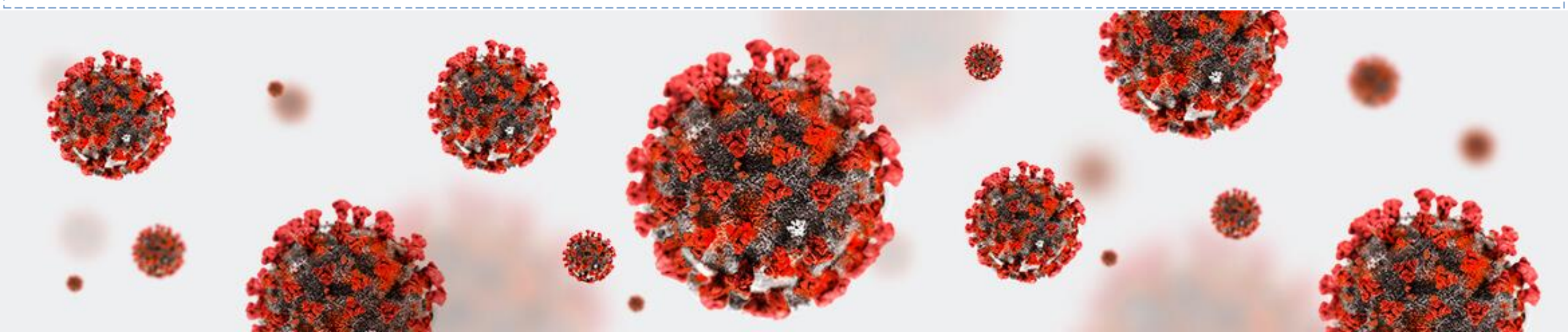
COVID19 CLINICIANS Network

Webinar series: COVID-19 and inherited arrhythmia syndromes

Thursday 23 April at 17:30 CET, Brussels time



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IDIBAPS, Institut d'Investigació August Pi i Sunyer (IDIBAPS)

Centro de Investigación Biomédica en Red de Enfermedades Cardiovasculares (CIBERCV)

European Reference Networks

European Commission

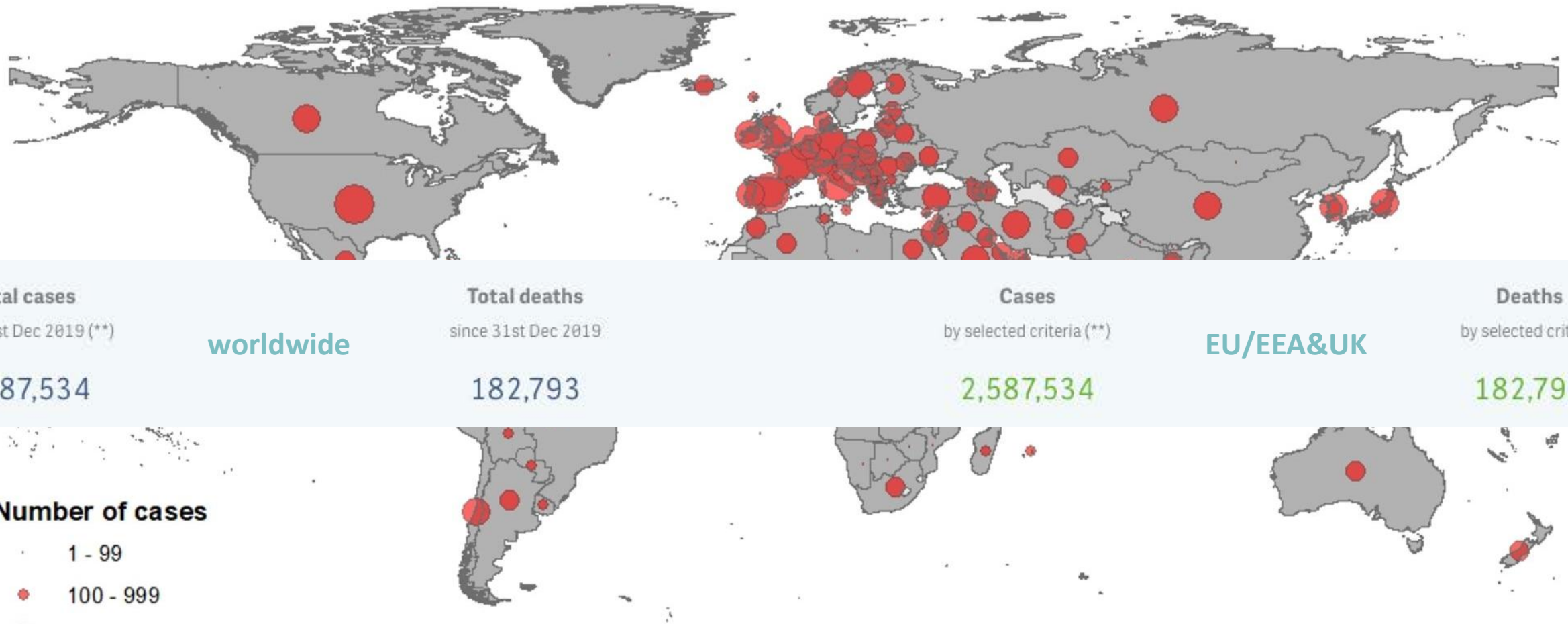
Science

Novel human virus? Pneumonia cases linked to seafood market in China stir concern

Normile D. Jan. 3, 2020

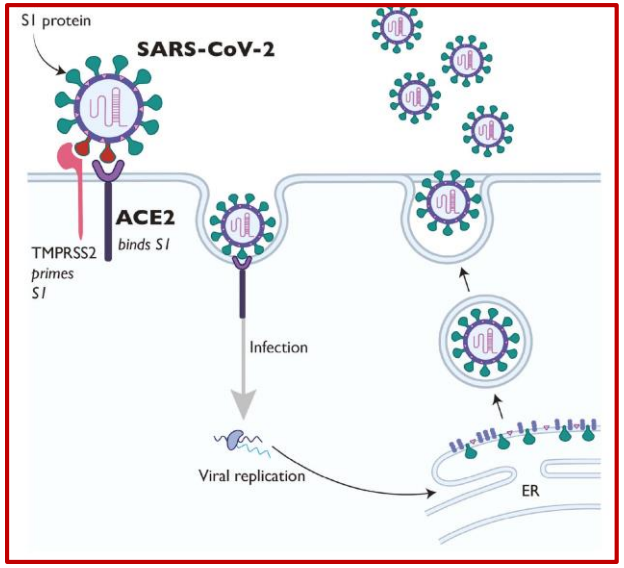
Widespread dissemination in our hyperconnected creates realtime challenges to prediction analyses

Geographic distribution of COVID-19 cases worldwide, as of 23 April 2020

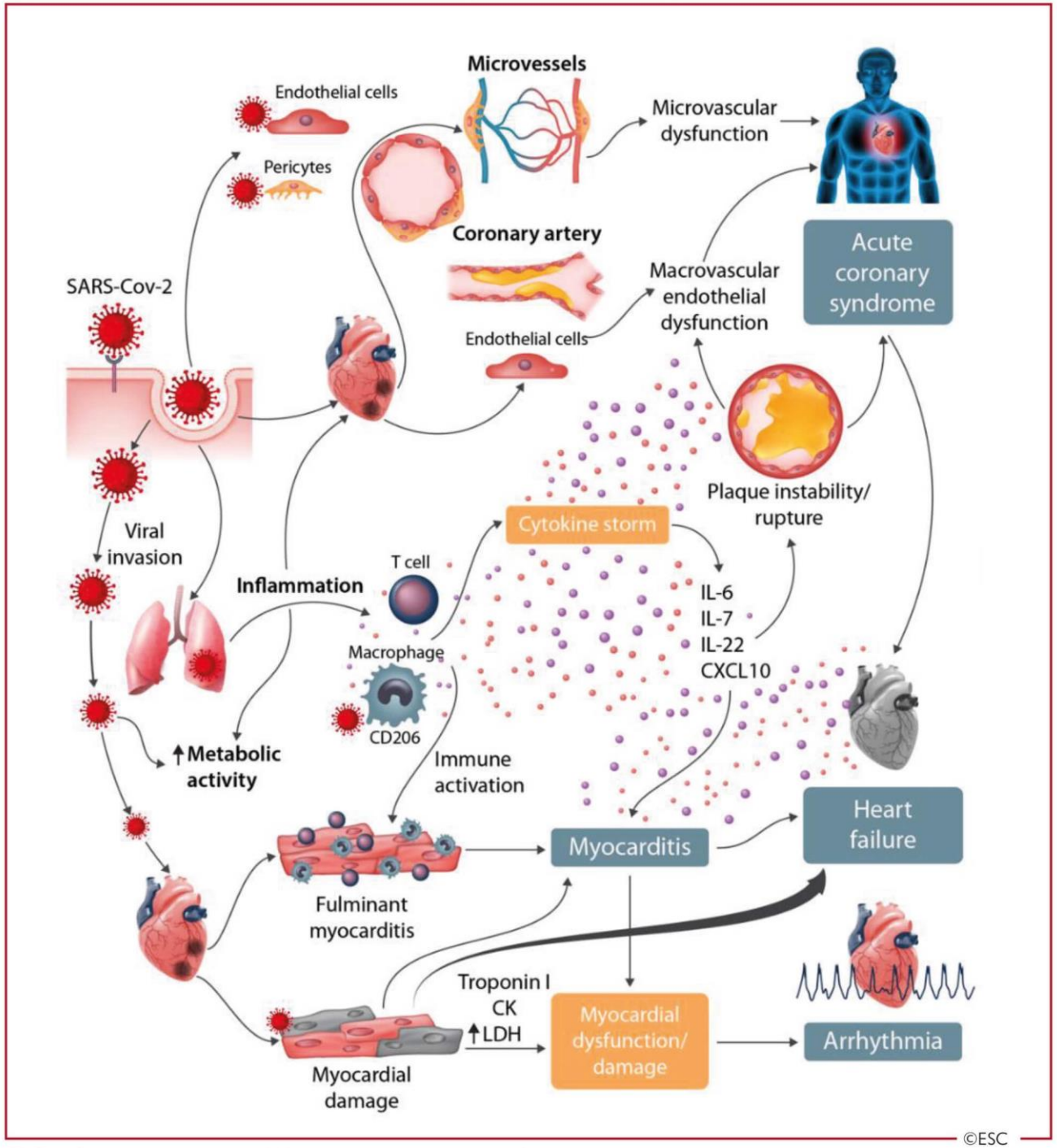


https://www.ecdc.europa.eu/en/geographical-distribution-2019-ncov-cases

Cardiovascular involvement in COVID-19



Cardiovascular manifestations and hypothetical mechanisms



ESC European Society of Cardiology

https://www.escardio.org/Education/COVID-19-and-Cardiology/ESC-COVID-19-Guidance

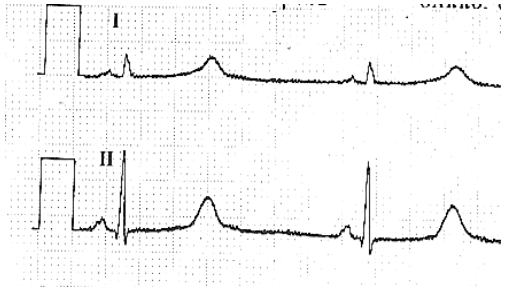
Possible cardiac effects of SARS-COV-2 coronavirus

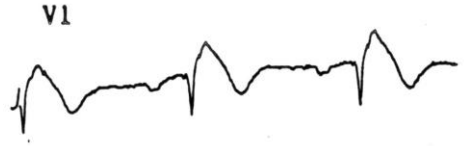
	Study	Patients	Outcomes
Arrhythmia	Wang 2020 [7], retrospective, single-center case series	138 hospitalized patients	Total events: 23 (16.7%) ICU vs non-ICU patients: 16 (44.4%) vs. 7 (6.9%), p<0.001)
	Liu 2020 [15], retrospective, nine- tertiary hospitals (cohort)	137 hospitalized patients	Total events: 10 (7.3%)*
Myocardial injury (elevated cTnI)	Huang 2020 [13], retrospective, cohort study	41 hospitalized patients	Overall: 5 (12%) ICU patients: 4 (31%) Vs. non-ICU patients: 1 (4%), p=0.017
	Wang 2020 [7], retrospective, single-center case series	138 hospitalized patients	Overall: 10 (7.2%) ICU patients: 8 (22.2%) Vs. non-ICU patients 2 (2.0%), p<0.001
	Zhou 2020 [11], retrospective, multicenter cohort study	191 hospitalized patients	Overall: 33 (17%) Survivors: 1 (1%) Vs. non survivors: 32 (59%), p<0.0001
Myocarditis	Ruan 2020 [20], retrospective, multicenter study	68 deaths from 150 hospitalized patients	5 (7%) deaths from myocardial damage and circulatory failure 22 (33%) deaths from myocardial damage and respiratory failure**
Heart Failure	Zhou 2020 [11], retrospective, multicenter cohort study	191 hospitalized patients	Overall: 44 (23%) Survivors: 16 (12%) Vs. non-survivors 28 (52%), p<0.0001

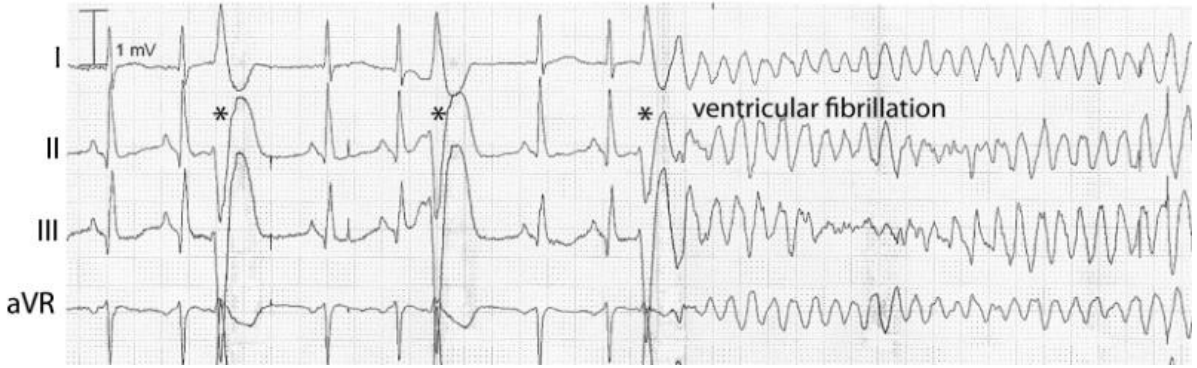
Vlachakis PK et al. Hellenic Journal of Cardiology. 2020.

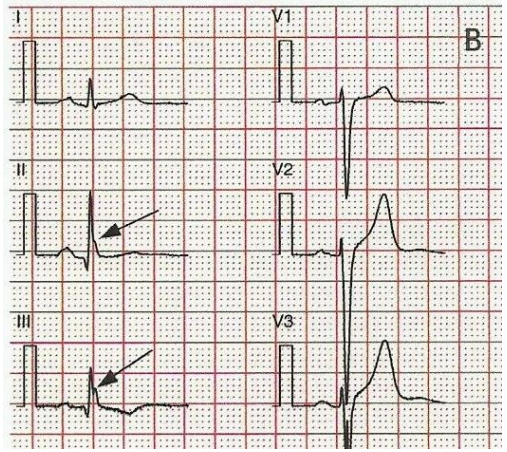
Inherited Arrhythmia Syndromes

- ✓Long QT syndrome (1-5/10.000)
- ✓Short QT syndrome (<1/10.000)
- ✓Brugada syndrome (1-5/10.000)
- ✓Catecholaminergic polymorphic ventricular tachycardia(<1/10.000)
- ✓Early repolarisation syndrome(<1/10.000)
- ✓Primary ventricular fibrillation (<1/10.000)

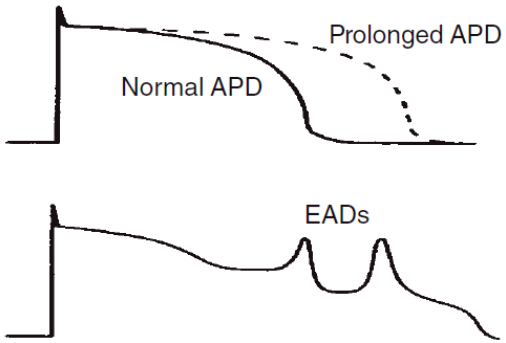


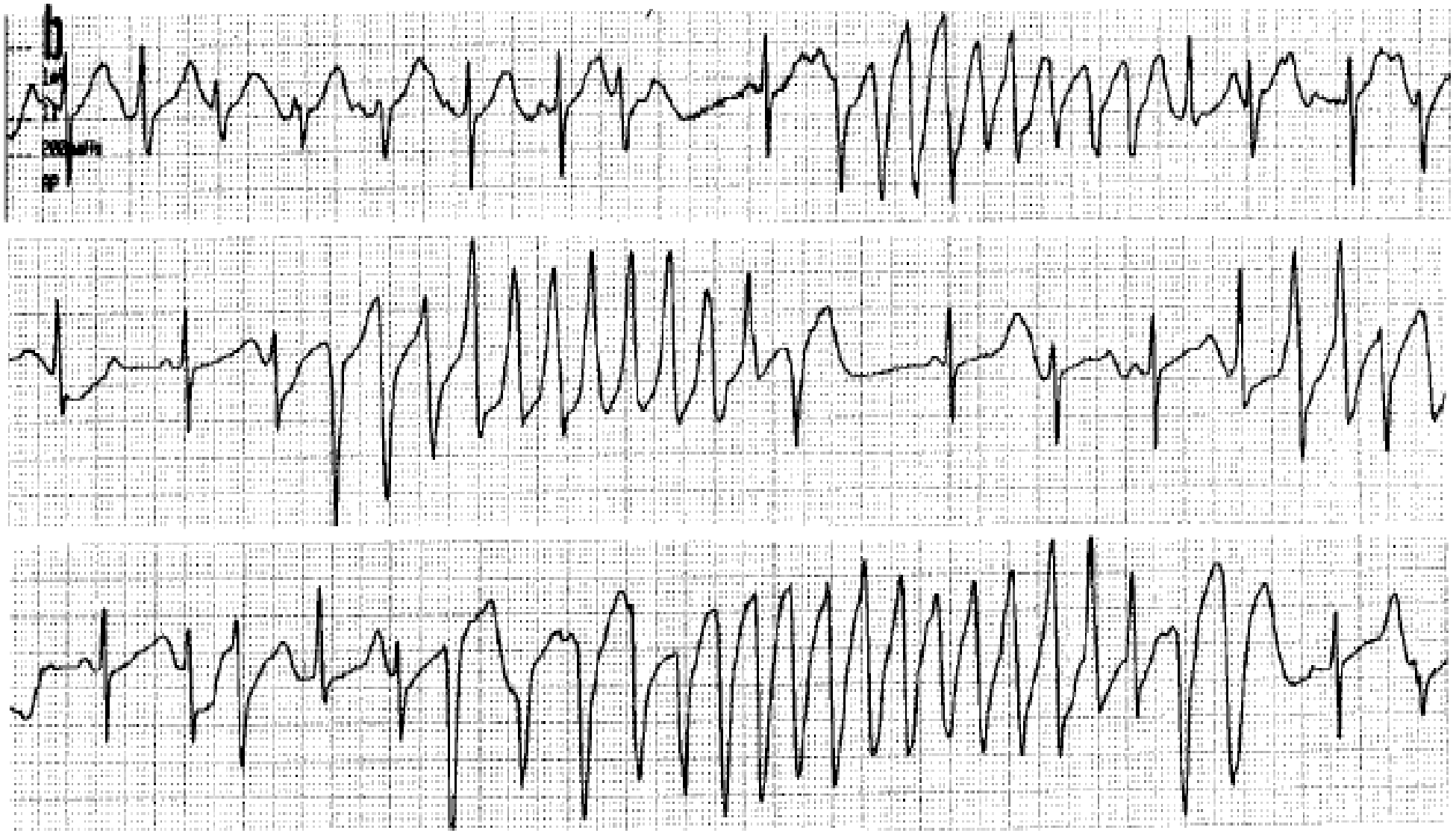






Long QT syndrome





Long QT syndrome

Leading cause of autopsy-negative SD in the young[1]

Prevalence: ≈ 1:2000[2]

Clinical manifestations:
- **Syncope:** early childhood or teenagers (≈12 yo)
- **Sudden death:** secondary to *torsade de pointes*

Electrocardiogram:
- **Prolonged QT interval**
- **T-wave alterations**

Suggested Bazett-Corrected QTc Values for Diagnosing QT Prolongation

Higher risk of TdP if QTc >500 ms (>550 ms if QRS >120 ms)

Prolonged	>460	>450	>470

1. *Tester DJ et al. Circulation 2011;49:240-6*
2. *Schwartz PJ et al. Circulation 2009*
3. *Gondenberg I et al.JCE 2006*

Long QT syndrome

Congenital LQTS:

- autosomal dominant (1/2000)
- autosomal recessive (1-6/10^6)

Acquired LQTS:

- Drugs (class I or III AADs, etc.)
- Metabolic disorders (hipoK^+, hipoCa^{2+}, hipoMg^{2+}, etc.)
- Bradycardia
- Others

- Genetic predisposition

Long QT syndrome

FACTORS THAT PREDISPOSE TO QTc PROLONGATION (and *Torsade de Pointes*)

Non-modifiable factors

- Female sex
- Significant underlying heart disease: severe hypertrophy, ischemic heart disease, decompensated heart failure
- Subarachnoid hemorrhage
- Congenital long QT syndrome
- Genetic polymorphisms

Modifiable factors

- Ionic disorders: hypokalemia, hypomagnesemia, hypocalcemia.
- Bradycardia
- Simultaneous administration of drugs associated with QTc prolongation.

An International, Multicentered, Evidence-Based Reappraisal of Genes Reported to Cause Congenital Long QT Syndrome

Table 2. Classification of Genetic Evidence for Genes Previously Reported as Causing LQTS (

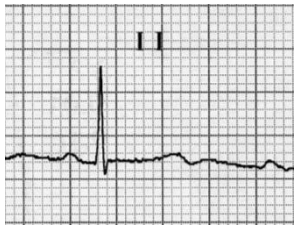
Gene	LQTS	aLQTS	Syndromic*
AKAP9	Disputed		
ANK2	Disputed		
CACNA1C	Moderate		Definitive (Timothy syndrome)
CALM1	Definitive†		
CALM2	Definitive†		
CALM3	Definitive†		
CAV3	Limited		
KCNE1	Limited	Strong	
KCNE2	Disputed	Strong	
KCNH2	Definitive		
KCNJ2	Limited		Definitive (Andersen-Tawil syndrome)
KCNJ5	Disputed		
KCNQ1	Definitive		
SCN4B	Disputed		
SCN5A	Definitive		
SNTA1	Disputed		
TRDN	Strong‡		

aLQTS indicates acquired long QT syndrome; and LQTS, congenital long QT syndrome.
* Multiorgan syndrome including QT prolongation and cardiac arrhythmias.
† LQTS presenting in infancy or early childhood with heart block and severe QT prolongation.
‡ QT prolongation, negative T waves in precordial leads, and exercise-induced arrhythmias in early childhood related to homozygous or compound heterozygous frameshift mutations.

85-90% of genotyped patients

Adler A et al. Circulation 2020;141:418–428

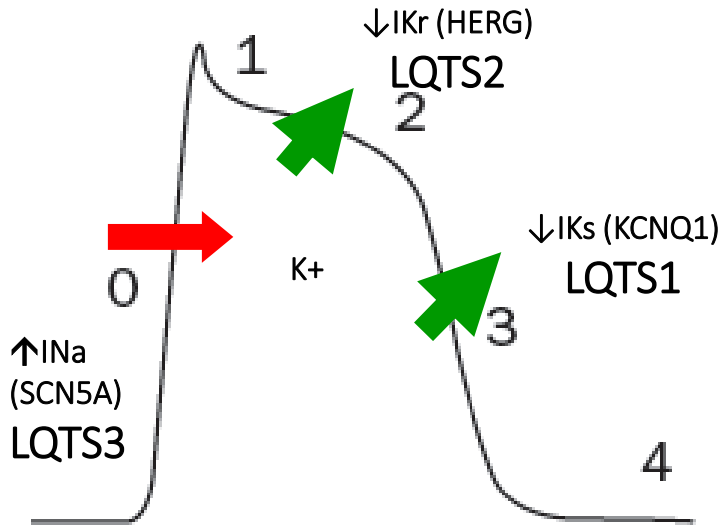
35%



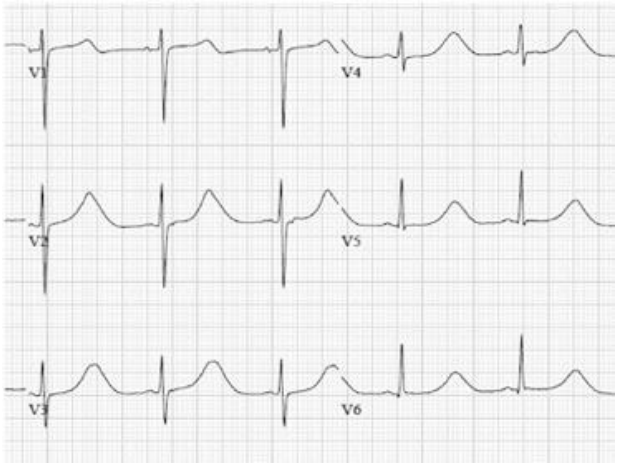
BB < LQTS1

10%

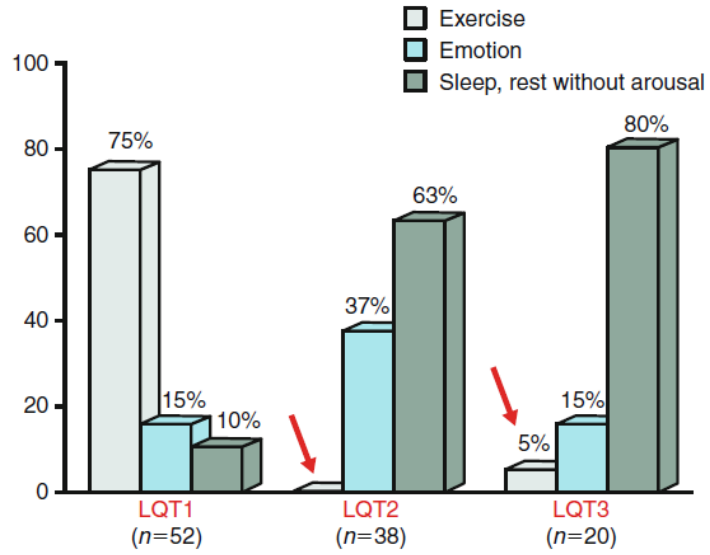
BB Incierta



50%



BB OK



Modif. Roden DM. N Engl J Med 2008; 358:169-79
Obeyesekere MN. Circ Arrhythm Electrophysiol. 2011;4:958-964.

Schwartz PJ et al. Circulation 2001;103:89-95

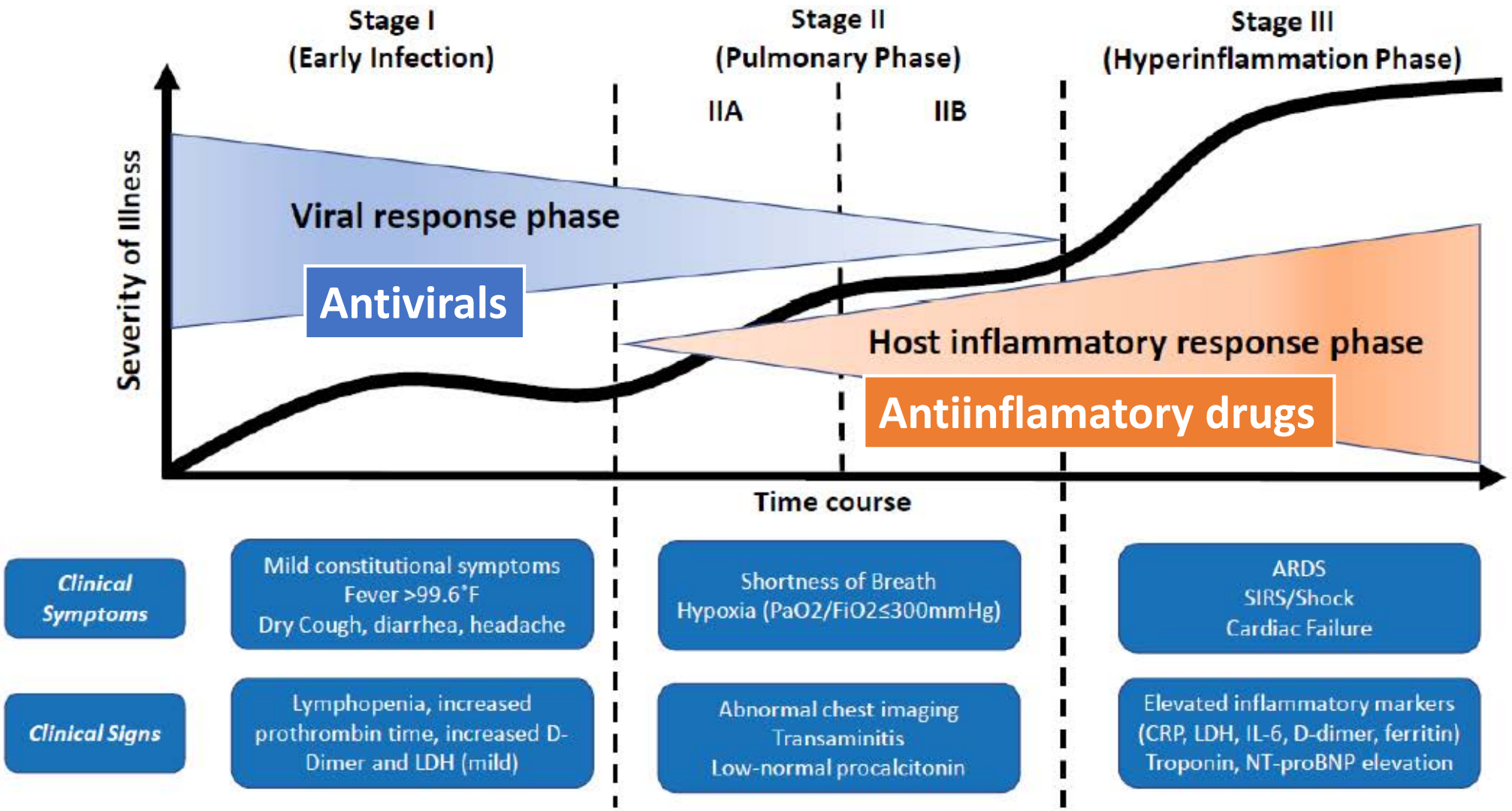
Long QT syndrome

Table 2. Risk Mechanisms and Genotype-Specific Therapy Based on Clinical and Experimental Data in LQT1, LQT2, and LQT3 Forms of Long QT (LQT) Syndrome

	LQT1	LQT2	LQT3
Exercise restriction	+++	++	?
β-blockers	+++	++	?
Potassium supplement	+	++	+
Mexiletine	+	+	++
Flecainide	No data	No data	+++ (ΔKPQ, D1790G)
Ranolazine	No data	No data	++ (ΔKPQ)
LCSD in high-risk patients	++	++	++
ICD in high-risk patients	+++	+++	+++

Moss AJ et al. Circ Arrhythm Electrophysiol 2008;1:219-226

Long QT syndrome and COVID-19: Treatment



Siddiqu HK, et al. J Heart Lung Transplant 2020. doi: 10.1016/j.healun.2020.03.012

https://clinicaltrials.org Accessed on April 22nd, 2020

Pro-arrhythmogenic effects of COVID-19 therapy

	HR	AV CONDUCTION	QRS INTERVAL	QTC INTERVAL	TDP RISK
CHLOROQUINE	Mild ↓	Mild ↑ Δ_{PR}= 14.8 ms[216]	Mild ↑ Δ_{QRS}= 9.9 ms[216]	Moderate ↑ Δ_{QTc}= 27- 51 ms[216-218] ↑ Δ_{QTc} in 14.2% of pts [219]	Very-low risk of TdP (72 cases of VF/VT/TdP/LQTS in FAERS registry)
HYDROXY-CHLOROQUINE	Mild ↓ [220, 221, 224]	Mild ↑	Mild ↑	Moderate ↑ Δ_{QTc}= 25 ms [220, 221]	Very-low risk of TdP (222 cases of VF/VT/TdP/LQTS in FAERS registry)
AZITHROMYCINE	Mild ↓ [226]	Mild ↑ [226]	Mild ↑ [226]	Moderate-Severe ↑ Δ_{QTc}= 5-32 ms[226-228]	Low risk of TdP Cumulative incidence SCD = 64.6/1 million[229] ROR for Tdp = 4.76 compared to other medication (2.81-7.98)[230] RR for SCD or VT= 3.40 compared to no macrolide use [229, 231, 232]
LOPINAVIR/ RITONAVIR	NR	Moderate↑ Δ_{PR}= 33.5 ms[216]	Mild ↑ Δ_{QRS}= 7 ms[235]	Moderate ↑ Δ_{QTc}= 20 ms[216]	Low risk of TdP (27 cases of VF/VT/TdP/LQTS in FAERS registry) HR for Tdp 1.02 (0.26-3.24)[227]

Two studies have evaluated the association of **chloroquine and azithromycin** for the *prevention and treatment for malaria* in Africa with 114 and 1445 individuals, respectively in the arm treated with the combination.

acceptable safety profile

Sagara I et al. Malaria Journal 2014;13(1):458.
Kimani J et al. PLOS ONE 2016;11(6):e0157045

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Pro-arrhythmogenic effects of COVID-19 therapy

	HR	AV CONDUCTION	QRS INTERVAL	QTC INTERVAL	TDP RISK
TOCILIZUMAB	No ECG changes described[236]				Unknown
FINGOLIMOD SIPONIMOD	Moderate-Severe ↓ Δ_{HR}= -23 bpm[237]	Mild-moderate ↑	Unknown	Mild ↑	Unknown
REMDESIVIR	Unknown	Unknown	Unknown	Unknown	Unknown
INTERFERON ALFACON-1	Unknown	Unknown	Unknown	Unknown	Unknown
RIBAVIRIN	Unknown	Unknown	Unknown	Unknown	Unknown
METILPRED-NISOLONE	Unknown	Unknown	Unknown	Unknown	Unknown

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Drug-to-drug interactions

COVID-19 drug	Antiarrhythmic drug											
	AMIODARONE	BEPRIDIL	DISOPYRAMIDE	DOFETILIDE	DRONEDARONE	FLECAINIDE	IVABRADINE	LIDOCAINE	MEXILETINE	PROPAFENONE	QUINIDINE	SOTALOL
CHLOROQUINE	**	**	**	**	**	**	*	*	*	*	**	**
HYDROXYCHLOROQUINE	**	**	**	**	**	**	*	*	*	*	**	**
AZITHROMYCINE	**	**	**	**	**	**	*	*	*	*	**	**
ATAZANAVIR	*	*	*	*	*	*					*	*
ATAZINAVIR/COBICISTAT	*	*	*	*	*	*					*	*
LOPINAVIR/RITONAVIR	*	*	*	*	*	*					*	*
RIBAVIRIN	*	*	*	*	*	*					*	*
REMDESIVIR	*	*	*	*	*	*					*	*
FAVIPIRAVIR	*	*	*	*	*	*					*	*
BEVACIZUMAB	*	*	*	*	*	*						
ECULIZUMAB	*	*	*	*	*	*						
TOCILIZUMAB	*	*	*	*	*	*					*	*
FINGOLIMOD	*	*	*	*	*	*					*	*
INTERFERON	*	*	*	*	*	*					*	*
PIRFENIDONE	*	*	*	*	*	*						
METHYLPREDNISOLONE	*	*	*	*	*	*					*	*
NITAZOXANIDE	*	*	*	*	*	*					*	*

Red: avoid combination

Orange: consider modification

Yellow: monitor therapy

Green: no action needed

Source: UpToDate – Lexicomp®

Long QT syndrome and COVID-19: QTc measurement

Airborne isolation

a. Anteroom/hall

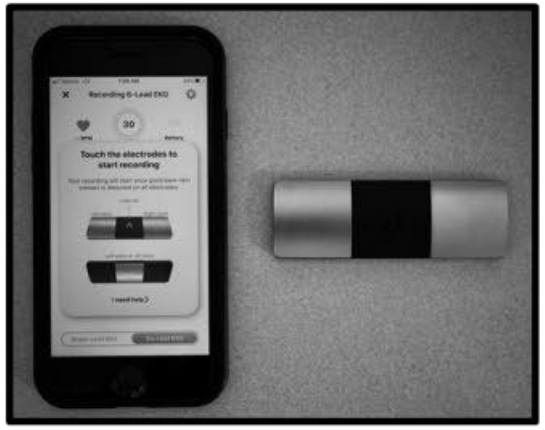
Place smartphone in biohazard bag. Nurse/provider in PPE helps patient record mobile ECG.*

Patient room

Carefully disinfect all equipment using product with known activity against SARS-CoV-2.

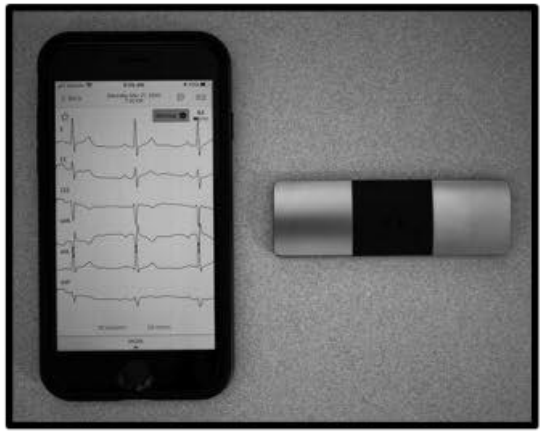
Anteroom/hall

b. Patient room



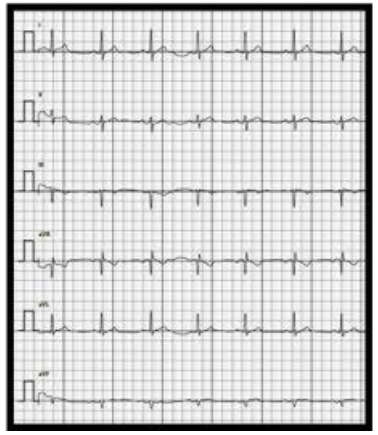
Patient records mobile ECG with own phone and personal/loaned mobile ECG device.

Patient room



Mobile ECG uploaded to remote monitoring platform or e-mailed directly to provider(s).

Remote review

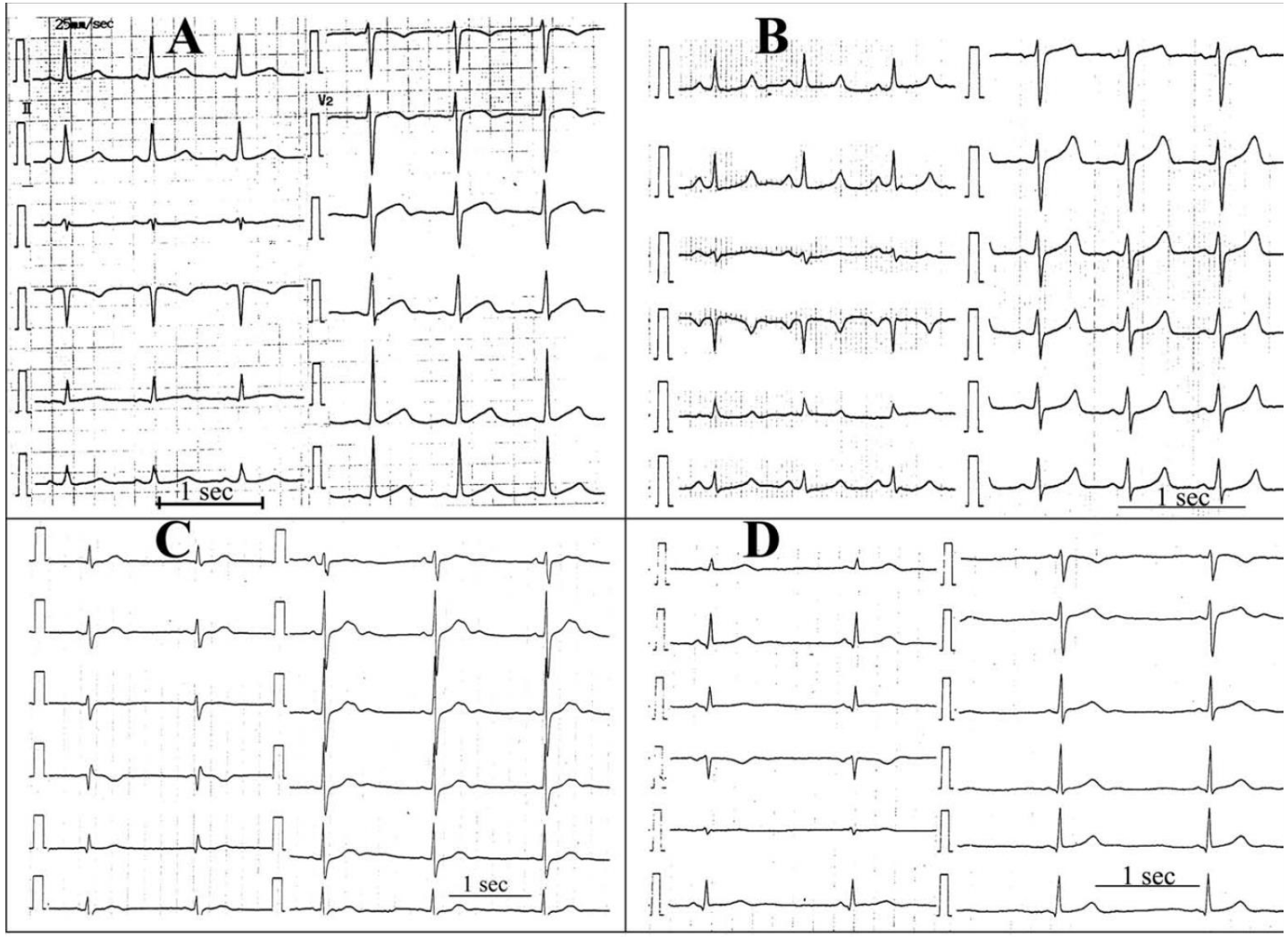


Giudicessi JR et al. Mayo Clinic Proceedings. 2020. https://doi.org/10.1016/j.mayocp.2020.03.024

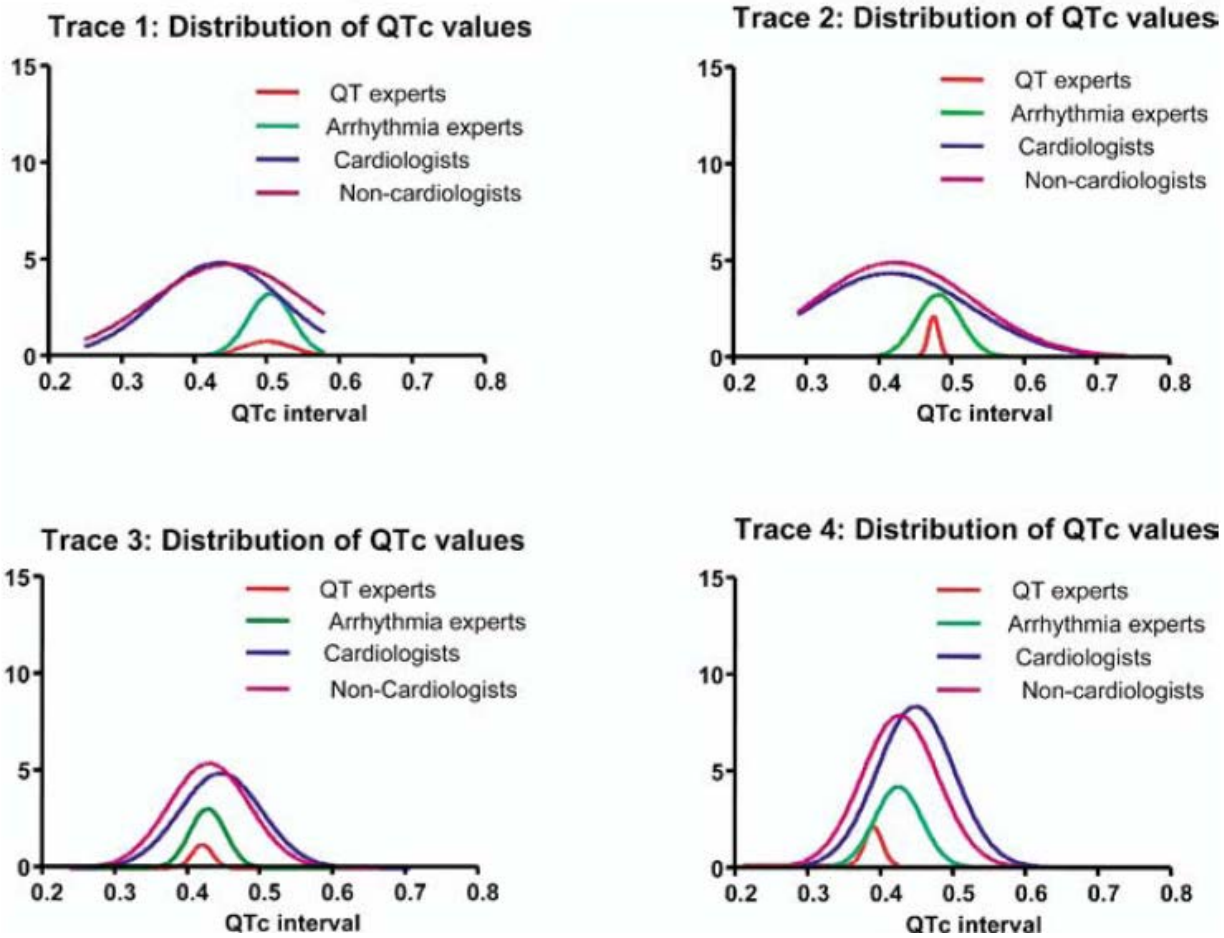
Long QT syndrome and COVID-19: QTc measurement

Appropriate QTc measurement

Inaccurate electrocardiographic interpretation of long QT: The majority of physicians cannot recognize a long QT when they see one



Viskin S et al. Heart Rhythm 2005; 2:569-574



Correct classification of QTc intervals

1. LQTS:
   - >80% arrhythmia experts
   - <50% cardiologists
   - <40% non-cardiologists
2. Normal ECGs:
   - 96% QT experts
   - 62% arrhythmia specialists
   - <25% of cardiologists and non-cardiologists

Interobserver agreement (Kappa coefficients)

- LQTS experts: 0.82
- Arrhythmia experts: 0.44
- Cardiologists: 0.3
- Non-cardiologists: 0.3

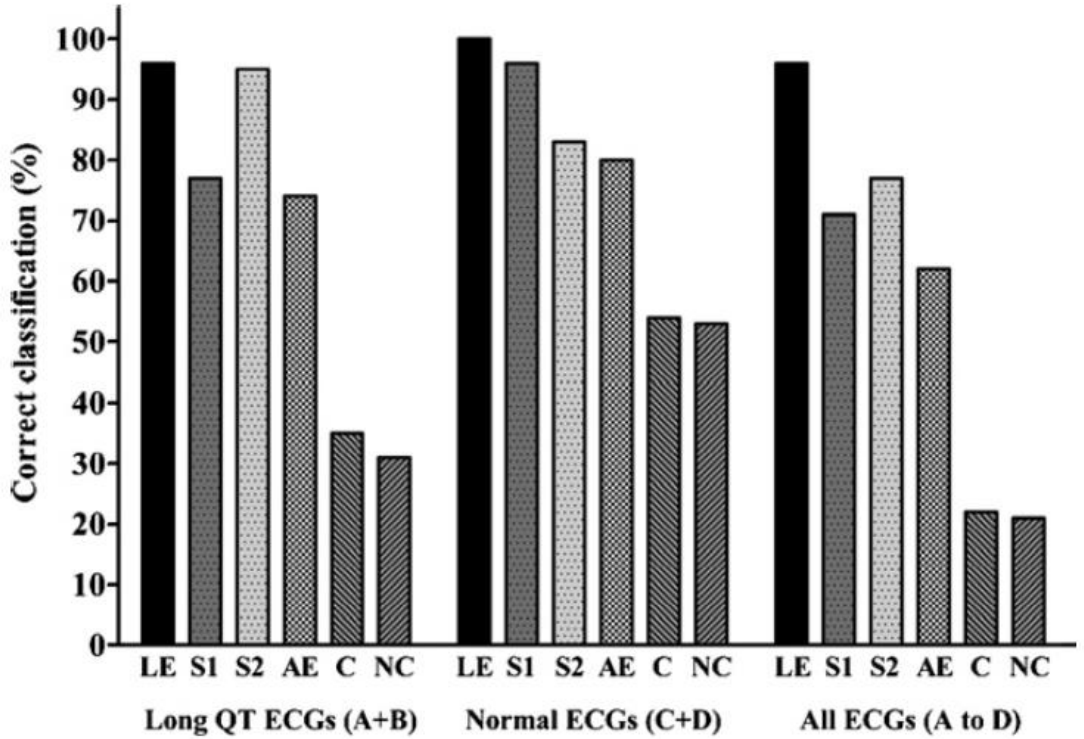
Viskin S et al. Heart Rhythm 2005; 2:569-574

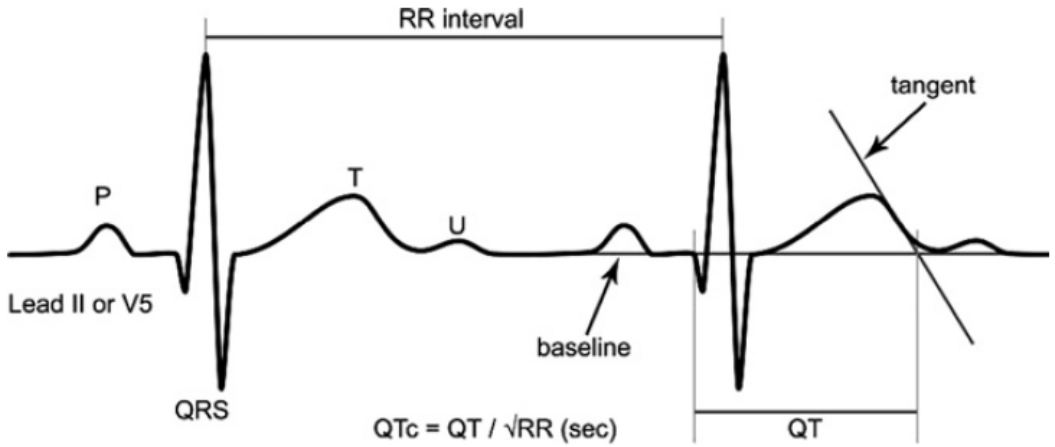
Accurate electrocardiographic assessment of the QT interval: Teach the tangent

Pieter G. Postema, MD, Jonas S.S.G. De Jong, MD, Ivo A.C. Van der Bilt, MD,
Arthur A.M. Wilde, MD, PhD

$$QTc(Bazett) = \frac{QT}{\sqrt{RR}}$$

$$QTc(Fridericia) = \frac{QT}{\sqrt[3]{RR}}$$



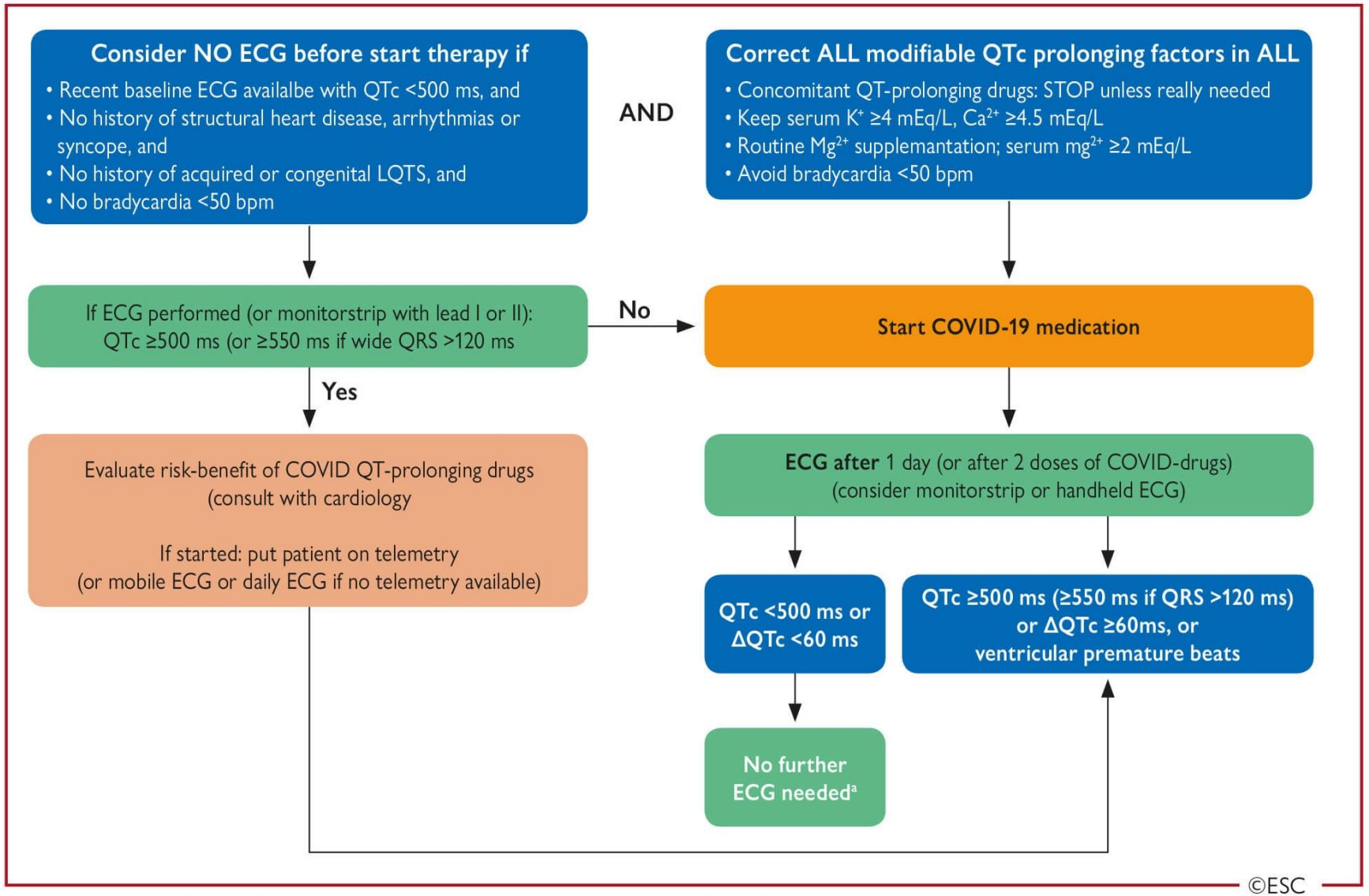


Interobserver agreement (Kappa coefficients)

- Students: 0.82 and 0.78
- LQTS experts: 0.82
- Arrhythmia experts: 0.44
- Cardiologists: 0.3
- Non-cardiologists: 0.3

Postema PG et al. Heart Rhythm 2008;5:1015-1018.

COVID-19: Recommendations to prevent QTc prolongation and *TdP*



[a]As long as the patient is clinically stable (e.g. no pronounced vomiting, diarrhoea, signs/symptoms of heart failure or deterioration of respiratory or other organ function).

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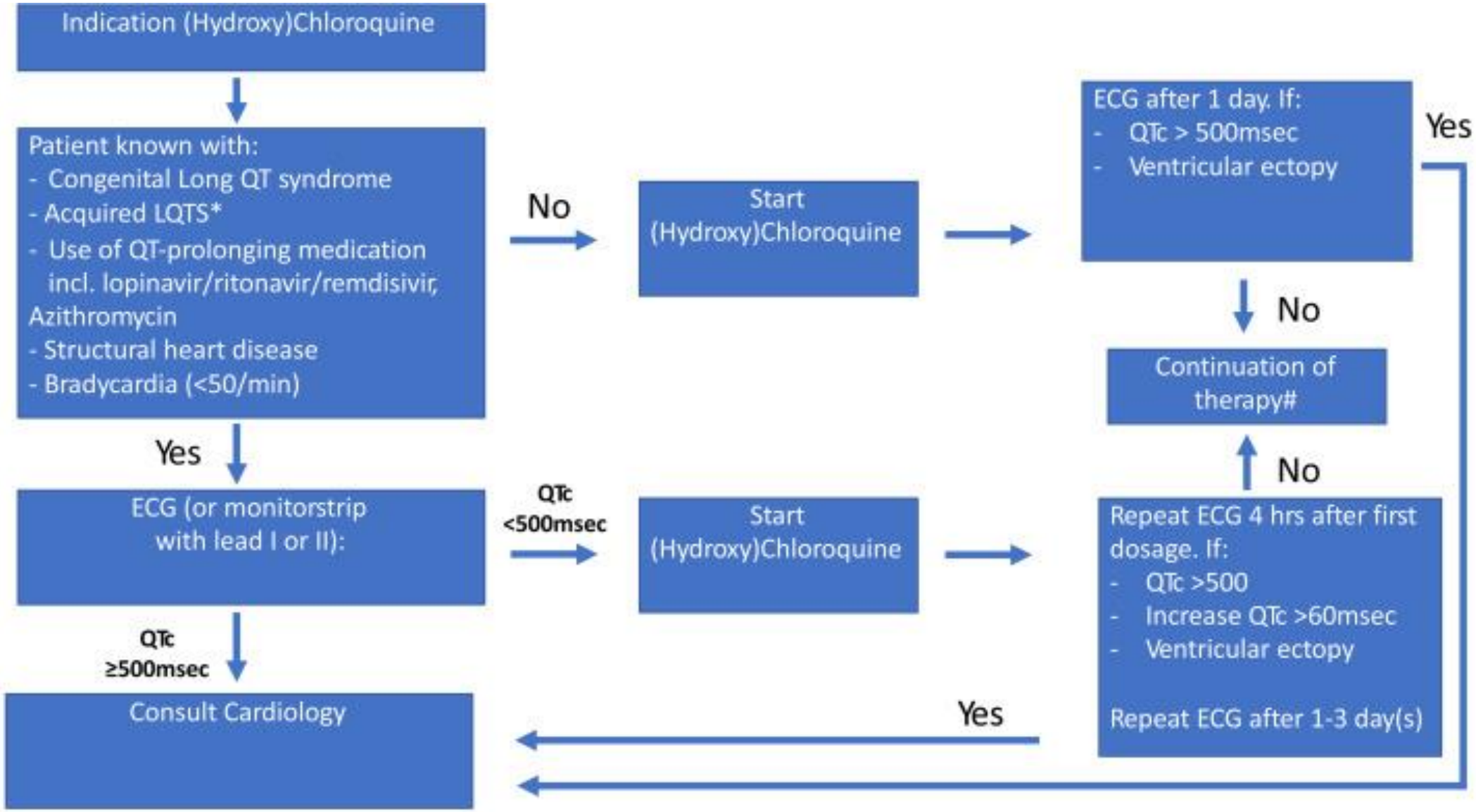
https://www.escardio.org/Education/COVID-19-and-Cardiology/ESC-COVID-19-Guidance

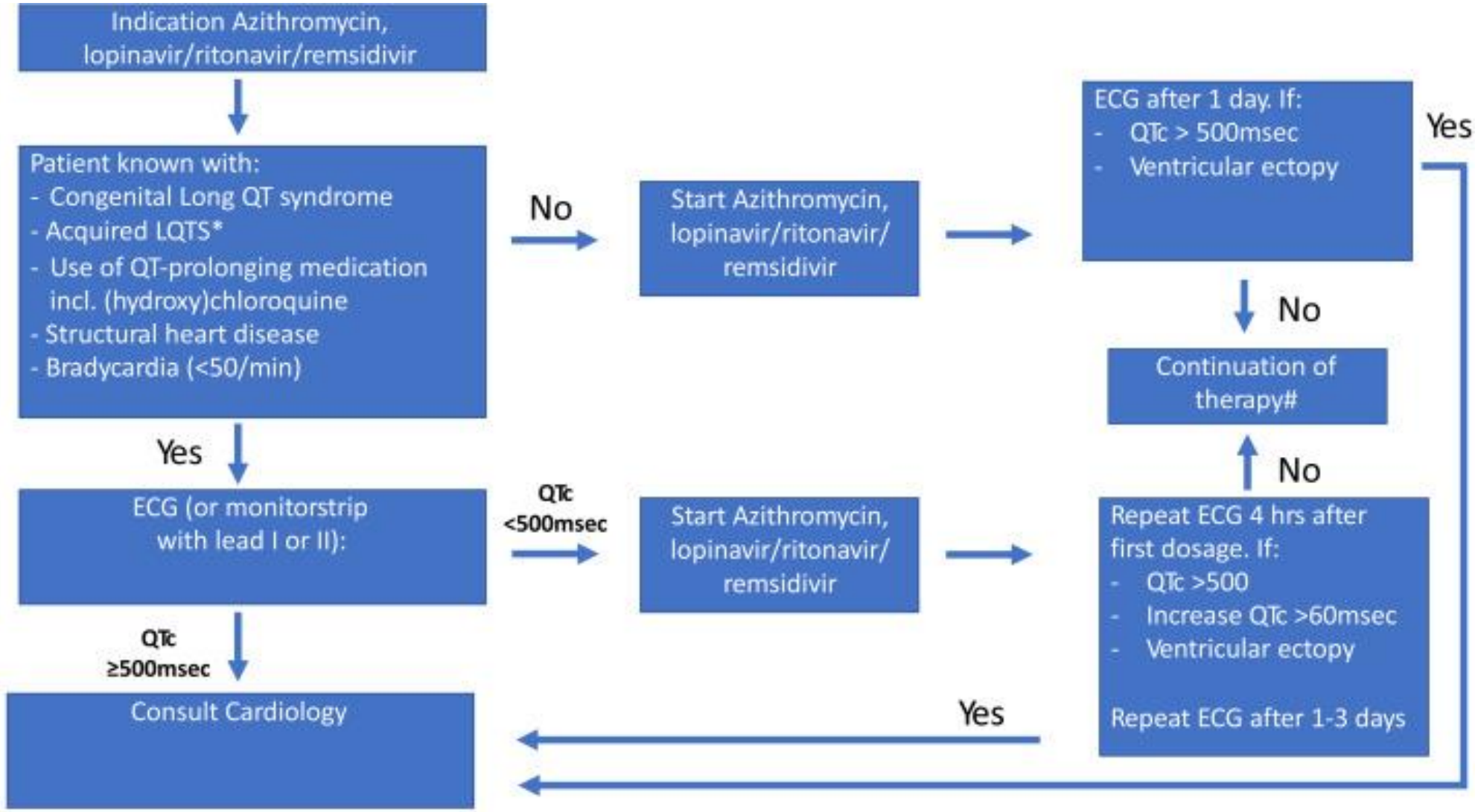
COVID-19 and cLQTS: Recommendations to prevent QTc prolongation and *TdP*



*: earlier QTc prolongation with medication; #: if ventricular ectopy, arrhythmia, dizziness or loss of consciousness: consult cardiology

Wu C-I et al. Heart Rhythm. 2020. Accepted – in press. https://doi.org/10.1016/j.hrthm.2020.03.024

COVID-19 and cLQTS: Recommendations to prevent QTc prolongation and *TdP*



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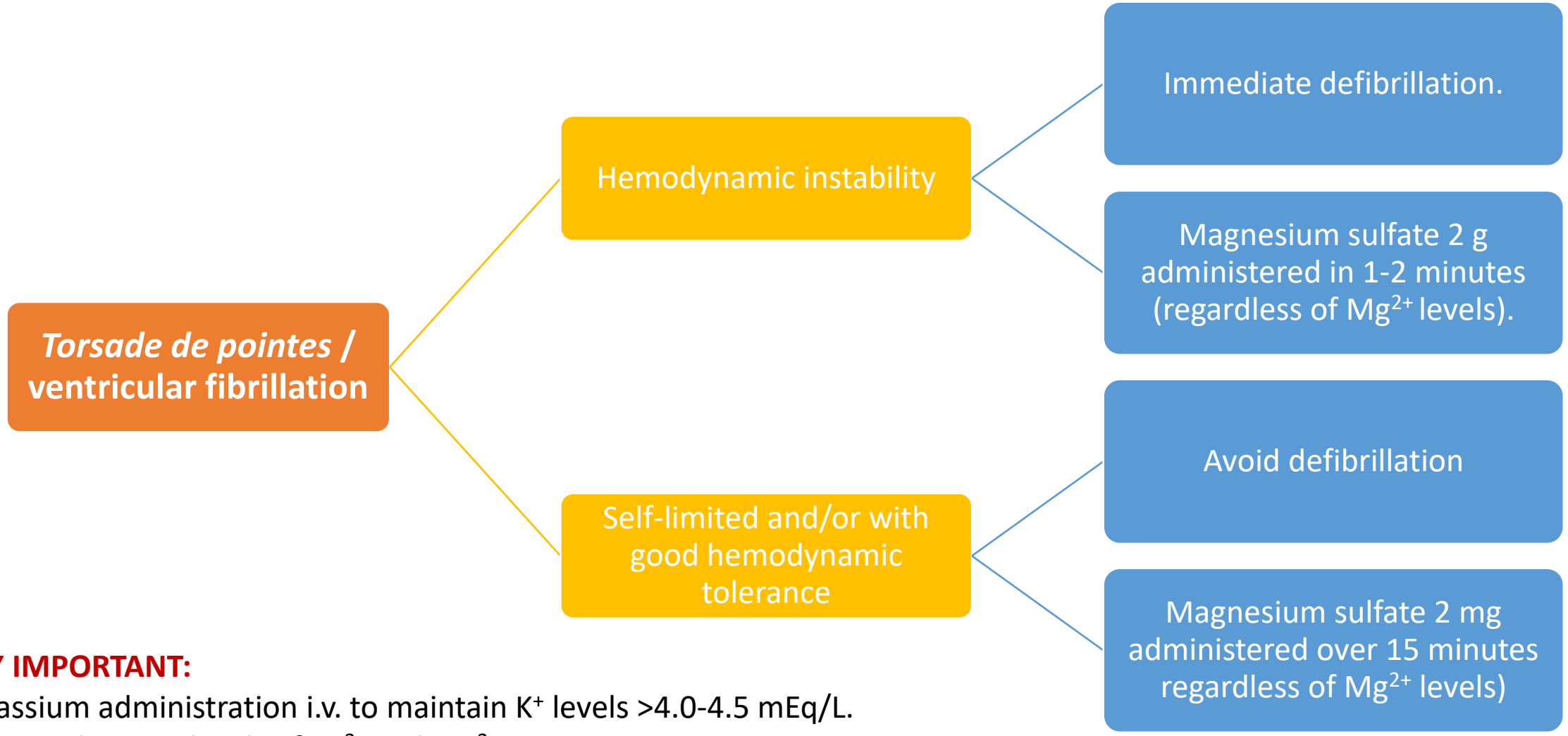
Wu C-I et al. Heart Rhythm. 2020. Accepted – in press. https://doi.org/10.1016/j.hrthm.2020.03.024

Management of sustained or recurring TdP/VF due to QTc prolongation

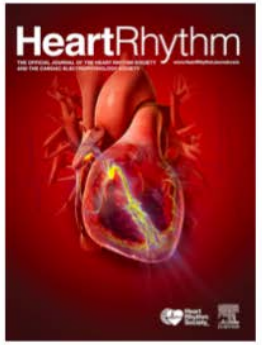


VERY IMPORTANT:

- Potassium administration i.v. to maintain K^+ levels >4.0-4.5 mEq/L.
- Ensure adequate levels of Ca^{2+} and Mg^{2+}
- Discontinue causing drugs as well as those that favor the presence of bradycardia.
- In case of non-control with the previous measures, consider temporary transvenous stimulation at frequencies >100 bpm until resolution of the QTc prolongation (isuprel an alternative but **NOT** in cLQTS)

Recommended reading

Journal Pre-proof



SARS-CoV-2, COVID-19 and inherited arrhythmia syndromes

Cheng-I. Wu, MD, Pieter G. Postema, MD, PhD, Elena Arbelo, MD, PhD, Elijah R. Behr, MBBS, MD, Connie R. Bezzina, PhD, Carlo Napolitano, MD, PhD, Tomas Robyns, MD, Vincent Probst, MD, PhD, Eric Schulze-Bahr, MD, PhD, Carol Ann Remme, MD, PhD, Arthur A.M. Wilde, MD, PhD.

PII: S1547-5271(20)30285-X

DOI: https://doi.org/10.1016/j.hrthm.2020.03.024

Reference: HRTHM 8332

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European Society of Cardiology › Education › COVID-19 and Cardiology

COVID-19 and Cardiology

ESC Guidance for the Diagnosis and Management of CV Disease during the COVID-19 Pandemic

Last updated on 21 April 2020

CLÍNIC BARCELONA Hospital Universitari

>2000 patients treated for COVID-19

GENERAL RECOMMENDATIONS TO PREVENT PROARRHYTHMIA
1. Correction of predisposing factors for QTc prolongation/TdP in ALL patients: a. Minimize non-essential drugs that potentially prolong QTc (www.qtdrugs.org) and/or significant drug interactions (UpToDate – Lexicomp®). b. Correction of ionic alterations at the level of K +, Mg2 + and Ca2 + (preferably maintain K + ≥4 mEq/L) **2. Measurement of baseline QTc on ECG (12-lead, telemetry strip or mobile device)*:** a. If the baseline QTc is ≤500 ms (or ≤550 ms in the presence of bundle branch block) the risk of proarrhythmia is low. b. If the baseline QTc is> 500 ms (or> 550 ms in the presence of bundle branch block), assess risk-benefit. **3. QTc measurement under ECG treatment (telemetry strip or mobile device):** a. If the baseline QTc is ≤500 ms (or ≤550 ms in the presence of bundle branch block) the risk of proarrhythmia is low. b. If the baseline QTc is> 500 ms (or >550 ms in the presence of bundle branch block), assess correctable factors and/or treatment adjustment.
**Can be skipped if no risk factor for QTc prolongation: cLQTS, prior aLQTS, structural heart disease, bradycardia <50 bpm*

It is important to adjust the monitoring needs according to the individual risk of QTc prolongation considering comorbidities (particularly, if they suffer from congenital long QT) and associated drugs.

ERN GUARD-Heart

European Reference Network for Rare and Low Prevalence Complex Diseases of the Heart

COVIDAR

CAPACITY

https://capacity-covid.eu

EHRA

European Heart Rhythm Association

European Society of Cardiology

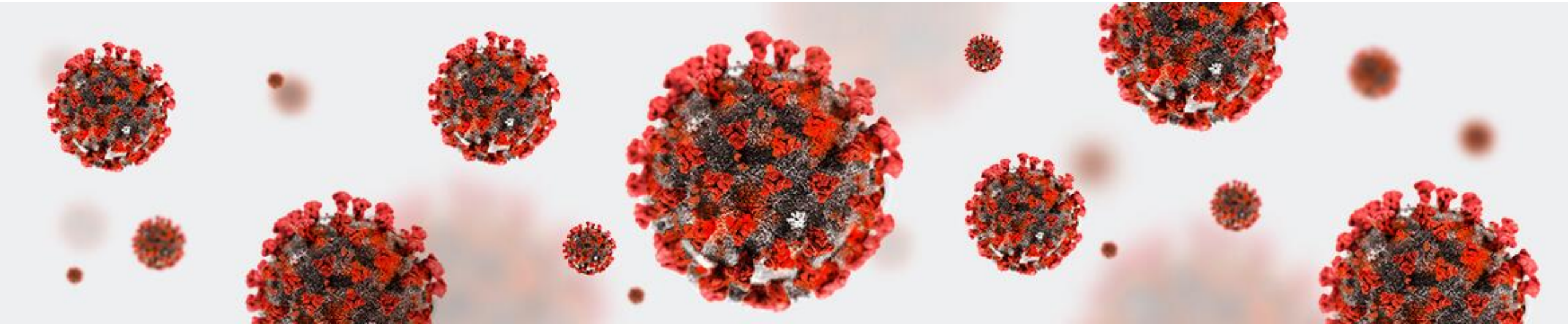
ECGen: European Cardiac Arrhythmia Genetics Focus Group of EHRA

European Reference Networks

GOBIERNO DE ESPAÑA
MINISTERIO DE ECONOMÍA, INDUSTRIA Y COMPETITIVIDAD
Instituto de Salud Carlos III

UNIÓN EUROPEA
Fondo Europeo de Desarrollo Regional

"Una manera de hacer Europa"



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