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Acute coronary syndromes and Covid-19: exploring the dark side of the outbreak.

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ABSTRACT

Since association between myocardial infarction (MI) and respiratory infections has been described for influenza-viruses and other respiratory viral agents, understanding possible physiopathological links between severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and acute coronary syndromes (ACS) is of the greatest importance. First data suggest an underestimation of ACS cases all over the world, but acute MI still represents a major cause of morbidity and mortality worldwide and should not be overshadowed during the coronavirus disease (Covid-19) pandemic. No common consensus regarding the most adequate healthcare management policy for ACS is currently available. Indeed, important differences have been reported between the measures employed to treat ACS in China during the first disease outbreak and what currently represents clinical practice across Europe and the USA. This review aims to discuss: pathophysiological links between MI, respiratory infections, and Covid-19; epidemiological data related to ACS at the time of the Covid-19 pandemic; what emerged so far from several catheterization labs and coronary care units all over the world, in order to shed some light on the current strategies for optimal management of ACS patients with confirmed or suspected SARS-CoV-2 infection.

KEYWORDS: acute coronary syndromes; myocardial infarction; STEMI; Covid-19, infectious disease; respiratory infections; pathophysiology; percutaneous coronary intervention; thrombolysis; drug treatment.

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INTRODUCTION

In December 2019 an outbreak of pneumonia caused by a novel coronavirus occurred in Wuhan, Hubei province, and has spread rapidly first throughout China and subsequently across Europe, United States (US) and the rest of the world [1–3], reaching the total number of 3.435.894 confirmed cases worldwide, as of May 5, 2020 [4]. On January 30, 2020, the World Health Organization (WHO) declared the Covid-19 outbreak a public health emergency of international concern and on March 12, 2020 that it can be characterized as a pandemic. Patients exposed to this virus, named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), frequently present with fever, cough and shortness of breath within 2 to 14 days after exposure and then usually develop coronavirus disease (Covid-19) related pneumonia [5]. Although respiratory symptoms prevail among all clinical manifestations of Covid-19, preliminary studies showed that some patients may develop severe cardiovascular (CV) damage and some patients with underlying CV diseases might have an increased risk of death [5–7].

Moreover, the Covid-19 outbreak has put a lot of pressure on the overloaded healthcare systems, especially in Lombardy (Italy) and more general in Northern Italy, where Covid-19 has spread very rapidly, giving concerns regarding the capacity of the system to respond to the need of intensive care treatments [8]. All possible efforts have been made in order to give the maximum number of patients the chance to be admitted and treated in hospitals. All non-urgent procedures have been shut down and routine clinical practice has been completely modified. In the context of an overwhelmed healthcare system, screening and elective treatments of coronary artery disease (CAD) have been underestimated, and dealing with acute coronary syndromes (ACS) has become more complicated and apparently less frequent. Nevertheless, ACS still remain a major cause of morbidity and mortality worldwide and are responsible for more than 1 million hospital admissions in the US annually, while ischaemic heart disease accounts for almost 1.8 million annual deaths, or

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20% of all deaths in Europe, although with large variations between different European countries [9,10].

During this pandemic, links between SARS-CoV-2 and ACS have not been established yet and a common guidance to handle ACS in Covid-19 and non-Covid-19 patients are needed. Aim of this review is to shed some light on those issues, analysing possible physiopathological links between Covid-19 and ACS and evaluating the best strategy to balance optimal ACS management and infectious risks related to Covid-19 outbreak.

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ACUTE CORONARY SYNDROMES AND COVID-19

Pathophysiology

Acute coronary syndromes (ACS) reflect a spectrum of pathological conditions compatible with acute myocardial ischaemia and/or infarction that are usually due to an abrupt reduction in coronary blood flow [11]. The clinical spectrum of ACS may range from myocardial infarction with ST-segment elevation (STEMI), that generally reflects an acute total coronary occlusion, to myocardial infarction without ST-segment elevation (NSTEMI) or unstable angina (UA) - with or without myocardial injury, respectively [12]. The current fourth universal definition defines myocardial infarction (MI) in the presence of acute myocardial injury, detected by elevated cardiac Troponin value above the 99th percentile of the upper reference limit (URL), in the setting of evidence of acute myocardial ischaemia, related to symptoms, electrocardiogram (ECG) or imaging changes and/or angiographic findings [13]. Cardiac troponin (cTn) I and T, regulatory components of the contractile apparatus of myocardial cells, are the preferred biomarkers for the evaluation of myocardial injury and have been used worldwide. It should be underlined that any type of myocardial injury can result in release of cTn into the blood but cTn elevation does not allow to discriminate the underlying pathophysiological mechanisms [14]. Several clinical condition related to the mismatch between oxygen supply and/or demand, such as respiratory failure (predominantly hypoxaemia) and infectious disease (particularly sepsis), may induce or lead to myocardial injury or to type 2 MI [13,15,16]. Causes related to myocardial injury are summarized in Tab. 1.

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Tab. 1 - Mechanisms of myocardial injury.
Adapted from Thygesen et al - Fourth universal definition of myocardial infarction (2018) [13].

<table>
<tr><th colspan="3"><u>MYOCARDIAL INJURY</u></th></tr>
<tr><th>Related to primary acute myocardial ischaemia</th><th>Related to oxygen supply/demand imbalance</th><th>Other causes</th></tr>
<tr><td rowspan="3">Plaque rupture - erosion with occlusive thrombosis</td><td>Reduced myocardial perfusion</td><td>Cardiac conditions</td></tr>
<tr><td>Coronary artery spasm
Microvascular dysfunction
Coronary embolism
Coronary artery dissection
Sustained bradyarrhythmia
Hypotension or shock
Respiratory failure with hypoxaemia
Severe anaemia</td><td>Heart failure
Myocarditis
Cardiomyopathy (any type)
Takotsubo syndrome
Coronary revascularization procedure
Cardiac procedure other than revascularization
Catheter ablation
Defibrillator shocks
Cardiac contusion</td></tr>
<tr><td>Increased myocardial oxygen demand</td><td>Systemic conditions</td></tr>
<tr><td>Plaque rupture - erosion with occlusive thrombosis</td><td>Sustained tachyarrhythmia
Severe hypertension with or without left ventricular hypertrophy</td><td>Sepsis, infectious disease
Chronic kidney disease
Stroke, subarachnoid haemorrhage
Pulmonary embolism, pulmonary hypertension
Infiltrative diseases, e.g. amyloidosis, sarcoidosis
Chemotherapeutic agents
Critically ill patients
Strenuous exercise</td></tr>
</table>

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Identification of type 2 MI can be more challenging due more frequent atypical clinical presentations (such as with dyspnoea), higher prevalence of comorbidities that may mask ischaemia [17], and lower frequency of ischaemic electrocardiographic findings (Q waves or new ST-T wave changes) and new regional wall motion abnormalities. Moreover, culprit lesions can be identified in a small percentage of cases by coronary angiography [18–21]. Nowadays, it is well accepted that sepsis and other infections are associated with CV events, especially ACS [22,23]. In particular, the risk of MI in the context of respiratory infectious disease reaches a peak at the onset of infections and it is proportional to the severity of illness [22]. Acute respiratory failure with consequent severe hypoxaemia contributes to reduce oxygen supply and determines activation of sympathetic system that increases heart rate, cardiac output and contractility, factors which in turn increase myocardial oxygen demand [24,25]. Incidence of myocardial injury or infarction in critical ill patients may go unrecognized [26], since autoptic studies have observed a prevalence of undiagnosed post-mortem acute myocardial infarction (AMI) ranging from 5% to 25% in patients died for acute respiratory failure [27,28].

Another possible mechanism implicated in the association between respiratory tract infections and ACS is the pro-inflammatory state. Since this association has been established with a variety of pathogens and sites of infection, it is likely that the causal agent and the host response could have a crucial role in eliciting an inflammatory pattern that may trigger ACS [22]. Atherosclerotic plaques contain inflammatory cells that proliferate and secrete cytokines that stimulate smooth muscle cells to form a fibrous cap [29]. An inflammatory state at any site elsewhere generates circulating cytokines, such as interleukins 1, 6, and 8 and tumor necrosis factor α, that can activate inflammatory cells in atherosclerotic plaques [30]. Studies in murine models [31] and autoptic studies in humans [32] have shown that inflammatory activity in atheromatous plaques increases after an infectious stimulus. When activated, intraplaque inflammatory cells, especially macrophages and T-cells, up-regulate host response proteins, including metalloproteinases and peptidases, that degrade components of the extracellular matrix and promote an oxidative burst, all

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of which contribute to destabilization of plaques [33,34]. When plaque surface becomes disrupted, thrombogenic elements (collagen, phospholipids, tissue factor and platelet-adhesive matrix molecules) are exposed and this process leads to the acute formation of a thrombus, which is the characteristic mechanism related to type 1 MI [35]. Moreover, inflammation promotes a prothrombotic state, which could further increase the risk of coronary thrombosis at sites of plaque disruption [36]. The inflammatory reaction in the coronary arteries impairs fibrinolysis through the inhibition of action of antithrombin, protein C system, and tissue factor pathway inhibitor, three major coagulation-inhibiting proteins that facilitates thrombosis [37,38]. Finally, influenza-viruses and other respiratory viruses infections are associated with expression of genes that have been linked to platelet activation and a risk of MI [39].

ACS and other acute respiratory infections

In the early 20th century, an excess mortality during influenza and pneumonia epidemics was first recognized [40], but the specific association with influenza or other respiratory infections and MI was not described until decades later (see Tab. 2).

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Tab. 2 – Acute coronary syndromes and other acute respiratory infection: main studies.

STUDY, YEAR, JOURNAL	INFECTION	POPULATION AND TIMELINE	CASES WITH MYOCARDIAL INFARCTION	CASES WITH RESPIRATORY INFECTIOUS DISEASE
Smeeth et al., 2004, New England Journal of Medicine [41]	Systemic respiratory tract infection (pneumonia, acute bronchitis, chest infections, and influenza)	MI diagnosed 91days after infection exposure	N = 3254	N = 20921
Kwong et al., 2018, New England Journal of Medicine [42]	Influenza A/B, RSV, adenovirus, CoV, enterovirus (including rhinovirus), HPIV, and HMPV	Admission for MI within 7 days after laboratory confirmation of influenza	N = 364	N = 19045
Warren-Gash et al., 2013, British Medical Journal [43]	Influenza A H1N1	Respiratory tract infection developed within one month before admission for MI	N = 134	N = 13
Violi et al., 2017, Clinical infectious diseases [44]	CAP	MI during hospitalization for CAP	N = 89 (NSTEMI = 78 STEMI = 11)	N = 1182
Musher et al., 2007, Clinical infectious diseases [45]	Pneumococcal pneumonia	MI diagnosed at hospital admission for pneumonia	N = 12 (NSTEMI = 9 STEMI = 3)	N = 170
Corrales-Medina et al., 2015, Journal of American Medical Association [46]	Pneumonia	MI and fatal coronary heart disease over 10 years after pneumonia hospitalization	N = 247 (MI = 137 Fatal coronary heart disease = 110)	N = 1271
Vejpongsa et al., 2019, The American Journal of Medicine [47]	Acute influenza and other viral respiratory infections	Acute influenza and other viral infections in hospital admission for MI	N = 1884985	N = 21370 (Acute influenza = 9885 Other = 11485)
Peiris et al, 2003, The Lancet [48]	SARS-CoV	Deaths for MI in hospitalized patients with SARS	N = 2	N = 75
Chong et al., 2004, Archives of Pathology & Laboratory Medicine [49]	SARS-CoV	MI in post-mortem examinations for confirmed SARS infections	N = 2	N = 8
No data available	MERS	NA		

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Abbreviations: CAP: community acquired pneumonia, CoV: coronavirus, HMPV: human metapneumovirus, HPIV: human parainfluenza virus, MERS: Middle East respiratory syndrome, MI: myocardial infarction, NA: not available, NSTEMI: myocardial infarction without ST-segment elevation, RSV: respiratory syncytial virus, SARS-CoV: severe acute respiratory syndrome coronavirus, STEMI: ST-segment elevation myocardial infarction.

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More recent studies have well documented an increase of risk of MI with influenza, pneumonia, acute bronchitis and other chest infections [41–43]. In retrospective and prospective case series, a rate of CV events of about 30% and a rate of MI of about 8%, were found among patients who were hospitalized for community-acquired pneumonia [44,45]. Other retrospective studies suggested that hospitalization for pneumonia was associated with both short and a long term increased risk of CV events: in an analysis performed by Medina et al., 318 out of 1271 patients (25%) developed CV events over 10 years after pneumonia hospitalization [46]. A meta-analysis of 10 case-control studies conducted by Barnes et al. demonstrated a twofold increased risk of AMI in patients with recent influenza infection or respiratory tract infection: a recent influenza infection, influenza-like illness, or respiratory tract infection were significantly more likely in AMI cases, with a pooled odds ratio (OR) of 2.01 (95% confidence interval -CI- 1.47 to 2.76) [50]. From a large national database in the US, among 1.884.985 admissions for AMI from January 2013 to December 2014, influenza or other viral respiratory infections accounted for 1.1% of the patients (9885 and 11485 patients respectively) and were associated with worse outcomes and higher in-hospital case fatality (approximately 13%) [47]. Vejpongsa et al. also showed that AMI patients with concomitant influenza infection or other viral respiratory infections were less likely to receive cardiac catheterization across all age groups when compared with patients with AMI alone (22% vs 43.8% vs 58.8%, $p<0.001$); however, more than half of these patients required revascularization [47]. This interesting finding should be highlighted and related to what is currently happening during this Covid-19 pandemic, given that patients infected with SARS-CoV-2 virus seem to undergo cardiac catheterization less likely due to high risk of infection spreading.

Acute coronary syndromes and MI were noted also to occur in severe acute respiratory syndrome (SARS), an infectious disease that has afflicted a total of 8096 people in 29 countries in 2003, with a mortality around 9.6% [51]. In a prospective study of 75 patients hospitalized with SARS, AMI was the cause of death in 2 out of 5 fatal cases [48]. An autoptic study from Singapore reported post-mortem examinations in 8 patients who died suddenly and unexpectedly from SARS:

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1 out of 8 patient had subendocardial infarction with occlusive coronary disease (who had AMI on presentation with SARS), while 4 patients had pulmonary thromboembolism and 1 patient had marantic valvular vegetations, along with infarction in heart, kidneys, spleen, and brain [49]. This findings suggest a possible link between severe acute respiratory syndromes, thrombophilia and subsequently ACS. Also Middle East respiratory syndrome (MERS), that has been first reported in 2012 in Saudi Arabia and that has afflicted 2519 patients with 866 associated deaths (case-fatality rate: 34.4%) in 27 countries [52], has been related to CV diseases. A systematic analysis of 637 MERS patients showed that 30% of cases had underlying cardiac diseases, 50% had hypertension, 50% had diabetes, and 16% had obesity [53]. The clinical risk factors for mortality in MERS were older age, male sex and CV-related underlying medical conditions including hypertension, diabetes, cardiac diseases, chronic kidney disease [54–56]. Data on incidence of ACS in the context of MERS infection are lacking. Alhogbani reported a case of a 60-year-old patient with MERS Coronavirus (MERS-CoV) infection, presented with respiratory symptoms, chest pain, TnT elevation, diffuse T-wave inversion, and severe left ventricular (LV) dysfunction; acute myocarditis was then diagnosed with cardiac magnetic resonance that excluded an ischaemic cardiomyopathy [57].

Moreover, the pooled results of the aforementioned meta-analysis from Barnes et al. demonstrated an association between influenza vaccination and a lower risk of composite CV events, with a pooled OR of 0.71 (95% CI 0.56 to 0.91), equating to an estimated vaccine effectiveness of 29% (95% CI 9% to 44%) against AMI [50]. This finding is in line with other results from another meta-analysis from Udell et al. that showed that the influenza vaccine given to high-risk patients, such as patients with CAD, reduced their risk of a major adverse cardiovascular event (MACE) (patients treated with influenza vaccine and MACE 2.9% vs patients treated with placebo or control and MACE 4.7%; RR, 0.64 [95% CI, 0.48-0.86], P = 0.003) [58]. Therefore, current European Guidelines for the diagnosis and management of chronic coronary syndromes

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recommend annual influenza vaccination in order to improve prevention of AMI in patients with CAD and decrease CV mortality [59–61].

Myocardial injury and ACS in patients with Covid-19: what we know

Although the clinical manifestations of Covid-19 are dominated by respiratory symptoms, evidence of myocardial injury, was recognized in early cases in China (see Tab. 3).

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Tab.3 - Myocardial injury and ACS in patients with Covid-19: main studies.

STUDY, YEAR, JOURNAL	POPULATION	EVALUATION AND TIMELINE	CASES WITH MYOCARDIAL IINJURY	SUSPECTED ACS	IN HOSPITAL MORTALITY
Huang et al., 2020, The Lancet [5]	N = 41 ICU = 13 Non-ICU = 28	Myocardial injury = increased cardiac biomarkers or new ECG – echo abnormalities during hospitalization	N = 5 (12%) ICU = 4 (31%); Non-ICU = 1 (4%)	NA	N = 6 (15%)
Wang et al., 2020, Journal of American Medical Association [1]	N = 138 ICU = 36 Non-ICU = 102	Myocardial injury = increased cardiac biomarkers or new ECG – echo abnormalities during hospitalization	N = 10 (7.2%) ICU = 8 (22.2%) Non-ICU = 2 (2%)	NA	N = 6 (43%)
Zhou et al., 2020, The Lancet [62]	N = 191 Non-survivor = 54 Survivor = 137	Myocardial injury = increased cardiac biomarkers or new ECG – echo abnormalities during hospitalization	N = 33 (17%) Non-survivor = 32 (59%) Survivor = 1 (1%)	First autopsy performed = findings were consistent with AMI	N = 54 (28.3%)
Shi et al., 2020, Journal of American Medical Association: Cardiology [63]	N = 416	Myocardial injury = increased cardiac biomarkers regardless of new ECG – echo abnormalities during hospitalization	N = 82 (19.7%)	ECG features consistent with myocardial ischaemia – NSTEMI: N = 14 (3.36%)	N = 57 (13.7%) With cardiac injury = 42 (51.2%) Without cardiac injury = 15 (4.5%)

Abbreviations: AMI: acute myocardial infarction, ECG: electrocardiogram, ICU: intensive care unit, NA: not available, NSTEMI: myocardial infarction without ST-segment elevation, STEMI: ST-segment elevation myocardial infarction.

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Huang et al. first reported a prevalence of acute myocardial injury of 12% as major complications in 41 hospitalized patients infected with SARS-CoV-2 [5]. In another study from Wang et al. conducted on 138 hospitalized patients with Covid-19, cardiac injury was found in 7.2% of patients overall and in 22.2% of patients who were treated in the intensive care unit (ICU) [1]. This findings could suggest that acute myocardial injury may have a relevant role in worsening clinical outcomes in Covid-19 patients, even without a clear evidence of myocardial ischaemia. Indeed, Zhou et al., in a retrospective report of 191 patients admitted with SARS-Cov-2 pneumonia, diagnosed acute myocardial injury in 33 out of 191 (17%) patients of their cohort [62]. Interestingly, they found that non-survivors were more likely to develop acute myocardial injury than survivors (n=32, 59% vs n=1, 1%; p<0.0001). Notably, the first autopsy in this cohort was performed on a 53-year-old woman with chronic renal failure and findings were consistent with AMI (data resulting from personal communication between a pathologist and the Chinese Academy of Science, not available in a published manuscript). In a single-center retrospective study by Shi et al., conducted on a cohort of 416 consecutive Covid-19 patients in Wuhan, China, cardiac injury was found in 19.7% patients (n=82) [63]. Those patients were older and had more CV comorbidities (hypertension, diabetes, cerebrovascular disease and heart failure) and presented with more severe acute illness than patients without cardiac injury. This study demonstrated that myocardial injury was independently associated with an increased risk of mortality in patients with Covid-19. It should be underlined that among those 82 patients with cardiac injury, only 22 (26.8%) underwent electrocardiogram (ECG) after admission, and only 14 out of 22 ECGs (63.6%) were performed during the periods of elevation of cardiac biomarkers. All ECGs were described as abnormal, with findings compatible with myocardial ischaemia, such T-wave depression and inversion, ST-segment depression, and Q waves. All those findings may suggest that 14 out of 416 patients in this cohort (3.36%) may have developed myocardial ischaemia, with features consistent with NSTEMI. No evidence of STEMI in this cohort was provided, even if limited availability of ECGs may have led to underestimation of AMI cases. In addition, the National Health Commission of China,

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reported that, among people who died from Covid-19, 11.8% of patients without underlying CV diseases had substantial heart damage, with elevated levels of cTnI or cardiac arrest during hospitalization [64]. What seemed to emerge from a metanalysis from Lippi et al. that included a total number of 341 patients (123 with severe disease, 36%), was that cTnI values were significantly increased in patients with severe SARS-CoV-2 infection compared to those with milder forms of disease [65].

Several mechanisms that could explain the onset of acute myocardial injury related to myocardial ischaemia in SARS-CoV-2 infection have been proposed. Some of them may resemble the ones identified for others respiratory infectious agents, such a pro-inflammatory state and a cytokine storm (that could cause plaque instability), a prothrombotic state and a hypoxaemia-related damage due to acute respiratory failure. The rise in cTn tracks with other inflammatory biomarkers, such as D-dimer, interleukin-6, lactate dehydrogenase, raising the possibility that this may reflect cytokine storm more than isolated myocardial injury [66]. On the other hand, some reports of patients presenting with cardiac symptoms, ECG changes or new wall motion abnormalities, may suggest a different pattern, such as viral myocarditis and stress cardiomyopathy. The underutilization of coronary angiography in these outbreaks, due to the high infectious risk, makes more difficult to establish a definite differential diagnosis in many cases.

Furthermore, specific damages caused by SARS-CoV-2 infection might be related to angiotensin-converting enzyme 2 (ACE2) receptors, that have been shown to represent the entry point into human cells for some coronaviruses, like SARS-CoV and SARS-CoV-2. ACE2 receptors are widely expressed not only in the lungs but also in the CV system and, therefore, ACE2- related signalling pathways might also have a role in myocardial injury. At the time of writing, a lot of studies are ongoing all over the world, and hopefully they will tell us more about the link between ACE2 receptors, Covid-19 and CV diseases.

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Critical issues in management and treatment of ACS patients

Where did all the STEMIs go?

A relevant impact of Covid-19 pandemic is related to the diagnosis and management of patients with ACS, that were not hospitalized for confirmed or suspected Covid-19. Diagnosis and treatment of ACS - especially STEMI - start from the point of first medical contact (FMC), defined as the time point when the patient is initially assessed by a physician, paramedic, nurse or trained medical personnel who can interpret the ECG and deliver medical interventions, in the prehospital or in-hospital setting [67]. Prompt activation of emergency medical service (EMS) is crucial since ischaemic time duration is a major determinant of infarct size in patients with STEMI, and prompt recognition alongside an early management is critical to reduce morbidity and mortality related to ACS [68]. It has been postulated that, in the midst of this healthcare crisis, hospital admissions for ACS has dramatically reduced, mostly due to the fact that patients do not activate EMS, because of the “do not come to the hospital” policy and due the fact that hospital are now perceived as dangerous places. Prof. B. Casadei, Professor of Cardiovascular Medicine at the University of Oxford and European Society of Cardiology (ESC) president, stated that, in the worst hit areas, hospital admissions for ACS has reduced by up to 75% [69]. In the US and in Spain respectively, an estimated 38% and 40% reduction in cardiac catheterization laboratory STEMI activations was experienced [70,71], while in Italy a reduction of about 50% in coronary care units (CCUs) admission was initially reported [72]. Those findings were corroborated by De Filippo et al. that performed a retrospective analysis on consecutive patients who were admitted at 15 hospitals in northern Italy for ACS. They showed that the mean admission rate for ACS during the study period (February 20, 2020 to March 31, 2020) was 13.3 admissions per day vs 18.0 admissions per day during the earlier period in the same year vs 18.9 admissions per day during the same timeframe of the previous year [73].

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Are we really prioritizing and treating STEMI patients the way we should?

In Hong Kong, Tam et al. described a small number of patients with STEMI seeking medical help (n=7) and found large delays in presentation, after institution of infection control measures in their country, when compared to 2018-2019 presentation time during office and non-office hours, respectively: median symptom onset to first medical contact = 318 mins (IQ range 75-448) vs 82.5 mins (IQ range 32.5-195) vs 91.5 mins (IQ range 32.25-232.75) [74]. Reason proposed to understand these delays vary, and are mostly related to hesitancy to go to the emergency department (ED) or to activate the EMS, introducing a first “Covid-19-related delay” in the so-called “total ischaemia time” (Fig.1).

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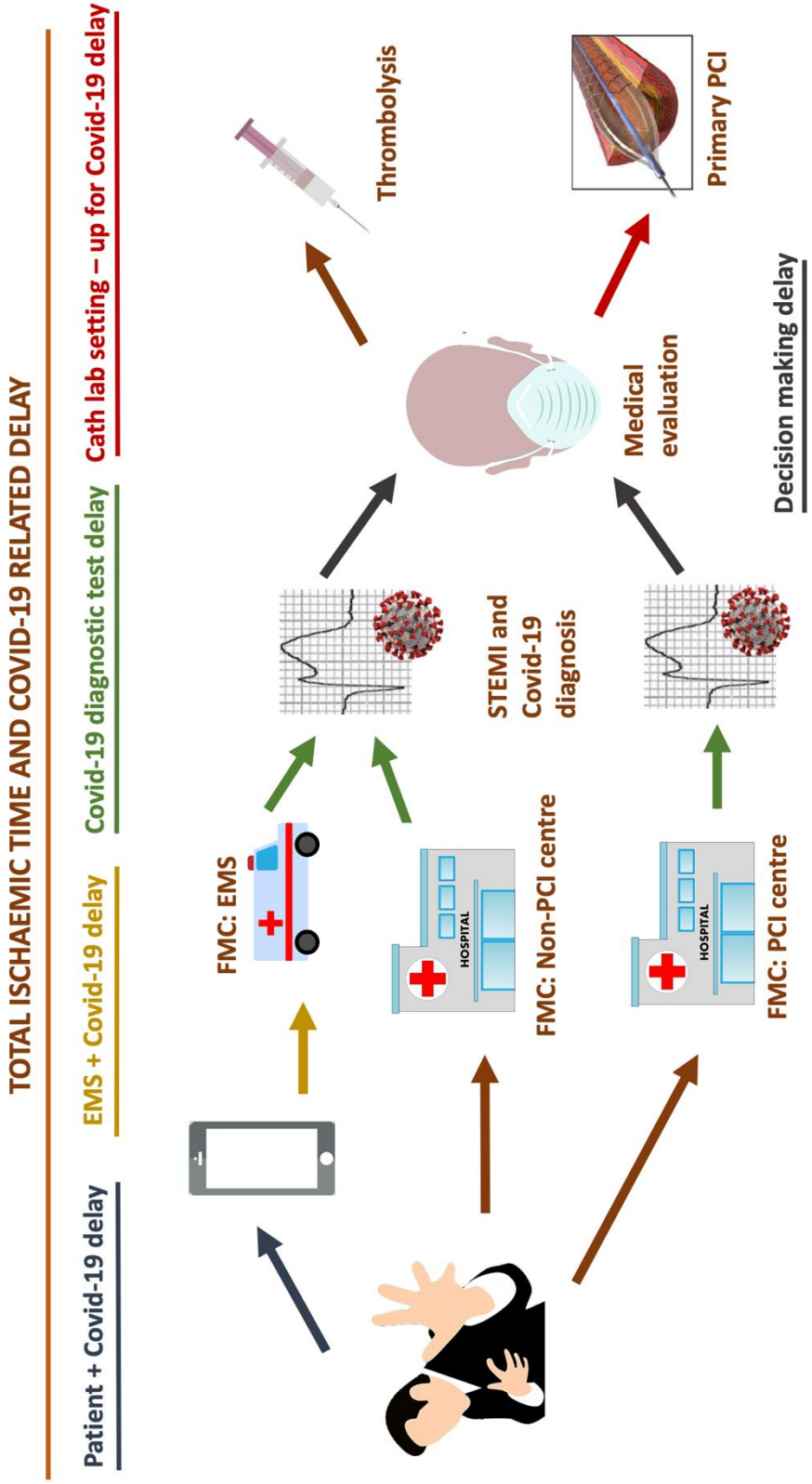
Fig. 1 –"Covid-19 related delays" in treating STEMI patients.
Adapted from Ibanez et al - 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation [67].



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Tam et al. also postulated that many STEMI patients do not seek care at all and this may contribute to a global underestimation of ACS cases [74]. In Italy - particularly in Lombardy -, like in several other European countries and US states, healthcare systems has also been facing a huge overload with unbearable consequences on resources for cardiology, since the availability of ward and cardiology care unit (CCU) beds have been drastically reduced as well as suspension of admissions for elective procedures (such as coronary catheterizations). EMS is now focused on facing Covid-19 outbreak, so less resources are available to cope with other emergencies such as ACS, due to limited means of support or healthcare staff, which is either sick or committed to handle Covid-19 emergency. In order to avoid SARS-CoV-2 spreading, on March 8, 2020, the government of Lombardy identified 13 hospitals with catheterization laboratories acting as "*hubs"* for ACS, with the remaining hospitals acting as *"spokes"*, in order to gather cardiovascular emergencies in few CCUs all across the region [75]. About 10 million people live in Lombardy, representing one-sixth of Italy's population, so that this reorganization – yet essential – introduced another "Covid-19-related delay" (fig.1) in managing patients with STEMI, being potentially more distant from a *"Hub"* catheterization laboratory when activating EMS. Moreover, "*Hubs"* must have more than 1 catheterization lab and at least 1 of those should be dedicated for suspected or diagnosed Covid-19 patients, so that the more appropriate protocol can be followed. Major impact of these healthcare policy is expected, since delays in seeking and delivering care due to patient fears of contracting an infection from the healthcare system and longer time to reach *"Hubs,"* could have a harmful impact on outcomes of ACS patients.

During this pandemic, finding a balance between risks related to untimely treatment of ACS patients and SARS-CoV-2 infection control has become a global challenge. Commonly, regional reperfusion strategies are established to maximize efficiency in treatments, since primary percutaneous coronary intervention (PCI) – bypassing the ED – is the routine treatment for STEMI patients [76]. Several trials and metanalysis, endorsed by European and American Guidelines, have clearly established the superiority of primary PCI compared to thrombolysis over the years. As

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early as 1997, a quantitative review published by Weaver et al., based on outcomes at hospital discharge or at 30-days, demonstrated that primary PCI was superior to thrombolytic therapy for treatment of patients with AMI (n=2606), in case of high-rate success PCI [mortality at 30 days or less was 4.4% for patients treated with primary PCI (n=1290), compared with 6.5% for patients treated with thrombolysis (n=1316), with 34% reduction (OR, 0.66; 95% CI, 0.46-0.94; P = 0.02)] [77]. More recently, a pooled analysis of 22 randomized trials (total patients n=6763) from Boersma et al. demonstrated that primary PCI was associated with significantly lower 30-days mortality rate compared to thrombolysis [adjusted OR, 0.63; 95% CI (0.42–0.84)], regardless of treatment delay [78].

Despite this clinical evidence, to cope with Covid-19 abrupt outbreak, case decisions has been individualized at the beginning of the pandemic, taking into account the risk of SARS-CoV-2 exposure versus the risk of delaying diagnosis or therapy. Subsequently, Peking Union Medical College Hospital and Sichuan Provincial People's Hospital proposed recommendations in China, summarized as follows [79,80]: with regard to STEMI patients they recommended thrombolytic therapy over primary PCI, if Covid-19 was confirmed or could not be excluded within a short time, while for NSTEMI – UA the priority was to exclude SARS-CoV-2 infection first, since door-to-balloon time is less crucial in those patients than in STEMIs. Those recommendations were endorsed by Daniels et al., that stated that thrombolysis might be the best compromise of prompt reperfusion for the patient, buying time for a complete diagnosis to be made [81]. According to Peking's protocol, blood tests, pharyngeal swab or sputum specimen or blood sample for detection of SARS-CoV-2 nucleic acid, chest computed tomography (CT) and evaluation by infectious disease specialists should be performed before starting treatment [79], while Sichuan's protocol relies on rapid nucleic acid test before starting care. Those recommendations are undoubtedly useful to minimize and control the spreading of SARS-CoV-2 infection, but data on the outcomes of ACS patients are needed to confirm that delaying treatment and using thrombolysis as a first therapy to treat STEMI, in confirmed or suspected Covid-19 patients, is not associated with a worse outcome.

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Indeed, despite Lombardy has been considered as an area with cluster transmission of SARS-CoV-2 since the last days of February 2020, most *"Hubs"* are performing primary PCI without waiting for screening test results in order to avoid important delays and without relying on thrombolysis. Dr. A. Chieffo, from "IRCSS Ospedale Scientific Institute" (Milan, Italy), during an interview for the ESC TV [82], stated that, from a primary analysis performed in Lombardy on 33 patients with Covid-19 who underwent urgent coronary angiography (90.9%) or coronary computed tomography angiography, CCTA (9.1%) from February 21 to March 18, 2020, 60.6% of these patients did not have a culprit lesion requiring treatment, suggesting a possible link between SARS-CoV-2 and type 2 MI and/or myocarditis – stress cardiomyopathy in more than a half of those patients. Stefanini et al. performed a retrospective analysis on 28 Covid-19 patients who were admitted for STEMI: they found that 24 patients (85.7%) did not have a SARS-CoV-2 test result at the time of coronary angiography and that 11 patients (39.3%) did not have obstructive CAD [83]. In line with the aforementioned experiences, in our tertiary care centre ("Ospedale Luigi Sacco", Milan, Italy), located in the heart of the Italian epidemic, no cases of ACS requiring PCI were reported among more than 900 patients admitted for SARS-CoV-2 infection, as of May 5, 2020. A case report from Hu et al. described a 37-years-old male patient presenting with chest pain and dyspnea with ST-segment elevation in the inferior leads, elevation of TnT and severe depression of LV ejection fraction (27%), in which an emergency CCTA revealed no coronary stenosis and a diagnosis of fulminant myocarditis was made [84]. Another case report from Inciardi et al. described a patient infected with SARS-CoV-2 that had severe fatigue, no chest pain, minimal diffuse ST-segment elevation (more prominent in the inferior and lateral leads) and an ST-segment depression with T-wave inversion in lead V1 and aVR, severe LV dysfunction and no evidence of obstructive CAD at urgent coronary angiography, that was then diagnosed with acute myopericarditis [85]. A first case-series from New York City (US) described 18 Covid-19 patients with ST-segment elevation indicating potential AMI: among those, 9 patients (50%) underwent coronary angiography, 6 out of 9 (67%) had obstructive disease, and 5 (56%) underwent PCI [86]. All these findings should be

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underlined considering that in such cases, thrombolytic therapy – if used – may have increased the haemorrhagic risk without adding any benefit on the ischaemic side. Since reperfusion seems not to be mandatory in a great number of patients, maybe due to the previously highlighted link between respiratory infections and type 2 MI, relying on systematic thrombolysis seem not to be justified from these initial European and American reports [83,86]. Hence, also based on those findings, Society for Cardiovascular Angiography and Interventions (SCAI), American College of Cardiology (ACC), American College of Emergency Physicians (ACEP) and American Heart Association (AHA) published guidance on the management of AMI during Covid-19 pandemic in the US [87,88]. Those guidelines state that, after a first evaluation in the ED to assess the infectious risks, STEMI patients should undergo primary PCI whenever possible, if it can be provided within an adequate time frame from the symptoms onset and STEMI diagnosis. Thrombolytic therapy should not be the standard of care strategy and should be limited to particular situations, such as in non-PCI capable hospital or when PCI cannot be performed within an acceptable time frame. Those latest recommendations are more consistent with general European and American Guidelines on STEMI [67,89], confirming that primary PCI remains the reperfusion therapy of choice if feasible within an acceptable time frame from STEMI diagnosis.

To sum up, protocols should guarantee the feasibility to perform PCI in facilities approved for treatment of Covid-19 patients, avoiding potentially harmful thrombolysis, in compliance with adequate safety measure to protect healthcare workers *(see after).* An even more efficacious strategy could be to organize separated catheterization labs and subsequently CCUs or cardiology wards for patients with and without SARS-CoV-2 infections, although this may be possible only in high volume hospitals. On April 3, 2020, SCAI and the Canadian Association of Interventional Cardiology (CAIC) have announced the formation of the North American Covid-19 ST-Segment Elevation Myocardial Infarction Registry (NACMI) [90], that hopefully will tell us more about this topic, since further data are needed to detect and characterize patients with STEMI and Covid-19 and optimize treatment.

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Organization issues for workers and catheterization lab

Catheterization lab staff need time to set protective gear. According to latest recommendations, appropriate personal protective equipment (PPE) should include gowns, surgical gloves, protective eyewear, full face shields, disposable caps, shoe covers and a N95/99/100 masks [91–93]. However, this perspective has mostly been shared from the experience with SARS in 2005. Although protection of healthcare workers is essential, especially during this outbreak that is seeing high rates of infections among healthcare personnel, this setting-up may contribute to introduce another "Covid-19 related delay" in treating STEMI (fig.1). Tam et al. – in a letter previously mentioned - found that catheterization lab from device time was higher during Covid-19 outbreak when compared to 2018-2019 times during office and non-office hours, respectively: catheterization lab 33 mins (IQ range 21-37) vs 20.5 mins (IQ range 16-27.75) vs 24 mins (IQ range 18-30) [74]. Importantly, most catheterization labs have either normal or positive ventilation systems and are not designed for infection isolation so that terminal clean following the procedure is needed, leading to eventual further delays for subsequent procedures [91]. If possible, in order to avoid SARS-CoV-2 spreading, critical patients should be intubated - if needed - prior to arrival to the catheterization laboratory.

Drug treatment

Among drugs commonly used to treat ACS patients, care should be taken when administering antiplatelet therapy. Clopidogrel and Ticagrelor have specific interactions with Lopinavir/Ritonavir, a combination of anti-viral drugs that have previously been used to treat SARS and MERS, having in vitro and in an animal models inhibitory activity against SARS-CoV and MERS-CoV [94,95]. Even if a randomized, controlled, open-label trial conducted by Cao et al. in hospitalized adult patients with severe Covid-19, showed no benefit with Lopinavir/Ritonavir treatment beyond standard care, this drug combination is still used worldwide, waiting for future trials that may help to confirm or exclude the possibility of a treatment benefit [96].

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Lopinavir/Ritonavir should not be used in combination with Clopidogrel or Ticagrelor due to their potent CYP3A4 inhibition [97], that determines a diminished effect of Clopidogrel and an increased effect of Ticagrelor; Prasugrel should be used if no contraindications are present or a testing-guided approach to evaluate platelet function may be considered [98]. Aspirin may be safely used as antiplatelet drug in Covid-19 patients.

Also Atorvastatine and Rosuvastatine should be started at lowest possible dose when co-administered with Lopinavir/Ritonavir, since this antiviral drugs inhibit CYP3A4, OATTP1B1 and BCRP that have a role in the metabolism of statins [98]. Beta-blockers – especially metoprolol - should be administered cautiously in patients assuming Chloroquine or Hydroxychloroquine due to CYP2D6 inhibition [99] and for the potential role of Hydroxychloroquine in reducing heart rate [100].

Renin–angiotensin–aldosterone system (RAAS) related drugs (such as ACE-inhibitors and Angiotensin II receptor blockers, ARBs) are a cornerstone of therapy after MI since maintenance of therapy in the days to weeks after the index event has been shown to reduce early mortality [101]. Despite evidence on drugs assumption or discontinuation in these patients included in the previous mentioned studies are lacking, it has been hypothesized that abrupt withdrawal of RAAS inhibitors in high-risk patients, especially those who have heart failure or previous MI, may result in clinical instability and adverse outcomes [102,103], and may eventually be related to myocardial injury.

Antivirals drugs used for SARS-CoV-2 infection treatment may have potential interactions with oral anticoagulants (OACs). Several case reports have highlighted the necessity of augmented doses of warfarin in patients treated with ribavirin; international normalized ratio (INR) should be monitored carefully in these patients [104,105]. Due to Lopinavir/Ritonavir inhibitory effect on CYP3A4, that is involved in the hepatic clearance of some novel OACs, Rivaroxaban should be avoided and Apixaban should be administered at 50% of dose [98]. Given those potential interactions, low molecular weight heparins, or unfractionated heparin should be preferred over OACs; moreover, first evidences showed decreased mortality in most severe Covid-19 patients with

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coagulopathy [106]. Drugs potentially useful for treatment of acute coronary syndromes and coronary artery disease and their potential interactions are summarized in Tab. 4.

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Tab.4 – Drug treatment of acute coronary syndromes and coronary artery disease: evidence and potential interactions with drugs used to treat SARS-CoV-2 infection.

THERAPY	POTENTIAL INTERACTIONS	EVIDENCE	NOTES
P2Y12 inhibitor: - Clopidogrel - Ticagrelor - Prasugrel	Lopinavir/Ritonavir	When coadministered with Lopinavir/Ritonavir: diminished effect of clopidogrel, increased effect of ticagrelor [98].	Use Prasugrel if no contraindications. Contraindications to prasugrel: previous intracranial haemorrhage, previous ischaemic stroke or TIA, or ongoing bleeds; prasugrel is not recommended for patients >_75 years of age or with a body weight <60 kg: or in NSTE-ACS if coronary anatomy is not known. Contraindications for ticagrelor: previous intracranial haemorrhage or ongoing bleeds [107].
Aspirin	-	Despite first conflicting information on the media that aspirin (and generally NSAIDS) could worsen Covid-19, currently there is lack of evidence on discontinuation of aspirin.	Aspirin can be safely used as antiplatelet drug in Covid-19 patients.
Statins: - Atorvastatin - Rosuvastatin - Lovastatin - Simvastatin	Lopinavir/Ritonavir	When coadministered with Lopinavir/Ritonavir: increased effect of Atorvastatine and Rosuvastatine.	Start at lowest possible dose of rosuvastatin and atorvastatin and titrate up. Otherwise use Pravastatin [98].
Beta-blockers: - Metoprolol - Carvedilol - Propranolol - Labetalol	Chloroquine / Hydroxychloroquine Fingolimod	Hydroxychloroquine has a potential role in reducing heart rate [100], and may increase effect of beta-blockers.	When coadministered with Chloroquine or Hydroxychloroquine, beta-blockers dose reduction may be required.
ACEi/ARbs	-	No human evidence establishing a link between the use of these medications with an increased risk of Covid-19 acquisition or illness severity [103].	Abrupt withdrawal in high-risk patients, especially those who have heart failure or have had MI, may result in clinical instability and adverse outcomes [102,103].
Heparin	-	First evidences showed decreased mortality in severe Covid-19 patients with coagulopathy [106].	Given the interactions between some antiviral drugs and OACs, low molecular weight heparins, or unfractionated heparin should be preferred over OACs [98].

Abbreviations: ACEi: ACE- inhibitors; ARBs: angiotensin receptor blockers; Covid-19: coronavirus disease; MI: myocardial infarction; NSAIDS: nonsteroidal anti-inflammatory drugs; NSTE-ACS: acute coronary syndromes without ST-segment elevation; OACs: oral anticoagulants; TIA: transient ischaemic attack.

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CONCLUSION

Despite being eclipsed by Covid-19 outbreak, acute coronary syndromes are still a major cause of morbidity and mortality worldwide and should not be overshadowed in this era, especially because of the possible physiopathological links – yet unexplored - with SARS-CoV-2 infection.

Given limited heterogeneity of data published in these months, the potential overlapping symptomatology between ACS and SARS-CoV-2 infection and the underestimation of ACS cases during Covid-19 outbreak, further more reliable data are needed to estimate the real prevalence of ACS and to evaluate properly features of ACS patients during this pandemic.

All efforts made during the last decades to develop strategies to facilitate transfer of ACS patients in whom AMI is suspected directly to the hospital offering 24/7 PCI-mediated reperfusion therapy, should not be forgotten. Specific protocols to balance infective risks related to Covid-19 and optimal ACS management, especially STEMI, without delays and with preferential PCI treatment – whenever possible – should be implemented.

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M.S., C.G., M.M and G.B.F. conceived of this review.

M.S., C.G. and A.G. structured and organized this review.

M.S. and C.G. revised the literature and synthesized study data.

M.S. and C.G. wrote the original draft of this paper.

M.M. and G.B.F supervised the entire work as senior authors.

G.B.Z., F.D.A., A.P., M.V., F.F. and M.M. provided expert commentary on how to manage ischemic patients during Covid-19 pandemic due to their expertise in treating coronary artery disease and myocardial infarction.

M.G. provided expert commentary on links between respiratory infections and myocardial involvement and on infectious risk in ischemic patients during Covid-19 pandemic due to his expertise in infectious disease.

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