

CONTEMPORARY REVIEW

# Guidance on Short-Term Management of Atrial Fibrillation in Coronavirus Disease 2019

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**ABSTRACT:** Atrial fibrillation is a common clinical manifestation in hospitalized patients with coronavirus disease 2019 (COVID-19). Medications used to treat atrial fibrillation, such as antiarrhythmic drugs and anticoagulants, may have significant drug interactions with emerging COVID-19 treatments. Common unintended nontherapeutic target effects of COVID-19 treatment include potassium channel blockade, cytochrome P 450 isoenzyme inhibition or activation, and P-glycoprotein inhibition. Drug-drug interactions with antiarrhythmic drugs and anticoagulants in these patients may lead to significant bradycardia, ventricular arrhythmias, or severe bleeding. It is important for clinicians to be aware of these interactions, drug metabolism changes, and clinical consequences when choosing antiarrhythmic drugs and anticoagulants for COVID-19 patients with atrial fibrillation. The objective of this review is to provide a practical guide for clinicians who are managing COVID-19 patients with concomitant atrial fibrillation.

**Key Words:** antiarrhythmic drug ■ atrial fibrillation ■ COVID-19

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2, which was first reported in 2019 in Wuhan, Hubei, China.<sup>1,2</sup> It infects host cells through angiotensin-converting enzyme 2 membrane receptors, which are highly expressed in heart and lungs, especially in patients with underlying cardiovascular disease.<sup>3</sup> COVID-19 patients with underlying cardiovascular disease have increased risk of morbidity and mortality from complicated myocardial injury, myocarditis, congestive heart failure (CHF), thromboembolism, and arrhythmias.<sup>4</sup> Atrial fibrillation (AF) is the most common arrhythmia seen in critically ill patients.<sup>5</sup> Several potential pharmacotherapies are emerging.<sup>4,6</sup> Risks of arrhythmogenic effects of COVID-19 pharmacotherapies have been noted<sup>4,7</sup> (Table). The overall objective of this review is to provide practical guidance for clinicians who are managing COVID-19 patients with concomitant AF recommendations (Figure 1) based on the

pharmacological characteristics of COVID-19 pharmacotherapies, anticoagulants, and antiarrhythmic drugs (AADs) in the setting of limited clinical data.

## AF IN COVID-19

The prevalence of cardiac arrhythmias was up to 16.7% in hospitalized patients and as high as 44.4% in the intensive care unit in Wuhan.<sup>8</sup> In New York City, arrhythmias were reported in 24 of 130 patients (18.5%) who required invasive mechanical ventilation, of whom 23 of 24 patients (95.8%) had atrial arrhythmias.<sup>9</sup> In an Italian cohort of 99 patients hospitalized with COVID-19, AF was found in 19% of all cases and in 36% of patients with underlying cardiovascular disease, and AF was more common in patients who did not survive (42.1% versus 32.5%).<sup>10</sup> In a small Italian report, 75% of hospitalized COVID-19 geriatric patients in Italy had a medical history of AF.<sup>11</sup>

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## Nonstandard Abbreviations and Acronyms

<b>AAD</b>	antiarrhythmic drug
<b>AF</b>	atrial fibrillation
<b>CHF</b>	congestive heart failure
<b>COVID-19</b>	coronavirus disease 2019
<b>CYP</b>	cytochrome P
<b>I<sub>K</sub></b>	potassium channel
<b>I<sub>Na</sub></b>	sodium channel

Evidence of myocardial injury was noted in 19.7% of 416 hospitalized COVID-19 patients, leading to a higher mortality rate compared with those without myocardial injury (51.2% versus 4.5%, respectively).<sup>12</sup> Viral activated cytokine storm syndrome in fulminant myocarditis could play a major role in COVID-19 mortality.<sup>13</sup> CHF was present in up to 23.0% of COVID-19 patients and was more prevalent in non-survivors compared with survivors (52% versus 12%;  $P < 0.0001$ ).<sup>14</sup> AF is associated with in-hospital mortality and morbidity in patients with acute myocarditis.<sup>15</sup> Inflammatory cytokines, including CRP (C-reactive protein), interleukin-6, and tumor necrosis factor- $\alpha$ , may have an important role in AF pathogenesis.<sup>16</sup> Guidelines for the management of AF in various conditions and populations have been published<sup>17,18</sup>; however, guidance for managing AF in COVID-19 patients is currently not available.

## OVERVIEW OF MECHANISMS AND PHARMACOKINETICS AND DYNAMICS OF THE EMERGING COVID-19 PHARMACOTHERAPY

A list of emerging COVID-19 pharmacotherapies is summarized in Table. Pharmacokinetics and pharmacodynamics of AADs (Figure 2) and anticoagulants (Figure 3), focused on known and plausible drug-drug interactions with emerging COVID-19 pharmacotherapies, are discussed. Major interactions are illustrated in Figure 4.

### Hydroxychloroquine and Chloroquine

Chloroquine and hydroxychloroquine (less toxic metabolite of chloroquine) block viral entry into cells, reduce cytokines, and inhibit autophagy and lysosomal activity in host cells<sup>19</sup> (Table). They are metabolized by cytochrome P (CYP) 2C8, CYP3A4, CYP2D6, and CYP1A1. They are both CYP2D inhibitors, have a long half-life, have a large volume of distribution, and are renally excreted (chloroquine, 51%; and hydroxychloroquine, 21%).<sup>20</sup> They also block potassium channel

(I<sub>Kr</sub>), potentially prolonging QT, leading to drug-induced torsade de pointes (Figure 4) in those with concomitant use of drugs prolonging QT and drugs with CYP metabolic inhibition, and patients with reduced repolarization reserve (concealed or manifested congenital long-QT syndrome).<sup>4</sup>

### Macrolide

Azithromycin and hydroxychloroquine in combination increase viral clearance compared with hydroxychloroquine monotherapy.<sup>21</sup> The mechanism is likely caused by induction of interferon and interferon-related genes.<sup>22</sup> Major drug interaction with AADs is QT prolongation from I<sub>Kr</sub> blockade effect of azithromycin<sup>23</sup> (Figure 4). Unlike other macrolides, which are strong CYP3A4 inhibitors, azithromycin minimally inhibits CYP3A4. Azithromycin is a P-glycoprotein substrate and a weak to moderate P-glycoprotein inhibitor, which may interact with anticoagulants (Figure 3).

### Antiviral Therapy

Lopinavir, a protease inhibitor, is extensively metabolized by CYP3A4 and was therefore combined with ritonavir, a strong CYP3A inhibitor, to enhance its efficacy. Lopinavir/ritonavir has strong drug interactions with AADs (Figure 2). Lopinavir is metabolized by the liver and excreted in the gastrointestinal tract, with minimal renal excretion but significant nephrotoxicity (Table). Ritonavir is also a strong P-glycoprotein inhibitor and may potentially interact with anticoagulants<sup>24</sup> (Figure 4).

Nucleotide analogs that inhibit RNA-dependent RNA polymerase, such as remdesivir (adenosine analog), ribavirin (guanosine analog), and favipiravir (purine analog), are being studied in COVID-19 patients. Remdesivir is mainly metabolized by hydrolase and partially metabolized by CYP2C8, CYP2D6, and CYP3A4. Remdesivir is a CYP3A4 inhibitor in vitro, but no clinically significant drug interaction is documented, likely because of its rapid clearance<sup>25</sup> (Table). Ribavirin is metabolized by non-organ-specific phosphorylation and renally excreted without CYP metabolism.<sup>4,26</sup> Ribavirin does not have documented interaction with AAD but elevates international normalized ratio when used with warfarin by unclear mechanisms.<sup>4,27</sup> Favipiravir was approved for influenza treatment in Japan. It is metabolized by oxidase and excreted in the urine.<sup>28</sup> Cardiovascular adverse effects are not yet established.<sup>4</sup>

Umifenovir inhibits membrane fusion of viral envelope targeting the S-protein/angiotensin-converting enzyme 2 interaction. It is approved in China and Russia. It is mainly metabolized by CYP3A4 and excreted by gastrointestinal tract.<sup>29</sup> There is no documented evidence of drug interaction between AAD

**Table. Mechanisms, Pharmacokinetics, and Dynamics of the Emerging COVID-19 Pharmacotherapy**

Pharmacotherapy	Mechanism of Action	Metabolism	Mechanism of Interaction	Clinical Manifestation	
				Interaction With AADs	Interaction With Anticoagulants
Chloroquine/hydroxychloroquine	<ul style="list-style-type: none"> <li>Block viral entry into cells</li> <li>Reduce cytokines and inhibit autophagy and lysosomal activity in host cells</li> </ul>	CYP2C8, CYP3A4, CYP2D6, and CYP1A1	<ul style="list-style-type: none"> <li>Blocks <math>I_{kr}</math></li> <li>CYP2D inhibitors</li> <li>Long half-life</li> </ul>	<ul style="list-style-type: none"> <li>QT prolongation (TdP)</li> </ul>	None
Azithromycin	<ul style="list-style-type: none"> <li>Induction of interferon and interferon-related genes</li> </ul>	MRP2 and ABCB (minimally by CYP3A4)	<ul style="list-style-type: none"> <li>Blocks <math>I_{kr}</math></li> <li>Weak CYP3A4 inhibitor</li> <li>Moderate P-glycoprotein inhibitor</li> </ul>	<ul style="list-style-type: none"> <li>QT prolongation (TdP)</li> </ul>	<ul style="list-style-type: none"> <li>Increases serum DOAC</li> </ul>
Lopinavir/ritonavir	<ul style="list-style-type: none"> <li>Protease inhibitor</li> </ul>	CYP3A4	<ul style="list-style-type: none"> <li>Strong CYP3A4 inhibitor</li> <li>Moderate CYP2D6 inhibitor</li> <li>Strong P-glycoprotein inhibitor</li> </ul>	<ul style="list-style-type: none"> <li>QT prolongation (TdP)</li> <li>Nephrotoxicity (may increase serum sotalol and dofetilide)</li> </ul>	<ul style="list-style-type: none"> <li>Increases serum DOAC</li> <li>Nephrotoxicity (may increase serum apixaban, rivaroxaban, dabigatran, and LMWH)</li> </ul>
Remdesivir	<ul style="list-style-type: none"> <li>Adenosine analog (inhibits RNA-dependent RNA polymerase)</li> </ul>	Mainly by phosphorylation in nonspecific organ and partially by CYP2C8, CYP2D6, and CYP3A4	<ul style="list-style-type: none"> <li>CYP3A4 inhibitor (in vitro without clinical significance)</li> </ul>	None	None
Ribavirin	<ul style="list-style-type: none"> <li>Guanosine analog (inhibits RNA-dependent RNA polymerase)</li> </ul>	Mainly by hydrolase and partially by CYP2C8, CYP2D6, and CYP3A4	None	None	None
Favipiravir	<ul style="list-style-type: none"> <li>Purine analog (inhibits RNA-dependent RNA polymerase)</li> </ul>	Oxidase and renally excreted	None	None	None
Umifenovir	<ul style="list-style-type: none"> <li>Inhibits membrane fusion of viral envelope targeting the S-protein/ACE2 interaction</li> </ul>	CYP3A4	<ul style="list-style-type: none"> <li>CYP3A4 substrate</li> </ul>	<ul style="list-style-type: none"> <li>Plasma concentration may be increased with amiodarone, diltiazem, and verapamil (no documented evidence)</li> </ul>	None
Interferon	<ul style="list-style-type: none"> <li>Interfering with viral replication and promoting activation of the adaptive immune system</li> </ul>	Proteolytic degradation by lysosomal enzymes, which are excreted in urine	None	None	None
Tocilizumab	<ul style="list-style-type: none"> <li>Interleukin-6 inhibitors</li> </ul>	Unknown (expected to undergo catabolism)	<ul style="list-style-type: none"> <li>Increases mRNA expression of CYP enzymes</li> </ul>	None	<ul style="list-style-type: none"> <li>May increase warfarin metabolism</li> </ul>
Sarilumab	<ul style="list-style-type: none"> <li>Interleukin-6 inhibitors</li> </ul>	Unknown (expected to undergo catabolism)	<ul style="list-style-type: none"> <li>Increases mRNA expression of CYP enzymes</li> </ul>	None	<ul style="list-style-type: none"> <li>May increase warfarin metabolism</li> </ul>
Pirfenidone	<ul style="list-style-type: none"> <li>Interleukin-<math>\beta</math>1 and interleukin-4 inhibitors</li> </ul>	CYP1A2 and renally excreted	None	<ul style="list-style-type: none"> <li>Amiodarone, a CYP1A2 inhibitor, may increase pirfenidone plasma concentration</li> </ul>	None
Bevacizumab	<ul style="list-style-type: none"> <li>VEGF inhibitor monoclonal antibody</li> </ul>	The reticuloendothelial system	None	None	None
Eculizumab	<ul style="list-style-type: none"> <li>Complement inhibitor monoclonal antibody</li> </ul>	The reticuloendothelial system	None	None	None
Lenzilumab	<ul style="list-style-type: none"> <li>GM-CSF inhibitor monoclonal antibody</li> </ul>	The reticuloendothelial system	None	None	None

(Continued)

**Table. Continued**

Pharmacotherapy	Mechanism of Action	Metabolism	Mechanism of Interaction	Clinical Manifestation	
				Interaction With AADs	Interaction With Anticoagulants
Methylprednisolone	<ul style="list-style-type: none"> <li>• Anti-inflammatory agent</li> <li>• Alters gene expression</li> </ul>	CYP3A4	<ul style="list-style-type: none"> <li>• CYP3A4 substrate</li> </ul>	<ul style="list-style-type: none"> <li>• Plasma concentration may increase with amiodarone, diltiazem, and verapamil (no documented evidence)</li> <li>• Hypokalemia-induced digoxin toxicity</li> </ul>	<ul style="list-style-type: none"> <li>• May interfere with warfarin metabolism and bioavailability</li> </ul>
Fingolimod	<ul style="list-style-type: none"> <li>• Sphingosine 1-phosphate receptor modulator</li> </ul>	CYP4F2	<ul style="list-style-type: none"> <li>• Blocks <math>I_{K_{ACH}}</math> and <math>I_{CaL}</math></li> </ul>	<ul style="list-style-type: none"> <li>• QT prolongation (TdP)</li> <li>• Atrioventricular block</li> </ul>	None

AAD indicates antiarrhythmic drug; ABCB, ATP binding cassette subfamily B; ACE2, angiotensin-converting enzyme 2; COVID-19, coronavirus disease 2019; CYP, cytochrome P; DOAC, direct oral anticoagulant; GM-CSF, granulocyte-macrophage colony-stimulating factor;  $I_{CaL}$ , L-type calcium channel;  $I_{K_{ACH}}$ , acetylcholine-dependent potassium channels;  $I_{Kr}$ , potassium channel; LMWH, low-molecular-weight heparin; MRP2, multidrug resistance-associated protein 2; TdP, torsade de pointes; and VEGF, vascular endothelial growth factor.

and umifenovir. However, given its CYP3A4 substrate, plasma concentration of umifenovir may be increased with amiodarone, diltiazem, and verapamil (Table).

Interferon is a cytokine that has antiviral activity by interfering with viral replication and promoting activation of the adaptive immune system. Interferons undergo proteolytic degradation by lysosomal enzymes and are excreted in urine.<sup>30</sup> The cardiovascular adverse effects include nonspecific arrhythmias, myocardial infarction, cardiomyopathy, and hypotension. Their interaction with AADs is unknown.<sup>4</sup>

### Interleukin Inhibitor

Critically ill COVID-19 patients have elevated inflammatory cytokines, including interleukin, granulocyte/macrophage colony-stimulating factor, interferon, and tumor necrosis factor- $\alpha$ .<sup>1</sup> Tocilizumab and sarilumab are interleukin-6 inhibitors. They were found to increase mRNA expression of CYP 450 isoenzymes by reversing the CYP inhibition effect of interleukin-6.<sup>31</sup> Pirfenidone inhibits interleukin- $\beta$ 1 and interleukin-4. Its cardiovascular adverse effects and interaction with AADs are unknown.<sup>4</sup> It is metabolized by CYP1A2 and renally excreted.<sup>32</sup> Amiodarone, a CYP1A2 inhibitor, may increase pirfenidone plasma concentration (Table).

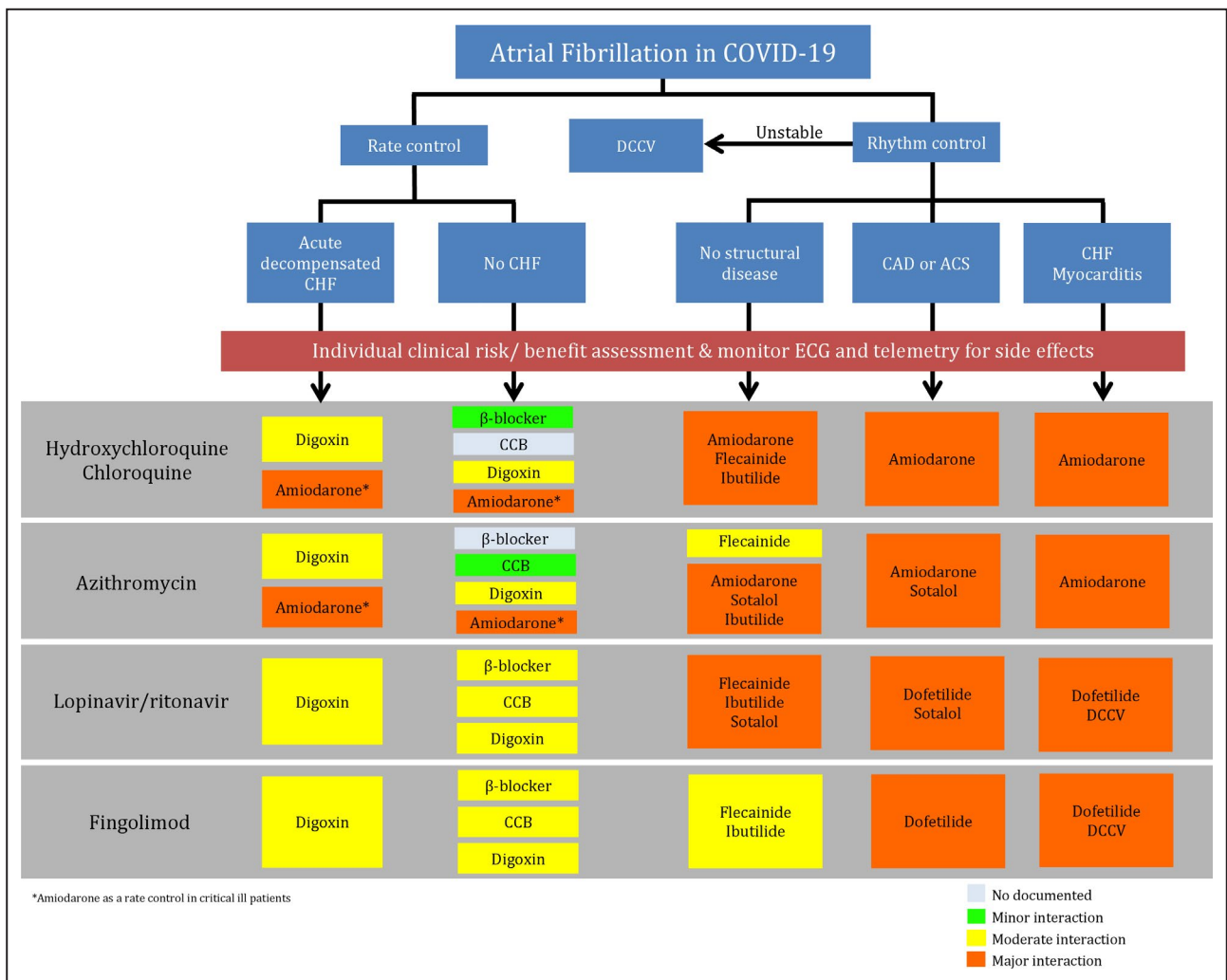
### Monoclonal Antibody

Bevacizumab (vascular endothelial growth factor inhibitor), eculizumab (complement inhibitor), and lenzilumab (granulocyte/macrophage colony-stimulating factor inhibitor) are under investigation.<sup>33</sup> Mechanism of action includes inhibiting inflammatory cytokines. They are metabolized by the reticuloendothelial system, and a common cardiovascular adverse effect is hypertension. However, their interaction with AADs is unknown. Bevacizumab can cause myocardial toxicity and thromboembolic events, and eculizumab may cause tachycardia and peripheral edema.<sup>4</sup>

### Immunosuppression

Methylprednisolone is an anti-inflammatory agent that alters gene expression. It is metabolized by CYP3A4 and renally excreted but does not affect CYP3A4 activity.<sup>34</sup> No significant drug interaction with AADs is reported.

Fingolimod is an immunosuppressive agent through sphingosine 1-phosphate receptor modulator, which reduces lymphocyte migration. Fingolimod has L-type calcium channel blockade effect, causing prolongation of PR, RR, and QT intervals. It also activates acetylcholine-dependent potassium channels in sinoatrial node, causing dose-dependent bradycardia.<sup>35</sup> Fingolimod is



**Figure 1. Management guidance algorithm for atrial fibrillation and concomitant coronavirus disease 2019 (COVID-19).** ACS indicates acute coronary syndrome; CAD, coronary artery disease; CCB, calcium channel blocker; CHF, congestive heart failure; and DCCV, direct current cardioversion.

not recommended in patients with recent myocardial infarction, decompensated CHF, stroke, high-grade atrioventricular block, corrected QT interval >500 ms, or concomitant use of class IA or class III AADs.<sup>36</sup> It is metabolized by hepatic CYP4F2 and excreted in gastrointestinal tract.

### ANTIARRHYTHMIC AND RATE CONTROL DRUGS FOR AF AND INTERACTIONS WITH COVID-19 PHARMACOTHERAPY

Antiarrhythmic drug-drug interactions were reported as the most common cause of drug-related life-threatening ventricular arrhythmias, and 84% of these cases were associated with CYP inhibition and 74% were QT prolongation related.<sup>37</sup> Most COVID-19 pharmacotherapies under investigation have unintended nontherapeutic

target effects, including I<sub>Kr</sub> blockade, CYP inhibition, and P-glycoprotein inhibition (Figure 4). Lopinavir/ritonavir is the only drug that has nephrotoxicity. A summary of AADs used in AF and their interactions with COVID-19 pharmacotherapies are shown in Figure 2. Dosages and routes of administration are provided in Table S1. A stepwise approach in managing COVID-19 patients who present with AF is shown in Figure 1.

#### Class IA

Quinidine is a vagolytic and α-blocker with use-dependent sodium channel (I<sub>Na</sub>) blockade and I<sub>Kr</sub> reverse use-dependent blockade,<sup>38</sup> therefore prolonging the QT interval.<sup>39</sup> It is primarily metabolized by CYP3A4. Plasma concentration of quinidine can be decreased with CYP3A4 inducers (tocilizumab and sarilumab) and can be increased with CYP3A4 inhibitors (lopinavir/ritonavir)<sup>40</sup> (Figure 2).

				COVID-19 Drugs								
				Hydroxychloroquine/ Chloroquine	Azithromycin	Lopinavir/ Ritonavir	IL-6 inhibitor (Tocilizumab and Sarilumab)	Fingolimod	Methylprednisolone	Remdesivir and Umifenovir	Pirfenidone	Favipiravir and Ribavirin
Antiarhythmic/ rate control drug	Drug	Mechanism (Channels blocked)	Primary route(s) of metabolism/elimina- tion and mechanism of drug interaction	Hepatic CYP3A/ CYP2D6 With I <sub>Kr</sub> blockade and CYP2D6 inhibitor	I <sub>Kr</sub> blockade and mild CYP3A4 inhibitor	Hepatic CYP3A with strong P-glycoprotein and CYP3A4 inhibitor, moderate CYP2D6 inhibitor, and nephrotoxicity	Increased m-RNA expression of CYP enzymes	Hepatic CYP4F2 With I <sub>CaL</sub> activation, I <sub>CaL</sub> blockade, and I <sub>Kr</sub> blockade	Hepatic CYP3A	Hepatic CYP3A	Hepatic CYP1A2	Renal
IA	Procainamide	I <sub>Na</sub> , I <sub>Kr</sub>	Hepatic/Renal CYP2D6	QT prolongation	QT-prolongation**	QT prolongation	Decrease AAD plasma concentration	QT prolongation	NDI	NDI	NDI	NDI
	Disopyramide	I <sub>Na</sub> , I <sub>Kr</sub> , I <sub>CaL</sub>	Renal/hepatic CYP3A4	QT prolongation	QT-prolongation**	QT prolongation		QT prolongation				
	Quinidine	I <sub>Na</sub> , I <sub>Kr</sub> , I <sub>K</sub> , I <sub>CaL</sub> , α	Renal/hepatic CYP3A4	QT prolongation	QT-prolongation**	QT prolongation		QT prolongation				
IC	Flecainide	I <sub>Na</sub>	Renal/hepatic CYP2D6 (age- related)	QRS prolongation QT prolongation	QRS prolongation QT prolongation	QRS prolongation QT prolongation	Decrease AAD plasma concentration	QRS prolongation QT prolongation	NDI	NDI	NDI	NDI
	Propafenone	I <sub>Na</sub> , I <sub>CaL</sub> , β	Hepatic CYP2D6/CYP3A4/ CYP1A2	QRS prolongation QT prolongation	QRS prolongation QT prolongation	QRS prolongation QT prolongation		QRS prolongation QT prolongation				
II	Carvedilol	β	Hepatic CYP3A4/CYP2D6/ CYP1A2/ CYP2C	Prolong PR, second- and third-degree heart block	NDI	Prolong PR, second- and third-degree heart block	Decrease AAD plasma concentration	Bradycardia, heart block	May increase methylprednisolone plasma concentration	May increase antiviral plasma concentration	May increase IL inhibitor plasma concentration	NDI
	Metoprolol	β	Hepatic CYP2D6	Prolong PR, second- and third-degree heart block	NDI	Prolong PR, second- and third-degree heart block		Bradycardia, heart block				
	Esmolol	β	Red blood cell	NDI	NDI	Prolong PR, second- and third-degree heart block		Bradycardia, heart block				
III	Amiodarone*	I <sub>Na</sub> , I <sub>Kr</sub> , I <sub>CaL</sub> , I <sub>Ca</sub> , α, β	Hepatic CYP3A4/CYP2C8 with moderate CYP3A4/CYP1A2 inhibitor	QT prolongation	QT-prolongation**	QT prolongation	Decrease AAD plasma concentration	QT prolongation	Increase methylprednisolone plasma concentration	May increase antiviral plasma concentration	May increase IL inhibitor plasma concentration	NDI
	Dronedarone*	I <sub>Na</sub> , I <sub>Kr</sub> , I <sub>CaL</sub> , I <sub>Ca</sub> , α, β	Renal/hepatic/ gastrointestinal CYP3A4/CYP2D6	QT prolongation	QT-prolongation**	QT prolongation		QT prolongation				
	Dofetilide*	I <sub>Kr</sub>	Renal/hepatic CYP3A4	QT prolongation	QT-prolongation**	QT prolongation		QT prolongation				
	Ibutilide*	I <sub>Kr</sub> , I <sub>Na</sub> agonist	Renal/hepatic CYP3A4/CYP2D6	QT prolongation	QT-prolongation**	QT prolongation		QT prolongation				
	Sotalol*	β, I <sub>Kr</sub>	Renal	QT prolongation	QT-prolongation**	QT prolongation		QT prolongation				
IV	Diltiazem	I <sub>Ca</sub>	Hepatic CYP3A4/CYP2C1	May increase hydroxychloroquine/ chloroquine plasma concentration	QT-prolongation**	Prolong PR, second- and third-degree heart block	Decrease AAD plasma concentration	Bradycardia, heart block	Increase methylprednisolone plasma concentration	May increase antiviral plasma concentration	May increase IL inhibitor plasma concentration	NDI
	Verapamil	I <sub>Ca</sub>	Hepatic CYP3A4/CYP3A5/ CYP2C8 with CYP3A4 inhibitor	May increase hydroxychloroquine/ chloroquine plasma concentration	NDI	Prolong PR, second- and third-degree heart block		Bradycardia, heart block				
NDI	Digoxin	Na/K ATPase	Renal	Increase digoxin concentration (nuclear mechanism)	Increase digoxin concentration	Increase digoxin concentration	NDI	Bradycardia, heart block	Hypokalemia induced digoxin toxicity	NDI	NDI	NDI

\*Dose-dependent QT prolongation  
 \*\*Unlike clarithromycin, erythromycin, and troleandomycin inhibits CYP3A4, azithromycin minimally inhibits CYP3A4 (no documented evidence of drug interaction)  
 There is no documented drug interaction between Favipiravir, Remdesivir, or Lenzilumab and antiarrhythmic drugs in atrial fibrillation

Abbreviations: AAD: antiarrhythmic drugs; b.i.d.: twice a day; CHF: congestive heart failure; CYP: cytochrome P450; I<sub>Ca</sub>: calcium channel; I<sub>CaL</sub>: inward-rectifying potassium channel; I<sub>K</sub>: potassium channel; I<sub>Na</sub>: sodium channel; IV: intravenous; Na/K: sodium/potassium; NDI: notdocumented interaction; RNA: ribonucleic acid; t.i.d.: three times a day; TdP: torsades de pointes.

- No documented interaction
- Minor interaction
- Moderate interaction
- Major interaction
- Not recommended (no data or contraindicated)

**Figure 2. AADs Used in AF and Their Drug Interaction With COVID-19 Therapy.** AF indicates atrial fibrillation; and COVID-19, coronavirus disease 2019.

Disopyramide is also a use-dependent I<sub>Na</sub> blocker and a reverse use-dependent I<sub>Kr</sub> blocker. Disopyramide has potent anticholinergic effects and should be avoided in glaucoma, prostatic hyperplasia, and myasthenia gravis patients.<sup>38</sup> Given its negative inotropic effect, disopyramide is not recommended in patients with CHF.<sup>41</sup> Plasma concentration of disopyramide can be decreased through CYP3A4 metabolism<sup>40</sup> (Figure 2).

Procainamide is an I<sub>Na</sub> and I<sub>Kr</sub> blocker. It is available in the intravenous form and can be useful in patients with Wolff-Parkinson-White syndrome presenting with preexcited AF.<sup>17</sup> Procainamide is partially metabolized by CYP2D6<sup>42</sup> and mainly (60%) excreted by the kidney.<sup>43</sup> Plasma concentration of procainamide can be decreased with CYP2D6 inducers (tocilizumab and sarilumab) (Figure 2).

Because chloroquine, hydroxychloroquine, azithromycin, and fingolimod have I<sub>Kr</sub> blocking effect, concomitant use of a class IA AAD could potentiate QT prolongation.<sup>39</sup> Interactions of class IA AADs with lopinavir/ritonavir, interleukin-6 inhibitors, and azithromycin are at the CYP metabolic level. Any class IA AAD should be used with caution when combined with hydroxychloroquine, chloroquine, macrolides, or lopinavir/ritonavir (Figures 1 and 2). Documentation

of baseline and sequential QT intervals following initiation of an AAD is recommended. Class IA AAD is not recommended in patients who are treated with fingolimod attributable to QT prolongation and risk of torsade de pointes.<sup>35,36</sup> Class IA AADs are not used often in the contemporary management of AF because of less than desired efficacy, cardiac and extracardiac adverse effects, and multiple potential drug-drug interactions.

### Class IC

Flecainide is a use-dependent I<sub>Na</sub> blocker with moderate negative inotropic effect. Because of specific blocking effect on I<sub>Na</sub>, unlike class IA, flecainide delays depolarization (prolonging QRS duration) with minimal effect on ventricular repolarization (QT interval).<sup>38</sup> However, there are several case reports stating that flecainide can lead to prolonged QT and torsade de pointes.<sup>44</sup> Flecainide is predominantly metabolized by CYP2D6.<sup>45</sup> Flecainide is reasonable for pharmacological cardioversion in the short-term setting and can be used to maintain sinus rhythm in patients without coronary artery disease or structural heart disease.<sup>17</sup> Because of possible increases in plasma concentration of flecainide when administered with

Anticoagulation			COVID-19 drugs interaction										
			Hydroxychloroquine/Chloroquine	Azithromycin	Lopinavir/Ritonavir	IL-6 inhibitor (Tocilizumab and Sarilumab)	Fingolimod	Methylprednisolone	Remdesivir and Umifemovir	Pirfenidone	Favipiravir and Ribavirin		
Class	Drug	Primary route(s) of metabolism/elimination and mechanism of drug interaction	Hepatic CYP3A/CYP2D6 with I <sub>Kr</sub> blockade and CYP2D inhibitor	Weak-moderate P-glycoprotein and mild CYP3A4 inhibitor	Hepatic CYP3A with strong P-glycoprotein and CYP3A4 inhibitor, moderate CYP2D6 inhibitor, and nephrotoxicity	Increased m-RNA expression of CYP enzymes	Hepatic CYP4F2	Hepatic CYP3A	Hepatic CYP3A	Hepatic CYP1A2	Renal		
Factor Xa inhibitor	Apixaban	CYP3A4 renally excreted	NDI	NDI	Increase DOAC serum concentration	NDI	NDI	NDI	NDI	NDI	NDI		
	Rivaroxaban	CYP3A4 and CYP2J2 renally excreted		Increase DOAC serum concentration	Increase DOAC serum concentration (contraindicated)								
	Edoxaban	CES1, CYP3A4, CYP3A5			Increase DOAC serum concentration (no data)								
Thrombin inhibitor	Dabigatran	Esterase-catalyzed hydrolysis and renally excreted		Increase the of effect warfarin	Decrease the of effect warfarin	May increase warfarin metabolism						May interfere warfarin metabolism and bioavailability	Decrease the of effect warfarin
Vitamin K antagonist	Warfarin	Liver CYP2C9/CYP2C19/CYP2C8/CYP2C18/CYP1A2/CYP3A4			NDI	NDI							
Heparin	Unfractionated heparin	Reticuloendothelial system and endothelial cells		NDI	Nephrotoxicity	NDI						NDI	NDI
	Low molecular weight heparin	Non-saturable renal excretion											

Abbreviation: CYP: cytochrome P450; IL: interleukin; LMWH: Low molecular weight heparin; NDI: not documented interaction.

- No documented interaction
- Minor interaction
- Moderate interaction
- Major interaction
- Not recommended (no data or contraindicated)

**Figure 3. Anticoagulation Drugs Used in AF and Potential Drug-Drug Interactions With COVID-19 Therapy.** AF indicates atrial fibrillation; and COVID-19, coronavirus disease 2019.

hydroxychloroquine/chloroquine and lopinavir/ritonavir (CYP2D6 inhibitors), we recommend sequential electrocardiographic monitoring before and after drug initiation.

Propafenone is an I<sub>Na</sub> blocker with mild β-blocking effect (negative inotropic and chronotropic effect) and predominantly metabolized by CYP2D6. Similar to flecainide, propafenone has minimal effect on repolarization. We recommend monitoring for QRS/QT prolongation when administered with hydroxychloroquine/chloroquine and lopinavir/ritonavir (CYP2D6 inhibitors). Given documented prolonged QT from I<sub>Kr</sub> blockade by azithromycin,<sup>23</sup> we also recommend ECG monitoring when azithromycin is used with class IC AADs.

Because myocarditis and CHF are common clinical manifestations in critically ill COVID-19 patients, the use of class IC AADs in this population needs to be exercised with caution. Their interactions with CYP2D6 inducers (tocilizumab and sarilumab) and CYP2D6 inhibitors (lopinavir/ritonavir) need to be recognized by closely monitoring any ECG changes. Fingolimod increases the risk of bradycardia and heart block through L-type calcium channel and acetylcholine-dependent potassium channel blockade. ECG before starting AADs, ECG at 6 hours after

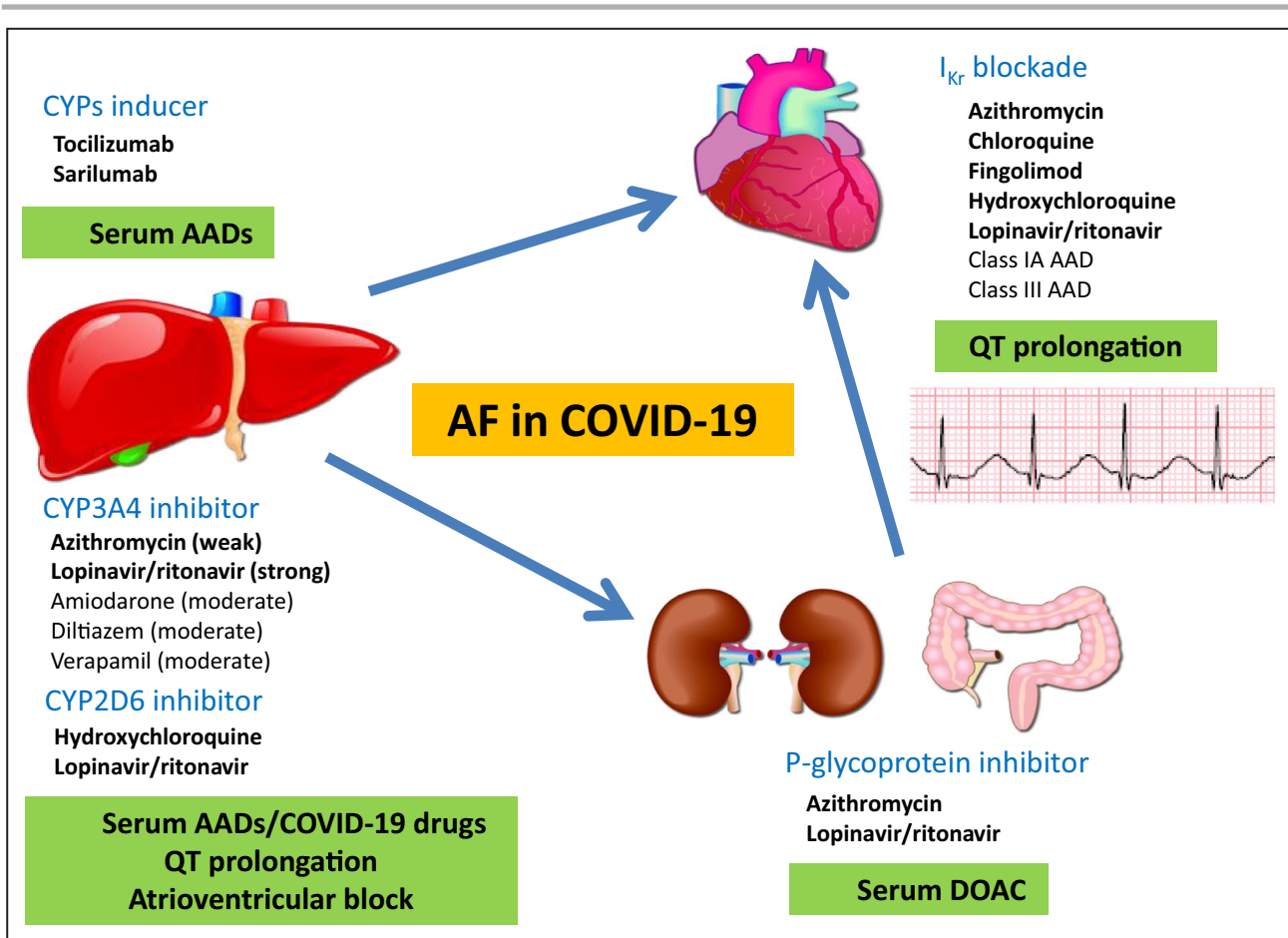
first dose, and continuous telemetry monitoring are recommended.<sup>36</sup>

### Class II

β Blockers are recommended as a first-line therapy for rate control in AF with COVID-19 infection.<sup>46</sup> All β blockers may have drug interactions with lopinavir/ritonavir, including PR prolongation, second-degree heart block, and third-degree heart block.<sup>24,47</sup> Lopinavir/ritonavir may increase carvedilol and metoprolol serum concentration through CYP2D6 inhibition,<sup>47</sup> and telemetry should be monitored closely (Figure 1).

Hydroxychloroquine and chloroquine inhibit CYP2D6 and may increase plasma concentration of metoprolol<sup>48</sup>; a similar effect may be observed in carvedilol but has never been studied.

Carvedilol is a nonselective β blocker. Only immediate release is recommended in AF guidelines and only oral form is available, which limits its utility in acute AF with rapid ventricular response.<sup>17,49</sup> Metoprolol and esmolol are cardioselective β blockers.<sup>50</sup> Metoprolol comes in both intravenous and oral forms,<sup>17</sup> whereas esmolol only has intravenous preparation. Both are effective when administered in AF, with rapid ventricular



**Figure 4.** Drug-drug interactions between antiarrhythmic drugs/anticoagulants in atrial fibrillation (AF) and emerging coronavirus disease 2019 (COVID-19) pharmacotherapies. AAD indicates antiarrhythmic drug; CYP, cytochrome P; DOAC, direct oral anticoagulant; and I<sub>Kr</sub>, potassium channel.

response.<sup>17</sup>  $\beta$  Blockers should also be avoided in acute decompensated CHF and bronchospasm.<sup>49</sup>

### Class III

Amiodarone blocks multiple ion channels, including I<sub>Na</sub>, I<sub>Kr</sub>, calcium channel, and acetylcholine-dependent potassium channel, as well as  $\alpha$  and  $\beta$  receptors.<sup>38</sup> It prolongs QT but is rarely associated with torsade de pointes (<0.5%).<sup>51</sup> Amiodarone is the most effective and most common AAD used in AF.<sup>52</sup> It is preferred for AF rate and rhythm control in critically ill COVID-19 patients with significant CHF or borderline blood pressure.<sup>46</sup> However, information on amiodarone and COVID-19 pharmacotherapy interactions is limited. Surveillance for liver, lung, and thyroid toxicity is recommended for long-term amiodarone therapy and for short-term use if clinically indicated. Long- and short-term presentations of amiodarone toxicity have been reported.<sup>53,54</sup> Pulmonary toxicity may be a concern for COVID-19 patients with severe pneumonia who require prolonged mechanical ventilation. Amiodarone should

be used with extreme caution when coadministered with lopinavir/ritonavir (QT prolongation).

Dronedaron shares similar pharmacokinetics with amiodarone<sup>38</sup>; however, its use is contraindicated in patients with CHF or left ventricular dysfunction.<sup>55</sup> Dronedaron is contraindicated with lopinavir/ritonavir because of dependence on CYP3A4 for clearance and risk of life-threatening arrhythmia.<sup>47</sup> Therefore, the utility of dronedaron may be limited for AF in COVID-19 patients.

Amiodarone and dronedaron may cause QT prolongation, particularly when used with hydroxychloroquine, chloroquine, or macrolides. Plasma concentration of amiodarone and dronedaron can be decreased when administered with tocilizumab or sarilumab (CYP3A4 inducers) (Figure 4).

Dofetilide is an I<sub>Kr</sub> blocker and predominantly excreted by the kidney (Figure 2). Hospitalization for ECG monitoring is required for the 3-day loading period.<sup>38</sup> Dofetilide is more effective than cardioversion in maintaining sinus rhythm<sup>56</sup> and proved to be safe in patients with underlying CHF and myocardial infarction.<sup>57</sup> Information is not available on any



long-term use of dofetilide in patients on COVID-19 pharmacotherapy.

Ibutilide is an  $I_{Kr}$  blocker and late inward  $I_{Na}$  agonist. Ibutilide is used for pharmacological cardioversion (Figure 1) of AF or atrial flutter. QT interval must be monitored for 2 to 6 hours after the infusion.<sup>58</sup> Ibutilide is metabolized by CYP3A4 and CYP2D6.

Dofetilide and ibutilide use may be limited in COVID-19 patients already receiving hydroxychloroquine, chloroquine, macrolides, or lopinavir/ritonavir because of their intrinsic dose-dependent QT prolongation. However, the use of ibutilide may be a good option for conversion of acute symptomatic AF (Figure 1).

Sotalol is an  $I_{Kr}$  blocker (dose dependent) with moderate  $\beta$ -blockade effect.<sup>38</sup> Sotalol is renally excreted (Figure 2).<sup>38</sup> If sotalol is used in the presence of lopinavir/ritonavir, which is nephrotoxic, QT interval should be followed closely. Sotalol may be used with lopinavir/ritonavir, tocilizumab, or sarilumab, given lack of interaction on CYP3A4 or CYP2D6. However, there are dose-dependent QT prolongation drug interactions with hydroxychloroquine, chloroquine, and macrolides, so monitoring should be implemented. Class III AADs are generally contraindicated in patients who are treated with fingolimod because of QT prolongation and risk of torsade de pointes.<sup>36</sup>

## Class IV

Nonhydropyridine calcium channel blockers are used as first-line rate-control agents in AF.<sup>17</sup> Diltiazem and verapamil block L-type calcium channels and are contraindicated in patients with decompensated CHF or significantly reduced ejection fraction because of negative inotropic effect<sup>17,49</sup> (Figure 1).

Diltiazem is metabolized by CYP2C19 and CYP3A4. The use of diltiazem (P-glycoprotein inhibitor) with azithromycin (P-glycoprotein substrate) has been reported to prolong QT interval, leading to torsade de pointes.<sup>59</sup> Lopinavir/ritonavir may cause prolonged PR and second- or third-degree heart block when used with calcium channel blockers.<sup>24</sup> Lopinavir/ritonavir can increase calcium channel blocker plasma concentration through CYP3A4 inhibition and should be closely monitored<sup>47,60</sup> (Figure 1).

## Digoxin

Digoxin is a sodium/potassium ATPase pump inhibitor. It could be considered in CHF patients given lack of negative inotropic effect<sup>17</sup> and in patients with marginal blood pressure who do not tolerate calcium channel blockers or  $\beta$  blocker.

Lopinavir/ritonavir increases serum digoxin concentration and toxicity through inhibition of P-glycoprotein.<sup>61</sup> Lopinavir/ritonavir may cause prolonged PR and second- or third-degree heart block when used with

digoxin.<sup>24</sup> Routine monitoring of digoxin levels should be considered.

COVID-19 patients treated with both fingolimod and digoxin should receive ECG before medication initiation, sequential ECG, and telemetry monitoring for bradycardia and QT prolongation.<sup>36</sup>

## CONCOMITANT USE OF ANTICOAGULATION THERAPY AND COVID-19 DRUG THERAPY

Coagulopathy has been reported in critically ill COVID-19 patients, and anticoagulation with heparin has shown some mortality benefit.<sup>62</sup> The prevalence of drug-drug interactions from anticoagulation was reported as up to 26.3% in the AF population.<sup>63</sup> The interaction increased risk of bleeding up to 7-fold<sup>63</sup> and is expected to be higher in COVID-19 patients. The guiding principles for anticoagulation in COVID-19 patients with AF are the same as in patients without COVID-19, although little is known about potential drug-drug interactions with COVID-19 pharmacotherapy. We aim to review the choice of anticoagulation on the basis of possible drug interactions with COVID-19 pharmacotherapy, as summarized in Figure 3.

## Direct Oral Anticoagulation

### Direct Factor Xa Inhibitor

Apixaban is predominantly metabolized by CYP3A4 with a minor (27%) component of renal elimination. Lopinavir/ritonavir is a strong CYP3A4 and P-glycoprotein inhibitor. Coadministration is generally not recommended, but if necessary, the dose can be reduced by 50% (discontinue if on 2.5 mg twice a day) (Table S1).<sup>4</sup>

Rivaroxaban is metabolized in the liver by CYP3A4, with 30% excreted in the urine. It also has a drug interaction with lopinavir/ritonavir (strong CYP3A4 and P-glycoprotein inhibitor), and coadministration is not recommended.<sup>4</sup> However, rivaroxaban can be used in patients who receive azithromycin (weak CYP3A4 inhibitor) with caution (Figure 3).<sup>64</sup>

Edoxaban is mainly excreted in the urine, with <4% metabolized by liver CYP3A4. The dose should be reduced with concomitant use of azithromycin (P-glycoprotein inhibitor) (Table S1).<sup>65</sup> Concurrent treatment with ritonavir/lopinavir (strong P-glycoprotein) and edoxaban is not recommended, given lack of adequate data on interaction.<sup>66</sup>

### Direct Thrombin Inhibitor

Dabigatran is hydrolyzed and 80% renally excreted. However, there are no data on any interaction with azithromycin or ritonavir.<sup>67</sup>

## Vitamin K Antagonist

Azithromycin increases the effect of warfarin,<sup>68</sup> whereas ribavirin and lopinavir/ritonavir diminish warfarin's effect by unclear mechanisms. In several case reports, the dose of warfarin needed to be increased up to 40% with ribavirin and 125% with ritonavir to maintain international normalized ratio goal.<sup>27,69</sup> Tocilizumab and sarilumab can potentially increase warfarin metabolism through induced CYPs. Steroids may increase the bioavailability of warfarin,<sup>70</sup> affecting international normalized ratio. We recommend regular international normalized ratio monitoring in patients who are treated with COVID-19 pharmacotherapy.

## Heparin

Unfractionated heparin and enoxaparin potentiate antithrombin III activity. They have no documented drug interaction with COVID-19 pharmacotherapy. Unfractionated heparin is metabolized by the reticuloendothelial system and endothelial cells, and enoxaparin metabolites are renally excreted.<sup>71</sup>

Therefore, we recommend heparin as an anticoagulant of choice in COVID-19 patients with AF in the short-term setting. Direct oral anticoagulants can be used in AF patients with COVID-19 after hospital discharge without lopinavir/ritonavir.

## Clinical Approach

Stepwise approach in COVID-19 patients with AF is summarized in Figure 1.

## General Considerations

1. QT interval should be monitored closely when class IA, IC, and III AADs are administered with hydroxychloroquine/chloroquine, macrolide, or lopinavir/ritonavir.
2. Classes IA and IC are contraindicated in COVID-19 patients on fingolimod.
3. For patients on fingolimod, we recommend obtaining an ECG before AAD initiation, ECG at 6 hours after first dose, periodic ECG, and continuous telemetry monitoring.
4.  $\beta$  Blockers are recommended as a first-line therapy for rate control strategy.
5. Calcium channel blockers are not recommended in myocarditis patients with acute decompensated CHF.
6. Digoxin can be used in CHF or in combination with  $\beta$  blockers or calcium channel blockers to achieve rate control.
7. Heparin is the anticoagulant of choice in hospitalized COVID-19 patients with AF, especially if patients are being treated with lopinavir/ritonavir.
8. Direct oral anticoagulants can be used in AF patients with COVID-19 after discharge without lopinavir/ritonavir.

## Rhythm Control

1. Amiodarone can be useful for rhythm and rate control in critically ill COVID-19 patients with CHF. Close monitoring with caution is recommended with concurrent lopinavir/ritonavir use. It is not recommended in patients undergoing treatment with fingolimod.
2. Flecainide is a preferred option for pharmacological cardioversion in patients with no structural heart disease or coronary artery disease who are on fingolimod.
3. Ibutilide can be used for cardioversion in the patient is not on fingolimod.

## CONCLUSIONS

The use of AADs or anticoagulants in AF may have significant adverse effects because of drug-drug interactions with emerging COVID-19 pharmacotherapy, including  $I_{Kr}$  blockade, CYP inhibition or enhanced activity, and P-glycoprotein inhibition. Drug-drug interactions may lead to increased propensity for bradycardia, tachyarrhythmias, or severe bleeding. The choice of AADs and anticoagulants for COVID-19 patients with AF should be individualized on the basis of drug interactions, mechanisms of drug metabolism, and potential consequences. A baseline ECG before the initiation of AAD in addition to continuous rhythm monitoring after AAD initiation are recommended. If anticoagulation is started, extra caution should be exercised when used in combination with azithromycin or lopinavir/ritonavir. It is crucial for clinicians to be aware of the indications, contraindications, and key drug-drug interactions between AADs, anticoagulants, and emerging COVID-19 pharmacotherapies in this challenging cohort of patients to achieve optimal clinical outcomes.

## ARTICLE INFORMATION

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None.

### Supplementary Material

Table S1

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# **SUPPLEMENTAL MATERIAL**

**Table S1. Doses and common side effects of antiarrhythmic drugs and anticoagulants used in atrial fibrillation.**

Antiarrhythmic/ Anticoagulant		Doses for Atrial Fibrillation	Toxicity	
Class	Drug		Non-cardiotoxicity	Cardiotoxicity
IA	Procainamide	IV Loading: up to 17 mg/kg at 20 to 50 mg/min or 100 mg every 5 min; administer until arrhythmia is controlled Maintenance IV: 1 to 4 mg/min CrCl 10-50: reduce continuous IV 25-50% CrCl <10: reduce continuous IV 50-75%	Positive ANA titer, lupus like syndrome	Hypotension
	Disopyramide	100-200 mg q 6 hr; maximum 800 mg/d (immediate release)	Anticholinergic	CHF exacerbation, TdP
	Quinidine	200-300 mg Q6 -8 hr maximum 600 mg t.i.d.	Thrombocytopenia, cinchonism, pruritus, rash	QRS prolongation, TdP
IC	Flecainide	50-100 mg b.i.d.; maximum 300-400 mg/d	Dizziness, headache, visual blurring,	1:1 atrial flutter, ventricular tachycardia, unmask Brugada pattern
	Propafenone	150-300 mg q 8hr (immediate release)	Metallic taste, dizziness	
II	Carvedilol	Immediate release: 3.125-25 mg b.i.d., extended release 10-80 mg/day daily	Dizziness, fatigue, weight gain, diarrhea	Bradycardia, heart block, hypotension
	Metoprolol	Oral:25-100 mg b.i.d.(immediate release) 50-400 mg daily (extended release) IV:2.5-5 mg over 2 min;repeat dose every 5 min as needed; maximum 15 mg	Dizziness, fatigue, depression	Bradycardia, heart block, hypotension
	Esmolol	IV loading dose: 500 mcg/kg over 1 min, follow by 50-300 mcg/kg/min	Dizziness, nausea	Bradycardia, heart block, hypotension
III	Amiodarone	IV: 300 mg over 1h, then 10-50 mg/h over 24 h Oral maintenance: 100-200 mg daily	Pulmonary, hepatitis, thyroid toxicity, photosensitivity, skin discoloration, nausea, ataxia, tremor, alopecia	Bradycardia
	Dronedarone	400 mg b.i.d.	Anorexia, nausea, hepatotoxicity	Bradycardia
	Dofetilide	CrCl>60:500 µg b.i.d., CrCl 40-60: 250 µg b.i.d., CrCl 20-39: 125 µg b.i.d.	Nausea, headache	TdP
	Ibutilide	IV 0.01 mg/kg (<60 kg) or 1 mg (≥60 kg) over 10 min	Nausea, headache	TdP
	Sotalol	Oral:80-120 b.i.d.; maximum 240 mg b.i.d. (daily dose if CrCl 30-60) IV: 75 mg b.i.d.; maximum 150 mg b.i.d. (daily dose if CrCl 40-60)	Fatigue, dizziness, dyspnea, weakness	Bradycardia, TdP
IV	Diltiazem	Oral:120-360 mg/d (3-4 divided doses in immediate release/ daily in extended release) IV 0.25 mg/kg bolus over 2 min , then 5-15 mg/h	Peripheral edema, dizziness,	Bradycardia, heart block, hypotension, vasodilation
	Verapamil	Oral: 40-480 mg/d (b.i.d. in immediate release/daily in extended release) IV: 0.075–0.15 mg/kg bolus over 2 min; then 0.005 mg/kg/min	Headache, gingival hyperplasia, fatigue, dizziness	Bradycardia, heart block, hypotension
Na/K ATPase inhibitor	Digoxin	IV loading 0.25-0.5 mg, repeat doses of 0.25 mg q 6 hr; maximum 1.5 mg per day, followed by oral maintenance dose of 0.125 to 0.25 mg daily	Nausea, visual disturbance	Bradycardia, heart block, ventricular arrhythmias
Factor Xa inhibitor	Apixaban	5 mg b.i.d. 2.5 mg b.i.d. if at least 2 of (age ≥80 years, BW 60 kg, or Cr ≥1.5 mg/dL) 2.5 mg b.i.d. when co-administered with Ritonavir	Nausea	Hemorrhagic shock
	Rivaroxaban	CrCl >50 mL/min: 20 mg daily CrCl 15 - 50 mL/min: 15 mg daily	Insomnia, pruritus	Hemorrhagic shock
	Edoxaban	60 mg daily 30 mg daily if met one of the following criteria; CrCL 30-50 mL/min, BW <60 kg, or concomitant use of azithromycin (P-glycoprotein inhibitors)	Rash, abnormal liver function tests	Hemorrhagic shock
Thrombin inhibitor	Dabigratan	CrCl >30 mL/min: 50 mg daily CrCl 15-30 mL/min: 75 mg daily	Dyspepsia	Hemorrhagic shock
Vitamin K antagonist	Warfarin	Titrate for INR goal 2-3	Diarrhea, bloating, rash	Hemorrhagic shock, vasculitis
Heparin	Unfractionated heparin	Bolus 60 to 80 units/kg (maximum: 5,000 units), followed by IV 12-18 units/kg/h (maximum: 1,000 units/h)	Thrombocytopenia	Hemorrhagic shock
	Low molecular weight heparin	1 mg/kg every 12 hours; adjust dose based on anti-Xa monitoring	Edema, nausea	Hemorrhagic shock

ANA: antinuclear antibody; b.i.d.: twice daily; BW: body weight; Cr: creatinine; CHF: congestive heart failure; CrCl: creatinine clearance; INR: the international normalized ratio; IV: intravenous; Na/K: sodium/potassium; t.i.d.: three times daily; TdP: torsades de pointes.