Cardiovascular Considerations for Patients, Health Care Workers, and Health Systems During the Coronavirus Disease 2019 (COVID-19) Pandemic

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Drug Therapy and COVID-19: Interactions and Cardiovascular Implications

Data regarding antiviral therapies and other treatment strategies, as well as their potential interaction with CV medications and CV toxicities are summarized in Tables 3-5. Although currently there are no specific effective therapies for COVID-19, various pharmacologic agents are under activeinvestigation. As these drugs are being studied, it is important to review the potential CV side effects and interactions with other CV medications.

Antiviral Therapy: Antivirals are at the forefront of medications under study for the treatment COVID-19 and the clinical trial identifiers for each are listed in Table 3. Ribavirin and remdesivir are two such agents that bind to the active site on the RNA-dependent RNA polymerase on SARS-CoV2 (62), while lopinavir/ritonavir inhibits replication of RNA virus and has evidence of a synergistic effect *in vitro* with ribavirin (63). Ribavirin and lopinavir/ritonavir are under investigation in clinical trials for COVID-19 and have been used for years as components of treatment for hepatitis C and HIV, respectively (64,65). While ribavirin has no characterized direct CV toxicity, lopinavir/ritonavir may result in QT and PR interval prolongation, especially in patients who have a baseline abnormality (long QT) or those who are at risk for conduction abnormalities including those taking other QT prolonging drugs (65).

Anticoagulant drugs: Both ribavirin and lopinavir/ritonavir have the potential to affect anticoagulant dosing: ribavirin has variable effects on warfarin dosing (66) and lopinavir/ritonavir may require dose reductions or avoidance of CYP3A mediated drugs such as rivaroxaban and apixaban (67,68).

P2Y12 inhibitors: Lopinavir/ritonavir can also influence the activity of P2Y12 inhibitors through CYP3A4 inhibition, which results in decreased serum concentrations of the active metabolites of clopidogrel and prasugrel and increased serum concentrations of ticagrelor. Given the increase in serum ticagrelor levels with such medications (69,70), concomitant use with ticagrelor is discouraged in the United States and Canada due to excess in bleeding risk. Conversely, there is evidence that clopidogrel may not always provide sufficient platelet inhibition in the setting of concomitant administration of lopinavir/ritonavir, whereas this was not the case with prasugrel as assessed by the VerifyNow P2Y12 assay (71,72). If P2Y12 inhibition is needed during treatment with lopinavir/ritonavir, prasugrel can be used; however, if contraindicated (i.e. history of stroke or TIA, low body mass index, or active pathological bleeding), a testing-guided approach (e.g. with P2Y12 platelet function assays) may be considered with alternate antiplatelet agents. Details about switching between P2Y12 inhibitors have been described elsewhere (73). Finally, metabolism of the intravenous P2Y12 inhibitor, cangrelor, is independent of hepatic function, therefore a drug interaction is not expected (74).

Statins: HMG-CoA reductase inhibitors also have the potential to interact with the combination of lopinavir/ritonavir and can result in myopathy due to elevated statin levels when administered together. Lovastatin and simvastatin, in particular, are contraindicated for co-administration with lopinavir/ritonavir due to risk of rhabdomyolysis. Other statins, including atorvastatin and rosuvastatin, should be administered at the lowest possible dose but not to exceed the maximum dose stated in the package insert while on lopinavir/ritonavir (65). Remdesivir is an investigational drug previously evaluated in the Ebola epidemic and is now being studied in patients with COVID-19. The drug is currently available in clinical trials and through compassionate use from Gilead Sciences, Inc (Foster City, California). While extensive CV toxicities and medication interactions have yet to be reported, prior evaluation of this drug during the Ebola outbreak did note the development

of hypotension and subsequent cardiac arrest after loading dose in one patient (among 175 total) (75).

ACE2 and potential therapeutic implications: As the ACE2 receptor is the mechanism of entry for SARS-CoV2, some data suggest that ACE inhibitors (ACEi) and angiotensin receptor blockers (ARB) may upregulate ACE2, thereby increasing susceptibility to the virus (Figure 1) (5). In contrast other studies show that ACEi/ARB may potentiate the lung protective function of ACE2, which is an angiotensin II inhibitor (80-82). Thus, the therapeutic implications for ACEi/ARB therapy during COVID-19 infection is unclear. Overall, there is insufficient data to suggest any mechanistic connections between ACEi/ARB therapy with contracting COVID-19 or with severity illness once infected.