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# Cerebro-/Cardiovascular Collateral Damage During the COVID-19 Pandemic: Fact or Fiction?

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Numerous observational studies have identified a decline in cerebro-/cardiovascular (CV) admissions during the initial phase of the COVID-19 pandemic. Recent studies and meta-analyses indicated that the overall decrease was smaller than that found in initial studies during the first months of 2020. Two years later we still do not have clear evidence about the potential causes and impacts of the reduction of CV hospitalizations during the COVID-19 pandemic. It has becoming increasingly evident that collateral damage (i.e., incidental damage to the public and patients) from the COVID-19 outbreak is the main underlying cause that at least somewhat reflects the effects of imposed measures such as social distancing and self-isolation. However, a smaller true decline in CV events in the community due to a lack of triggers associated with such acute syndromes cannot be excluded. There is currently indirect epidemiological evidence about the immediate impact that the collateral damage had on excess mortality, but possible late consequences including a rebound increase in CV events are yet to be observed. In the present narrative review, we present the reporting milestones in the literature of the rates of CV admissions and collateral damage during the last 2 years, and discuss all possible factors contributing to the decline in CV hospitalizations during the COVID-19 pandemic. Healthcare systems need to be prepared so that they can cope with the increased hospitalization rates for CV events in the near future.

**Keywords** COVID-19 pandemic; collateral damage; stroke; acute coronary syndrome.

## INTRODUCTION

"Collateral damage" is defined as damage to persons, animals, and things that is incidental to the intended target, and was initially used as a military term.[1] This term is now widely used in nonmilitary applications, and has been borrowed mostly by the computing and medical communities. One of the first examples of collateral damage used in medicine was the ecological effects of antibiotics therapy or the immune responses to viral agents. Nowadays, during the COVID-19 pandemic, the term has been used in relation to deaths or disorders (biological or mental) caused as a result of policies implemented by authorities such as lockdowns, reorganization of health services, and cuts to research funding for non-COVID-19 research, or as a result of the behavioral changes of the public. Any other consequence caused directly or indirectly by the virus are excluded, such as myocarditis, deep vein thrombosis, and complications due to extended stay at an intensive care unit.

During the first phase of the pandemic, healthcare utilization decreased dramatically, which affected primary, elective, and emergency/urgent care.[2-4] Cardiologists and neurologists observed a reduction of cerebro-/cardiovascular (CV) hospitalizations, with admissions for both acute coronary syndrome (ACS) and acute stroke (AS) declining sharply.[5-7] The scientific community hypothesized that this significant reduction was mostly attributable to

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fewer people going to the hospital for fear of becoming infected. As a result, physicians considered collateral damage from CV disease a reality. However, the magnitude and impact of the problem on death and disability from CV disease was unknown, and 2 years later we still do not have clear evidence about the potential causes and impact of the reduction of CV admissions during the COVID-19 pandemic.

In this narrative review, we outline the data associated with possible CV collateral damage during the COVID-19 pandemic.

## THE FACT: REDUCTION IN CV ADMISSIONS

### Initial reports and data during the COVID-19 waves

On April 2, 2020, Rodríguez-Leor et al.[8] reported data from 73 centers in Spain that indicated a 40% reduction of percutaneous coronary interventions (PCIs) in patients with ST-segment elevation myocardial infarction (STEMI) during the third week of March compared with the last week of February (before the pandemic outbreak). Eight days after the first report Garcia et al.[9] reported data about a similar reduction (38%) in primary PCI for STEMI during March 2020 (compared with the previous 14 months). Data were extracted from nine high-volume cardiac catheterization laboratories in the USA. On April 14, 2020, neurologists from a hospital in a relatively small city in northern Italy observed a dramatic reduction in ischemic stroke admissions between February 21, 2020 (date of the first record of a patient with SARS-CoV-2 in Italy) and March 25, 2020. Each month there was an average of 51 ischemic stroke cases over the previous 5 years, whereas only 6 admissions were recorded during the investigation period. In their published letter, the authors wondered about the reasons for this phenomenon.[7] Up to that time, neurologists had focused on protecting the stroke units or departments and their personnel from COVID-19 infection and maintaining continuous open access to all patients with stroke[10] and with chronic neurological disorders.[11] In the second half of April 2020, two brief reports from two European countries described that the COVID-19 outbreak was associated with significant reductions in the rates of hospital admissions due to ACS: Metzler et al.[6] found a 40% reduction in Austria and De Filippo et al.[5] a 30% in northern Italy. Immediately, both the European Society of Cardiology and American College of Cardiology urged patients to seek help if they had symptoms of CV diseases. They hypothesized—reasonably but without any evidence—that many patients with CV did not reach emergency and hospital services.

Soon thereafter many other regional and national reports suggested a significant decline in admissions due to AS and ACS in many countries with different healthcare systems.[12-28] The reduction was larger during the various waves of COVID-19, and also after national lockdown conditions began, but was smaller than described in the initial reports. For example, a nationwide study in Germany found that hospitalizations for ischemic AS decreased by 10.9% during the first wave and by 4.6% during the second wave.[20] In the USA, data among Medicare fee-for-service beneficiaries aged ≥65 years indicated that stroke hospitalizations decreased by 22.3% during weeks 10–15 of 2020 compared with same period in 2019; while during weeks 24–44 they decreased by 12.1%. The percentage reduction in ischemic stroke hospitalizations was larger than that of hemorrhagic stroke. However, the reduction of ischemic and hemorrhagic stroke hospitalizations was reported to vary markedly between the states of the USA.[29] Data from Wenzhou, China indicated that patients admitted with intracerebral hemorrhage (ICH) at the beginning of 2020 had a higher incidence of a baseline score on the modified Rankin Scale (mRS) of ≥3 than did those admitted during the same period in 2019.[30] Since most published reports relate to data from countries with high epidemiological burdens from COVID-19, the question arose about whether this reduction was exclusively related to COVID-19 community transmission and the associated healthcare burden. Data from countries with low COVID-19 incidence rates during the first wave of the pandemic demonstrated varied rates of admission due to CV events, which did not always show a substantial decrease compared with previous years. In New Zealand, the admission rate for ACS was lower during their 5-week lockdown.[31] In Australia, in a geographically defined population, a stability in admissions for myocardial infarction and AS was reported during two waves of COVID-19 and two strict lockdowns.[32] In Greece, during a 6-week period of the COVID-19 outbreak, decreases were found in both AS and ACS admissions.[15]

It is worth noting that a reduction of CV admissions was detected despite COVID-19 itself possibly increasing the risk of CV events (both ACS and AS).[33-36] This risk was observable among both individuals who were hospitalized during the acute phase of the infection but also in nonhospitalized individuals. An increased 12-month incidence of CV diseases was observed in people with COVID-19. Since CV events often occur in the presence of other cardiovascular risk factors,[37] we do not know whether COVID-19 provokes or triggers CV events. The interaction between the viral spike protein on the virion surface and angiotensin-converting enzyme 2, which triggers the virus entering host cells, is likely to be involved in the CV manifestations of COVID-19.[34,38] A hypercoagulable state with elevated fibrinogen and factor VIII levels,[39] hyperactivation of platelets, and direct endothelial or vascular injury caused by SARS-CoV-2 infection might also increase the risk of thrombus formation and CV events, especially among critically ill patients.[40,41] Finally, genetic factors may contribute to the susceptibility and response to viral infection.[42] Compared with individuals who experienced a stroke independent of the infection, patients infected with SARS-CoV-2 who suffered a stroke were younger, had higher scores on the National Institutes of Health Stroke Scale (NIHSS), more often had strokes caused by large-artery occlusions, and had higher in-hospital mortality rates.[43] Ischemic AS in patients with COVID-19 was associated with severe disability.[44] Patients with stroke and COVID-19 had higher median mRS scores and a lower "favorable functional outcome" at 3 months. However, in the multivariable logistic regression analysis after adjusting for age, baseline NIHSS score, intensive care unit admission, and history of diabetes, COVID-19 infection was not independently associated with the probability of a poor functional outcome.[45]

## Meta-analyses

A meta-analysis by Baumhardt et al.[46] found that the number of hospital admissions for patients with myocardial infarction was lower during the first lockdown (incidence rate ratio [IRR]=0.516, 95% confidence interval [CI]=0.403–0.660). The investigation periods of most of the included studies (24/27) were very short: 1 or 2 months, up to the end of March or April 2020. Zhu et al.[47] analyzed data from 38 studies (79,753 patients) and found that the number of patients hospitalized with STEMI decreased by 26% during the initial phase of the COVID-19 pandemic. In a systematic review of 40 studies, Helal et al.[48] found that the reduction in the rate of admissions due to ACS was larger in patients with unstable angina than in those with non-STEMI or STEMI. They also found a significant correlation between the absolute risk reduction for the total number of ACS cases and the number of COVID-19 cases per 100,000 people. In a recent meta-analysis that included 79 articles among 57 countries, Sofi et al.[49] found that STEMI admissions significantly decreased during the COVID-19 pandemic, although to a smaller extent than initially reported (IRR over the reference period=0.80, 95% CI=0.76–0.84, $p<0.05$); moreover, there was a large variability across countries. Rattka et al.[50] also found a similar reduction in overall admission rates of patients with STEMI during the COVID-19 pandemic (IRR=0.789, 95% CI=0.730–0.852, $I^2$=77%, $p<0.01$).

Data from meta-analyses indicated that admissions due to AS were also lower during the pandemic. July and Pranata[51] found that the number of stroke alerts was reduced by 36% during the pandemic. However, their meta-analysis included subjects from only nine studies, and their defined "pandemic period" was very short (up to the end of March or the first 2 weeks of April). Romoli et al.[52] included 29 studies in a meta-analysis and found a 35% reduction in admissions due to stroke during the first phase of the COVID-19 pandemic (the "pandemic period" ended before the end of April in 24 out of the 29 studies, and was not defined clearly in 1). Reddy et al.[53] found a 15% reduction in overall admissions due to stroke for the first 6 months of 2020 (compared to the same period in 2019), while Katsanos et al.[54] found that differences in baseline characteristics and the severity of stroke attributed to large-vessel occlusion were observed during the COVID-19 pandemic. However, conflicting results were reported for hemorrhagic strokes. Although admissions were reduced during the pandemic period compared with before the pandemic, the proportion of hospitalizations due to hemorrhage to that due to ischemic stroke was increased.[55] Patients admitted with AS during the COVID-19 pandemic had higher in-hospital mortality rates. Similar to the reduction of admissions due to ischemic AS, the number of reperfusion therapies also decreased during the pandemic.[51] However, the likelihood of being treated with intravenous thrombolysis did not differ between the two periods in comprehensive stroke centers, and the likelihood of being treated with endovascular thrombectomy increased during the pandemic.[56] The latter may be secondary to higher rates of large-vessel occlusion among admissions due to AS,[54] and the reduced rates of patients admitted with milder AS symptoms.[56] Patients admitted with AS during the COVID-19 pandemic had higher in-hospital mortality rates.[54] The largest meta-analysis to date (which included 455,073 stroke admissions), which was recently presented at the International Stroke Conference in 2022, found that patients hospitalized due to stroke during the pandemic had a 42% higher risk of in-hospital mortality compared with those hospitalized during the prepandemic period.[57]

In summary, there is no doubt that during the COVID-19 pandemic, and especially during its first months (during lockdowns or periods with more COVID-19 community transmission), there was a decline in admissions due to CV events (Tables 1 and 2), although the decline was smaller than in initial reports. Both international and local registries have clearly illustrated that as the number of COVID-19 cases/hospitalizations increased, especially during the first phase of the pandemic (wave 1), there was a gradual decrease in patients presenting with AS or ACS; a similar decline was also observed during the second wave (last trimester of 2020), while in the period between the waves, the incidence rates of AS and ACS cases increased but they did not fully return to prepandemic levels.[20,26,58-60] Nevertheless, the question remains as to whether this reduction was due to patients fearing potential exposure to the novel SARS-CoV-2 and consequently avoiding seek-

**Table 1.** Representative reports on the reduction of patients that presented with AS during the COVID-19 pandemic compared with the corresponding control period

| Study | Setting | Population size (*n*): COVID-19 vs. control | Study period (COVID-19 pandemic) | Control period | Percentage reduction (endpoint) |
|---|---|---|---|---|---|
| Morelli et al.[7] | Italy | 6 vs. 51/month | Feb 21 to Mar 25, 2020 | Monthly average of previous 5 years | 88% (ischemic stroke) |
| Richter et al.[24] | Germany | 51,554 vs. 57,889 | Mar 1 to May 31, 2020 (wave 1) | Mar 1 to May 31, 2019 | 11% (ischemic stroke) |
| Richter et al.[20] | Germany | 47,043 vs. 49,318 | Oct 1 to Dec 31, 2020 (wave 2) | Oct 1–31, 2019 | 5% (ischemic stroke) |
| Yang et al.[29] | USA | 53,062 vs. 68,266 | Weeks 10–23, 2020 | Weeks 10–23, 2019 | 22% (stroke in Medicare fee-for-service aged ≥65 years) |
| Katsouras et al.[15] | Greece (three representative COVID-19 referral university hospitals) | 35 vs. 71 | Mar 2 to Apr 12, 2020 | Mar 2 to Apr 12, 2019 | 51% (AS) |
| July and Pranata[51] | Meta-analysis | 9 studies: 36,451 vs. 22,782 | COVID-19 pandemic (Mar & Apr 2020) | Same time period before the pandemic | 36% (stroke alerts) |
| Romoli et al.[52] | Meta-analysis | 29 studies: 212,960 total | First phase of the pandemic | Corresponding period | 31% (stroke) |
| Reddy et al.[53] | Meta-analysis | 29 studies: 32,640 total | COVID-19 pandemic | Historical period | 29% (stroke) |

AS, acute stroke.

**Table 2.** Representative reports on the reduction of patients that presented with ACS during the COVID-19 pandemic compared with the corresponding control period

| Study | Setting | Population size (*n*): COVID-19 vs. control | Study period (COVID-19) | Control period | Percentage reduction (endpoint) |
|---|---|---|---|---|---|
| Rodriguez-Leor et al.[8] | Spain | 260 vs. 433 | Mar 16–22, 2020 | Feb 24 to Mar 1, 2020 | 40% (PCI STEMI) |
| Garcia et al.[9] | USA | 138 vs. 2,970 | Mar 2020 | Jan 2019–Feb 2020 | 38% (PCI STEMI) |
| Metzler et al.[6] | Austria | 137 vs. 226 | Calendar week 13 (Mar 23–29) | Calendar week 10 (Mar 2–8) | 39% (STEMI and NSTEMI) |
| De Filippo et al.[5] | Northern Italy | 547 vs. 756 | Feb 20 to Mar 31, 2020 | Feb 20 to Mar 31, 2019 | 30% (ACS) |
| Chan et al.[31] | New Zealand | 525 vs. 3,648 | Mar 23 to Apr 26, 2020 (lockdown) | Mar 23 to Apr 26, 2015–2019 | 28% (ACS) |
| Katsouras et al.[15] | Greece (three representative COVID-19 referral university hospitals) | 123 vs. 168 | Mar 2 to Apr 12, 2020 | Mar 2 to Apr 12, 2019 | 27% (ACS) |
| Baumhardt et al.[46] | Meta-analysis | 27 studies: 10,102 vs. 71,061 | Lockdown | Before lockdown | 48% (STEMI and NSTEMI) |
| Zhu et al.[47] | Meta-analysis | 38 studies: 79,753 | 2020 | 2019 | 26% (STEMI) |
| Helal et al.[48] | Meta-analysis | 40 studies: 28,613 vs. 39,225 | 2020 pandemic months | 2019 | 28% (ACS) |
| Sofi et al.[49] | Meta-analysis | 79 studies/57 countries: 48,396 vs. 63,161 | Wave 1 of the COVID-19 pandemic | 2019 or average of previous years or immediately preceding period | 20% (STEMI) |
| Rattka et al.[50] | Meta-analysis | 10 studies: 14,861 vs. 35,262 | COVID-19 | Pre-COVID-19 | 21% (STEMI) |

ACS, acute coronary syndrome; MI, myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

ing medical care in hospitals, or a true reduction in CV events. In any case, we anticipate an increase in CV events and hospitalizations after the COVID-19 pandemic ends. However, if the former is true, increases in cardiovascular mortality and morbidity, including increased rates of hospitalizations for heart failure or recurrent AS, are anticipated in the near future.

## THE CAUSES

### Evidence supporting avoidance of medical care

Medical-care avoidance or delay is a problem for many diseases and has negative health consequences. Community interventions mostly focus on knowledge of symptoms and explaining the need to promptly treat the disease, without always being successful. Theoretically, multiple not-well-known factors and many types of information can influence the behaviors and decisions of patients to promptly ask for help regarding their symptoms. When confronted with a crisis (health problem), individuals (patients) make several considerations before acting upon the situation (symptoms). According to the crisis decision theory,[61] when humans face a negative event (e.g., symptoms), the first step is to assess the severity of the event, the second step is to determine how they will respond to the event, and the final step is to begin the process of choosing the best response while considering the direct and indirect consequences of that response. During the last pandemic , two major parameters may have especially affected the third step: 1) the fear of becoming infected with the virus and 2) the absence of a causative therapy against SARS-CoV-2. Based on that, the following data support the hypothesis that avoidance of seeking medical care for CV disease during the COVID-19 pandemic was a major causative factor in the reduction in hospital admissions (Fig. 1):

1) During the pandemic, and especially during the lockdown phases, similar decrease in hospital admissions were observed in CV and non-CV diseases among new patients who had not been previously diagnosed and for those with a known disease.[62] Lower hospital admission rates (compared with the prepandemic data) were reported for all major noninfectious disease groups.

2) Increased morbidity/mortality rates were found in nationwide population-based cohort studies, possibly indicating that inappropriate medical care was provided during medical emergencies due to delays.[62]

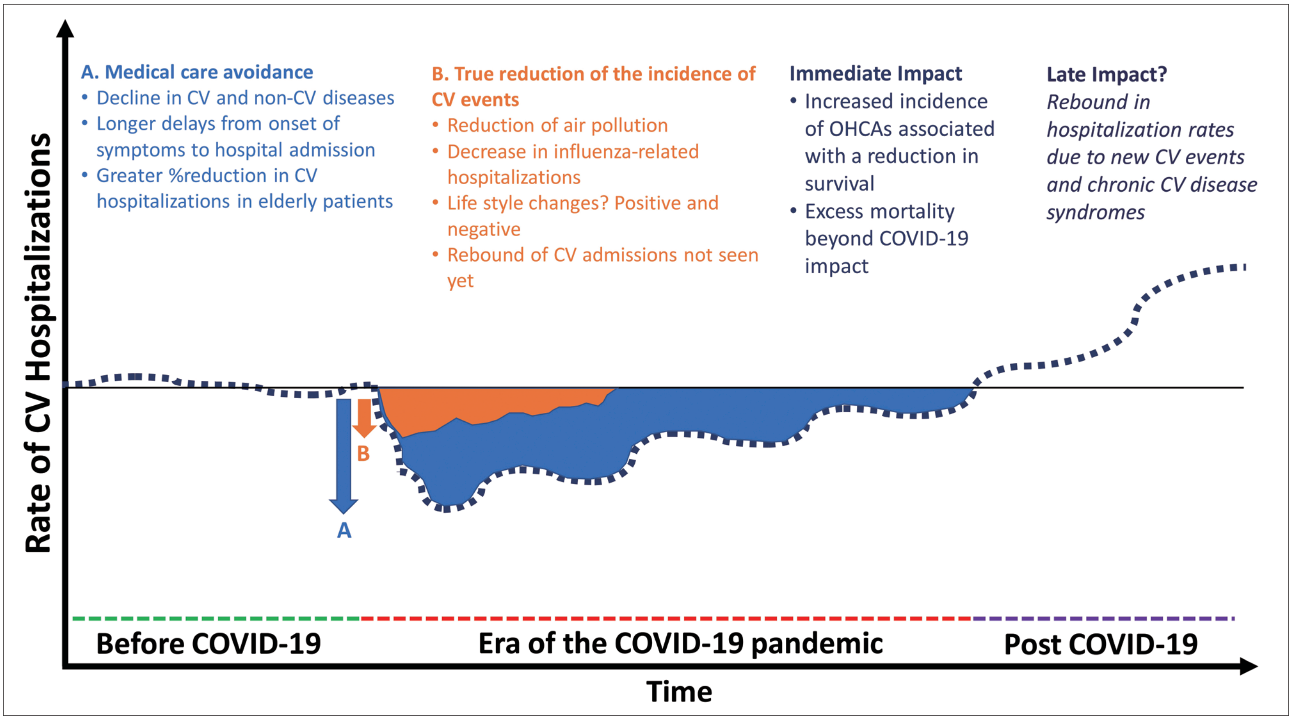


**Fig. 1.** Schematic representation of the rates of CV hospitalizations (blue dashed curve) over three periods: before (green dashed line), during (red dashed line), and after (purple dashed line) the COVID-19 pandemic. Overall, the hospitalization rate was reduced during the COVID-19 pandemic due to 'A' medical care avoidance behaviors of the patients (relatively large effect) and 'B' a true reduction of the incidence of CV events (relatively small effect). As a result, we observed an immediate impact on excess mortality. After the COVID-19 pandemic, there may be latent consequences (rebound effects) of a substantial increase in the hospitalization rate due to CV diseases from new CV events and chronic CV disease syndromes. CV, cerebro-/cardiovascular; OHCAs, out-of-hospital cardiac arrests.

3) Many studies found that, during the first months of the pandemic, the time from symptom onset to hospital admission in patients with STEMI and the gap between the last-known time without disease to presentation in patients with AS were significantly longer compared with the same periods in previous years.[63,64] However, not all studies confirmed this observation.[54]

4) Larger percentage reductions in CV hospitalizations were observed in elderly individuals.[19,54] This is indirect evidence of the avoidance or delay from seeking medical care since the elderly are considered to have a high risk of COVID-19 complications and were more concerned about becoming infected.

## Evidence supporting a true reduction in the incidence of CV events in the community

Acute CV events are often preceded by triggers, which include common daily activities, emotions, and environmental changes. These triggers are possible predisposing factors for the destabilization of other risk factors for CV diseases and atheromatous plaques, and contribute to artery thrombosis. Published studies support that many of these triggers were suppressed during the last pandemic, especially during the lockdown phases (Fig. 1):

1) There is evidence from epidemiological studies of a strong association between air pollution and CV diseases.[65] Lockdown during the COVID-19 pandemic in China resulted in a dramatic decrease in atmospheric nitrogen dioxide ($NO_2$) levels, as identified both by satellites and by observations from the ground.[66] Similar observations were reported in some European countries. Claeys et al.[67] found that during the lockdown in Belgium there was a 32% decrease in ambient $NO_2$ concentrations, while there was a 26% reduction in admissions due to STEMI during the same period. However, the coexistence of the decrease in ambient $NO_2$ concentrations and the reduction in admissions due to STEMI does not confirm the presence of a causal relationship. Moreover, Le et al.[66] found some unexpected effects of lockdown on air pollution in China such as high levels of particulate matter (PM) and severe haze formation in some areas. In Europe, although substantial decreases in $NO_2$ were reported shortly after the lockdown phase (within days or weeks), the reductions in $PM_{2.5}$ were smaller and less consistent.[68] Previous studies indicated that $PM_{2.5}$ air pollution is the most significant air pollution trigger for CV events, which can occur within a few days of a pollution event.[65] In summary, despite observations suggesting that air pollution decreased during the COVID-19 period, there is no reliable evidence for a causal link between this and the reduction of admissions due to CV events.

2) Following the COVID-19 pandemic, there was a significant decrease in influenza-related hospitalizations compared with the values predicted over the same time period.[69] This was due to a sharp decline in influenza transmission and influenza-like syndromes in most countries. Prepandemic observational studies found an association between influenza and acute myocardial infarction, while the incidence of acute myocardial infarction was also increased (to a lesser extent) after noninfluenza respiratory viruses.[70] Warren-Gash et al.[71] found that acute respiratory infection in influenza is a trigger for ACS that acts within a few days. Moreover, influenza-like syndromes increase the short-term risk of AS, particularly in young people.[72] Nonetheless, it should also be remembered that SARS-CoV-2 infection increases the risk of CV events,[73] and that the "total virus burden" (the sum of different virus infections) during the pandemic could be a more-accurate index of the risk of CV events. As a result, the "total virus burden" during the pandemic and the relative impact of COVID-19 and influenza or influenza-like syndromes on CV risk must be considered before it can be claimed that the remarkable decrease in the number of influenza infections resulted in a true reduction of CV events. The COVID-19 burden changed rapidly over time during the pandemic, and the influenza burden was not stable during recent years in many countries. Overall, it seems that the "total virus burden" was somewhat reduced during the first months of the COVID-19 pandemic, at least in some countries and for certain periods of time.[74,75] Regarding the relative impacts of COVID-19 and influenza or influenza-like syndromes on CV risk, indirect evidence supports that the AS risk was higher after COVID-19,[36,73,76] but the data were not clear since different values were reported and different methodological approaches were used.[36,70,71,73,77] The hypothesis of the reduction in CV events being due to a decline of influenza infections therefore cannot be excluded (or supported) easily.

3) Lifestyle changes have been reported during the waves of the COVID-19 pandemic. Changes in diet habits, physical activity, working hours, hours of sleep per day, relaxation periods, and alcohol consumption have been observed in the general population. However, it is difficult to conclude that the COVID-19 pandemic resulted in lifestyles that were either more or less healthy. Tsigkas et al.[78] observed an inverse association between lifestyle changes and the number of known CV risk factors. In a telephone survey they found reductions in passive smoking, working hours, and the consumption of alcohol, junk food, and salt, and an increase in sleeping hours, mostly in participants with smaller burdens from cardiovascular risk factors. They stated that this modification could have been one of the causes of the reduced admissions due to ACS (via avoidance of trigger activities). However, other studies found an increase in alcohol consumption dur-

ing the pandemic,[79] which may explain the relatively significant increase in ICH during the same period, since alcohol intake is an important risk factor for spontaneous ICH, but does not explain why the absolute incidence of ICH was rather reduced.[55] Moreover, an increased urgency to strengthen mental health systems in most countries was reported, and mental health status is known to influence the risk of CV events.[80] Finally, it is not easy to assess the result of the interaction between racial and socioeconomic disparities with these factors over a relatively short period of time. It is very interesting that during the pandemic, some racial and ethnic minority groups in polyethnic societies experienced disproportionate increases in CV deaths, suggestive that the collateral damage from CV diseases was more severe in these populations.[81] Other factors such as the unemployment rate may attenuate the possible positive effects of lifestyle changes on CV diseases, since unemployed persons are well known to have less access to vital health care than employed persons.[82]

4) From an epidemiological point of view, if the reduced admission rates for CV diseases during the pandemic was mostly explained by the avoidance of medical health care, there should be a rebound in admissions after a period of time (for new CV events and especially for chronic heart failure); this would be the result of patients with CV events who went untreated. New CV events and more-severe symptoms and signs (e.g., dyspnea and edema due to heart failure in cases of untreated myocardial infarctions) could lead to a surge of admissions for CV events. Throughout the pandemic, we anticipated such an increase that would possibly exceed the rates of previous years; however, such an increase was not observed. However, we cannot exclude the possibility that this will be observed in the near future.

## THE IMPACT

In order to obtain a complete picture of the collateral damage caused by the COVID-19 pandemic, we reviewed the literature referring to its impact on mortality and morbidity (Table 3), which revealed the following:

1) The incidence of out-of-hospital cardiac arrests (OHCAs) increased during the first phase of the pandemic. Significant correlations between the differences in OHCAs during 2020 and 2019 and the cumulative incidence rates of COVID-19 were also reported in Lombardia (Italy) and London (UK), and OHCAs were associated with a reduced survival rate.[83,84] The cause of these correlations cannot be determined as there was a paucity of data in systemic autopsy studies during the last pandemic. A possible explanation for cardiac arrest or CV complications is treatment delay.

2) Data for excess mortality (the number of deaths from all causes measured over a period, above what would be observed under "normal" conditions) during the COVID-19 pandemic in the European Union (EU) were very interesting. In 2020, the EU experienced two waves of excess mortality: the first between March and May 2020 (reaching a 25% excess rate in April), and then a longer one between August 2020 and February 2021 (reaching a 40% excess rate in November 2020). During 2021 excess mortality reached a new peak in April (21%), and then a second in early autumn, with the excess mortality throughout the EU reaching 17% in October.[85] This excess mortality was observed in most countries. Data from 24 European countries indicated that during the first few months of the pandemic, more deaths were reported, especially among the elderly population (90% of the excess deaths were among persons aged 65 years or older). Only some of the deaths in Europe, the UK, and the USA can be attributed to a respiratory condition such as COVID-19.[86-88] In the USA, deaths increased by 20% during March–July 2020, while COVID-19 was the cause of only 67% of these excess deaths.[88] Data from death certificates (from 50 states and the District of Columbia ) indicated a significant increase in total deaths during 2020 in three distinct waves compared with previous years. Again, only two-thirds of those total deaths were attributed to COVID-19. Deaths from heart disease increased by 4.8%, the largest increase since 2012, and deaths from stroke increased by 5.0%.[89] These deaths can be indirectly related to the pandemic; that is, "collateral damage."

3) While excess mortality during the COVID-19 pandemic was observed in most countries around the world, another question emerged regarding the true incidence of deaths

**Table 3.** Representative reports on the impacts of the COVID-19 pandemic on mortality and morbidity

| Setting | Study period | Endpoint | Percentage increase |
|---|---|---|---|
| Italy (Lombardia) | First phase of the pandemic | OHCA | 52 |
| UK (London) | First phase of the pandemic | OHCA | 81 |
| EU | Mar–May 2020 | Excess mortality | Up to 25 (Apr 2020) |
| EU | Aug 2020–Feb 2021 | Excess mortality | Up to 40 (Nov 2020) |
| EU | 2021 | Excess mortality | 21 (Apr 2021) |
| USA | Mar–July 2020 | Excess mortality | 20 |

EU, European Union; OHCA, out-of-hospital cardiac arrest.

from COVID-19. Researchers wondered if the mortality of the new virus could have been underestimated since it was mostly calculated from death certificates. Avoidance of or delay in receiving health care, false-negative tests, and delays in reporting deaths to public-health systems are some of the possible reasons for this. Indeed, different studies that used different regression model approaches and methodologies found that a proportion of all-cause deaths during the last pandemic, especially those during the first phases and during peaks in SARS-CoV-2 transmission, could be reclassified as "unrecognized" COVID-19 deaths.[90,91] The rates of "unrecognized" COVID-19 deaths were higher in very old people. However, even if the proportion of underrecognized deaths was high, the total number of COVID-19-related deaths did not entirely explain the excess mortality. For 2020, the World Health Organization (WHO) used data from 50 European and 15 American countries to estimate excess mortality at 1.11–1.21 million in Europe and 1.34–1.46 million in the Americas.[86] Only about 50% and 60% of these deaths, respectively, were reported as COVID-19-related deaths, but the gap between COVID-19-related mortality and excess all-cause deaths varied among regions.[92] It is therefore impossible that unrecognized deaths from COVID-19 were responsible for all of the excess mortality during the pandemic. However, COVID-19 could have been responsible for most of the excess deaths in some countries and for particular periods of time. The number of excess all-cause deaths in the USA from March to May 2020 was 28% higher than the official number of COVID-19-related deaths reported during that period. Iuliano et al.[93] stated that 24% of the total estimated COVID-19-related deaths in the USA from March 2020 to May 2021 were not reported through death certificates. An overwhelmed health system and low diagnostic capacity during that time might have played significant roles. Finally, many regions of the world are known to lack the capacity to provide accurate data, with WHO data indicating that almost 40% of worldwide deaths (irrespective of cause, and in nonpandemic periods) are not registered.

## FUTURE DIRECTIONS

Many public-health leaders have supported that a new pandemic is inevitable in the near future, possibly involving zoonotic diseases. It is now realized that pandemics such as that of COVID-19 create a complex crisis ("mega-crisis") that includes the combination and interdependence of health, economic, political, national, and global crises. The prolepsis and overall handling of this situation was outside the scope of this review. However, if a pandemic occurs, one of the main expected problems to be resolved is an increase in collateral damage, especially those related to CV diseases. We have already learnt that the treatment of infectious disease at the expense of other diseases generates major health problems and excess total mortality. Pandemics demand immediate changes to the practices in health-care systems, making it important to dedicate hospitals (and supplies) for new infections, reorganize health infrastructures, and continue providing the medical community and the general public with education. Dedicated hospitals will not only protect many medical workers from the transmission of the disease but also help patients suffering from other diseases (e.g., CV events) to visit nondedicated hospitals without the fear of becoming infected. Reorganization of the health infrastructures involves changes in primary care and hospitals. In primary care, telemedicine (e.g., video telemedicine, new devices for patient follow-up, and telerehabilitation) will help to improve the control of the risk factors and avoid unnecessary visits to hospitals, especially in areas with no purely nondedicated (e.g., non-COVID-19) hospitals.[94-96] In hospitals, better spaces in emergency departments will also help to both reduce the transmission of the disease and reduce the fear of becoming infected for people suffering from other diseases. Smart campaign strategies distributed by digital media will be needed in order to eliminate avoidable harm in health care or reduce the prehospital time delay of patients with CV events, since many community interventions in the past had no major effect on patient behavior. Unfortunately, these interventions have not been investigated in a randomized manner during the last pandemic, since communities are often unprepared for emergencies and instead improvise in the presence of great pressure.

## CONCLUSION

It is difficult to obtain accurate data regarding the exact reasons behind the decline in admissions due to CV events and its impact on mortality and morbidity during the COVID-19 pandemic. This decrease seems to be less than what was indicated in initial reports. Indirect evidence supports that the main reason was the reluctance of the public to seek medical aid, although a small true decline in CV events cannot be excluded. The impacts of the CV collateral damage due to COVID-19 on CV mortality and morbidity appear to be highly detrimental, even though it is not possible to estimate them accurately. A systematic effort is needed to appropriately and promptly reorganize health-care systems in order to cope with the anticipated increased rates of hospitalizations for CV events in the near future.

## Availability of Data and Material

Data sharing not applicable to this article as no datasets were generated or analyzed during the study.

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## Conflicts of Interest

The authors have no potential conflicts of interest to disclose.


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