Dual antiplatelet therapy in patients with acute coronary syndrome during the coronavirus disease of 2019 pandemic: the right choice at the right time
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The rapid spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the resulting Coronavirus disease 2019 (COVID-19) have placed an enormous strain on the healthcare systems, with unique implications on medical practice. These implications include major modifications of our standard healthcare management of patients, either who are suspected or who are affected by COVID-19. A systematic analysis of current available literature describing clinical features of COVID-19-infected patients in China reported a high prevalence of preexisting cardiovascular disease (CVD) among SARS-CoV-2 infected patients. A meta-analysis of more than 1500 COVID-19 patients from China reported a prevalence of cardiovascular and cerebrovascular disease ranging between 4 and 40% with a median of 16%\textsuperscript{1}; notably, data obtained outside of China are still limited, but in Western countries, the presumed prevalence of CVD associated with COVID-19 could be even higher than reported in China because of the higher median age of the population.

Currently, data regarding prevalence and management of acute coronary syndrome (ACS) in the context of COVID-19 are scarce. The profound inflammatory response and hemodynamic changes associated with COVID-19 may confer the risk for prothrombotic status, and potentially coronary thrombosis, in susceptible patients. Of note, during acute respiratory failure because of influenza and noninfluenza viral illness, the risk of myocardial infarction has been reported to increase.\textsuperscript{2} For all these reasons, among COVID-19-infected patients, the occurrence of ACS is a high probable clinical scenario.

Dual antiplatelet therapy (DAPT) is a cornerstone of antithrombotic treatment in patients undergoing percutaneous coronary intervention (PCI) for ACS. In the absence of targeted therapies, antithrombotic drugs, used for years as part of treatment for HCV, HIV or Ebola virus diseases, are currently largely employed for treatment of COVID-19 patients. Drugs used for autoimmune diseases, such as chloroquine and hydroxychloroquine, are currently being tested worldwide in COVID-19 patients. Moreover, several ongoing clinical trials have been registered with the intention of discovering effective treatments; among these, the most intriguing are analyzing the effectiveness of plasma-based therapy (CONCOVID study, NCT04342182) and of immunomodulators such as tocilizumab (TOCIVID-19 trial, NCT04317092).

Multiple drug-drug interactions (DDIs) of these medications with cardiovascular drugs have been described (Table 1). Despite the cardiovascular scientific community being active in drawing up a consensus document about the management of CVD during the COVID-19 pandemic, specific suggestions regarding DAPT have not been provided. We advise that a ‘revised’ DAPT strategy during COVID-19 pandemic should be taken into consideration.

Despite the absence of specific therapeutic agents capable of targeting SARS-CoV-2, a small randomized clinical trial using antiviral drugs in COVID-19 patients reported no benefit in the primary endpoint, but an intriguing result for certain secondary endpoints, such as mortality and intensive care stay length.\textsuperscript{3} On the basis of this study and several other reports,\textsuperscript{4,5} in addition to hydroxychloroquine with azithromycin,\textsuperscript{6} antiviral therapy is at the forefront of SARS-CoV-2 management. Several of these antiviral agents are known for multiple DDIs. In particular, protease inhibitors, such as lopinavir/ritonavir, atazanavir and darunavir/atavidistat, are reported to inhibit hepatic CYP3A4 and influence the activity of P2Y\textsubscript{12} platelet receptor inhibitors.

The concomitant administration of ticagrelor with strong inhibitors of CYP3A4, such as protease inhibitors, increases its serum concentration; hence, the use of ticagrelor in this setting is contraindicated because of the high bleeding risk. Conversely (through CYP3A4 inhibition), the same antiviral agents impair the bioactivation of clopidogrel, reducing its active metabolite and, thereby, platelet inhibition\textsuperscript{7} with consequently associated high thrombotic risk.\textsuperscript{8} Similarly, prasugrel metabolism is affected by the co-administration of antiretroviral therapy. Despite this, a preserved, potent platelet inhibition persists.\textsuperscript{7} Among the not-oral antiplatelets drugs, cangrelor, an intravenous P2Y\textsubscript{12} inhibitor, is not influenced by liver function;
therefore, a DDI with antiviral agents is neither demonstrated nor expected.

Taking all this in consideration, DAPT selection for ACS management in the COVID-19 pandemic era is challenging. Virtually, all ACS patients admitted to hospital should be considered at risk of SARS-CoV-2 infection. The syndrome of COVID-19 can be preexisting the ACS or it could develop during hospital stay or weeks thereafter. For these reasons, all ACS patients should be

Table 1 Drug-drug interactions between experimental COVID-19 therapies and antithrombotic agents

<table>
<thead>
<tr>
<th>Interaction mechanism</th>
<th>Aspirin</th>
<th>Clopidogrel</th>
<th>Prasugrel</th>
<th>Ticagrelor</th>
<th>Cangrelor</th>
<th>Tirofiban</th>
<th>Eptifibate</th>
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<tbody>
<tr>
<td>Lopinavir/ritonavir</td>
<td>CYP3A4 inhibition</td>
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<td>Darunavir/cobicistat</td>
<td>CYP3A4 inhibition</td>
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<td>Atazanavir</td>
<td>CYP3A4 inhibition</td>
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<tr>
<td>Favipiravir</td>
<td>No expected interaction</td>
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<tr>
<td>Remdesivir</td>
<td>No expected interaction</td>
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<tr>
<td>Ribavirin</td>
<td>No expected interaction</td>
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<tr>
<td>Chloroquine or hydroxychloroquine</td>
<td>No expected interaction</td>
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<tr>
<td>Azithromycin</td>
<td>No expected interaction</td>
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<tr>
<td>Tocilizumab</td>
<td>CYP3A4 inhibition via IL-6</td>
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<td>Interferon-β</td>
<td>No expected interaction</td>
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Modified from https://www.covid19-druginteractions.org (Liverpool Drug Interactions Group). Decreased conversion to active metabolite leading to high residual platelet reactivity. Decreased conversion to active metabolite but without significant reduction in platelet inhibition. Increased serum concentration. Potential interaction likely to be of weak intensity. Additional action/monitoring or dosage adjustment unlikely to be required. No significant effect.

Fig. 1

Proposed algorithm for the choice of an oral P2Y12 receptor inhibitor for COVID-19 patients with an acute coronary syndrome.

Accurate and dynamic evaluations of ischemic and bleeding risks are mandatory.
considered potential candidates for antiviral therapy in the short or middle period, and therefore, the use of ticagrelor and clopidogrel should be carefully evaluated. Recently, the ISAR-REACT 5 trial demonstrated the superiority of prasugrel over ticagrelor in preventing major adverse ischemic events in ACS patients. These data and the known DDIs with antiviral agents should be taken into account while selecting the DAPT regimen during the COVID-19 pandemic. Moreover, a proper use of platelet function tests could also be considered. In this context, an accurate and dynamic evaluation of patient bleeding and ischemic risks is mandatory. Notably, cangrelor infusion may be considered to reduce the risk of peri procedural myocardial infarction, repeat coronary revascularization, and stent thrombosis in P2Y12 inhibitor-naïve patients undergoing PCI, especially for those with a contraindication to prasugrel, given the potential ticagrelor DDIs and the expected delayed and variable efficacy of clopidogrel in ACS patients.

Another, and perhaps, more frequent scenario refers to patients admitted for COVID-19 with DAPT ongoing because of a prior ACS or PCI. In that case, these patients are treated with antiviral agents, and switching from clopidogrel or ticagrelor to prasugrel should be considered, if DAPT is still needed after thoughtful guidelines-informed re-evaluation.

In the upcoming future, we will witness the introduction of several novel therapies to combat SARS-CoV-2 infection. The cardiovascular scientific community should consider as priority the intricate interplay between pharmacological strategies for COVID-19 and CVD.

If no contraindications exist, we propose to consider prasugrel as an important medication of choice for DAPT in the majority of ACS patients undergoing PCI during the COVID-19 pandemic (Fig. 1, flow chart). In addition, we should keep in mind that, although platelet reactivity-guided antithrombotic therapy failed to demonstrate to be effective in the prevention of major cardiovascular events in routine practice, in specific and selected settings, such as the concomitant administration of antiviral drugs for COVID-19, a “tailored” antiplatelet therapy including the evaluation of on-treatment residual platelet reactivity, might allow the risk of both ischemic and bleeding complications to be minimized.

Acknowledgements

Conflicts of interest

G.P. reported receiving consulting or lecture fees from AstraZeneca, Bayer, Chiesi, Daiichi Sankyo/Eli Lilly, and Merck Sharp Dohme. F.S. has no conflict of interest to disclose.

References