Canadian Heart Rhythm Society
Société canadienne de rythmologie

Guidance on Minimizing the Risk of Antimicrobial Drug-induced Ventricular Arrhythmia During Treatment of COVID-19: A Statement from the Canadian Heart Rhythm Society

The COVID-19 pandemic is causing wide-spread illness and has no proven therapies. Some proposed treatments may lead to drug-induced proarrhythmia. This Canadian Heart Rhythm Society position statement proposes risk minimization strategies to identify those at highest risk while minimizing unnecessary testing, which may increase exposure of other patients and caregivers to infectious risk.

The Canadian Heart Rhythm Society is an Affiliate organization of the Canadian Cardiovascular Society.

John L. Sapp MD, Wael Alqarawi MD, Ciorsti J. MacIntyre MD, Rafik Tadros MD, Christian Steinberg MD, Jason D. Roberts MD, Zachary Laksman MD, Jeff S. Healey MD, Andrew D. Krahn MD

Abstract

The COVID-19 pandemic has led to efforts at rapid investigation and application of drugs which may improve prognosis, but for which safety and efficacy are not yet established. This document attempts to provide reasonable guidance for use of antimicrobials which have uncertain benefit but may increase risk of QT prolongation and ventricular proarrhythmia, notably, chloroquine, hydroxychloroquine, azithromycin, and lopinavir/ritonavir. During the pandemic, efforts to reduce spread and minimize effects on health care resources mandate minimization of unnecessary medical procedures and testing.

We recommend that the risk of drug proarrhythmia be minimized by:

1. discontinuing unnecessary medications which may also increase the QT interval,
2. identifying outpatients who are likely at low risk and do not need further testing (no history of prolonged QT, unexplained syncope or family history of premature sudden cardiac death, no medications which may prolong the QT interval, and/or prior known normal QTc), and
3. performing baseline testing in hospitalized patients or those who may be at higher risk. If baseline ECG testing reveals a moderately prolonged QTc, optimization of medications and electrolytes may permit therapy. If the QTc is markedly prolonged, drugs which further prolong it should be avoided, or expert consultation may permit administration with mitigating precautions.

These recommendations are made while there are no known effective treatments for COVID-19 and should be revisited when further data on efficacy and safety becomes available.

Background

The emergence of COVID-19 has prompted rapid investigation of potential therapeutic options. Some early candidates have included chloroquine, hydroxychloroquine, azithromycin, lopinavir/ritonavir, remdesivir, ribavirin and others.[1] Some of these are known to pose a risk of ventricular arrhythmia. With an uncertain degree of potential for benefit, an assessment of risk of therapy should be undertaken. During the pandemic, avoidance of non-essential testing, including ECG, reduces exposure of health care workers and other patients to infectious risk, and is recommended when possible.[2] It should be noted that the advice included here is offered during a health care crisis when access to some medical tests may increase population infection risk, the potential for benefit of these drugs is unknown, and there are no treatments with clear efficacy beyond supportive care. These recommendations should be reevaluated when these factors change.

Chloroquine and hydroxychloroquine	The current data supporting the use of chloroquine or hydroxychloroquine for treatment of infection with SARS-CoV-2 includes evidence of *in vitro* activity against SARS-CoV-2,[3-5] and limited evidence from non-comparative clinical research.[6, 7] Clinical trial results from China[6] have not yet been published in peer-reviewed form at time of writing, and data from France[7] are useful, but are preliminary. The study was nonrandomized and the preliminary report included only viral RNA detection from nasopharyngeal swabs as its primary endpoint, rather than clinical outcomes. Although limited, the data has been sufficient to prompt recommendations for treatment from national agencies in China and Italy.[8, 9] The overall safety of these drugs has been established over several decades of use, with good cardiovascular safety profiles in small studies.[10] However, cases of QT prolongation and torsade de pointes (TdP) have been reported.[11, 12] Larger cohort studies have focused on the low risk of retinopathy associated with chronic administration.[13] Rare cases of cardiomyopathy, AV block and bundle branch block have been reported during both acute and chronic administration.
Azithromycin	Azithromycin has been suggested to have in vitro antiviral activity against other viruses,[14, 15] and is effective in treating bacterial pneumonia. In the French series,[7] 6 patients were treated with azithromycin in addition to hydroxychloroquine, and had further reductions in detectable viral load. Azithromycin is known to have increased risk of QT prolongation[16],TdP and sudden cardiac death (SCD)[17] however, the absolute risk is small[17] and it has been shown to be used safely in clinical practice without routine ECG-based QT interval surveillance.[18]
Lopinavir/ritonavir	Lopinavir is a protease inhibitor developed to treat HIV infection, often combined with ritonavir, which prolongs its plasma half-life, and was shown to have in vitro, as well as clinical activity against SARS-CoV[19, 20] and in vitro activity against MERS-CoV.[21] It has been evaluted in small observational series[22-24] and has been tested in a prospective randomized controlled trial against COVID-19 for patients with radiographic evidence of pneumonia and impaired oxygen exchange, in which it did not demonstrate a measurable improvement in clinical course.[25]
Combinations of drugs	Data regarding combinations of drugs used to treat COVID-19 are insufficient to draw reliable conclusions about the safety of this approach. It is important to note that combining more than one proarrhythmic medication is known to increase the risk of significant QT prolongation[26] however, the risk of medication-induced TdP is quite variable with an incidence that ranges between 0.001% to 8%; depending on medication used.[27]
Other candidate drugs	Other drugs which are being investigated for activity to treat COVID-19 include remdesivir, favipiravir, ribavirin, sarilumab, and baricitinib and have limited data available regarding effects on cardiac arrhythmias.[28]

Patients with higher clinical risk

Some patients may be at elevated clinical risk for drug-induced ventricular arrhythmia. Patients with inherited long QT syndrome are known to be at increased risk. Expert opinion may be helpful in determining how best to mitigate risk for patients with prolonged baseline QTc interval who have COVID-19.[29] The use of other drugs or medical conditions that may prolong the QT interval or otherwise interact with these medications may increase risk of adverse events. Drug-induced prolongation of the QT interval in vulnerable patients may be exacerbated in older patients, by coexistent cardiac conditions such as cardiomyopathy, ischemia, heart failure, or bradycardia, and by other conditions such as diabetes, electrolyte abnormalities, hypoglycemia or renal failure. It is possible that severe cases of COVID-19 would be more vulnerable to QT prolongation as well. It is likely that patients at higher clinical risk of drug-induced arrhythmia will also be at higher risk for more severe infectious complications and are more likely to be treated as in-patients, in which case ECG monitoring will more likely be indicated for supportive medical care. This is reflected in the recommendations below.

Putting arrhythmic risk in context

The anticipated risk of life-threatening arrhythmia from the medications included here is likely to be low; the potential for benefit remains uncertain. Methods to mitigate risk are warranted, but should not impose undue increased risk of infection to other patients, health care workers, or place undue increase in demand on medical resources during a time of crisis with potential restrictions on access to personal protective equipment, drug therapy and even care providers.[2]

If COVID-19 antimicrobial drugs reduce mortality rate by even 5%, it is likely that this would constitute a substantial net benefit in comparison to the risk of drug-induced sudden death, recognizing that the absolute levels of risk and benefit are unclear at present. Clinical risk scores may be useful in minimizing risk,[26] but ultimately the decision whether to require extra testing and monitoring will require balancing of potential individual benefit against the risk of individual and population harm. This includes the local prevalence of COVID-19 infection and associated risk of subjecting patients to important albeit discretionary testing such as an ECG. It is recognized that assessment of the balance of risks may differ in different jurisdictions.[30]

Alternative testing methods

Single-use or easily sterilized hand-held cardiac rhythm monitoring devices have become increasingly available and may permit reliable recording of cardiac intervals. Availability of means to perform these recordings may obviate the need for obtaining a standard 12-lead ECG and may not pose an infectious risk. If available, this may be utilized to confirm a patient's risk status prior to initiation of antimicrobial therapy, and may reduce personal risk without a meaningful increase in concomitant population risk.[31, 32]

Recommendations

The use of medications with unproven benefit for treatment of COVID-19 should primarily focus on robust evaluation within a clinical trial whenever possible. We recommend that clinical trials include an effort to mitigate the risk of treating patients with a known predictably high risk of torsade de pointes with drugs which may further prolong the QT interval.
If drugs with the potential to cause ventricular arrhythmia through prolongation of repolarization, including azithromycin, chloroquine, hydroxychloroquine, lopinavir/ritonavir are contemplated for treatment of COVID-19, the following precautions should be observed:

1. Review medications and discontinue unnecessary medications that may prolong QT.[28]
2. For patients with known inherited long QT syndrome or a history of drug-induced torsade de Pointes, use of these drugs should be undertaken only after consultation with a heart rhythm specialist. Potential mitigations could include use of cardiac monitoring, or repeated QTc interval checks. Risk and potential benefit should be individually assessed.
3. For patients with no history of prolonged QT, unexplained syncope or family history of premature sudden cardiac death, who are not taking other medications which may prolong the QT interval, and for patients with a prior known normal QTc, it may be reasonable to proceed with antimicrobial drug administration without a baseline or follow-up ECG, if obtaining an ECG may increase population risk of infection.
4. For hospitalized patients, or for those not fulfilling the above criteria
    a) Obtain baseline assessment of:
        i. ECG to assess QTc if not performed within last 3 months
        ii. electrolytes (Ca^{++}, Mg^{++}, K^{+}) if possible
    b) If QTc ≥ 500 ms, reassess after correction of electrolyte abnormalities or discontinuation of other QT prolonging drugs. If QTc remains ≥ 500 ms, recommend expert consultation and careful evaluation of benefits and risks.
    c) If QTc is ≥470 ms (male) or QTc is ≥480 ms (female), but < 500 ms, initiate antimicrobial drugs and consider repeat ECG in 48 hours.
    d) If patients have clinically severe disease, or are taking multiple medications which may prolong QT, recheck QTc 48 hours after initiation of antimicrobial drugs.
    e) If follow-up QTc increases by ≥ 60 ms OR is ≥ 500 ms, discontinue antimicrobial or seek expert consultation.

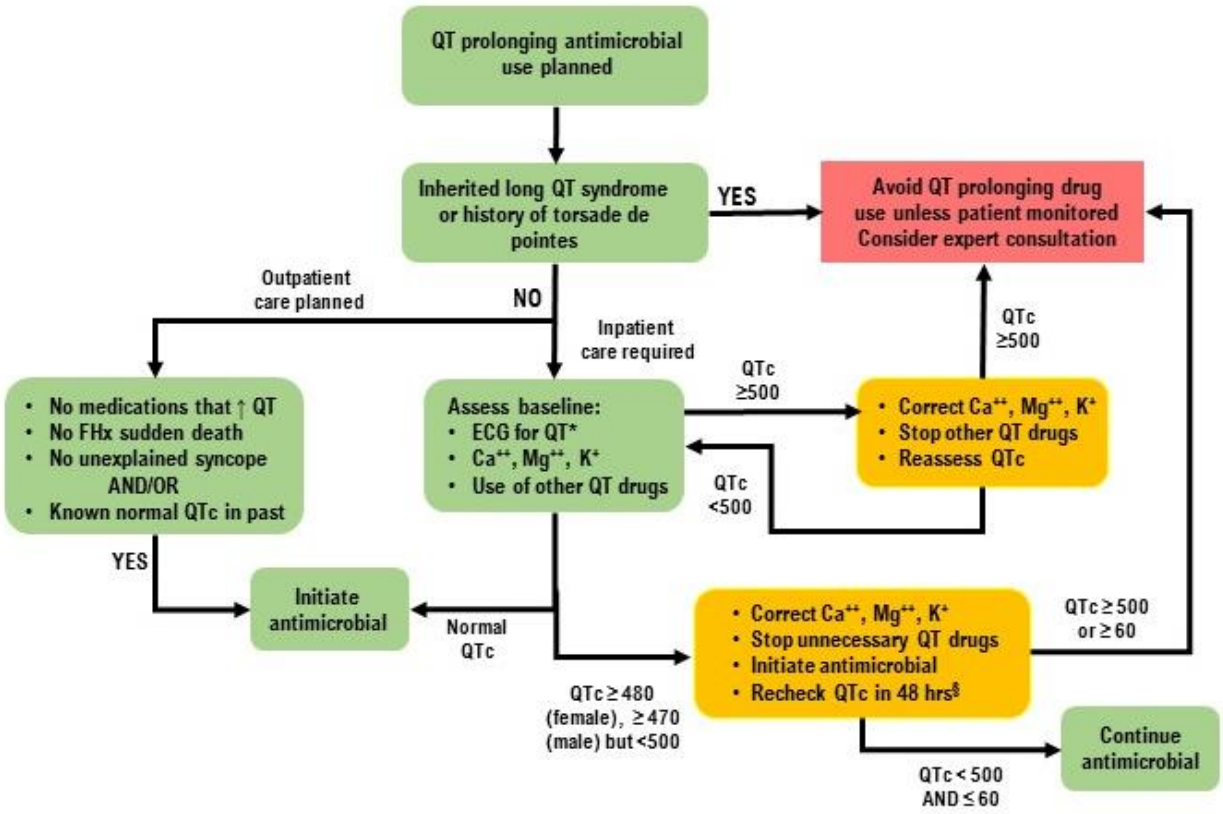

Figure 1: Treatment algorithm for COVID-19 therapies which may prolong QT. We recommend that use of these drugs for treating COVID-19 be within evaluative clinical trials. Note that this approach applies during a pandemic and may differ when the population risk of routine testing changes.
**See figure 2 for a review of how to measure the QT interval and calculate QTc.*
§ Consider rechecking the QTc interval at 48 hours for inpatients with high risk features (see text) or in those with borderline QTc prolongation at baseline.

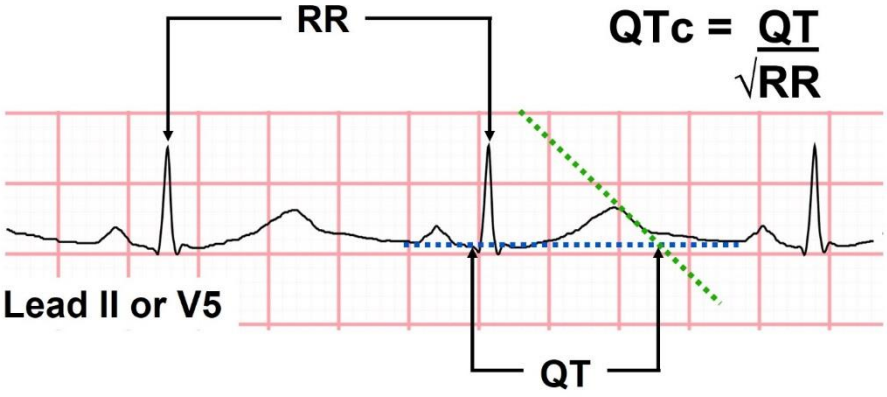

Figure 2: How to measure the corrected QT (QTc) interval. The QT interval is measured from the onset of the QRS (where it first deviates from baseline) to the intersection of the tangent of the downslope (dotted green line) with the baseline (TP segment, dotted blue line). This is corrected for heart rate by dividing by the square root of the RR interval, measured in seconds. In the presence of QRS widening (e.g. bundle branch block or paced ventricular rhythm) the QTc can be adjusted by subtracting the QRS duration (QRSd) which is in excess of 100 ms as in the following formula:[31,33]

QTc(adjusted)= QTc(measured) – (QRSd-100)

If the patient is in atrial fibrillation, the QTc interval can be determined from 10-averaged AF beats.[34]

References

1. Jin Y, Yang H, Ji W, Wu W, Chen S, Zhang W and Duan G. Virology, Epidemiology, Pathogenesis, and Control of COVID-19. *Viruses*. 2020;12.

2. Guidance From the CCS COVID-19 Rapid Response Team: Reducing in-hospital spread and the optimal use of resources for the care of hospitalized cardiovascular patients during hte COVID-19 pandemic. 2020;2020.

3. Liu J, Cao R, Xu M, Wang X, Zhang H, Hu H, Li Y, Hu Z, Zhong W and Wang M. Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. *Cell Discov*. 2020;6:16.

4. Yao X, Ye F, Zhang M, Cui C, Huang B, Niu P, Liu X, Zhao L, Dong E, Song C, Zhan S, Lu R, Li H, Tan W and Liu D. In Vitro Antiviral Activity and Projection of Optimized Dosing Design of Hydroxychloroquine for the Treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). *Clin Infect Dis*. 2020.

5. Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, Shi Z, Hu Z, Zhong W and Xiao G. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Res*. 2020;30:269-271.

6. Gao J, Tian Z and Yang X. Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. *Biosci Trends*. 2020;14:72-73.

7. Gautret P, Lagier JC, Parola P, Hoang VT, Meddeb L, Mailhe M, Doudier B, Courjon J, Giordanengo V, Vieira VE, Dupont HT, Honore S, Colson P, Chabriere E, La Scola B, Rolain JM, Brouqui P and Raoult D. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *Int J Antimicrob Agents*. 2020:105949.

8. Dong L, Hu S and Gao J. Discovering drugs to treat coronavirus disease 2019 (COVID-19). *Drug Discov Ther*. 2020;14:58-60.

9. Nicastri E, Petrosillo N, Bartoli TA, Lepore L, Mondi A, Palmieri F, D'Offizi G, Marchioni L, Murachelli S, Ippolito G and Antinori A. National Institute for the Infectious Diseases "L. Spallanzani", IRCCS. Recommendations for COVID-19 clinical management. *Infect Dis Rep*. 2020;12:8543.

10. Morita S, Takahashi T, Yoshida Y and Yokota N. Population Pharmacokinetics of Hydroxychloroquine in Japanese Patients With Cutaneous or Systemic Lupus Erythematosus. *Ther Drug Monit*. 2016;38:259-67.

11. Stas P, Faes D and Noyens P. Conduction disorder and QT prolongation secondary to long-term treatment with chloroquine. *Int J Cardiol*. 2008;127:e80-2.

12. O'Laughlin JP, Mehta PH and Wong BC. Life Threatening Severe QTc Prolongation in Patient with Systemic Lupus Erythematosus due to Hydroxychloroquine. *Case Rep Cardiol*. 2016;2016:4626279.

13. Levy GD, Munz SJ, Paschal J, Cohen HB, Pince KJ and Peterson T. Incidence of hydroxychloroquine retinopathy in 1,207 patients in a large multicenter outpatient practice. *Arthritis Rheum*. 1997;40:1482-6.

14. Retallack H, Di Lullo E, Arias C, Knopp KA, Laurie MT, Sandoval-Espinosa C, Mancia Leon WR, Krencik R, Ullian EM, Spatazza J, Pollen AA, Mandel-Brehm C, Nowakowski TJ, Kriegstein AR and DeRisi JL. Zika virus cell tropism in the developing human brain and inhibition by azithromycin. *Proc Natl Acad Sci U S A*. 2016;113:14408-14413.

15. Madrid PB, Panchal RG, Warren TK, Shurtleff AC, Endsley AN, Green CE, Kolokoltsov A, Davey R, Manger ID, Gilfillan L, Bavari S and Tanga MJ. Evaluation of Ebola Virus Inhibitors for Drug Repurposing. *ACS Infect Dis*. 2015;1:317-26.

16. Choi Y, Lim HS, Chung D, Choi JG and Yoon D. Risk Evaluation of Azithromycin-Induced QT Prolongation in Real-World Practice. *Biomed Res Int*. 2018;2018:1574806.

17. Ray WA, Murray KT, Hall K, Arbogast PG and Stein CM. Azithromycin and the risk of cardiovascular death. *The New England journal of medicine*. 2012;366:1881-90.

18. Trac MH, McArthur E, Jandoc R, Dixon SN, Nash DM, Hackam DG and Garg AX. Macrolide antibiotics and the risk of ventricular arrhythmia in older adults. *CMAJ*. 2016;188:E120-E129.

19. Chu CM, Cheng VC, Hung IF, Wong MM, Chan KH, Chan KS, Kao RY, Poon LL, Wong CL, Guan Y, Peiris JS, Yuen KY and Group HUSS. Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings. *Thorax*. 2004;59:252-6.

20. Chen F, Chan KH, Jiang Y, Kao RY, Lu HT, Fan KW, Cheng VC, Tsui WH, Hung IF, Lee TS, Guan Y, Peiris JS and Yuen KY. In vitro susceptibility of 10 clinical isolates of SARS coronavirus to selected antiviral compounds. *J Clin Virol*. 2004;31:69-75.

21. de Wilde AH, Jochmans D, Posthuma CC, Zevenhoven-Dobbe JC, van Nieuwkoop S, Bestebroer TM, van den Hoogen BG, Neyts J and Snijder EJ. Screening of an FDA-approved compound library identifies four small-molecule inhibitors of Middle East respiratory syndrome coronavirus replication in cell culture. *Antimicrob Agents Chemother*. 2014;58:4875-84.

22. Young BE, Ong SWX, Kalimuddin S, Low JG, Tan SY, Loh J, Ng OT, Marimuthu K, Ang LW, Mak TM, Lau SK, Anderson DE, Chan KS, Tan TY, Ng TY, Cui L, Said Z, Kurupatham L, Chen MI, Chan M, Vasoo S, Wang LF, Tan BH, Lin RTP, Lee VJM, Leo YS, Lye DC and Singapore Novel Coronavirus Outbreak Research T. Epidemiologic Features and Clinical Course of Patients Infected With SARS-CoV-2 in Singapore. *Jama*. 2020.

23. Kim JY, Choe PG, Oh Y, Oh KJ, Kim J, Park SJ, Park JH, Na HK and Oh MD. The First Case of 2019 Novel Coronavirus Pneumonia Imported into Korea from Wuhan, China: Implication for Infection Prevention and Control Measures. *J Korean Med Sci*. 2020;35:e61.

24. Lim J, Jeon S, Shin HY, Kim MJ, Seong YM, Lee WJ, Choe KW, Kang YM, Lee B and Park SJ. Case of the Index Patient Who Caused Tertiary Transmission of COVID-19 Infection in Korea: the Application of Lopinavir/Ritonavir for the Treatment of COVID-19 Infected Pneumonia Monitored by Quantitative RT-PCR. *J Korean Med Sci*. 2020;35:e79.

25. Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, Ruan L, Song B, Cai Y, Wei M, Li X, Xia J, Chen N, Xiang J, Yu T, Bai T, Xie X, Zhang L, Li C, Yuan Y, Chen H, Li H, Huang H, Tu S, Gong F, Liu Y, Wei Y, Dong C, Zhou F, Gu X, Xu J, Liu Z, Zhang Y, Li H, Shang L, Wang K, Li K, Zhou X, Dong X, Qu Z, Lu S, Hu X, Ruan S, Luo S, Wu J, Peng L, Cheng F, Pan L, Zou J, Jia C, Wang J, Liu X, Wang S, Wu X, Ge Q, He J, Zhan H, Qiu F, Guo L, Huang C, Jaki T, Hayden FG, Horby

PW, Zhang D and Wang C. A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19. *The New England journal of medicine*. 2020.

26. Tisdale JE, Jaynes HA, Kingery JR, Mourad NA, Trujillo TN, Overholser BR and Kovacs RJ. Development and validation of a risk score to predict QT interval prolongation in hospitalized patients. *Circ Cardiovasc Qual Outcomes*. 2013;6:479-87.

27. Drew BJ, Ackerman MJ, Funk M, Gibler WB, Kligfield P, Menon V, Philippides GJ, Roden DM, Zareba W, American Heart Association Acute Cardiac Care Committee of the Council on Clinical Cardiology tCoCN and the American College of Cardiology F. Prevention of torsade de pointes in hospital settings: a scientific statement from the American Heart Association and the American College of Cardiology Foundation. *Circulation*. 2010;121:1047-60.

28. CredibleMeds.org. 2020.

29. Wu C, Postema PG, Arbelo E, Behr ER, Bezzina CR, Napolitano C, Robyns T, Probst V, Schulze-Bahr E, Remme CA and Wilde AAM. SARS-CoV-2, COVID-19 and inherited arrhythmia syndromes. *Heart Rhythm*. 2020;doi: https://doi.org/10.1016/j.hrthm.2020.03.024.

30. Lakkireddy D, Chung M, Gopinathannair R, Patton KK, Gluckman TJ, Turagam M, Cheung J, Patel PJ, Sotomonte J, Lampert R, Han JK, Rajagopalan B, Eckhardt L, Joglar JA, Sandau K, Olshansky B, Wan E, Noseworthy PA, Leal M, Kaufman E, Gutierrez A, Marine JM, Wang PJ and Russo AM. Guidance for Cardiac Electrophysiology During the Coronavirus (COVID-19) Pandemic from the Heart Rhythm Society COVID-19 Task Force; Electrophysiology Section of the American College of Cardiology; and the Electrocardiography and Arrhythmias Committee of the Council on Clinical Cardiology, American Heart Association. *Heart Rhythm*. 2020.

31. Giudicessi JR, Noseworthy PA, Friedman PA and Ackerman MJ. Urgent guidance for navigating and circumventing the QTc prolonging and torsadogenic potential of possible pharmacotherapies for COVID-19. *Mayo Clin Proc*. 2020;https://doi.org/10.1016/j.mayocp.2020.03.024.

32. Cheung CC, Davies B, Gibbs K, Laksman ZW and Krahn AD. Multi-lead QT Screening is Necessary for QT Measurement: Implication for Management of Patients in the COVID-19 Era. *JACC Clin Electrophysiol*. 2020;In Press.

33. McLaughlin NB, Campbell RW and Murray A. Comparison of automatic QT measurement techniques in the normal 12 lead electrocardiogram. *Br Heart J*. 1995;74:84-9.

34. Tooley J, Ouyang D, Hadley D, Turakhia M, Wang P, Ashley E, Froelicher V and Perez M. Comparison of QT Interval Measurement Methods and Correction Formulas in Atrial Fibrillation. *The American Journal of Cardiology*. 2019;123:1822-1827.