Cardiovascular injuries and SARS-COV-2 infection: focus on elderly people

Claudia Colombo1,*, Laura Garatti1,2,*, Giulia Ferrante3, Francesca Casadei1, Claudio Montalto4, Gabriele Crimi5, Chiara Cogliati6, Enrico Ammirati7, Stefano Savonitto8, Nuccia Morici1,✉

1. Department of Cardiology De Gasperis Cardio Center, ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy; 2. School of Medicine and Surgery, University of Milano Bicocca, Italy; 3. Division of Cardiology, Heart and Lung Department, San Paolo Hospital, ASST Santi Paolo and Carlo, University of Milan, Italy; 4. Division of Cardiology, University of Pavia, Pavia, Lombardia, Italy; 5. Interventional Cardiology Unit, Cardio Thoraco Vascular Department (DICATOV), IRCCS Policlinico San Martino, Genova, Italy; 6. Internal Medicine, Department of Medicine and Riabilitation, ASST Fatebenefratelli-Sacco, Luigi Sacco Hospital, Milan, Italy; 7. De Gasperis Cardio Center and Transplant Center, Niguarda Hospital, Milan, Italy; 8. Division of Cardiology, Ospedale Manzoni, Lecco, Italy

*The authors contributed equally to this manuscript
✉Correspondence to: nuccia.morici@ospedaleniguarda.it
https://doi.org/10.11909/j.issn.1671-5411.2021.07.001

ABSTRACT The novel coronavirus disease (COVID-19) has hit the healthcare system worldwide. The risk of severe infection and mortality increases with advancing age, especially in subjects with comorbidities such as cardiovascular disease, hypertension, diabetes, obesity and cancer. Moreover, cardiovascular complications such as myocardial injury, heart failure and thromboembolism are frequently observed in COVID-19 cases, and several biomarkers (troponin, NTproBNP and D-Dimer) have been identified as prognostic indicators of disease severity and worst outcome. Currently, there is no specific therapy against SARS-CoV-2, although many medications are under investigation. The aim of this review will be to explore the intertwined relationship between COVID-19 disease and the cardiovascular system, focusing on elderly population. The available supportive treatments along with the related concerns in elderly patients, due to their comorbidities and polypharmacotherapy, will be explored.

The novel coronavirus type 2 (SARS-CoV-2) infection, which leads to severe acute respiratory syndrome in its most severe forms, has been first reported in December 2019 in the Chinese province of Hubei and subsequently designated as a pandemic by the World Health Organization (WHO) on March 11th 2020. Globally, as of 13 January 2021, there have been 90,054,813 confirmed cases of COVID-19, including 1,945,610 deaths, reported to WHO.[1] After the Chinese outbreak, Europe overtook China with the highest number of reported cases and deaths. The pandemic now is propagating across Americas, where over 25,958,213 cases and 717,028 deaths has been reported in November 2020.[1]

The case-fatality rate (CFR, i.e., number of deaths/number of diagnosed cases) differ significantly around the world, showing increased prevalence with advancing age. In particular, the CFR is < 1% for patients < 50 years of age, 1.3% for 50-year-old patients, 3.6% for 60-year-old patients, 8% for 70-year-old patients, and 14.8% for octogenarians.[2]

A number of key comorbidities are associated with worse clinical outcomes and CFR in patients with COVID-19. While CFR in patients with no medical history is low (0.9%), it raises to 5%-10% when frailty conditions are present [10.5% for cardiovascular disease (CVD), 7.3% for diabetes mellitus (DM), 6.3% for chronic obstructive pulmonary disease, 6% for arterial hypertension, and 5.6% for cancer].[2]

Among the predictors of outcome, age has consistently been reported as an independent and strong covariate associated with mortality.[3] Focusing on elderly patients, a recent cohort study of nursing home residents with COVID-19 has found impaired cognitive physical function as independent predictors of mortality in this population.[4]
A number of studies suggest an association between pre-existing CVD and severe COVID-19,[3,5−7] but the viral infection leads itself to CV complications or exacerbation of pre-existing CVD,[6,7] particularly in the geriatric population.[8]

PATHOPHYSIOLOGY

COVID-19 and Cardiovascular System: Hypothesis of Interaction and Mechanisms of Damage

COVID-19 interacts with various systems, being responsible for a wide spectrum of clinical manifestations. Angiotensin converting enzyme-2 (ACE2) has been demonstrated to be the SARS-CoV-2 cell entry receptor, after activation of the viral surface spike protein S by transmembrane protease serine 2 (TMPRSS2).[9] ACE2 is highly expressed in the lung (principally type II alveolar cells), but has also been found in multiple tissues, including heart, intestinal epithelium, vascular endothelium and kidneys.[6] Relevantly, by cleaving angiotensin II (Ang II), ACE2 generates Ang 1-7, which counteracts the pro-inflammatory and pro-oxidant effects of Ang II.[10,11]

Beyond direct cell damage due to viral infiltration, SARS-CoV-2 seems to downregulate ACE2 expression and Ang 1-7 production, leading to increased levels of Ang II.[12] Consequently, alveolar apoptosis and fibrosis together with cytokine storm and systemic inflammation can result in acute respiratory distress syndrome (ARDS) and multiorgan dysfunction.[13]

Cardiovascular complications are often observed in patients with COVID-19, especially those with severe manifestations. The mechanisms of cardiac injury remain under investigation, but it has been supposed to involve three possible mechanisms: direct myocardial infection through ACE2 receptors expressed in myocardial tissue, indirect injury due to the systemic inflammatory response and increased cardiac stress due to hypoxemia (Figure 1).[14−16]

Evidence suggests that ACE2 plays a double role in cardiovascular complication of COVID-19. First, ACE2 is largely expressed by myocardial pericytes,[17] therefore representing a potential portal of viral entry, resulting in cellular death and inflammation. On the other hand, viral replication seems to induce ACE2 downregulation.[18] This may alter the ACE/ACE2 balance leading to hyperactivation of the ACE/Ang II/AT1 system, responsible of vaso-constrictive, pro-inflammatory and pro-oxidant effects, potentially culminating in acute heart failure, endothelial dysfunction and intravascular coagulopathy.[19]

The cardiovascular damage mediated by SARS-CoV-2 can also result from the immune-mediated pathway caused by activated T and B cells, leading to a cytokine storm (i.e., interleukin-1 (IL-1), IL-6, and TNF-α)[20] that can exert a negative inotropic ef-
fect, promote cardiomyocyte apoptosis and fibrosis and induce the release of pro-coagulant factors.\textsuperscript{[21−23]} Generally, the rise in cardiac biomarkers tracks with inflammatory markers elevation, suggesting the relationship between cytokine storm and myocardial injury.\textsuperscript{[24]}

Even though Tavazzi, \textit{et al.}\textsuperscript{[25]} published a case of acute cardiac injury directly linked to SARS-CoV-2 myocardial localization, needs to be clarify if myocardial localization implies a viraemic phase or, alternatively, the migration of infected alveolar macrophages in extra-pulmonary tissues. Regardless the underlying mechanism, inflammatory infiltrates and necrosis were observed in cardiomyocytes of patients with COVID-19 and suspected myocarditis.\textsuperscript{[26,27]}

In addition, prolonged hypoxia due to respiratory failure leads to cardiomyocytes apoptosis,\textsuperscript{[28]} pulmonary hypertension,\textsuperscript{[29]} and pressure overload of the right ventricle. Finally, the endothelial damage caused by SARS-CoV-2 causes vascular injury with severe consequences as acute release of cytokines, plasminogen activator (responsible for high levels of D-dimers) and von Willebrand factor, leading to a pro-thrombotic status and to a thrombotic microangiopathy.\textsuperscript{[30−33]}

Interestingly, older adults and subjects with diabetes and pre-existing CVD have lower levels of ACE2.\textsuperscript{[34,35]} The ACE2 downregulation with subsequent increased levels of Ang II and proinflammatory state predisposes older individuals with cardiovascular comorbidities to experience a more aggressive SARS-CoV2 infection, which can explain the higher CFR reported in the studies.\textsuperscript{[36]}

Moreover, aging leads to a disruption of the immune system and to a vascular pro-inflammatory state with dysregulated production of cytokines and other inflammatory mediators, that can further explain the worst outcome of patients affected by COVID-19 disease.\textsuperscript{[37,38]}

**Myocardial Injury and Myocarditis**

Myocardial injury is generally defined by the elevation of cardiac troponin (cTn) above the 99\textsuperscript{th} percentile of its upper limit of normal (ULN). It can occur in the context of myocardial ischemia (type 1 or type 2 myocardial infarction according to fourth universal definition) or non-ischemic myocardial processes (myocarditis, stress-induced cardiomyopathy or cytokine release syndrome).\textsuperscript{[39]} Irrespectively from the underlying mechanism, cTn elevation was observed in 7.2\% to 17\% of hospitalized patients with COVID-19.\textsuperscript{[6,40]} and has important prognostic implications. Indeed, as showed in several observational studies (Table 1) troponin elevation among patients hospitalized with COVID-19 is associated with higher risk of mortality, especially in elderly with an history of CVD.\textsuperscript{[41]} The pattern in the rise of cTn levels is also significant: various reports from China showed that cTn values for survivors did not change significantly during follow-up, while they continued to rise until death in non-survivors.\textsuperscript{[6,28]}

In absence of obstructive coronary artery disease, whether the myocardial injury is secondary to oxygen supply-demand imbalance (Type 2 MI), acute myocarditis, stress cardiomyopathy or cardiac involvement in cytokine release syndrome is a challenging issue. Despite some argued that up to 7\% of COVID-19– related deaths were attributable to myocarditis,\textsuperscript{[42]} the prevalence of acute myocarditis among COVID-19 patients is still unclear.\textsuperscript{[43]} The Chinese National Health Commission firstly reports autopsy specimens characterized by degenerated and necrotized cardiomyocytes and monocytes, lymphocytes and/or neutrophils in the myocardium,\textsuperscript{[44]} making a diagnosis of suspected myocarditis. Considering that in the clinical scenario of COVID-19 patients cardiac magnetic resonance or endomyocardial biopsy are rarely feasible, the diagnosis of myocarditis is mainly based on troponin elevation in association with echocardiographic abnormalities and ECG changes compatible with acute myocarditis.\textsuperscript{[45]} Cases of acute cardiomyopathies with clinical, echocardiographic and ECG features of Tako-Tsubo syndrome have also been reported, especially in elderly individuals and in critically ill patients with prolonged mechanical ventilation.\textsuperscript{[46,47]}

**Acute Coronary Syndrome**

Despite the effects of COVID-19 on acute coronary syndromes (ACS) is still under investigation, it is known that profound systemic inflammatory responses may contribute to destabilize plaques in COVID-19 patients.\textsuperscript{[48]} In this regard, Kwong \textit{et al.}
RESEARCH ARTICLE

JOURNAL OF GERIATRIC CARDIOLOGY

Table 1  
Studies exploring relationship between myocardial injury and mortality in patients with COVID-19.

| First Author | Number of patients myocardial injury/total (%) | Definition of myocardial injury | Age, mean ± SD or median (IQR) | Impact of myocardial injury on outcomes |
|--------------|----------------------------------------------|--------------------------------|---------------------------------|----------------------------------------|
| Aquino[24]   | 73/254 (29%)                                  | Hs-cTnI > 99th URL              | 53.8 ± 12.7                     | Multivariate cox proportional hazards analysis showed that primary endpoint (mortality) is determined by several variables including myocardial injury (OR = 3.764, 95% CI: 1.307–10.838; P = 0.014). |
| Arcari[25]   | 39/103 (38%)                                  | Hs-cTnI >URN                    | 79 ± 13                         | In-hospital death is 11% in patients with Hs-troponine < URN and 31% in patients with Hs-troponine > URN (P = 0.012). |
| Barman HA[26]| 150/607 (24.7%)                                | Hs-cTnI > 99th percentile URL   | 68.5 ± 13.4                     | Mortality rate is higher in patients with cardiac injury vs. patients without myocardial injury (42% vs. 8%; P < 0.01). |
| Cipriani[27] | 41/109 (38%)                                  | Hs-cTnI > 99th URL              | 71 (60–81)                      | Compared with survivors, non-survivors presented with higher median levels of Hs-Ctnl (64 vs. 6 ng/L; P < 0.001). |
| Du[28]       | NA/179 (NA)                                   |                                 | 57.6 ± 13.7                     | Univariate and multivariate logistic regression analysis revealed that cardiac troponin I > 0.05 ng/mL (OR = 4.077, 95% CI: 1.66–14.253; P < 0.001) is associated with an increase in risk of mortality. |
| Guo[29]      | 52/187 (27.8%)                                 | TnT > 99th percentile URL       | 58.5 ± 14.66                    | TnT elevation is associated with increased risk of mortality (59.6% vs. 8.9%, P < 0.001). |
| Lala[30]     | 985/2,736 (36%)                                | Tn > 0.03 ng/mL                 | 66.40 ± 15.80                   | Elevated troponin levels were associated with an increased in-hospital mortality (37% vs. 13%; HR = 1.71 [95% CI: 1.13–2.59]; P = 0.01 via multivariable Cox regression analysis), and this is independent from concomitant cardiac disease. |
| Li[31]       | 181/2,068 (9%)                                 | Hs-cTnI > 99th URL              | 63 (51–70)                      | When compared to non-critically ill patients critically ill have more frequent cardiac injury on admission (30.3% vs. 2.3%, P < 0.001), with increased mortality during hospitalization (38.4% vs. 0%, P < 0.001). |
| Lombardi[32] | 278/614 (45.3%)                                | TnT or Tn > 99th percentile URL | 64±13.6                         | The development of cardiac injury is significantly associated with a higher inhospital mortality rate compared to those with normal troponin levels (40.9% vs. 11.1%, P < 0.001). |
| Lorente-Ros[33] | 147/700 (21%)                          | Tn > 99th percentile URL        | 66.76 ± 15.7                    | cTnI is associated with worse clinical outcomes, including all-cause mortality within 30 days (45.1% vs. 23.2%; P = 0.005). |
| Karbala[34]  | 118/386 (30%)                                  | Hs-cTnI > 99th URL              | 59 ± 16                         | Patients with elevated troponin have significantly increased odds of death for mildly elevated compared with normal troponin (adjusted OR = 2.06; 95% CI: 1.68–2.53; P < 0.001). |
| Majure[35]   | 1821/6,247 (29%)                               | Hs-cTnI > 99th percentile URL   | 66 (56–77)                      | Multivariable logistic regression analysis identified cTnI concentration (OR = 1.92 [95% CI: 1.41–2.59]) as one of the independent risk factors for death in patients with COVID-19. |
| Nie[36]      | 103/311 (33%)                                  | Tn > 99th percentile URL        | 63 (54–70)                      | Elevation of hs-cTnI is associated with increased 28 days mortality (adjusted HR 7.12 [95% CI: 4.60–11.03]; P < 0.001). |
| Qin[37]      | 95/1,462 (6.5%)                                | Hs-cTnI > 99th percentile URL   | 57 (45–66)                      | The rate of mortality is higher in patients with elevated hs-Tnl (22.5%, OR = 4.35, 95% CI: 1.72 to 11.04). |
| Stefanini[38] | 90/397 (22%)                                | Hs-Tn > 99th percentile URL     | 67 (55–76)                      | Tn > 0.026 ng/mL is associated with increased risk of in-hospital mortality (adjusted OR = 4.56; 95% CI: 1.28–16.28). |
| Shi[39]      | 106/671 (15.8%)                                | Tn > 99th percentile URL        | 63 (50–72)                      | Tn elevations is associated with increased mortality (51.2% vs. 4.5%, P < 0.001) also after multivariable adjustment (adjusted HR = 3.41; 95% CI: 1.62–7.16). |
| Shi[40]      | 82/416 (19.7%)                                 | Tn > 99th percentile URL        | 64 (21–95)                      | Elevated troponin is associated with a higher rate of mortality (37.2% vs. 14.8%, P < 0.001). |
| Tan[41]      | NA/115 (NA)                                    | NA                              | 63 (55–70)                      | Multivariable regression showed increasing odds of in-hospital critical-ill events associated with hypersensitive cTnI greater than 0.04 ng/mL (OR = 20.98, 95% CI: 3.51–125.31). |
| Wei[42]      | 16/101 (16%)                                   | Hs-TnT > 99th percentile URL    | 49 (34–62)                      | Log hs-TnT is associated with disease severity (OR = 6.63, 95% CI: 2.24 to 19.65). |
| Woo[43]      | NA/415 (NA)                                    | Hs-cTn > 99th URL Hs-cTn > 99th URL | 66 (54–77)                      | Elevation of hs-TnT is associated with the primary endpoint (mortality) is determined by several variables including myocardial injury (OR = 3.764, 95% CI: 1.307–10.838; P = 0.014). |
| Yang[44]     | 45/463 (10%)                                   | Hs-cTnI > 99th URL              | 60 (50–69)                      | Multivariable cox proportional hazards analysis showed that primary endpoint (mortality) is determined by several variables including myocardial injury (OR = 3.764, 95% CI: 1.307–10.838; P = 0.014). |

Hs-TnI: high sensitive troponone I; NA: not available; TnI: Troponine I; TnT: troponine T; URL: upper range limit; URN: upper range normality.
demonstrated that patients with acute respiratory infections are more prone to develop acute MI after influenza and after non-influenza viral illnesses including other coronavirus species. Moreover, inflammation promotes a prothrombotic state, which could further increase the risk of microangiopathy, and coronary thrombosis at sites of plaque disruption. As already mentioned, although reports suggest that cTn elevation in COVID-19 may be related more to myocardial injury or type 2 MI than to type 1 MI, more data are needed to properly understand all mechanisms that may induce ACS in SARS-CoV-2 infection. In the setting of supraventricular arrhythmias, as assessed by Colon et al., compared with patients without atrial tachyarrhythmias, those with atrial fibrillation, flutter, or tachycardia tended to be older with higher concentrations of CRP and D-dimer (55 ± 17 vs. 64.6 ± 12.8, P = 0.028). Heart Failure Although few data exists on incidence of heart failure in COVID-19 patients, as reported by Zhou, et al., acute heart failure (AHF) was observed in 23.0% of infected patients and was more common in patients who died compared to survivors (51.9% vs. 11.7%). Similar rates were observed in other studies. Whether AHF is most commonly due to exacerbation of pre-existing cardiovascular disease or to new cardiomyopathy (such as myocarditis or stress cardiomyopathy) is not clear. In elderly individuals with left ventricular (LV) dysfunction, coronary artery disease, hypertension or diabetes, AHF is more likely to result from the exacerbation of these conditions, sometimes previously undiagnosed. Moreover, diastolic LV dysfunction is a common condition related to senescence, particularly in patients with hypertension, overweight and chronic obstructive pulmonary disease (COPD). These patients are prone to develop heart failure with preserved ejection fraction (HFpEF), triggered by fever, tachycardia and impaired renal function. Routine monitoring of N-terminal pro-brain natriuretic peptide (NTproBNP) or BNP levels may be helpful to timely detection of patients with LV systolic or diastolic dysfunction, which is essential to avoid aggressive fluid replacement. However, since natriuretic peptides circulation levels are significantly influenced by age, their diagnostic and prognostic accuracy may be limited in the elderly population. Therefore, diagnostic age-adjusted cut-off values have been proposed and should be taken into account in the management of these patients.

Coagulation Abnormalities COVID-19 patients are at increased risk of thrombotic complications such as venous and arterial thromboembolism and microvasculature thrombosis. Data suggests that rates of thrombotic complications may involve almost 1/3 of critically ill patients. Hypercoagulability in COVID-19 is primary the result of direct effects of the virus able to infect endothelial cells and cause perturbation of the cellular homeostasis, leading to plasminogen activator release, and high molecular size multimeric von Willebrand factor causing thrombotic microangiopathy. Furthermore, severe inflammatory response, critical illness, and underlying traditional risk factors may all predispose to thrombotic events, similar to prior coronavirus outbreaks. Venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism (PE), is a common complication in critically ill patients.
patients with COVID-19, especially when admitted to ICU (Table 2). Case series of hospitalized patients with COVID-19 reported VTE in 20% to 85% of ICU-patients and in 2% to 15% of non-ICU patients. In some studies, VTE was associated with an increased mortality rate and longer duration of mechanical ventilation. Whereas prophylactic anticoagulation is generally effective in preventing DVT, many patients experienced PE despite adequate prophylaxis, usually without evidence of DVT. This evidence, together with autopsy studies descriptions of thrombotic microangiopathy in pulmonary and systemic vessels, suggest that pulmonary thrombi, rather than emboli from peripheral veins, may be the hallmark of severe COVID-19.

Table 2 Prevalence of VTE in hospitalized patients with COVID-19.

| First Author | Patient population | VTE n/total (%) | Age, mean ± SD or median (IQR) | All cause mortality, n/total (%) |
|--------------|--------------------|-----------------|---------------------------------|-------------------------------|
| Bilaloglu    | ICU and non-ICU    | ICU: 113/829 (13.6%) Non-ICU: 90/2505 (3.6%) | 64 (51–57) | 817/3334 (24.5%) |
| Criel        | ICU and non-ICU    | ICU: 4/30 (13.3%) Non-ICU: 2/52 (3.8%) | ICU: 64.5 ± 11.8 Non-ICU: 63.6 ± 14.4 | NR |
| Cui          | ICU                | 20/81 (24.7%) | VTE: 68.4 ± 9 Non-VTE: 57.1 ± 14 | 8/81 (10%) |
| Demelo-Rodriguez | Non ICU, with D-dimer > 1000 and CUS screening | 23/198 (11.6%) | DVT: 66.7 ± 15.2 Non-DVT: 68.4 ± 14.4 | NR |
| Desborough   | ICU                | 10/66 (15.2%) | VTE: 54 (45–63) Non-VTE: 59 (52–57) | 20/66 (30.3%) |
| Dubois-Silva | Non ICU            | 8/171 (4.9%)   | PE: 67 (58–74) | NR |
| Fraissè      | ICU                | 31/92 (33.7%)  | VTE: 62 (54–71) Non-VTE: 61 (55–69) | 38/92 (41%) |
| Helms        | ICU                | 28/150 (18.7%) | VTE: 55 ± 13 Non-VTE: 57 ± 17 | 39/91 (42.9%) |
| Hippensteel  | ICU                | 68/184 (37%)   | 64 ± 12 | 41/184 (22%) |
| Kolelait     | ICU and non-ICU, all underwent to LE venous duplexes | 18/135 (13.3%) | DVT: 59 (49–64) No-DVT: 64 (53–73) | DVT: 2/18 (11.1%) Non-DVT: 18/117 (15.4%) |
| Llitjos      | ICU                | 18/26 (69%)    | 68 (51.5–74.5) | 3/26 (12%) |
| Lodigiani    | ICU and non-ICU    | VTE: 61 (55–69) Non-ICU: 68 (55–77) | 92/388 (23.7%) |
| Longchamp    | ICU                | 8/25 (32%)     | 68 ± 11 | 5/25 (20%) |
| Mestre-Gomez | Non-ICU            | PE: 29/452 (6.4%) | PE: 65 (56–73) | PE: 1/29 (3.4%) |
| Middeldorp   | ICU and non-ICU    | VTE: 39/75 (52%) Non-ICU: 4/123 (3.3%) | VTE: 62 ± 10 Non-VTE: 60 ± 15 | NR |
| Nahum        | ICU                | 27/34 (79%)    | VTE: 62.9 ± 7.9 Non-VTE: 59.9 ± 11.2 | NR |
| Poissy       | ICU                | 22/107 (20.6%) | 60 (29–80) | NR |
| Soumagne     | ICU                | 79/375 (21%)   | PE: 61.1 ± 9.1 Non-PE: 63.9 ± 10.3 | PE: 16/55 (29%) Non-PE: 118/520 (57%) |
| Tavazzi      | ICU                | 12/54 (22.2%)  | VTE: 68 ± 7 | NR |
| Thomas       | ICU                | 6/63 (9.5%)    | 59 ±13 | NR |
| Wang         | ICU and non-ICU    | VTE: 19/88 (21.6%) | 61.5 (55–68.8) | DVT: 5/19 (26.3%) Non-DVT: 13/69 (18.8%) |
| Zhang        | Non-ICU            | 67/159 (42.1%) | VTE: 67 ± 12 Non-VTE: 59 ± 16 | VTE: 23/67 (34%) Non-VTE: 9/92 (9.7%) |

DVT: deep vein thrombosis; ICU: intensive care unit; LE: lower extremities; NR: not reported; PE: pulmonary embolism; VTE: Venous thromboembolism.
Arterial thrombosis was also reported as a complication of COVID-19. A large case series from New York, including 3334 patients, reported stroke in 1.6%, myocardial infarction in 8.9% and other arterial thrombotic events (i.e., acute limb ischemia, upper extremity arterial thrombosis, renal and splenic infarcts) in 1%. As predictable, arterial thrombotic events were associated with increased mortality (adjusted HR = 1.99; 95% CI: 1.65–2.40).[73]

The most common laboratory test abnormalities found in COVID-19 patients are thrombocytopenia and increased D-dimer levels, which are associated with a higher risk of requiring mechanical ventilation, ICU admission, or death.[66] In a multicenter retrospective cohort study from China, elevated D-dimer levels (> 1 g/L) were strongly associated with in-hospital death, even after multivariable adjustment.[61] As assessed by Tang, et al.[78] in a retrospective study of 183 COVID-19 patients, those who died presented levels of D-dimer and fibrin degradation products significantly increase (3.5- and ~1.9-fold increase, respectively) and PT prolongation. In addition, 71% of patients who died fulfilled the International Society on Thrombosis and Hemostasis criteria for DIC, compared with only 0.6% among survivors.

**TREATMENT CONSIDERATIONS**

Currently, there is no specific therapy against SARS-CoV-2, although many medications are under investigation. Therefore, we focused our review on supportive treatments and the related concerns in elderly COVID-19 patients, due to their comorbidities and polypharmacotherapy.

**Glucocorticoids**

Glucocorticoids are indicated for severely ill patients receiving respiratory support, as they counteract the immune system hyperactivation and mitigate the inflammatory multiorgan damage due to COVID-19.[79] This recommendation originates from several clinical trials, especially the RECOVERY Trial,[80] which showed that treatment with dexamethasone at a dose of 6 mg once daily reduced mortality in COVID-19 patients on supplemental oxygen or ventilatory support. Data are lacking about the possible role of glucocorticoids in preventing and treating the cardiovascular complications of COVID-19, which may constitute a supplemental indication to this treatment. Of note, in elderly patients, the benefits of a steroid therapy may be outweighed by higher risk of superinfections, induction or worsening of underlying psychiatric disorder and metabolic side effects (i.e., fluid retention, hypertension and hyperglycemia), which can precipitate pre-existing comorbidities including cardiovascular disease.[81] Caution should be used about corticosteroid administration in elderly STEMI patients with subacute admission, not a rare case during the current pandemic, due to the increased risk of myocardial rupture.[82]

**Anticoagulants**

Due to the high rate of venous and arterial thromboembolism, anticoagulation is a cornerstone in the management of COVID-19 patients. According to current guidelines,[83] all hospitalized patients should receive low-molecular-weight heparin (LMWH) at doses registered for prevention of venous thromboembolism, the only which have demonstrated an association with reduced risk of death.[84] LMWH is also known to exert anti-inflammatory and immunomodulant properties, by protecting glycocalyx from shedding.[85]

Anticoagulant interventions at increased doses (intermediate or therapeutic) have been proposed and used in patients hospitalized for COVID disease,[64] based on the hypothesis that higher dose of heparin could reduce mortality and morbidity by improving anti-inflammatory activity and decreasing the incidence of local thrombosis in vital organs, therefore preventing their disfunction. Comparisons between different anticoagulant dosing strategies are under investigation in several randomized controlled trials (RCTs), which have been described in a recent scoping review.[86] Of note, in three trials (REMAP-CAP, ACTV-4 and ATTAC) investigating therapeutic doses of anticoagulant drugs in COVID-19 patients, enrollment of ICU patients has been recently paused because of futility and safety concerns.[87]

Since high-quality data from randomized controlled trials will provide consistent evidence, any different approach compared to a thromboprophylaxis regimen, should be avoided in patients without a clear indication to full dose anticoagulant therapy.
An algorithm for the antithrombotic management of patients with SARS-CoV2 infection, with and without pre-existing indications to antithrombotic treatment, is suggested in Figure 2.

Currently, there is no sufficient evidence to recommend for or against intermediate and therapeutic dose regimens, which are obviously affected by a higher risk of bleeding.

**COVID-19 Specific Treatments and CV System: Side Effects and Drug-Drug Interaction**

Several clinical trials on antiviral and immunomodulant agents are currently ongoing. Advanced age is generally not an exclusion criterion *per se*, but patients with severe comorbidities (i.e., advanced liver, heart, or kidney disease) are usually excluded. Potential interactions of these therapies with the cardiovascular system and with other cardiovascular medications are summarized in (Table 3).

**Cardiovascular Drugs and COVID-19: Role of RAAS Inhibitors**

Besides the cardiovascular effects of SARS-CoV-2 treatments, early concern had been raised about the potential involvement of some cardiovascular drugs in the natural history of COVID-19. In particular,

---

**Figure 2  Flow chart of antithrombotic therapy in patients with COVID-19.** Proposed algorithm for the management of antithrombotic therapy during hospitalization and after discharge of patients with COVID-19. DAPT: dual antiplatelet therapy; DOAC: direct oral anticoagulant; LMWH: low molecular weight heparin; SAPT: single antiplatelet therapy; UFH: unfractioned heparin.
Table 3  Proposed COVID-19 treatment: concluded RCTs’ population age and CV interactions.

| Drug                          | Clinicaltrials.gov identifier | Age, mean ± SD or median (IQR) | Mechanism of action | CV side effects | CV drug interactions | Recommendations |
|-------------------------------|------------------------------|---------------------------------|---------------------|-----------------|----------------------|------------------|
| Chloroquine/hydroxychloroquine | NCT04316377, NCT04326961, NCT04332991, NCT043323527, NCT043812123, NCT04419194 | 62 (50-73) | Blockade of virus cell entry by changing endosomal pH | QTc prolongation, ventricular arrhythmias, AV/block direct cardio-toxicity with worsening of underlying cardiomyopathies | ↑Concentration Beta-blockers (CYP2D6 inhibition), and Digoxin (P-glycoprotein inhibition), QTc-prolonging antiarrhythmics | Monitor ECG; Monitor digoxin levels; Avoid in case of cardiomyopathy, conductive disorders, ventricular arrhythmias, prolonged QTc, concomitant QTc/PR-prolonging drugs |
| Lopinavir/Ritonavir           | NCT04276688, NCT04252885    | 52 (32–62) | Protease inhibition | QTc prolongation, AV blocks, ↑ serum cholesterol | ↑Metabolism of anticoagulants, statins, amiodarone, antiplatelets | Monitor ECG; Monitor INR; Avoid in case of structural heart disease and conduction disorders. Dabigatran and Warfarin: administer with caution; Apixaban half dose (do not administer if required 2.5 mg bid); edoxaban/ribavarin contraindicated; avoid statins; monitor digoxin level; antiplatelets: prefer prasugrel if not contraindicated |
| Ribavirin                     | NCT04276688                 | 52 (32–62) | RdRP inhibition | Hemolytic anemia | ↑Metabolism of Warfarin | Use with caution in ischemic heart disease. Monitor INR |
| Remdesivir                    | NCT04281075, NCT04292699, NCT04292730, NCT04415579 | 58.9 ± 15 | RdRP inhibition | Unknown | Unknown | - |
| Tocilizumab                   | NCT04356937                 | 59.8 (45–69) | IL-6 receptor inhibition | Hypertension, ↑ serum cholesterol | ↑Metabolism of anticoagulants, statins, amiodarone, antiplatelets | Monitor ECG; Monitor INR; No dose adjustment required |
| Sarilumab                     | NCT04324073, NCT04327388, NCT04322773 | 52 (32–62) | IL-6 receptor inhibitor | Unknown | ↑Metabolism of anticoagulants, statins, amiodarone, antiplatelets | Monitor ECG; Monitor INR; No dose adjustment required |
| Bevacizumab                   | NCT04275414                 | 61 ± 14 | VEGF inhibition | Direct cardiac toxicity vs worsening of cardiomyopathy, hypertension, thromboembolic events | None | Avoid in case of cardiomyopathy/heart failure |
| Interferon                    | NCT04276688, NCT04251400   | 52 (32–62) | Immune system activation | Direct cardiac toxicity vs worsening of cardiomyopathy, conduction disorders | ↑Concentration of Warfarin | Avoid in case of structural heart disease/conduction disorders. Monitor INR |
| Glucocorticoids               | NCT04372401, NCT04381936    | 61 ± 14 | Reduce inflammation | Fluid retention, hypertension, ↑ Concentration of Warfarin | Monitor BP and INR |
| Heparins (LMWH or UFH)        | NCT04362085, NCT04469834, NCT0444700, NCT04235707, NCT04377997, NCT04372589, NCT04410293, NCT04668389, NCT04394377, NCT04373517, NCT04366960, NCT04368181, NCT04367831, NCT04351724 | 52 (32–62) | All RCTs are still recruiting (no concluded RCTs available) | Bleeding; HIT | Other anticoagulants; antiplatelets (risk of bleeding) | Prophylactic doses in all hospitalized patients; Continue concomitant antiplatelet drugs; Monitor blood cell count and renal function |

ACS: acute coronary syndrome; ADHF: acute decompensated heart failure; ATIII: antithrombin III; AV: atrio-ventricular; BP: blood pressure; CV: cardiovascular; CYP: cytochrome; DOAC: direct oral anticoagulant; ECG: electrocardiogram; HIT: heparin-induced thrombocytopenia; INR: international normalized ratio; IL-1: interleukin-1; IL-6: interleukin-6; LMWH: low molecular weight heparin; QTc: corrected QT interval; RCT: randomized clinical trials; RdRP: RNA-dependent RNA polymerase; VEGF: vascular endothelial growth factor.
since ACEi and ARBs have been shown to upregulate ACE2 expression in animal models,\cite{88} it had been supposed that these drugs might cause a higher susceptibility and/or a more aggressive course of COVID-19.\cite{88,90} On the other hand, RAAS inhibitors could exert a beneficial effect by counteracting the pro-inflammatory role of Angiotensin II, as previously discussed, despite lack of evidence from clinical studies. Based on available data,\cite{90-92} major cardiology scientific societies recommend the continuation or initiation of ACEi/ARBs when indicated.\cite{93,94}

**Therapeutic Antibodies**

Antibodies taken from the blood of recovered patients serve as a therapeutic alternative that is currently under study. One of the first studies on the use of plasma in the treatment of patients with SARS-CoV2 infections was conducted on 5 COVID-19 patients\cite{95} and followed by other studies, mostly on a small number of patients.\cite{96} The main results of the observational studies conducted reported clinical and survival improvement in all patients after the end of the additional intervention with plasma and hyperimmune immunoglobulins. However, as recently demonstrated by RCTs, the use of convalescent plasma therapy in addition to standard treatment in patients with moderate to severe pneumonia due to COVID-19 did not reduce mortality or improve other clinical outcomes as compared with placebo.\cite{97,98}

**Vaccine**

Several observations support the concept that vaccination has the potential to prevent SARS-CoV-2 infection. In non-human primate studies, infection with wild-type SARS-CoV-2 virus protected against subsequent reinfection, indicating that infection can result in protective immunity.\cite{99} Vaccination of primates also protected against viral challenge allowing development of functional neutralizing antibodies correlated with protection.\cite{100} Epidemiologic studies in humans have also suggested that neutralizing antibodies are associated with protection from infection.\cite{101} SARS-CoV-2 vaccines are being developed using several different platforms.\cite{102} Some of these are traditional approaches, such as recombinant proteins and vectors.\cite{102} Some platforms, such as RNA and DNA vaccines, have never been employed in a licensed vaccine. Recently mRNA vaccines BNT162b2 (Pfizer-BioNTech COVID-19 Vaccine) and 1273 (Moderna COVID-19 Vaccine) have been granted emergency use authorization (EUA) for prevention of COVID-19. Of note, responses in participants ≥ 65 years old to mRNA vaccine (BNT162b2 Pfizer-BioNTech) were generally lower than in younger subjects, but still comparable to titers in convalescent plasma.\cite{103} As well as mRNA 1273 (Moderna COVID-19 Vaccine) vaccination in adults older than 55 years also elicited immune responses that were comparable to those seen in the younger populations.\cite{104}

**CONCLUSIONS**

From the beginning of the COVID-19 outbreak, the scientific world devote attention to the cardiovascular implication of SARS-COV-2 infection. Since cardiovascular biomarkers are recognized as prognostic indicators, the effort to complete understand the mechanisms of this interaction is still crucial. Despite current evidence of several interaction between viral infection and cardiovascular disease, the consideration for treatments, including ACEI or ARB, immunosuppression/modulation and anti-coagulation continue to evolve. Elderly people have been the proportion with worst outcome among those affected by SARS-CoV-2 infection. However, the need of turn off the effects of the immune system hyperactivation by therapy should adequately counterbalance the excess of adverse effects in the elderly population.

**REFERENCES**

[1] WHO Coronavirus Disease (COVID-19) Dashboard. https://covid19.who.int (accessed January 24, 2021).
[2] Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72,314 Cases From the Chinese Center for Disease Control and Prevention. JAMA 2020; 323: 1239.
[3] Guan W, Ni Z, Hu Y, et al. Clinical characteristics of 2019 novel coronavirus infection in China. Medrxiv 2020: 2020.02.06.20020974.
[4] Panagiotou OA, Kosar CM, White EM, et al. Risk
Factors Associated With All-Cause 30-Day Mortality in Nursing Home Residents With COVID-19. JAMA Intern Med 2021.

[5] Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. The Lancet 2020; 395: 497–506.

[6] Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. The Lancet 2020; 395: 1054–1062.

[7] Ruan Q, Yang K, Wang W, et al. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med 2020; 46: 846–848.

[8] Napoli C, Tritto I, Benincasa G, et al. Cardiovascular involvement during COVID-19 and clinical implications in elderly patients. A review. Ann Med Surg 2020; 57: 236–243.

[9] Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. Cell 2020; 181: 271–280.

[10] Rodrigues Prestes TR, Rocha NP, Miranda AS, et al. The Anti-Inflammatory Potential of ACE2/Angiotensin-(1-7)/Mas Receptor Axis: Evidence from Basic and Clinical Research. Curr Drug Targets 2017; 18: 1301–1313.

[11] Wang K, Gheblawi M, Oudit GY. Angiotensin converting enzyme 2: a double-edged sword. Circulation 2020; 142: 426–428.

[12] Sankrityayan H, Kale A, Sharma N, et al. Evidence for Use or Disuse of Renin-Angiotensin System Modulators in Patients Having COVID-19 With an Underlying Cardiorenal Disorder. J Cardiovasc Pharmacol Ther 2020; 25: 299–306.

[13] Zhou P, Yang XL, Wang XG, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature 2020; 579: 270–273.

[14] Akhmerov A, Marbán E. COVID-19 and the Heart. Circ Res 2020; 126: 1443–1455.

[15] Hendren Nicholas S, Drazner Mark H, Bokzurt Biykm, Cooper Leslie T. Description and Proposed Hypothesis of Thrombi in SARS-CoV-2 Infection: Time to Re-think. Thromb Haemost 2020; 120: 1339–1342.

[16] Clerkin Kevin J, Fried Justin A, Jayant R, et al. COVID-19 and Cardiovascular Disease. Circulation 2020; 141: 1648–1655.

[17] Chen L, Li X, Chen M, et al. The ACE2 expression in human heart indicates new potential mechanism of heart injury among patients infected with SARS-CoV-2. Cardiovasc Res 2020; 116: 1097–1100.

[18] Dijkman R, Jebbink MF, Dejjs M, et al. Replication-dependent downregulation of cellular angiotensin-converting enzyme 2 protein expression by human coronavirus NL63. J Gen Virol 2012; 93: 1924–9.

[19] Henry BM, Vikse J, Benoit S, et al. Hyperinflammation and derangement of renin-angiotensin-aldosterone system in COVID-19: A novel hypothesis for clinically suspected hypercoagulopathy and microvascular immunothrombosis. Clin Chim Acta Int J Clin Chem 2020; 507: 167–173.

[20] Mehta P, McAuley DF, Brown M, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. The Lancet 2020; 395: 1033–1034.

[21] Mann DL. Innate immunity and the failing heart: the cytokine hypothesis revisited. Circ Res 2015; 116: 1254–1268.

[22] Toldo S, Abbate A. The NLRP3 inflammasome in acute myocardial infarction. Nat Rev Cardiol 2018; 15: 203–214.

[23] Moccia F, Gerbino A, Lionetti V, et al. COVID-19-associated cardiovascular morbidity in older adults: a position paper from the Italian Society of Cardiovascular Researches. Gero Science 2020; 42: 1021–1049.

[24] Li C, Jiang J, Wang F, et al. Longitudinal correlation of biomarkers of cardiac injury, inflammation, and coagulation to outcome in hospitalized COVID-19 patients. J Mol Cell Cardiol 2020; 147: 74–87.

[25] Tavazzi G, Pellegrini C, Maurelli M, et al. Myocardial localization of coronavirus in COVID-19 cardiogenic shock. Eur J Heart Fail 2020; 22: 911–915.

[26] Zou X, Chen K, Zou J, et al. Single-cell RNA-seq data analysis on the receptor ACE2 expression reveals the potential risk of different human organs vulnerable to 2019-nCoV infection. Front Med 2020; 14: 185–192.

[27] Booth CM, Matukas LM, Tomlinson GA, et al. Clinical features and short-term outcomes of 144 patients with SARS in the greater Toronto area. JAMA 2003; 289: 2801–2809.

[28] Zheng YY, Ma YT, Zhang YJ, Xie X. COVID-19 and the cardiovascular system. Nat Rev Cardiol 2020; 17: 259–260.

[29] Netzer NC, Strohl KP, Högel J, et al. Right ventricle dimensions and function in response to acute hypoxia in healthy human subjects. Acta Physiol 2017; 219: 478–485.

[30] Varga Z, Flammer AJ, Steiger P, et al. Endothelial cell infection and endotheliitis in COVID-19. Lancet Lond Engl 2020; 395: 1417–1418.

[31] Ackermann M, Verleden SE, Kuehnel M, et al. Pulmonary Vascular Endotheliitis, Thrombosis, and Angiogenesis in Covid-19. N Engl J Med 2020; 383: 120–128.

[32] Morici N, Bottiroli M, Fumagalli R, et al. Role of von Willebrand Factor and ADAMTS-13 in the Pathogenesis of Thrombi in SARS-CoV-2 Infection: Time to Re-think. Thromb Haemost 2020; 120: 1339–1342.

[33] Giustino G, Pinney SP, Lala A, et al. Coronavirus and Cardiovascular Disease, Myocardial Injury, and Arrhythmia: JACC Focus Seminar. J Am Coll Cardiol 2020; 76: 2011–2023.

[34] Xie XD, Chen JZ, Wang XX, et al. Age- and gender-related difference of ACE2 expression in rat lung. Life Sci 2006; 78: 2166–2171.

[35] Lakatta EG. The reality of getting old. Nat Rev Cardiol 2020; 17: 2171–2178.

[36] Perrotta F, Corbi G, Mazzeo G, et al. COVID-19 and the elderly: insights into pathogenesis and clinical decision-making. Aging Clin Exp Res 2020; 32(8): 1599–608.

[37] Napoli C, Tritto I, Mansueto G, Coscioni E, Ambrosio G. Immunosenescence exacerbates the COVID-19.
Arch Gerontol Geriatr 2020; 90: 104174.

[38] Aw D, Silva AB, Palmer DB. Immunosenesence: emerging challenges for an ageing population. Immunology 2007; 120: 435–446.

[39] Thygensen K, Alpert JS, White HD, et al. Universal Definition of Myocardial Infarction. Circulation 2007; 116: 2634–2653.

[40] Wang D, Hu B, Hu C, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA 2020; 323: 1061.

[41] Lala A, Johnson KW, Januzzi JL, et al. Prevalence and Impact of Myocardial Injury in Patients Hospitalized With COVID-19 Infection. J Am Coll Cardiol 2020; 76: 533–546.

[42] Driggin E, Madhavan MV, Bikdeli B, et al. Cardiovascular Considerations for Patients, Health Care Workers, and Health Systems During the COVID-19 Pandemic. J Am Coll Cardiol 2020; 75: 2352–2371.

[43] Siripanthong B, Nazarian S, Muser D, et al. Recognizing COVID-19–related myocarditis: The possible pathophysiology and proposed guideline for diagnosis and management. Heart Rhythm 2020; 17: 1463–1471.

[44] Chinese Clinical Guidance for COVID-19 Pneumonia Diagnosis and Treatment (7th edition). http://kjfy.meetingchina.org/msite/news/show/cn/3337.html (accessed January 24, 2021).

[45] Ammirati E, Wang DW. SARS-CoV-2 inflames the heart. The importance of awareness of myocardial injury in COVID-19 patients. Int J Cardiol 2020; 311: 122–123.

[46] Fried IA, Kumudha R, Reema B, et al. The Variety of Cardiovascular Presentations of COVID-19. Circulation 2020; 141: 1930–1936.

[47] Sala S, Peretto G, Gramigna M, et al. Acute myocarditis presenting as a reverse Tako-Tsubo syndrome in a patient with SARS-CoV-2 respiratory infection. Eur Heart J 2020; 41: 1861–1862.

[48] Musher DM, Abers MS, Corrales-Medina VF. Acute Infection and Myocardial Infarction. N Engl J Med 2019; 380: 171–176.

[49] Kwong JC, Schwartz KL, Campitelli MA, et al. Acute Myocardial Infarction after Laboratory-Confirmed Influenza Infection. N Engl J Med 2018; 378: 345–353.

[50] Liu PP, Blet A, Smyth D, Li H. The Science Underlying COVID-19: Implications for the Cardiovascular System. Circulation 2020; 142: 68–78.

[51] Harskamp RE, van Ginkel MW. Acute respiratory tract infections: a potential trigger for the acute coronary syndrome. Ann Med 2008; 40: 121–128.

[52] Schiavone M, Gobbi C, Biondi-Zoccai G, et al. Acute Coronary Syndromes and Covid-19: Exploring the Uncertainties. J Clin Med 2020; 9: 1683.

[53] Baldi E, Sechi GM, Mare C, et al. Out-of-Hospital Cardiac Arrest during the Covid-19 Outbreak in Italy. N Engl J Med 2020; 383: 496–498.

[54] De Luca G, Verdoia M, Cercek M, et al. Impact of COVID-19 pandemic on mechanical reperfusion for patients with STEMI. J Am Coll Cardiol 2020; 76: 2321–2330.

[55] Bhatla A, Mayer MM, Adusumalli S, et al. COVID-19 and cardiac arrhythmias. Heart Rhythm 2020; 17: 1439–1444.

[56] Colon CM, Barrios JG, Chiles JW, et al. Atrial Arrhythmias in COVID-19 Patients. JACC Clin Electrophysiol 2020; 6: 1189–1190.

[57] Chen T, Wu D, Chen H, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. BMJ 2020; 368: m1091.

[58] Mehrara B, Ruschitzka F. COVID-19 Illness and Heart Failure: A Missing Link? JACC Heart Fail 2020; 8: 512.

[59] Owan TE, Hodge DO, Herges RM, et al. Trends in prevalence and outcome of heart failure with preserved ejection fraction. N Engl J Med 2006; 355: 251–259.

[60] Hogenhuis J, Voors AA, Jaarsma T, et al. Influence of age on natriuretic peptides in patients with chronic heart failure: a comparison between ANP/NT-ANP and BNP/NT-proBNP. Eur J Heart Fail 2005; 7: 81–86.

[61] Alehagen U, Goetze JP, Dahlström U. Reference intervals and decision limits for B-type natriuretic peptide (BNP) and its precursor (NT-proBNP) in the elderly. Clin Chim Acta Int J Clin Chem 2007; 382: 8–14.

[62] Januzzi JL, van Kimmenade R, Lainchbury J, et al. NT-proBNP testing for diagnosis and short-term prognostic value in acute destabilized heart failure: an international pooled analysis of 1256 patients: the International Collaborative of NT-proBNP Study. Eur Heart J 2006; 27: 330–337.

[63] Vergaro G, Januzzi JL, Solal AC, et al. NT-proBNP prognostic value is maintained in elderly and very elderly patients with chronic systolic heart failure. Int J Cardiol 2018; 271: 324–330.

[64] Klok FA, Kruip MJHA, van der Meer NJM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thromb Res 2020; 191: 145–147.

[65] Libby P, Lüscher T. COVID-19 is, in the end, an endothelial disease. Eur Heart J 2020; 41: 3038–3044.

[66] Bikdeli B, Madhavan MV, Jimenez D, et al. COVID-19 and Thrombotic or Thromboembolic Disease: Implications for Prevention, Antithrombotic Therapy, and Follow-Up: JACC State-of-the-Art Review. J Am Coll Cardiol 2020; 75: 2950–2973.

[67] Ranucci M, Sitzia C, Baryshnikova E, et al. COVID-19-Associated Coagulopathy: Biomarkers of Thrombin Generation and Fibrinolysis Leading the Outcome. J Clin Med 2020; 9: 3487.

[68] Li X, Guan B, Su T, et al. Impact of cardiovascular disease and cardiac injury on in-hospital mortality in patients with COVID-19: a systematic review and meta-analysis. Heart 2020; 106: 1142–1147.

[69] Shi Q, Qin M, Cai Y, et al. Characteristics and clinical significance of myocardial injury in patients with severe coronavirus disease 2019. Eur Heart J 2020; 41: 2070–2079.

[70] Ren B, Yan FF, Deng ZM, et al. Extremely High Incidence of Lower Extremity Deep Venous Thrombosis in 48 Patients With Severe COVID-19 in Wuhan. Circulation 2020; 142: 181–183.

[71] Lodigiani C, Iapichino G, Carenzo L, et al. Venous
and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy. *Thromb Res* 2020; 191: 9–14.

[72] Litjot J, Leclerc M, Chochois C, et al. High incidence of venous thromboembolic events in anticoagulated severe COVID-19 patients. *J Thromb Haemost* 2020; 18: 1743–1746.

[73] Bilaloglu S, Aphypananphongs Y, Jones S, et al. Thrombosis in Hospitalized Patients With COVID-19 in a New York City Health System. *JAMA* 2020; 324: 799.

[74] Zhang L, Feng X, Zhang D, et al. Deep Vein Thrombosis in Hospitalized Patients With COVID-19 in Wuhan, China: Prevalence, Risk Factors, and Outcome. *Circulation* 2020; 142: 114–128.

[75] Hippensteel JA, Burnham EL, Jolley SE. Prevalence of venous thromboembolism in critically ill patients with COVID-19. *Br J Haematol* 2020; 190: e134–e137.

[76] Menter T, Haslbauer JD, Nienhold R, et al. Postmortem examination of COVID-19 patients reveals diffuse alveolar damage with severe capillary congestion and variegated findings in lungs and other organs suggesting vascular dysfunction. *Histopathology* 2020; 77: 198–209.

[77] Birocchi S, Manzioni M, Podda GM, et al. High rates of pulmonary artery occlusions in COVID-19. A meta-analysis. *Eur J Clin Invest* 2021; 51: e13433.

[78] Levi M, Toh CH, Thachil J, Watson HG. Guidelines for the diagnosis and management of disseminated intravascular coagulation. British Committee for Standards in Haematology. *Br J Haematol* 2009; 145: 24–33.

[79] Information on COVID-19 Treatment Guidelines. https://www.covid19treatmentguidelines.nih.gov/ (access on January 8, 2021).

[80] The RECOVERY Collaborative Group. Dexamethasone in Hospitalized Patients with Covid-19 — Preliminary Report. *N Engl J Med* 2020: NEJMoa 2021436.

[81] Ben Dhauo B, Boussema F, Aydi Z, Baill L, Tira H, Cherif O, et al. Corticoid-associated complications in elderly. *Tunis Med* 2012; 90: 774–777.

[82] Silverman HS, Pfeifer MP. Relation between use of anti-inflammatory agents and left ventricular free wall rupture during acute myocardial infarction. *Am J Cardiol* 1987; 59: 363–364.

[83] Flaczyk A, Rosovsky RP, Reed CT, et al. Comparison of published guidelines for management of coagulopathy and thrombosis in critically ill patients with COVID-19: implications for clinical practice and future investigations. *Crit Care* 2020; 24: 559.

[84] Tang N, Bai H, Chen X, et al. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. *J Thromb Haemost* 2020; 18: 1094–1099.

[85] Li X, Ma X. The role of heparin in sepsis: much more than just an anticoagulant. *Br J Haematol* 2017; 179: 389–398.

[86] Tritschler T, Mathieu ME, Skeith L, et al. Anticoagulant interventions in hospitalized patients with COVID-19: A scoping review of randomized controlled tri-}

[87] COVID-19 Anticoagulation Trials ‘Paused’ for Futility, Safety. Medscape. http://www.medscape.com/viewarticle/943085 (accessed on January 8, 2021).

[88] Ferrario CM, Jewell J, Chappell MC, et al. Effect of Angiotensin-Converting Enzyme Inhibition and Angiotensin II Receptor Blockers on Cardiac Angiotensin-Converting Enzyme 2. *Circulation* 2005; 111: 2605–2610.

[89] Kuster GM, Pfister O, Burkard T, et al. SARS-CoV2: should inhibitors of the renin–angiotensin system be withdrawn in patients with COVID-19? *Eur Heart J* 2020; 41: 1801–1805.

[90] Reynolds HR, Adhikari S, Pulgarin C, et al. Renin-Angiotensin-Aldosterone System Inhibitors and Risk of Covid-19. *N Engl J Med* 2020; 382: 2441–2448.

[91] Mancia G, Rea F, Ludergnani M, et al. Renin-Angiotensin-Aldosterone System Blockers and the Risk of Covid-19. *N Engl J Med* 2020; 382: 2431–2440.

[92] Mehta N, Kalra A, Nowacki AS, et al. Association of Use of Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers With Testing Positive for Coronavirus Disease 2019 (COVID-19). *JAMA Cardiol* 2020; 5: 1020.

[93] Adamo M, Lombardi CM, Metra M. June 2020 at a glance: focus on COVID-19, quality of life and comorbidities. *Eur J Heart Fail* 2020; 22: 917–918.

[94] Han YL, Li YM, Ma CS. Scientific statement of the Chinese Society of Cardiology (CSC) on using of renin-angiotensin system blockers in patients with cardiovascular disease and COVID-19. *J Geriatr Cardiol* 2020; 17: 241–242.

[95] Shen C, Wang Z, Zhao F, et al. Treatment of 5 Critically Ill Patients With COVID-19 With Convalescent Plasma. *JAMA* 2020; 323: 1582.

[96] Valk SJ, Picchotta V, Chai KL, et al. Convalescent plasma or hyperimmune immunoglobulin for people with COVID-19: a rapid review. *Cochrane Database Syst Rev* 2020; 5: CD013600.

[97] Simonovich VA, Burgos Pratx LD, Scibona P, et al. A Randomized Trial of Convalescent Plasma in Covid-19 Severe Pneumonia. *N Engl J Med* 2021; 384: 619–629.

[98] Agarwal A, Mukherjee A, Kumar G, et al. Convalescent plasma in the management of moderate covid-19 in adults in India: open label phase II multicentre randomised controlled trial (PLACID Trial). *BMJ* 2020; 371.

[99] Deng W, Bao L, Liu J, et al. Primary exposure to SARS-CoV-2 protects against reinfection in rhesus macaques. *Science* 2020; 369: 818–823.

[100] Gao Q, Bao L, Mao H, et al. Development of an inactivated vaccine candidate for SARS-CoV-2. *Science* 2020; 369: 77–81.

[101] Addetia A, Crawford KHD, Dingens A, et al. Neutralizing Antibodies Correlate with Protection from SARS-CoV-2 in Humans during a Fishery Vessel Outbreak with a High Attack Rate. *J Clin Microbiol* 2020; 58: e02107–e02120.

[102] Dong Y, Dai T, Wei Y, et al. A systematic review of
SARS-CoV-2 vaccine candidates. *Signal Transduct Target Ther* 2020; 5: 1–14.

[103] Walsh EE, Frenck RW, Falsey AR, *et al.* Safety and Immunogenicity of Two RNA-Based Covid-19 Vaccine Candidates. *N Engl J Med* 2020; 383: 2439–2450.

[104] Anderson EJ, Rouphael NG, Widge AT, *et al.* Safety and Immunogenicity of SARS-CoV-2 mRNA-1273 Vaccine in Older Adults. *N Engl J Med* 2020; 383: 2427–2438.

[105] Heberto AB, Carlos PCJ, Antonio CRJ, *et al.* Implications of myocardial injury in Mexican hospitalized patients with coronavirus disease 2019 (COVID-19). *JFC Heart Vasc* 2020; 30: 100638.

[106] Arcari L, Luciani M, Cacciotti L, *et al.* Incidence and determinants of high-sensitivity troponin and natriuretic peptides elevation at admission in hospitalized COVID-19 pneumonia patients. *Intern Emerg Med* 2020; 15: 1467–1476.

[107] Cipriani A, Capone F, Donato F, *et al.* Cardiac injury and mortality in patients with Coronavirus disease 2019 (COVID-19): insights from a mediation analysis. *Intern Emerg Med* 2020; 16: 419–427.

[108] Du RH, Liang LR, Yang CQ, *et al.* Predictors of mortality for patients with COVID-19 pneumonia caused by SARS-CoV-2: a prospective cohort study. *Eur Respir J* 2020; 55: 2000524.

[109] Guo T, Fan Y, Chen M, *et al.* Cardiovascular Implications of Fatal Outcomes of Patients With Hospitalized Patients. *JAMA Cardiol* 2020; 5: 1–8.

[110] Lombardi CM, Carubelli V, Iorio A, *et al.* Association of Troponin Levels With Mortality in Italian Patients Hospitalized With Coronavirus Disease 2019: Results of a Multicenter Study. *JAMA Cardiol* 2020; 5: 1274.

[111] Lorente-Ros A, Ruiz JMM, Rincón LM, *et al.* Myocardial injury determination improves risk stratification and predicts mortality in COVID-19 patients. *Cardiol J* 2020; 27: 489–496.

[112] Karbalai Saleh S, Orai A, Soleimani A, *et al.* The association between cardiac injury and outcomes in hospitalized patients with COVID-19. *Intern Emerg Med* 2020; 15: 1415–1424.

[113] Majure DT, Gruberg L, Saba SG, *et al.* Usefulness of Elevated Troponin to Predict Death in Patients With COVID-19 and Myocardial Injury. *Am J Cardiol* 2021; 138: 100–106.

[114] Nie SF, Yu M, Xie T, *et al.* Cardiac Troponin I Is an Independent Predictor for Mortality in Hospitalized Patients With COVID-19. *Circulation* 2020; 142: 608–610.

[115] Qin JJ, Cheng X, Zhou F, *et al.* Redefining Cardiac Biomarkers in Predicting Mortality of Inpatients With COVID-19. *Hypertens Dallas Tex* 2020; 76: 1104–1112.

[116] Stefanini GG, Chiarito M, Ferrante G, *et al.* Early detection of elevated cardiac biomarkers to optimise risk stratification in patients with COVID-19. *Heart* 2020; 106: 1512–1518.

[117] Shi S, Qin M, Shen B, Cai Y, Liu T, Yang F, *et al.* Association of Cardiac Injury With Mortality in Hospitalized Patients With COVID-19 in Wuhan, China. *JAMA Cardiol* 2020; 5: 802.

[118] Tan WP, Zhu Y, Yi H, *et al.* Development a Nomogram to Predict Prognosis in Severe and Critically Ill Patients with COVID-19. DOI: 10.21203/rs.3.rs-34264/v1.

[119] Wei JF, Huang FY, Xiong TY, *et al.* Acute myocardial injury is common in patients with COVID-19 and impairs their prognosis. *Heart Br Card Soc* 2020; 106: 1154–1159.

[120] Woo SH, Rios-Diaz AJ, Kubey AA, *et al.* Development and Validation of a Web-Based Severe COVID-19 Risk Prediction Model. *Am J Med Sci* 2021; Published online first: May 21, 2021; DOI: 10.1016/j.amjms.2021.04.001.

[121] Yang S, Ma L, Wang YL, *et al.* Risk factors for critical ill events of patients with COVID-19 in Wuhan, China: a retrospective cohort study. medRxiv 2020.06.14.20130765; DOI: https://doi.org/10.1101/2020.06.14.20130765.

[122] Criel M, Falter M, Jaeken J, *et al.* Venous thromboembolism in SARS-CoV-2 patients: only a problem in ventilated ICU patients, or is there more to it? Published online first: Jul 30, 2020; DOI: 10.1183/139930 03.01201–2020.

[123] Cui S, Chen S, Li X, *et al.* Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia. *J Thromb Haemost JTH* 2020; 18: 1421–1424.

[124] Demelo-Rodríguez P, Cervilla-Muñoz E, Ordieres-Ortega L, *et al.* Incidence of asymptomatic deep vein thrombosis in patients with COVID-19 pneumonia and elevated D-dimer levels. *Thromb Res* 2020; 192: 23–26.

[125] Desborough MJR, Doyle AJ, Griffiths A, *et al.* Image-proven thromboembolism in patients with severe COVID-19 in a tertiary critical care unit in the United Kingdom. *Thromb Res* 2020; 193: 1–4.

[126] Dubois-Silva Á, Barbagelata-Lópex C, Mena Á, *et al.* Pulmonary embolism and screening for concomitant proximal deep vein thrombosis in noncritically ill hospitalized patients with coronavirus disease 2019. *Intern Emerg Med* 2020; 15: 865–870.

[127] Fraissé M, Logre E, Pajot O, *et al.* Thrombotic and hemorrhagic events in critically ill COVID-19 patients: a French monocenter retrospective study. *Crit Care* 2020; 24: 275.

[128] Helms J, Tacquard C, Severac F, *et al.* High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. *Intensive Care Med* 2020; 46: 1089–1098.

[129] Kolelait I, Galen B, Choinski K, *et al.* Clinical characteristics of acute lower extremity deep venous thrombosis diagnosed by duplex in patients hospitalized for coronavirus disease 2019. *J Vasc Surg Venous Lymphat Disord* 2021; 9: 36–46.

[130] Longchamp A, Longchamp J, Manzocchi-Besson S, *et al.* Venous thromboembolism in critically ill patients with COVID-19: Results of a screening study for deep vein thrombosis. *Res Pract Thromb Haemost* 2020; 4: 842–847.

[131] Mestre-Gómez B, Lorente-Ramos RM, Rogado J, *et al.* Incidence of pulmonary embolism in non-critically ill COVID-19 patients. Predicting factors for a challenging diagnosis. *J Thromb Thrombolysis* 2020; 1–7.
Middeldorp S, Coppens M, van Haaps TF, et al. Incid-
ence of venous thromboembolism in hospitalized pa-
tients with COVID-19. *J Thromb Haemost* 2020; 18:
1995–2002.

Nahum J, Morichau-Beauchant T, Daviaud F, et al.
Venous Thrombosis Among Critically Ill Patients
With Coronavirus Disease 2019 (COVID-19). *JAMA
Netw Open* 2020; 3: e2010478.

Poissy J, Goutay J, Caplan M, et al. Pulmonary Embol-
ism in Patients With COVID-19: Awareness of an In-
creased Prevalence. *Circulation* 2020; 142: 184–186.

Soumagne T, Lascarrou JB, Hraiech S, et al. Factors
Associated With Pulmonary Embolism Among Coro-
navirus Disease 2019 Acute Respiratory Distress Syn-
drome: A Multicenter Study Among 375 Patients. *Crit
Care Explor* 2020; 2: e0166.

Tavazzi G, Civardi L, Caneva L, et al. Thrombotic
events in SARS-CoV-2 patients: an urgent call for ul-
trasound screening. *Intensive Care Med* 2020; 46:
1121–1123.

Thomas W, Varley J, Johnston A, et al. Thrombotic
complications of patients admitted to intensive care
with COVID-19 at a teaching hospital in the United
Kingdom. *Thromb Res* 2020; 191: 76–77.

Wang W. Analysis of Risk Factors for the Throm-
boembolic Events from 88 Patients with COVID-19
Pneumonia in Wuhan, China: A Retrospective Report.
*Med Sci Monit* 2021; 27: e929708.

Please cite this article as: Colombo C, Garatti L, Ferrante G, Casadei F, Montalto C, Crimi G, Cogliati C, Ammirati E, Savonitto S, Morici N. Cardiovascular injuries and SARS-COV-2 infection: focus on elderly people. *J Geriatr Cardiol* 2021; 18(7): 534–548. DOI: 10.11909/j.issn.1671-5411.2021.07.001