PRESENT
AND FUTURE
APPROACHES TO
THE CONTROL OF
DYSLIPIDAEMIAS

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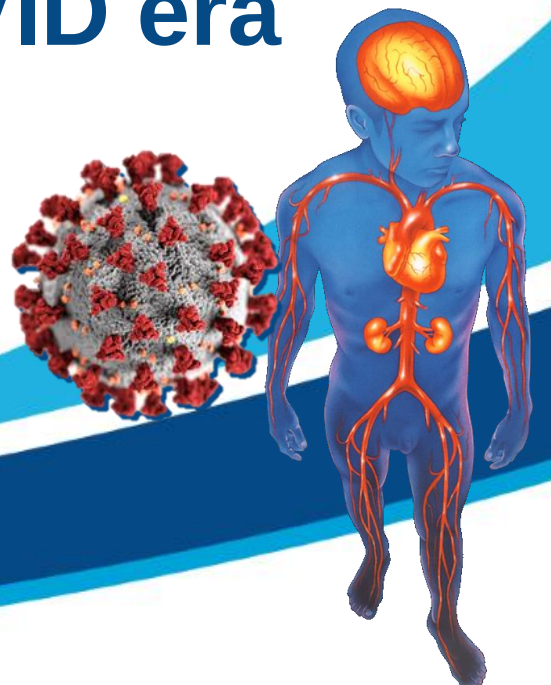
DYSLIPIDAEMIAS

Lipids and atherosclerosis in the COVID era

Lale Tokgözoğlu, MD, FACC, FESC
Professor of Cardiology
Hacettepe University, Ankara, Turkey
President, European Atheroscleoris Society

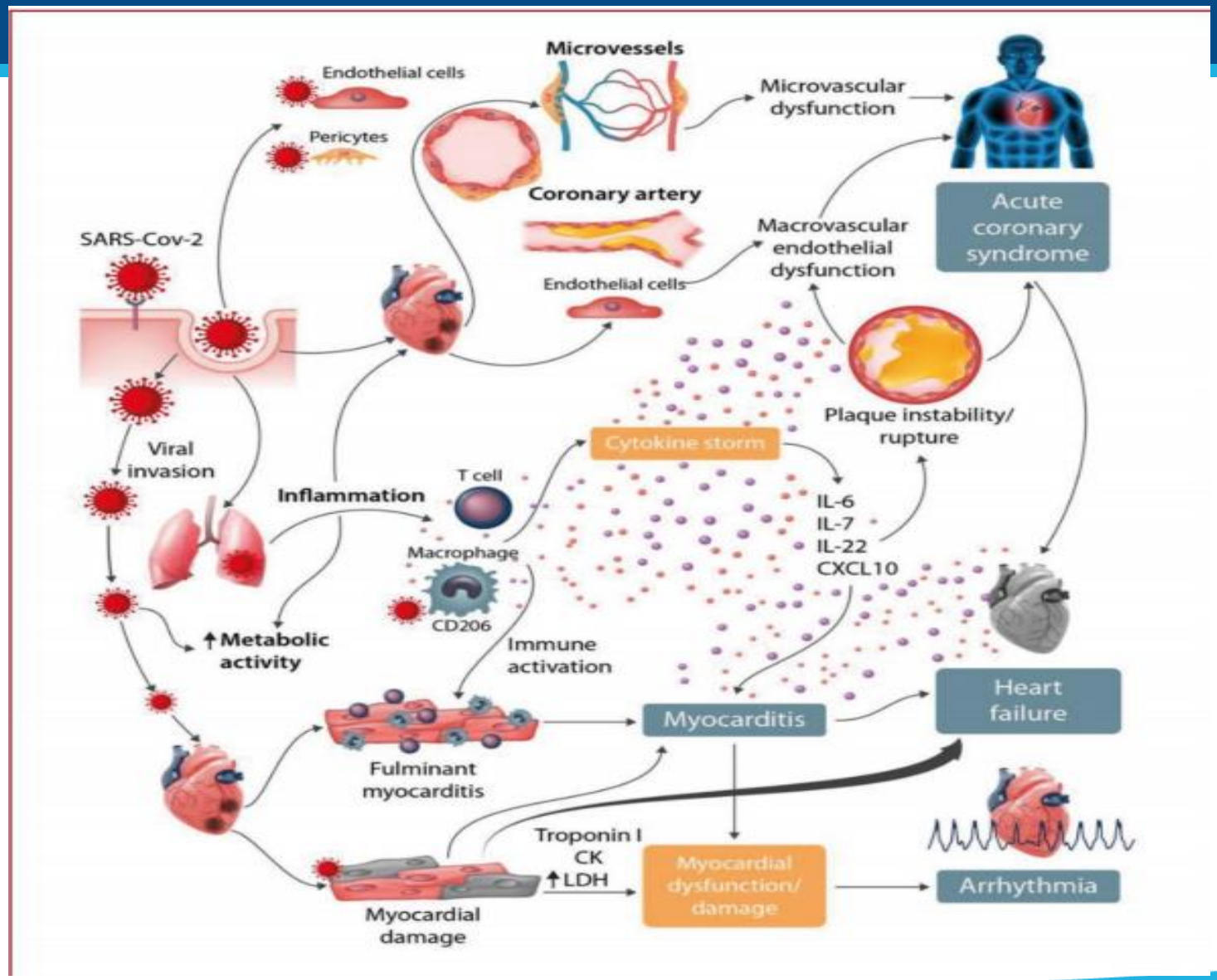


Disclosure of potential conflicts of interest

Lale Tokgözoğlu - Hacettepe University Hospitals, Ankara, Turkey

EMPLOYEMENT	None
RESEARCH GRANT / RESEARCH SUPPORT	Amgen
SPEAKER BUREAU	None
HONORARIA	Abbott,Actelion,Astra,Amgen,Bayer,Daiichi-Sankyo MSD,Mylan,Novartis, Novo Nordisk, Pfizer,Recordati, Sanofi,Sanovel,Servier
EXPERT WITNESS	None
OWNERSHIP INTEREST	None
CONSULTANT/ ADVISORY BOARD	Abbott, Bayer, Daiichi-Sankyo, Mylan, Novartis, Sanofi
OTHER	None

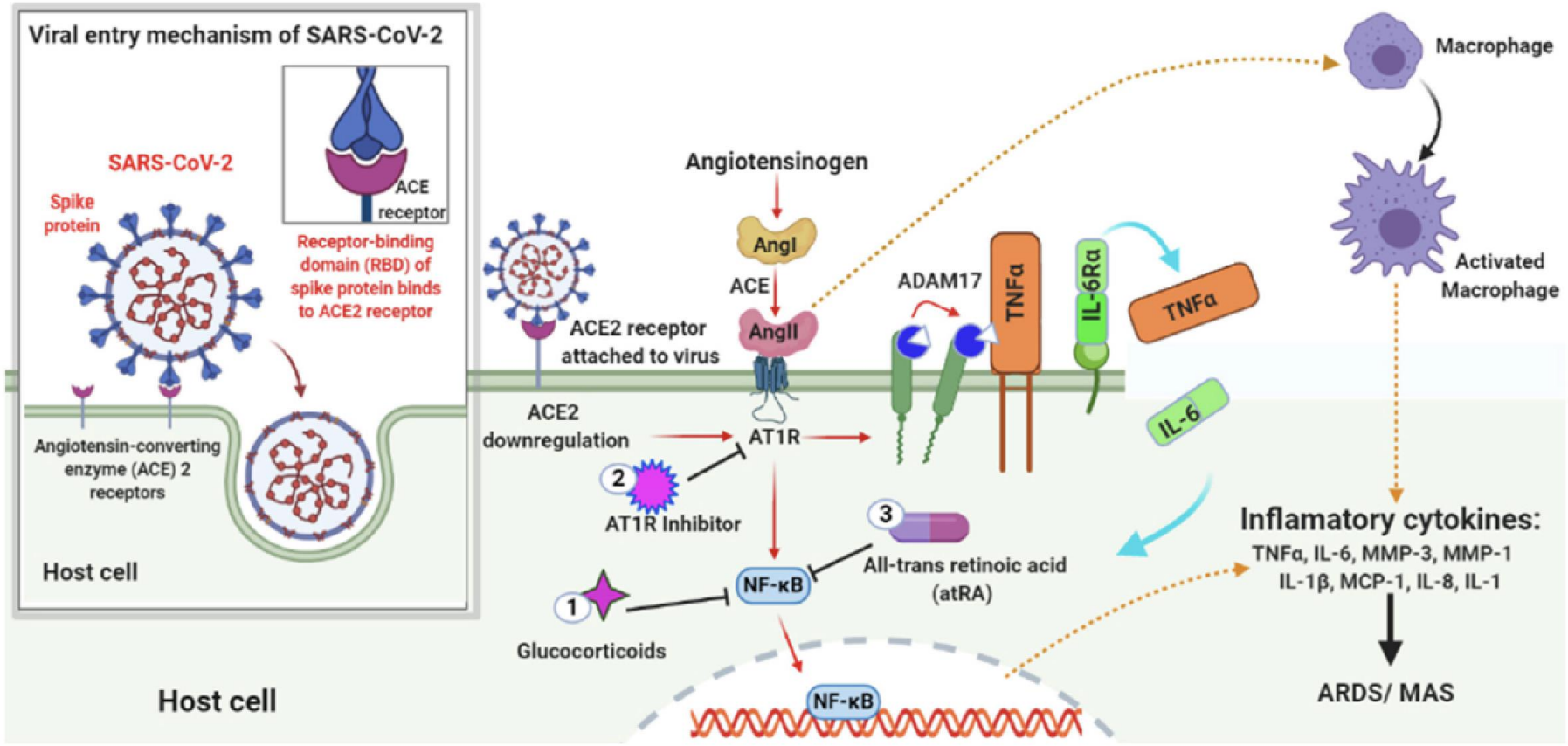
COVID-19 had a significant effect on CV health



- Systemic disease affecting endothelium,triggering inflammation and thrombosis
- Leading to multiorgan failure
- Leading to CV complications
- Patients with ASVD have increased risk of inflammation and thrombosis

SARS-Cov-2 enters endothelial,epithelial,myocardial cells via ACE2 receptor

N. Banu, et al. Life Sciences 256 (2020) 117905



Macrophage activation system

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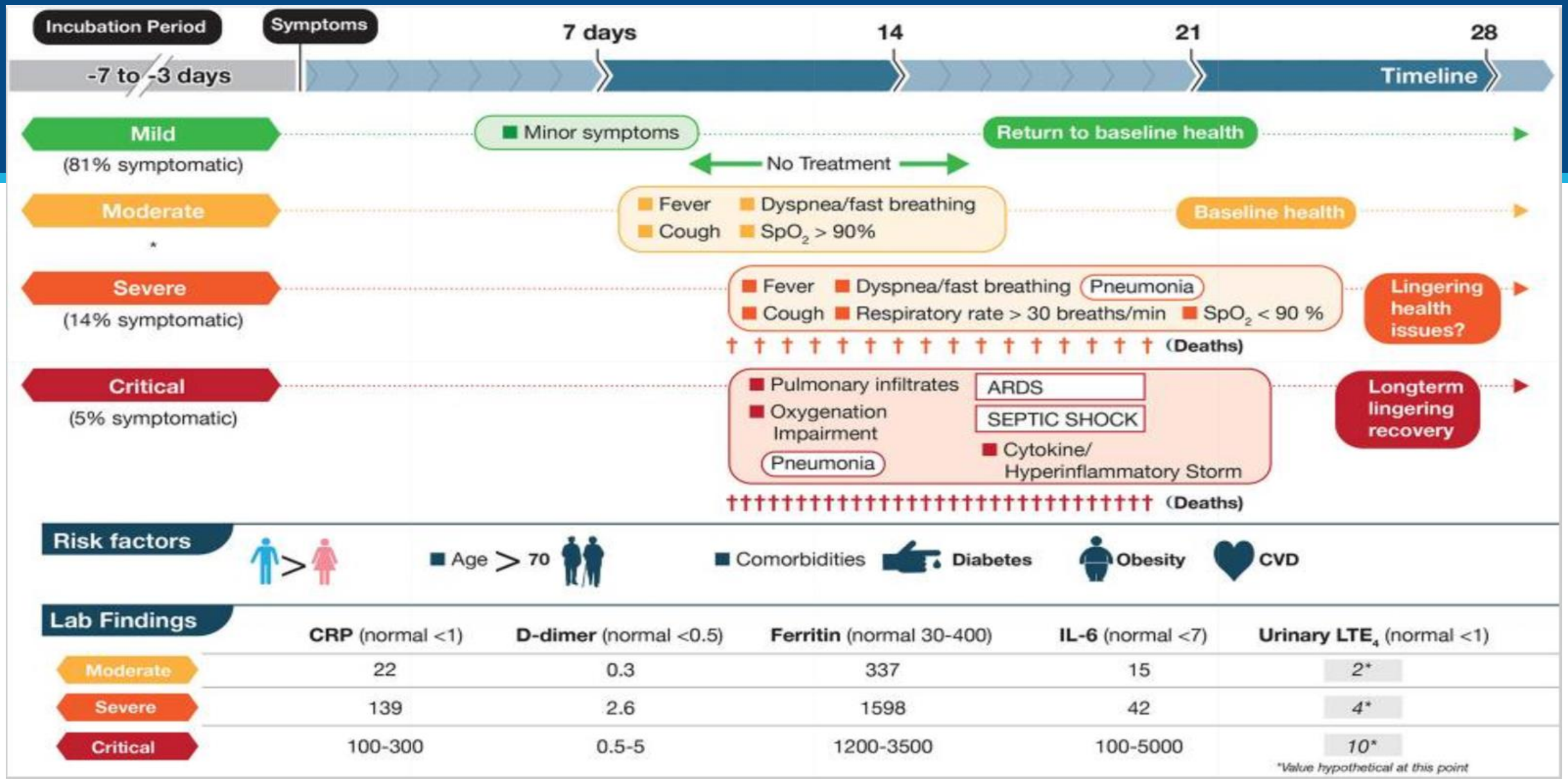

Funk et al. Front Pharmacol. 2020 Aug 6;11:1214

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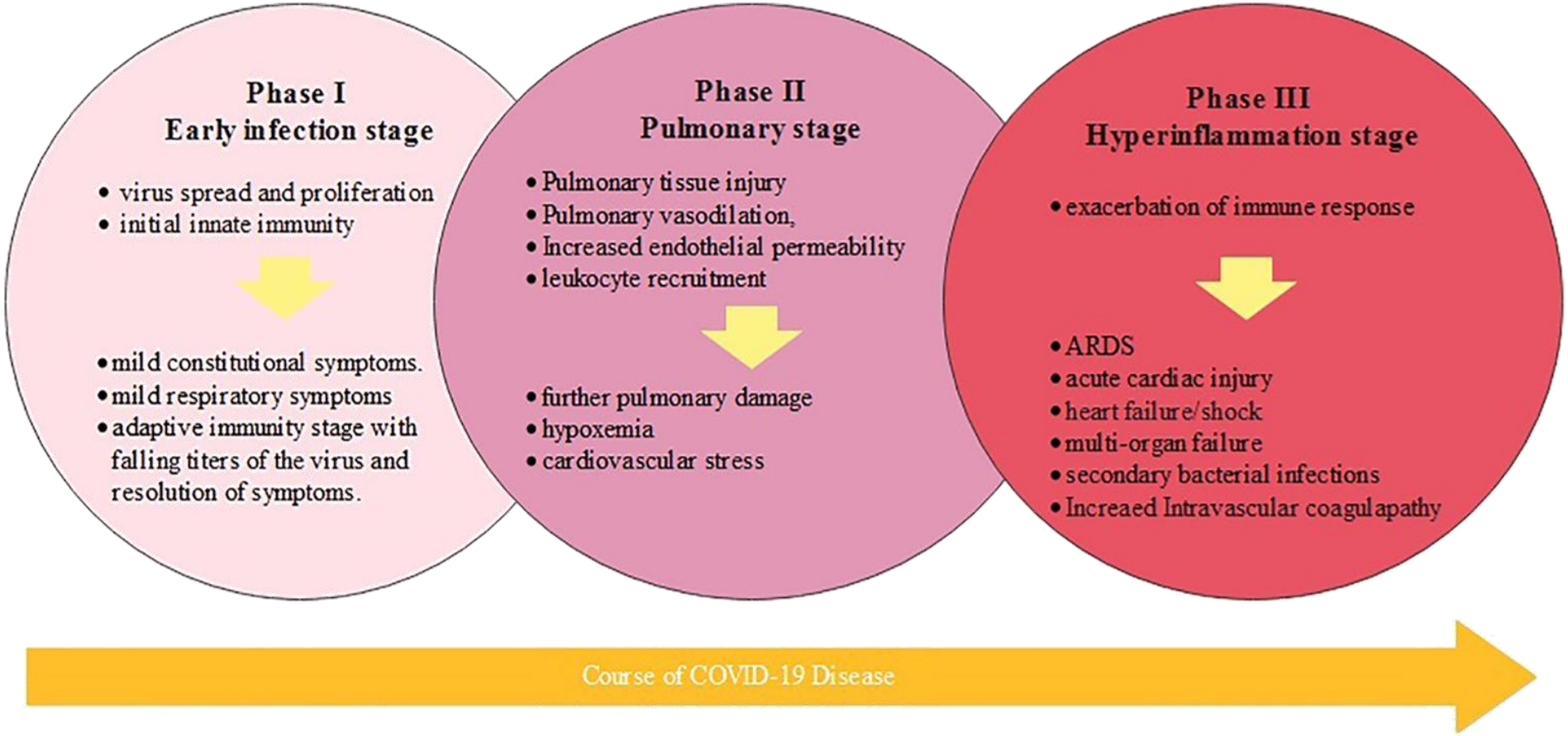
COVID-19 and the Heart:

Progression of COVID-19 infection



Clinical Cardiology, First published: 12 June 2020, DOI: (10.1002/clc.23406)

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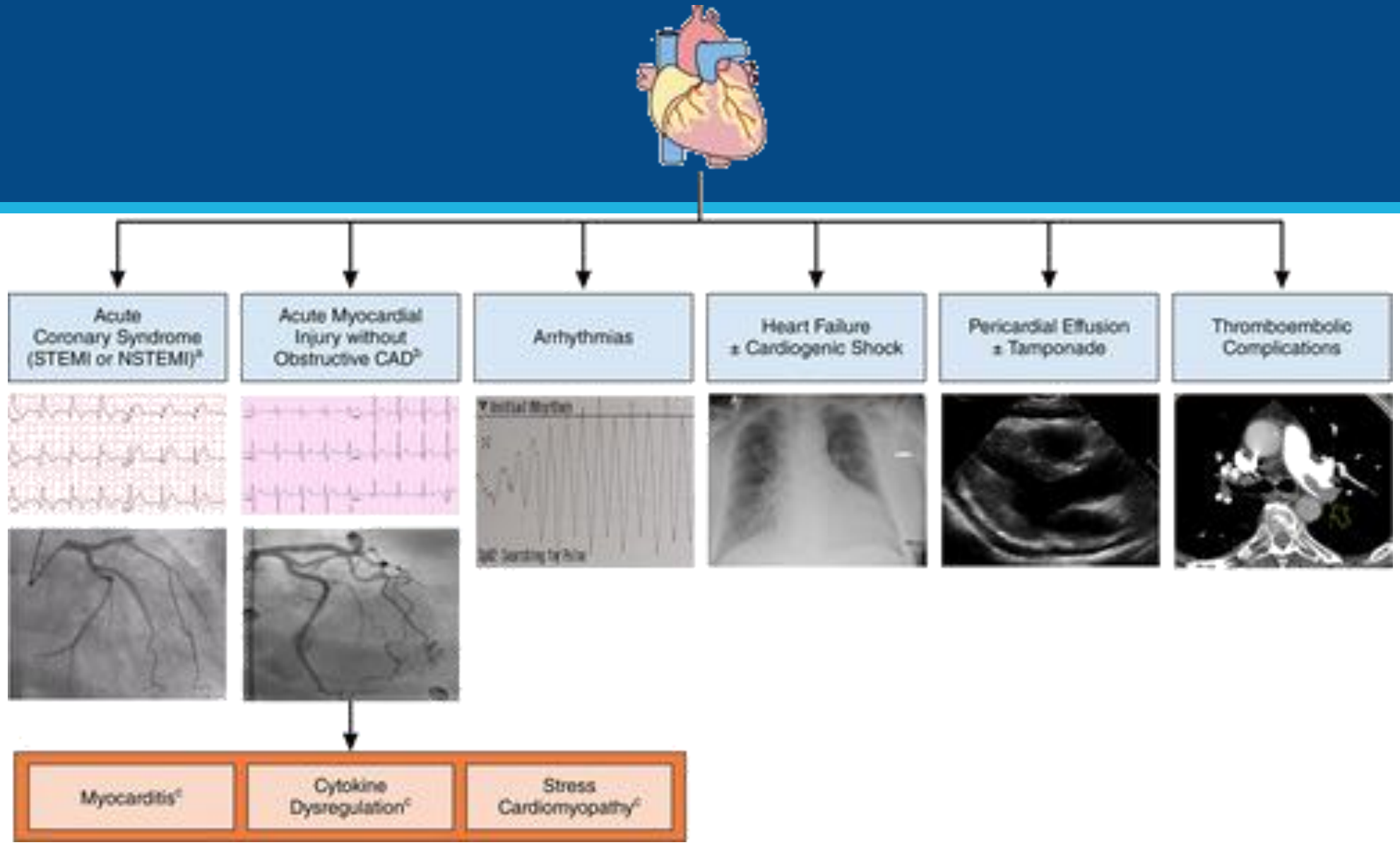

Nicholas S. Hendren. Circulation. Description and Proposed Management of the Acute COVID-19 Cardiovascular Syndrome, Volume: 141, Issue: 23, Pages: 1903-1914, DOI: (10.1161/CIRCULATIONAHA.120.047349)

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Patients with Atherosclerotic Vascular Disease and COVID-19:

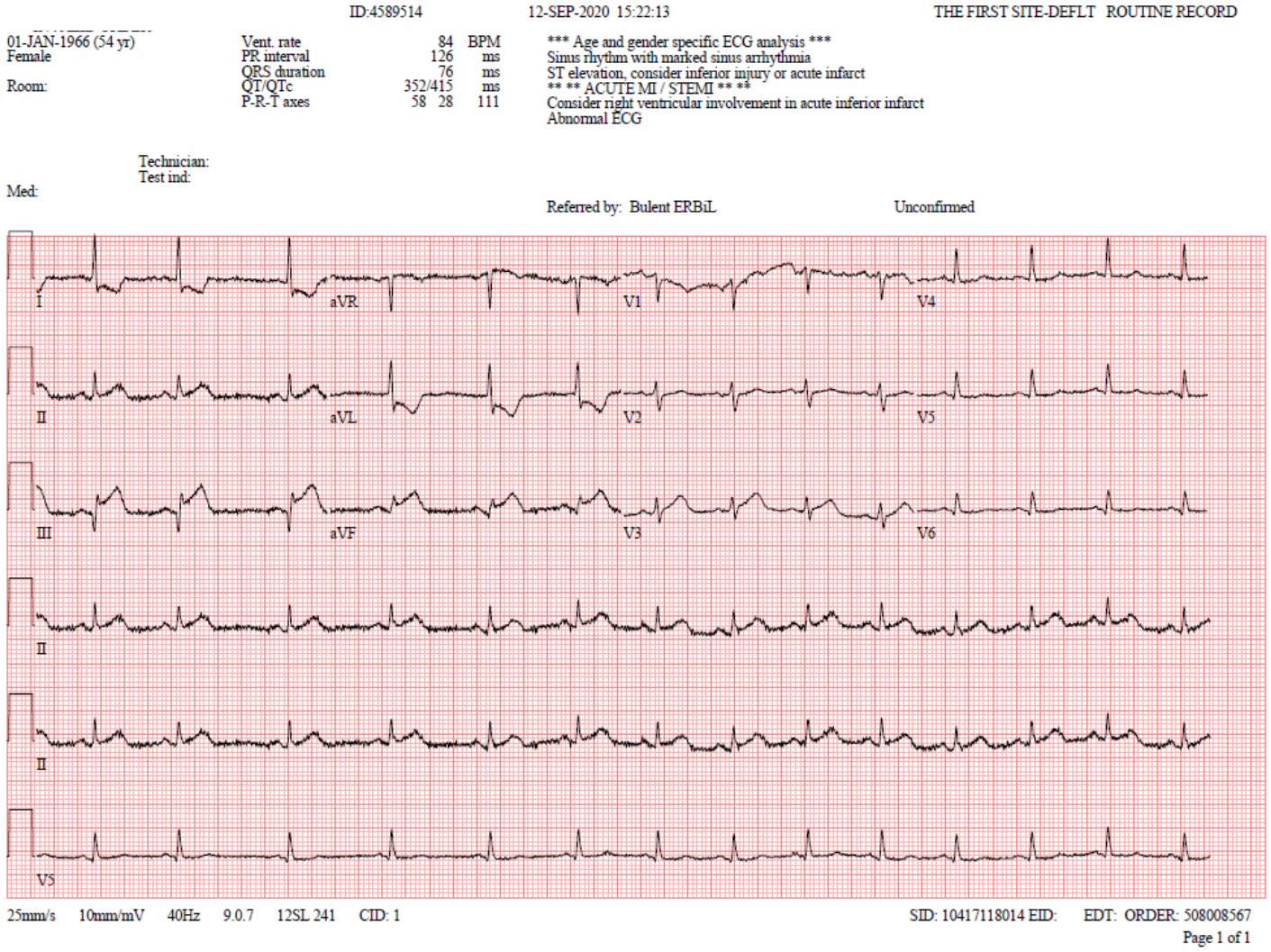
Direct risk:

- Higher risk of infection
- Higher risk of complications
- Risk from drug interactions

Collateral damage:

- Unhealthy lifestyle
- Less access to healthcare
- Less willingness to seek healthcare

- 54 yo female, Chest Pain
- No risk factors
- PCR +
  - TROPONIN-ı: 80,8 ng/L
- APTT, INR, D-DIMER normal
- BNP : 54,6 pg/mL



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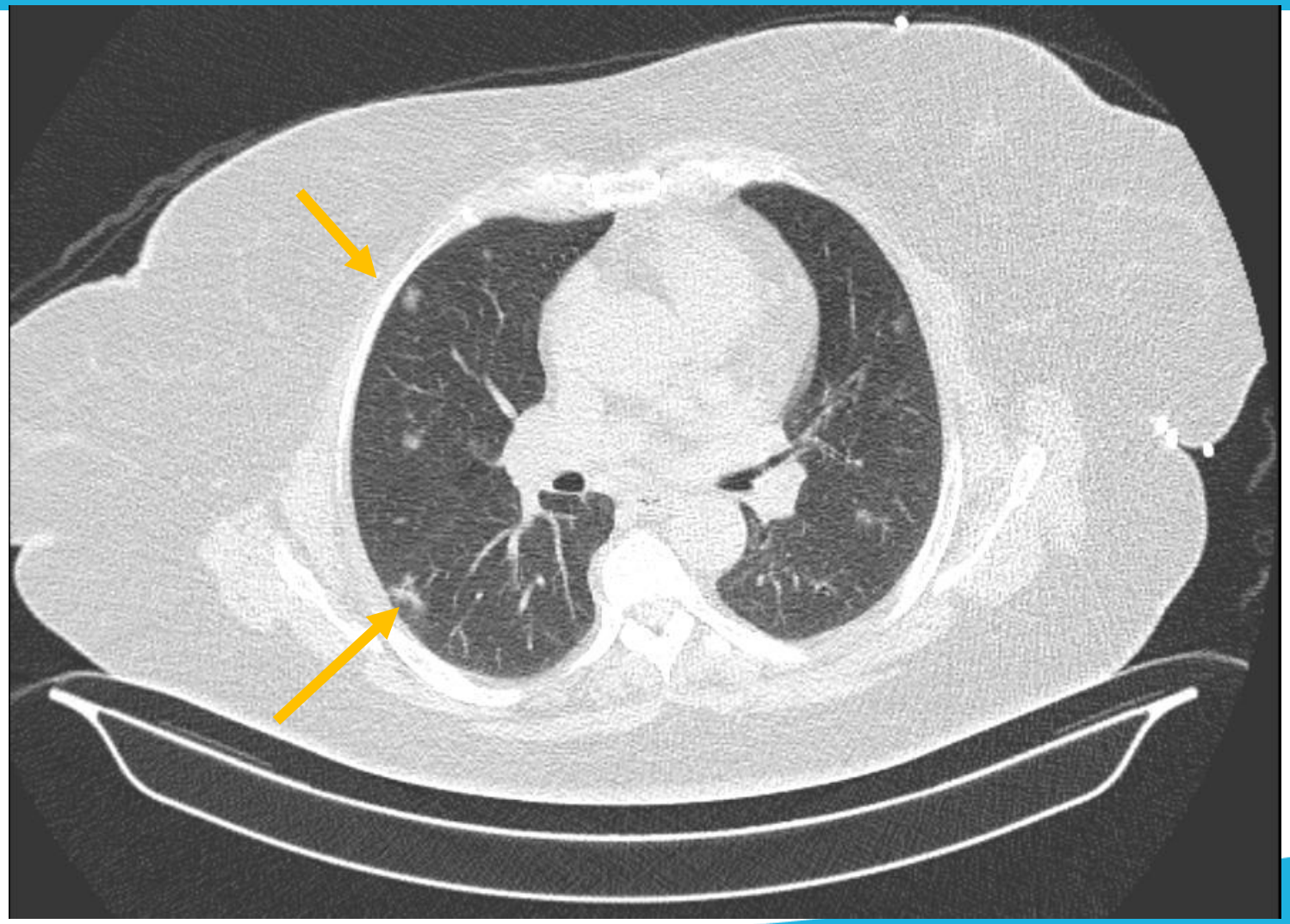
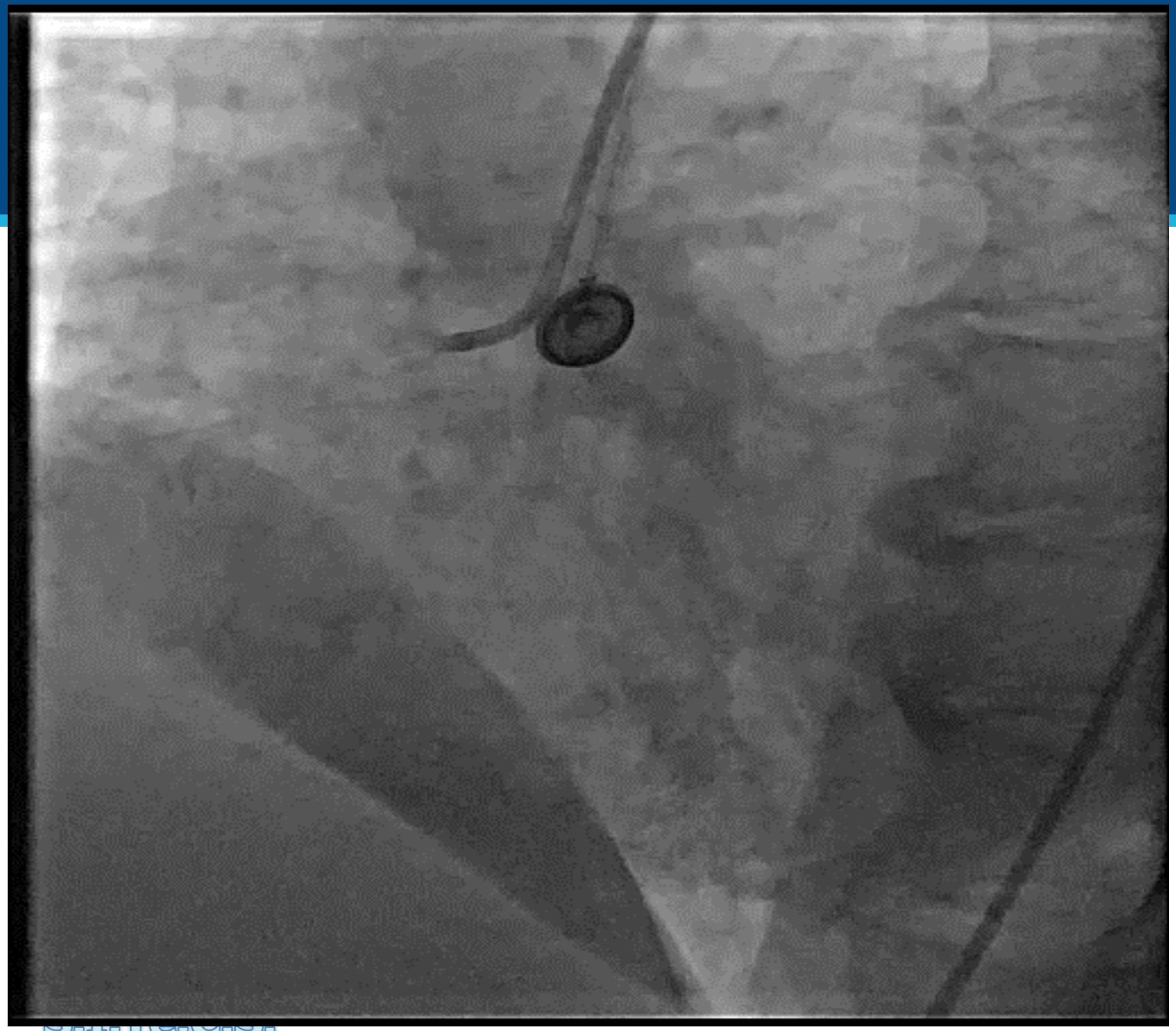
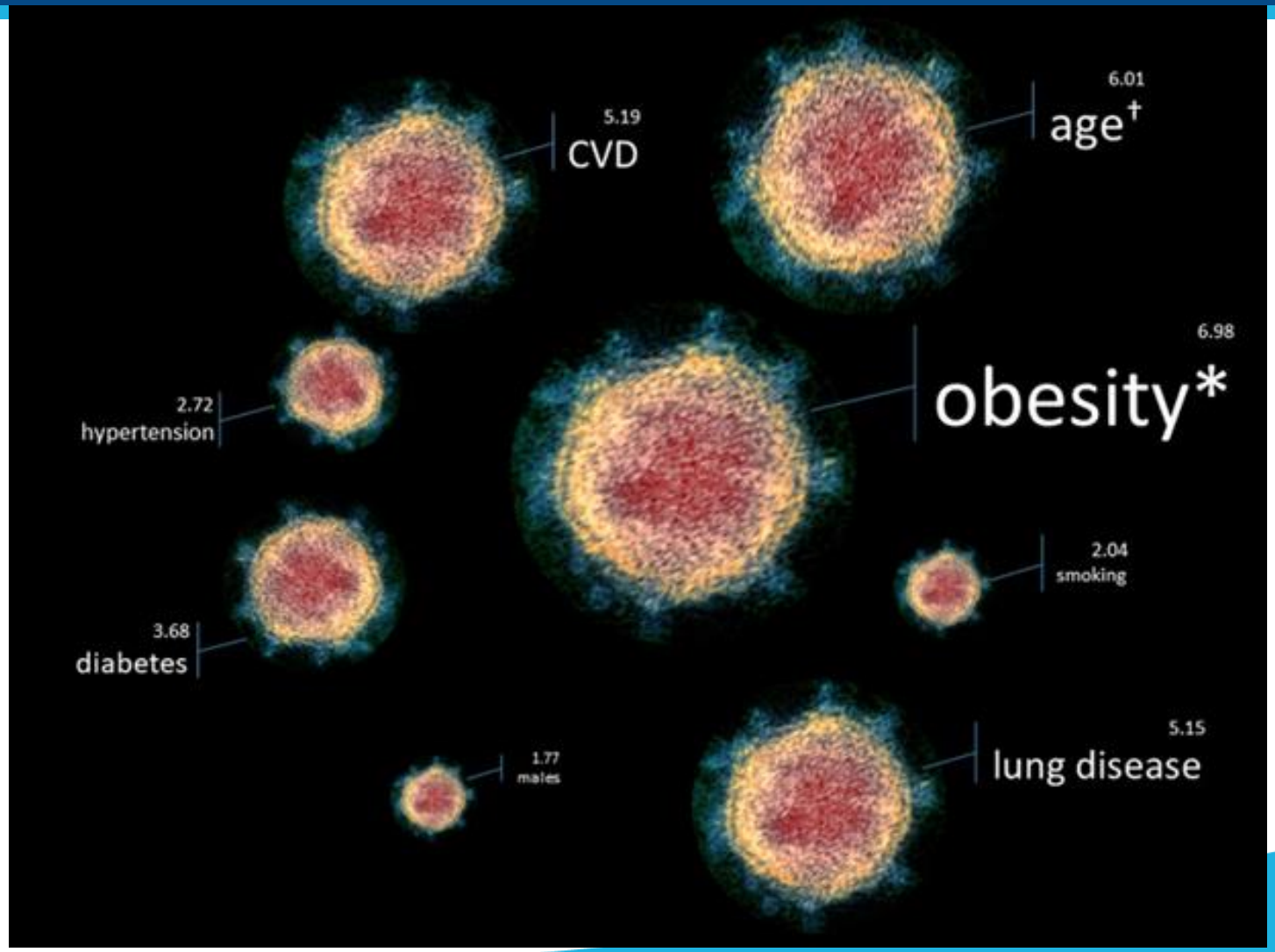




- PCI
- Favipravir
- Anticoagulation

Patients with ASVD and Risk Factors Have Worse Outcome (OR)

- Obesity 6.98
- Age 6.01
- CVD 5.19
- Lung disease 5.15
- Diabetes 3.68
- Hypertension 2.72
- Smoking 2.04
- Male 1.77



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Clin Obes. 2020;10:e12403.

Cholesterol and COVID-19 Relation:

Low LDL increases mortality vs cholesterol accelerates disease

The role of high cholesterol in age-related COVID19 lethality.

Hao Wang[1,2,3], Zixuan Yuan[1,2,3], Mahmud Arif Pavel[1,2], Scott B. Hansen[1,2,*]

Original Article

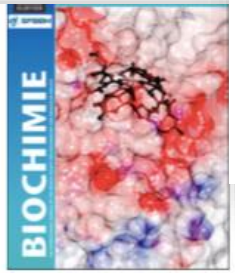
Hypolipidemia is associated with the severity of COVID-19

Xiuqi Wei, MD[#], Wenjuan Zeng, MD[#], Jingyu Su, MD, Huimin Wan, MD, Xinqin Yu, MD, Xiaoling Cao, MD, PhD, Wenbin Tan, MD, PhD[*,†], Hui Wang, MD[**,†]

Department of Laboratory Medicine, Cancer Center, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, P.R. China (Drs Wei, Su, Wan, and Yu); Department of Laboratory Medicine, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, P.R. China (Drs Zeng and Wang); Department of Cell Biology and Anatomy, School of Medicine, University of South Carolina, Columbia, SC, USA (Dr Cao and Tan); and Department of Biomedical Engineering, College of Engineering and Computing, University of South Carolina, Columbia, SC, USA (Dr Tan)

The endosomal lipid bis(monoacylglycero) phosphate as a potential key player in the mechanism of action of chloroquine against SARS-COV-2 and other enveloped viruses hijacking the endocytic pathway

Frédéric Carrière, Sonia Longhi, Michel Record



Potential COVID-19 therapeutics from a rare disease: Weaponizing lipid dysregulation to combat viral infectivity

Stephen L. Sturley[1,*], Tamayanthi Rajakumar[2], Natalie Hammond[2], Katsumi Higaki[3], Zsuzsa Márka[4], Szabolcs Márka[4], and Andrew B. Munkacsi[2,*]

[1]Department of Biology, Barnard College, 3009 Broadway, New York, NY 10027; [2]School of Biological Sciences and Centre for Biodiscovery, Victoria University of Wellington, Wellington, New Zealand 6012; [3]Division of Functional Genomics, Tottori University, Yonago, Japan 683-8503; [4]Department of Physics, Columbia University, 538 West 120th Street, 1009 Pupin, MC 5229, Box 29, New York, NY, 10027.

Cholesterol: A new game player accelerating vasculopothy caused by SARS-CoV-2?

Xiaoling Cao,[1] Rong Yin,[1] Helmut Albrecht,[2,3] Daping Fan,[1,4] and Wenbin Tan[1,4]

[1]Department of Cell Biology and Anatomy, School of Medicine, University of South Carolina, Columbia, South Carolina, USA

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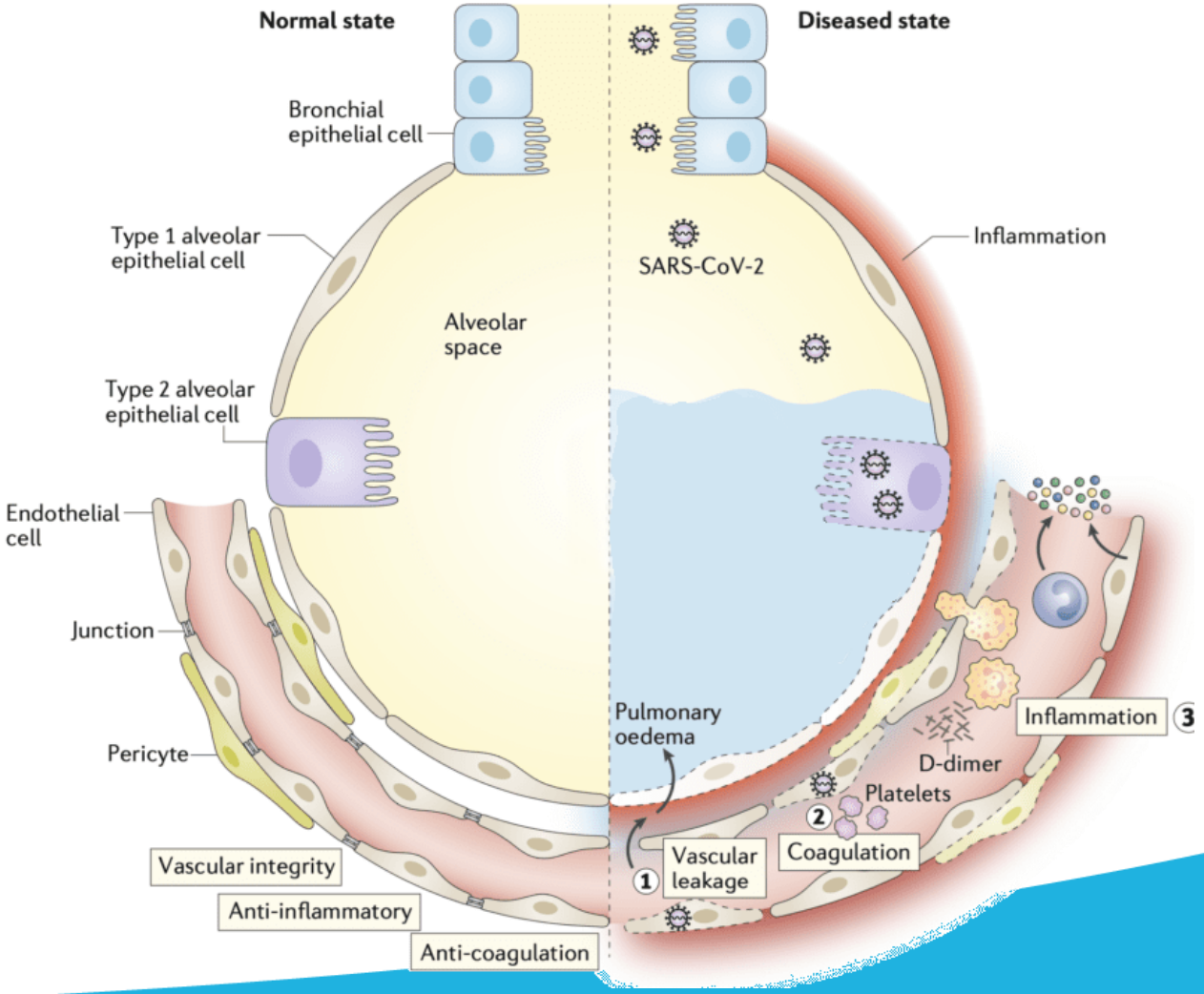
LLT and COVID:

- About 20 % of pts have HLP
- Hypolipidemia associated with severity of COVID: Lipid parameters often fall in cytokine-mediated inflammation as a consequence of the acute phase response rather than having a causative or pathological contribution towards infection.
- Statins may reduce proinflammatory cytokine release
- Previous reports suggested possible benefit of statin use in patients with viral pneumonias and MERS

Endothelium Plays a Key Role in COVID:

1. Oedema/Vasoplegia
2. Pathologic coagulation (Venous>Arterial)
3. Uncontrolled cytokine release

- Inflammation of the endothelium could explain the systemic impaired microcirculatory function in different vascular beds and their clinical sequelae in patients with COVID-19.



Nature Reviews Immunology 2020; 20: 389–391

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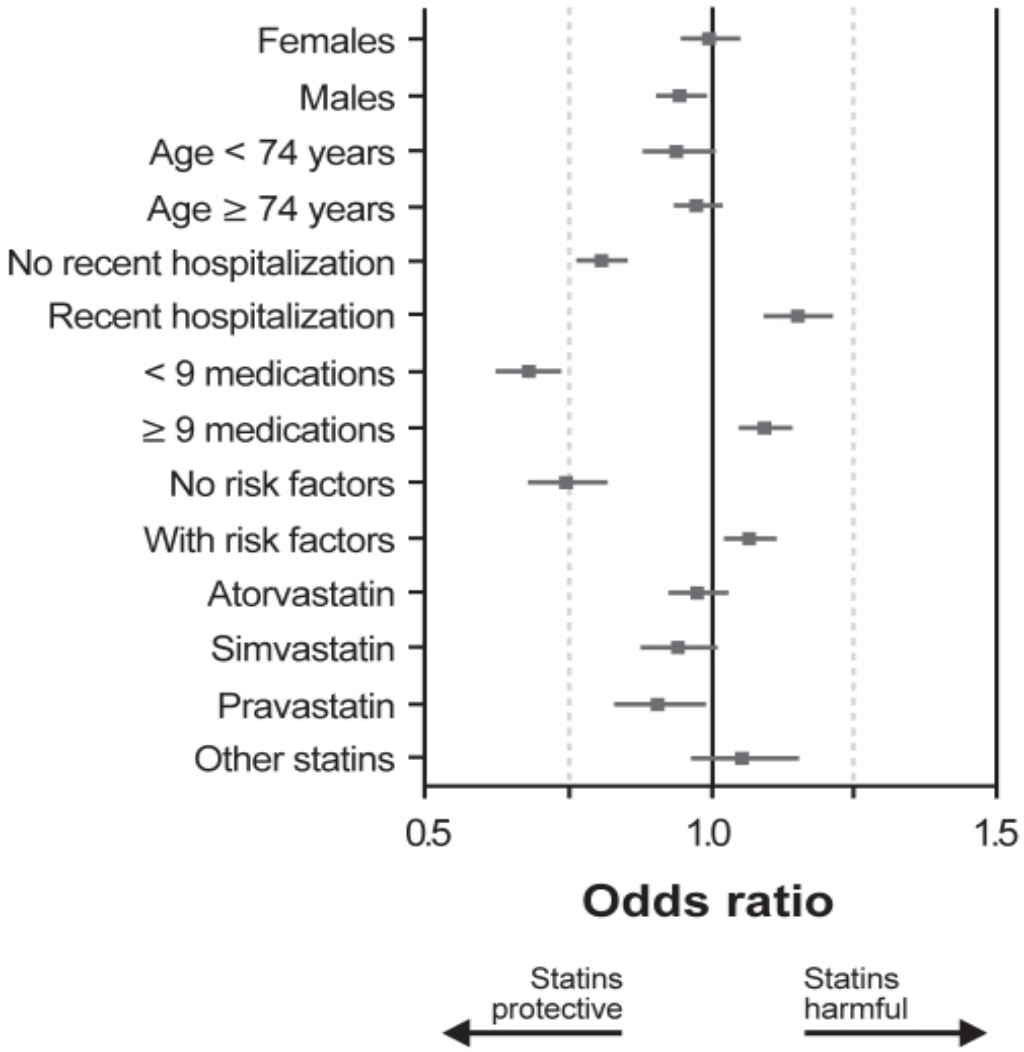
LLT in Viral Pneumonia:

- **Population-based cohort study over 10 influenza seasons, n= 2,240,638 patients**
  - **Half of whom received statins.**
- **Odd ratios for statin use and pneumonia hospitalization with patients not treated**
- **Statin use was associated with a statistically significant but minimal protective effect**

- **Statins might inhibit SARS-CoV-2 entry into host cells by directly binding the main protease of the coronavirus.**



Kwong JC et al. PLOS ONE 2009
Reiner et al., Arch. Med. Sci. 2020

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International Journal of Infectious Diseases 96 (2020) xxx–xxx

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Perspective

Potential role of statins in COVID-19

Ken Cheah Hooi Lee*, Duu Wen Sewa, Ghee Chee Phua

Department of Respiratory and Critical Care Medicine, Singapore General Hospital

ARTICLE INFO

Article history:
Received 12 May 2020
Received in revised form 27 May 2020
Accepted 28 May 2020

ABSTRACT

Patients with COVID-19 infection have an increased risk of cardiovascular complications and thrombotic events. Statins are known for their pleiotropic anti-inflammatory, antithrombotic and immunomodulatory effects. They may have a potential role as adjunctive therapy to mitigate endothelial dysfunction and dysregulated inflammation in patients with COVID-19 infection.

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Highlights

- Statins have anti-inflammatory effects including augmentation of ACE2 expression.
- Statins have an antithrombotic effect.
- Statins may improve endothelial function in patients with COVID-19 infection.

conversion of angiotensin II (AT II) to angiotensin-(1-7). AT-(1-7) opposes the effects induced by AT II, which left unopposed lead to increased oxidative stress, inflammation, and fibrosis.

Infection with SARS-CoV-2 causes downregulation of ACE2. This increases vulnerability to the damaging effects of AT II, which is thought to be responsible for the lung injury that is seen in many COVID-19 patients. The dual roles played by ACE2 as a protector against the harmful effects of the hyperinflammatory response

In-Hospital Use of Statins Is Associated with a Reduced Risk of Mortality among Individuals with COVID-19:

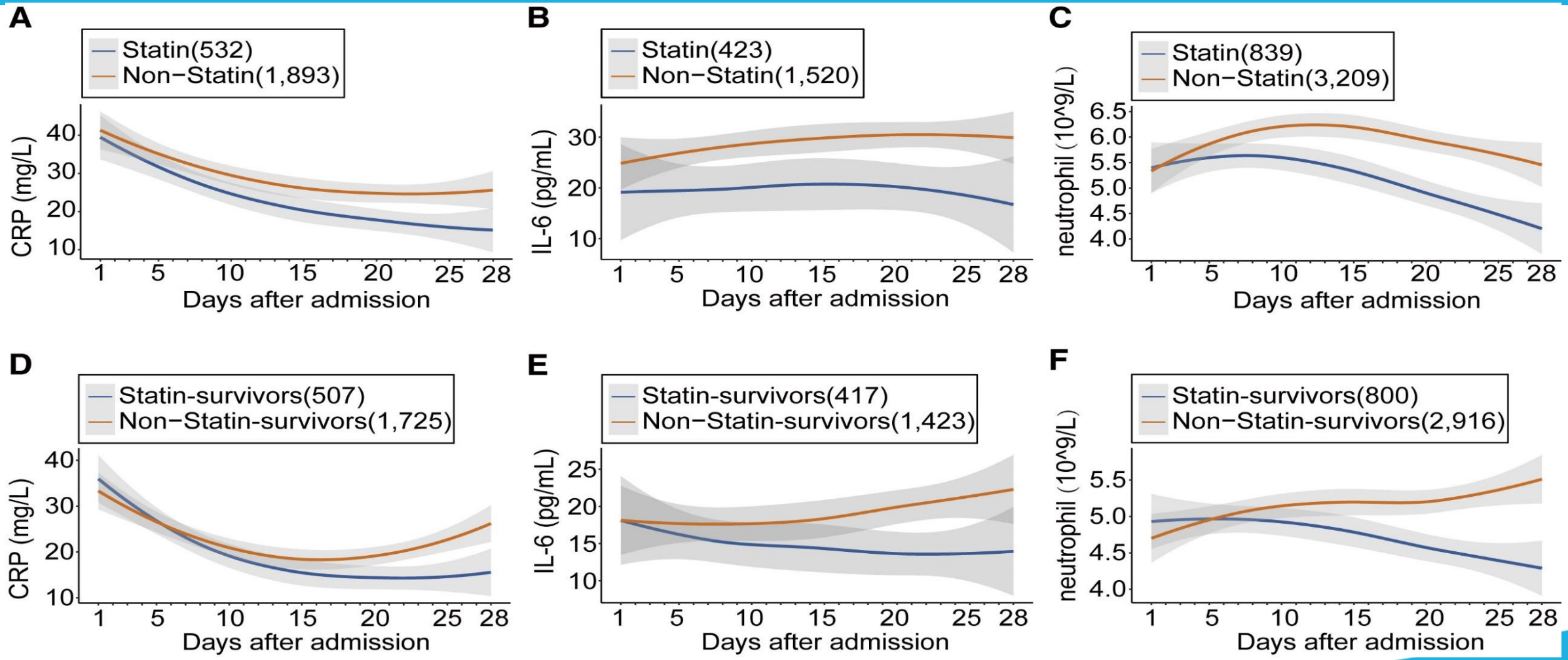
A total of 13,981 cases of confirmed COVID-19 admitted in 21 hospitals from Hubei Province, China.

- **1,219 on statins**
- **12,762 were not on statins**

Comorbidities	Statin	No statin	P value
COPD, n (%)	15 (1.2%)	138 (1.1%)	0.738
Hypertension, n (%)	993 (81.5%)	3,867 (30.3%)	<0.001
Diabetes, n (%)	414 (34.0%)	1,868 (14.6%)	<0.001
Coronary heart disease, n (%)	442 (36.3%)	729 (5.7%)	<0.001
Cerebrovascular disease, n (%)	107 (8.8%)	296 (2.3%)	<0.001
Chronic liver disease, n (%)	17 (1.4%)	268 (2.1%)	0.119
Chronic kidney disease, n (%)	63 (5.2%)	398 (3.1%)	<0.001

Zhang et al. Cell Metabolism 2020.

Changes in Inflammation Markers:



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Zhang et al. Cell Metabolism 2020.

Lipid Lowering Therapy During COVID19 Pandemic:

- Patients treated for hyperlipidaemia should continue with their advised diet and lifestyle measures and should not interrupt their pharmacologic treatment because of the COVID-19 pandemic
- Not enough evidence to start statin just for anti-inflammatory effect

Lipid Lowering Therapy During COVID19 Pandemic:

Managing Hyperlipidaemia in Patients with COVID-19 and During its Pandemic: An Expert Panel Position Statement from HEART UK

Statins: Continue unless

- ALT or AST is greater than 3 times the upper limit of normal (1, B-R).
- Consider dose reduction/change to another statin if significant drug-drug interaction identified (1, C-LD).
- Clinical or biochemical evidence of myopathy or myositis (1, B-R).

Fibrates: Continue unless

- A significant drug-drug interaction identified (1, C-LD).
- ALT or AST is greater than 3 times the upper limit of normal (1, B-R).
- clinical or biochemical evidence and/or biochemical evidence of myopathy or myositis (1, B-R).
- Acute kidney injury (1, B-NR).

PCSK9 monoclonal antibodies: Continue unless:

- If critically ill patients (1, E-EO).
- If treatment is suspended or delayed, a further individualised risk vs. benefit assessment should be conducted to restart treatment soon after patient's condition has stabilised (1, B-NR).

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Atherosclerosis 313 (2020) 126–136

Selected Drugs That May Increase Risk of Myopathy and Rhabdomyolysis When Used Concomitantly With Statins:

CYP3A4 Inhibitors/Substrates	Others
Amiodarone	Digoxin
Azole antifungals (fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole)	Fibrates (gemfibrozil)
Calcium antagonists (mibefradil, diltiazem, verapamil)	Niacin
Ciprofloxacin	
Colchicine	
Danazol	
Fusidic acid	
*Grapefruit juice	
Hepatitis C drugs (boceprevir, telaprevir)	
HIV medications (amprenavir, atazanavir, cobicistat, darunavir, delavirdine, efavirenz, elvitegravir, etravirine, fosamprenavir, indinavir, lopinavir, maraviroc, nelfinavir, nevirapine, rilpivirine, ritonavir, saquinavir)	
Immunosuppressants (cyclosporine, tacrolimus, sirolimus)	
Macrolides (azithromycin, clarithromycin, erythromycin, telithromycin)	
Midazolam	
Nefazodone	
Sildenafil	
Sitagliptin	
Ticagrelor	
Warfarin	

Grapefruit: should be avoided in combination with lovastatin/simvastatin.

Expert Opin Drug Saf. 2018 Jan;17(1):25-37

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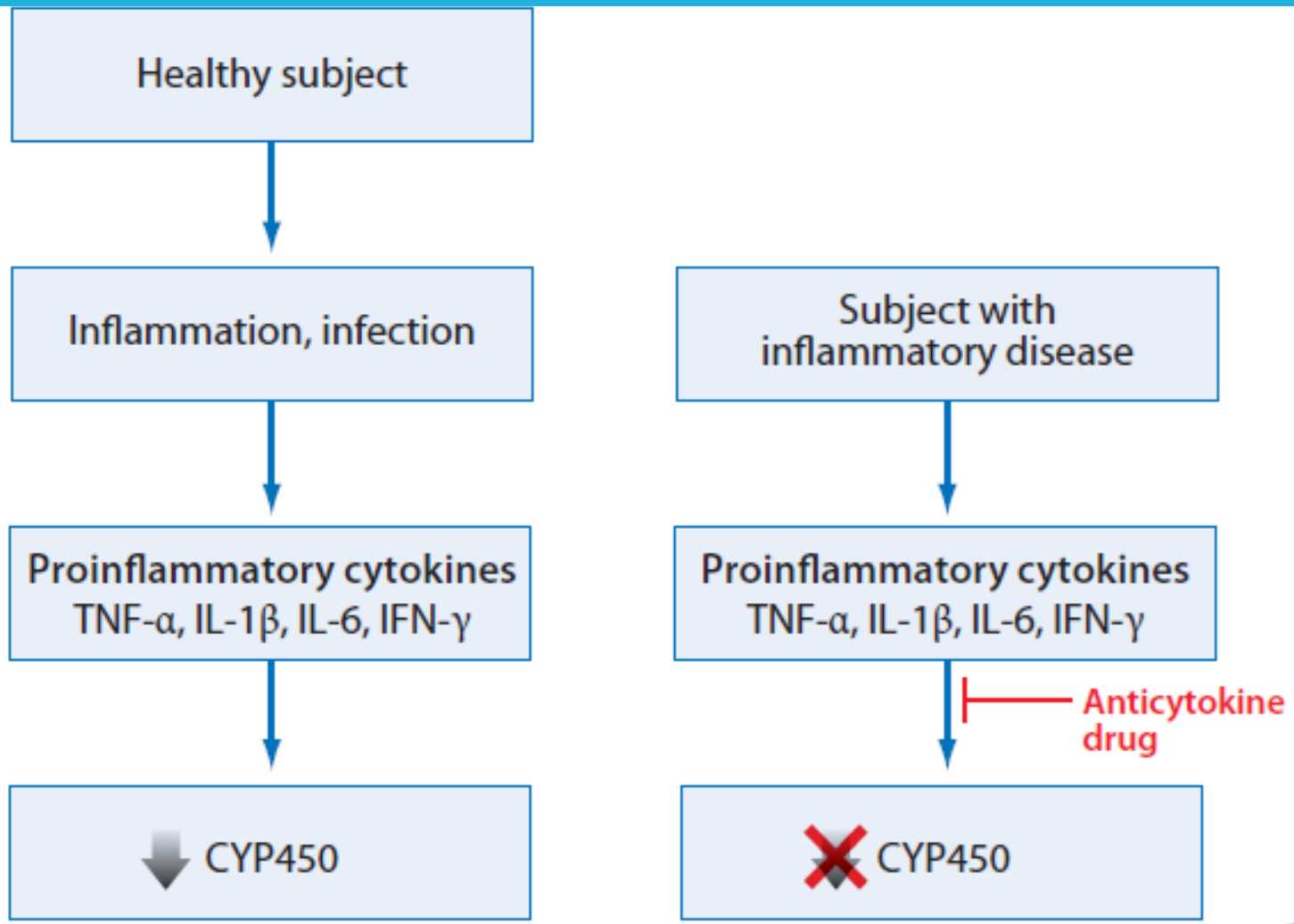
Effects of Inflammation and Anticytokine Treatment on CYP450 Activity:



Zhou H et al. *Ann Rev Pharmacol Toxicol* 2011;51:359-372

Interactions with Experimental COVID-19 Therapies

Please check www.covid19-druginteractions.org for updates.

Please note that if a drug is not listed it cannot automatically be assumed it is safe to coadminister. No recommendation to use experimental therapy for COVID-19 is made. Drug interaction data for many agents are limited or absent; therefore, risk-benefit assessment for any individual patient rests with prescribers.

Lipid Lowering Agents

	ATV	LPV/r	RDV	FAVI	CLQ	HCLQ	NITAZ	RBV	TCZ
Atorvastatin	↑	↑ 490%	↔	↔	↔	↔	↔	↔	↔
Bezafibrate	↔	↔	↔	↔	↔	↔	↔	↔	↔
Clofibrate	↔	↔	↔	↔	↔	↔	↔	↔	↔
Evolocumab	↔	↔	↔	↔	↔	↔	↔	↔	↔
Ezetimibe	↑	↔	↔	↔	↔	↔	↔	↔	↔
Fenofibrate	↔	↔	↔	↔	↔	↔	↔	↔	↔
Fish oils	↔	↔	↔	↔	↔	↔	↔	↔	↔
Fluvastatin	↑	↔	↔	↔	↔	↔	↔	↔	↔
Gemfibrozil	↔	↓ 41%	↔	↔	↔	↔	↔	↔	↔
Lovastatin	↑	↑	↔	↔	↔	↔	↔	↔	↔
Pitavastatin	↑ 31%	↓ 20%	↔	↔	↔	↔	↔	↔	↔
Pravastatin	↑	↑ 33%	↔	↔	↔	↔	↔	↔	↔
Rosuvastatin	↑	↑ 108%	↔	↔	↔	↔	↔	↔	↔
Simvastatin	↑	↑	↔	↔	↔	↔	↔	↔	↔

Key to abbreviations

ATV	Atazanavir	CLQ	Chloroquine
LPV/r	Lopinavir/ritonavir	HCLQ	Hydroxychloroquine
RDV	Remdesivir	NITAZ	Nitazoxanide
FAVI	Favipiravir	RBV	Ribavirin
		TCZ	Tocilizumab

Colour Legend

These drugs should not be coadministered
Potential interaction which may require a dose adjustment or close monitoring.
Potential interaction likely to be of weak intensity. Additional action/monitoring or dosage adjustment unlikely to be required.
No clinically significant interaction expected

© Liverpool Drug Interaction Group, University of Liverpool, Pharmacology Research Labs, 1st Floor Block H, 70 Pembroke Place, LIVERPOOL, L69 3GF

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Atorvastatin + ATV
Coadministration is not recommended. If the use of atorvastatin is considered necessary, use the lowest possible dose of atorvastatin with careful safety monitoring. The daily atorvastatin dose should not exceed 10 mg.

Atorvastatin + LPV/r
Do not exceed a daily dose of 20 mg with careful safety monitoring.

Evolocumab + TCZ
Avoid coadministration due to the enhanced immunosuppressive effect.

Rosuvastatin + ATV or LPV/r
Do not exceed rosuvastatin 10 mg/day.

Key to abbreviations

ATV	Atazanavir	CLQ	Chloroquine
LPV/r	Lopinavir/ritonavir	HCLQ	Hydroxychloroquine
RDV	Remdesivir	NITAZ	Nitazoxanide
FAVI	Favipiravir	RBV	Ribavirin
		TCZ	Tocilizumab

What about IPE ?

Novel Anti-inflammatory Effects of EPA in Human Pulmonary and Vascular Endothelium in Vitro

1. EPA Reduces Expression of Pulmonary ACE and ICAM-1 During Inflammation with IL-6[1]
2. EPA Preserves Vascular Endothelial Function Following IL-6 Exposure as Compared to DHA and AA[2]

[1]Presented at NLA 2020 (*Abstract #: 245*). Sherratt SCR, Dawoud H, Malinski T, Libby P, Bhatt DL, Mason RP.
[2]Presented at NLA 2020 (*Abstract #: 244*). Mason RP, Dawoud H, Sherratt SCR, Libby P, Bhatt DL, Malinski T.

ΣCLA SARS-CoV-2/COVID-19 Trials With IPE

PREPARE-IT 1

Prevention of COVID-19 With EPA in Healthcare Providers at Risk - Intervention Trial (Double-Blind)

Inclusion Criteria
- Doctors, nurses, ancillary/ cleaning staff working in ICU or EDs that care for COVID-19 patients
- Personnel performing aerosol-generating procedures on COVID-19 patients
- Relatives of confirmed COVID-19 patients who have been in contact
- Laboratory staff currently running COVID-19 tests
- General population at risk

R

n=1000 → **Icosapent Ethyl** 4 g PO BID x 3 days → **Icosapent Ethyl** 2 g PO BID x 57 days

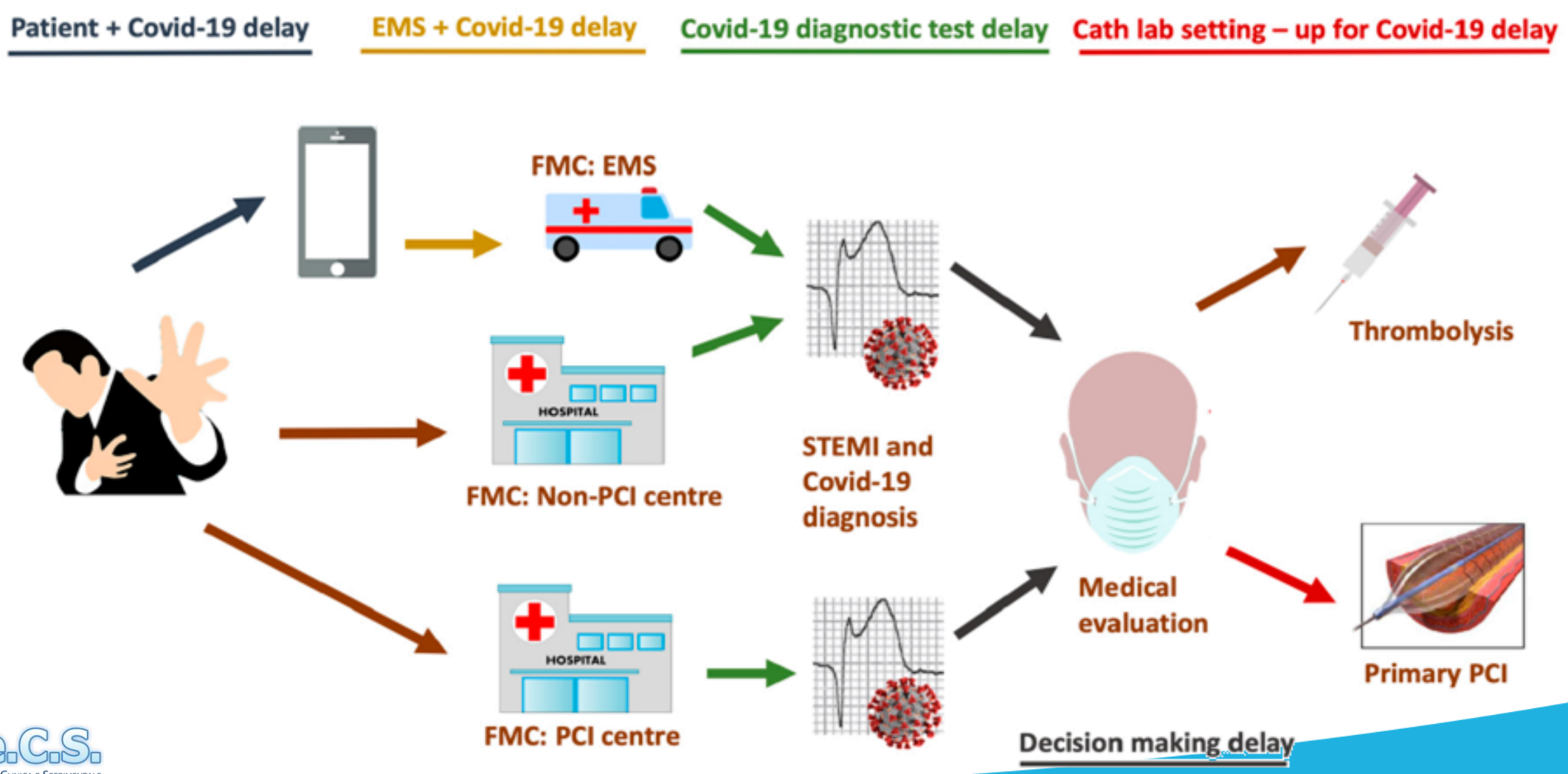
n=1000 → **Placebo** 4 g PO BID x 3 days → **Placebo** 2 g PO BID x 57 days

Primary Endpoints
- Percentage of patients positive for SARS-CoV-2 up to day 60
- Highest mean WHO descriptive score of COVID-19 in the icosapent ethyl group vs placebo group up to day 60

PREPARE-IT 1 - 1430 Patients Randomized as of 12/12/2020
PREPARE-IT 2 - 9 Patients Randomized as of 12/12/2020

BID, twice daily; ED, emergency department; ICU, intensive care unit; IPE, icosapent ethyl; WHO, World Health Organization.
https://clinicaltrials.gov/ct2/show/NCT04460651.

Toal Ischemic Time and COVID-19 Related Delay:



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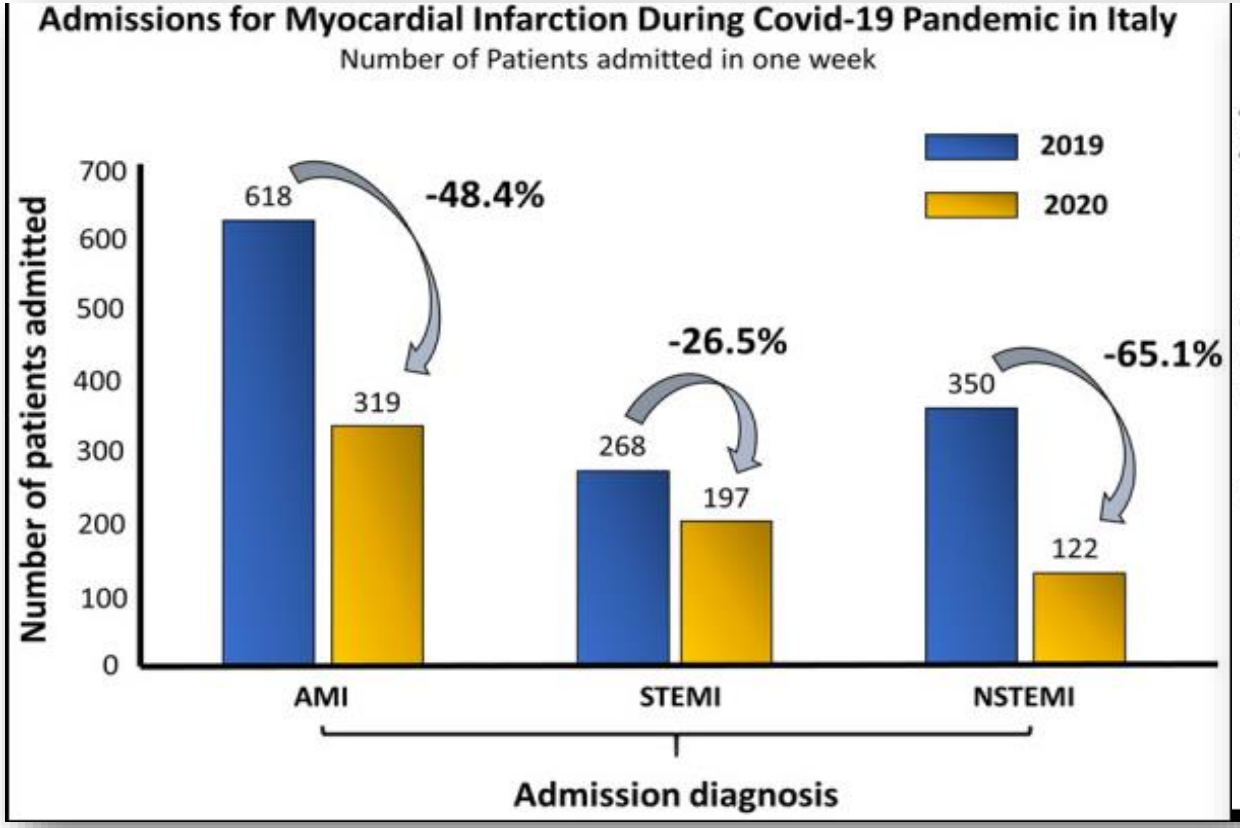
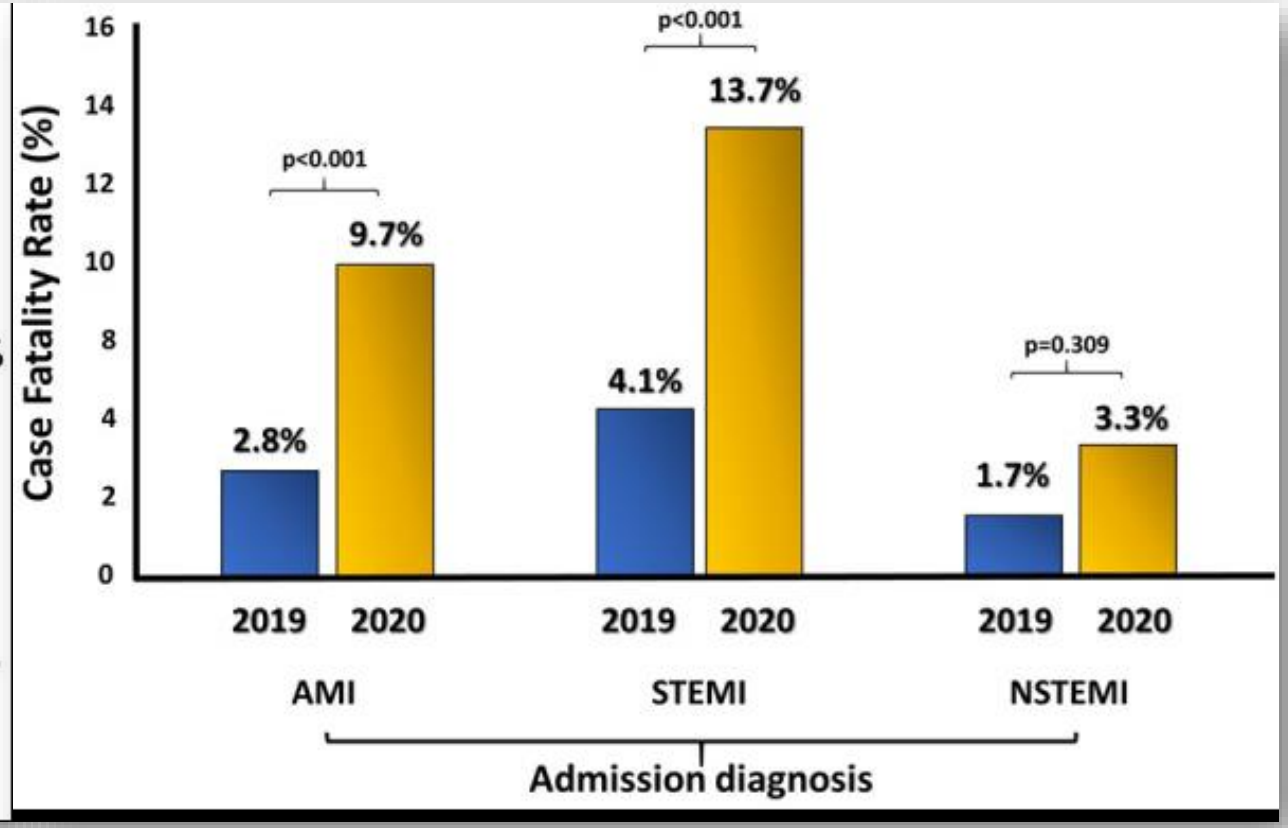
ESC European Society of Cardiology
European Heart Journal (2020) 0, 1–6
doi:10.1093/eurheartj/ehaa409
FASTTRACK CLINICAL RESEARCH

Did MI Admissions increase during COVID-19?

Reduction of hospitalizations for myocardial infarction in Italy in the COVID-19 era





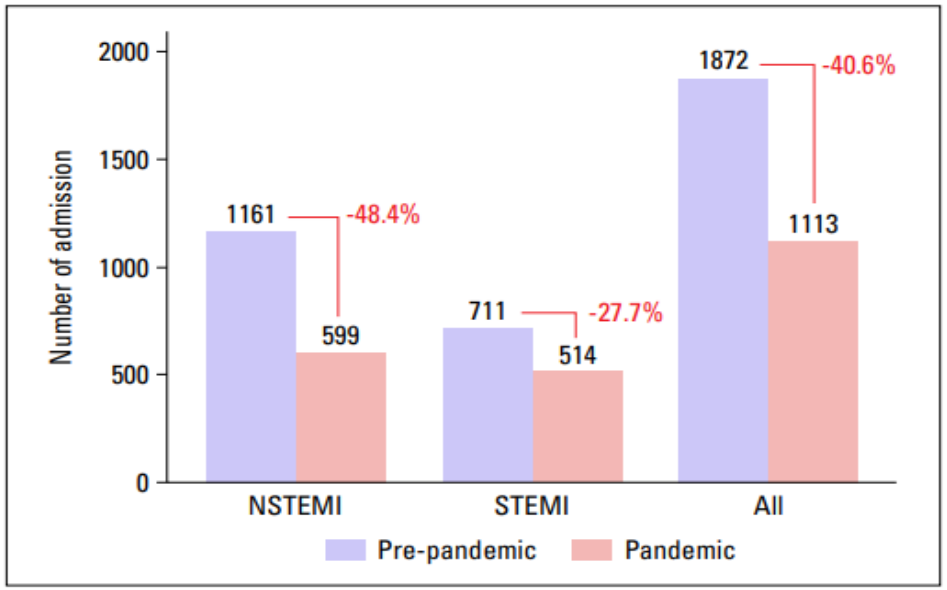
15 days snapshot AMI
48 centers
Same Inclusion criteria

Original Investigation

Treatment delays and in-hospital outcomes after acute myocardial infarction during the COVID-19 pandemic: A nationwide study

Mustafa Kemal Erol[1,*], Meral Kayıkçıoğlu[2,*], Mustafa Kılıçkap[3,*], Arda Güler[4], Abdullah Yıldırım[5], Fatih Kahraman[6], Veysi Can[7], Sinan İnci[8], Sadettin Selçuk Baysal[9], Okan Er[10], Utku Zeybey[11], Çağrı Kafkas[12], Çağrı Yayla[13], Can Baba Arın[14], İbrahim Aktaş[15], Ahmet Arif Yalçın[4], Ömer Genç[5], on the behalf TURKMI-2 Study Group

TURKMI-1: 1872 pts



eFigure 1. Change in the number of patients diagnosed with acute myocardial infarction during the pandemic period

TURKMI-2 - entire study population; STEMI - ST elevation myocardial infarction; NSTEMI - non ST-elevation myocardial infarction

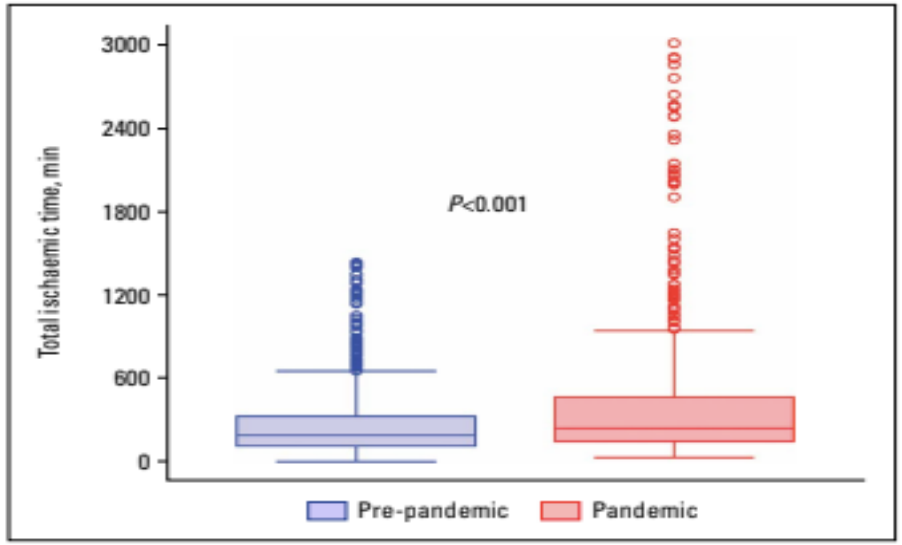


Figure 2. The total ischemic times for patients with ST elevation myocardial infarction who were treated with percutaneous coronary intervention were significantly longer during the pandemic period compared with the pre-pandemic period (median 195 min for TURKMI-1 vs. 245 min for TURKMI-2; p<0.001)

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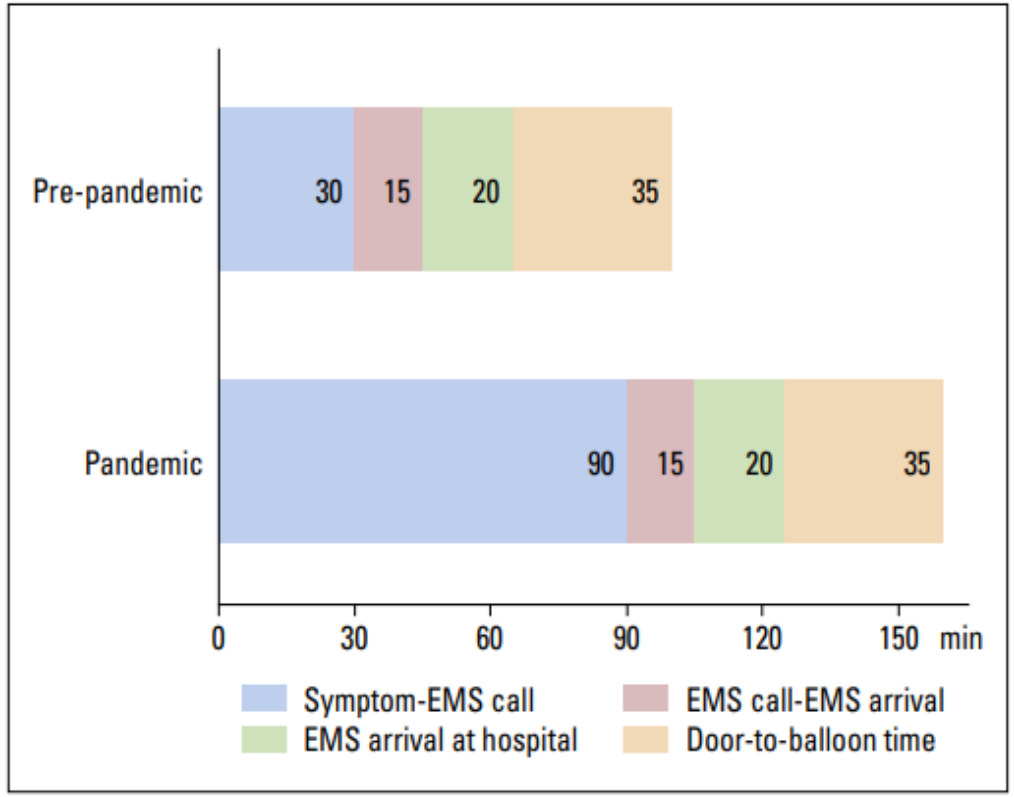
Società Italiana di Terapia Clinica e Sperimentale

Original Investigation

Treatment delays and in-hospital outcomes after acute myocardial infarction during the COVID-19 pandemic: A nationwide study

Mustafa Kemal Erol[1,*], Meral Kayıkçıoğlu[2,*], Mustafa Kılıçkap[3,*], Arda Güler[4], Abdullah Yıldırım[5], Fatih Kahraman[6], Veysi Can[7], Sinan İnci[8], Sadettin Selçuk Baysal[9], Okan Er[10], Utku Zeybey[11], Çağrı Kafkas[12], Çağrı Yayla[13], Can Baba Arın[14], İbrahim Aktaş[15], Ahmet Arif Yalçın[4], Ömer Genç[5], on the behalf TURKMI-2 Study Group



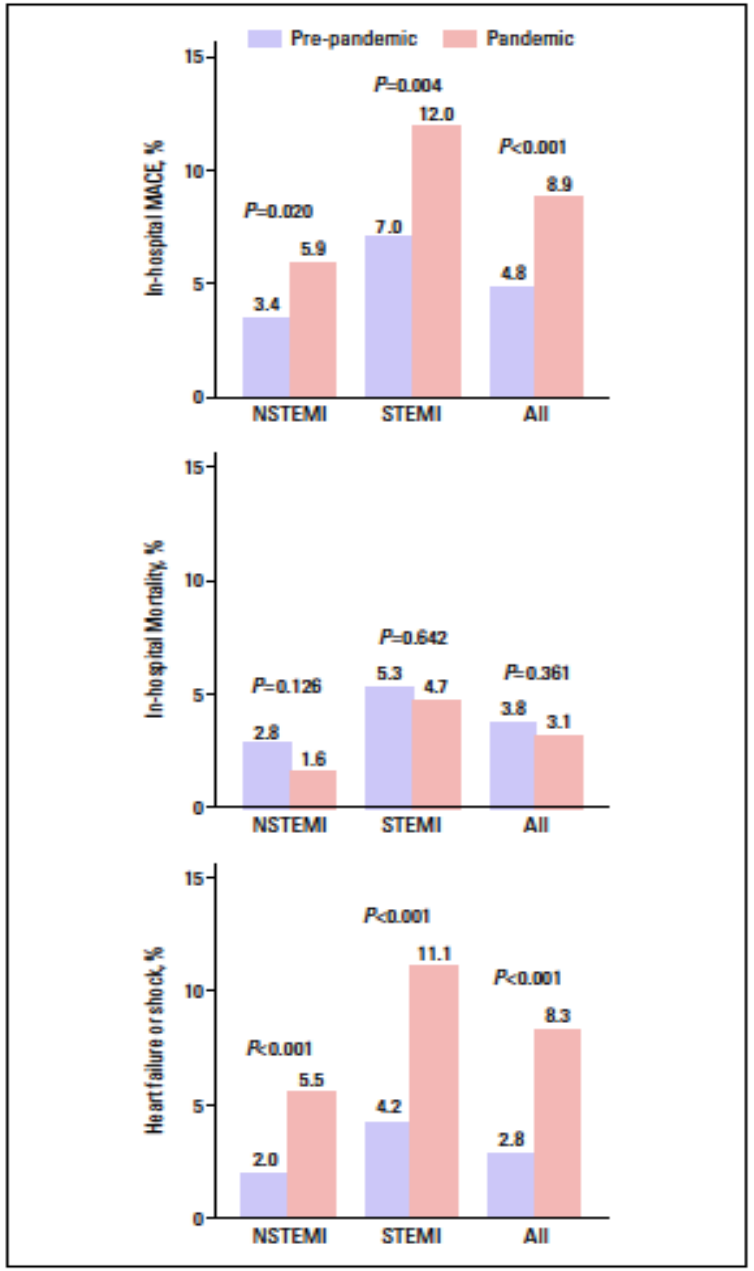


Figure 4. Comparison of the in-hospital major adverse events (defined as death, cardiogenic shock, or heart failure) between the pre-pandemic (TURKMI-1) and pandemic (TURKMI-2) periods
MACE - major adverse cardiac events, NSTEMI - non-ST elevation myocardial infarction STEMI - ST elevation myocardial infarction

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Negative impact of COVID-19 pandemic on the lifestyle and management of patients with Homozygous Familial Hypercholesterolemia

- Survey of 34 HoFH patients (mean age: 42.53±14.07 years, 55.9% female) during Covid-19 pandemics
- Fourteen (41.2%) were receiving regular weekly therapeutic lipid apheresis (LA)

Phone questionaire on;

- Heart healthy behavioral changes
- Increase in anxiety
- Awarenes of vulnerability to COVID-19
- Avoidance of seeking medical care
- Access to LA

RESULTS

Healty life-style behaviour disruption in 50.2%

Physical activity decrease in 56.2%

Reduced compliance to healthy diet in 40%

Anxiety level increase in 57%

Medical care avoidance in 70%

HoFH patients with regard to heart healthy lifestyle and access to LA have significantly deteriorated during the pandemic in a tertiary lipid center.

J Clin Lipidol. 2020 Sep

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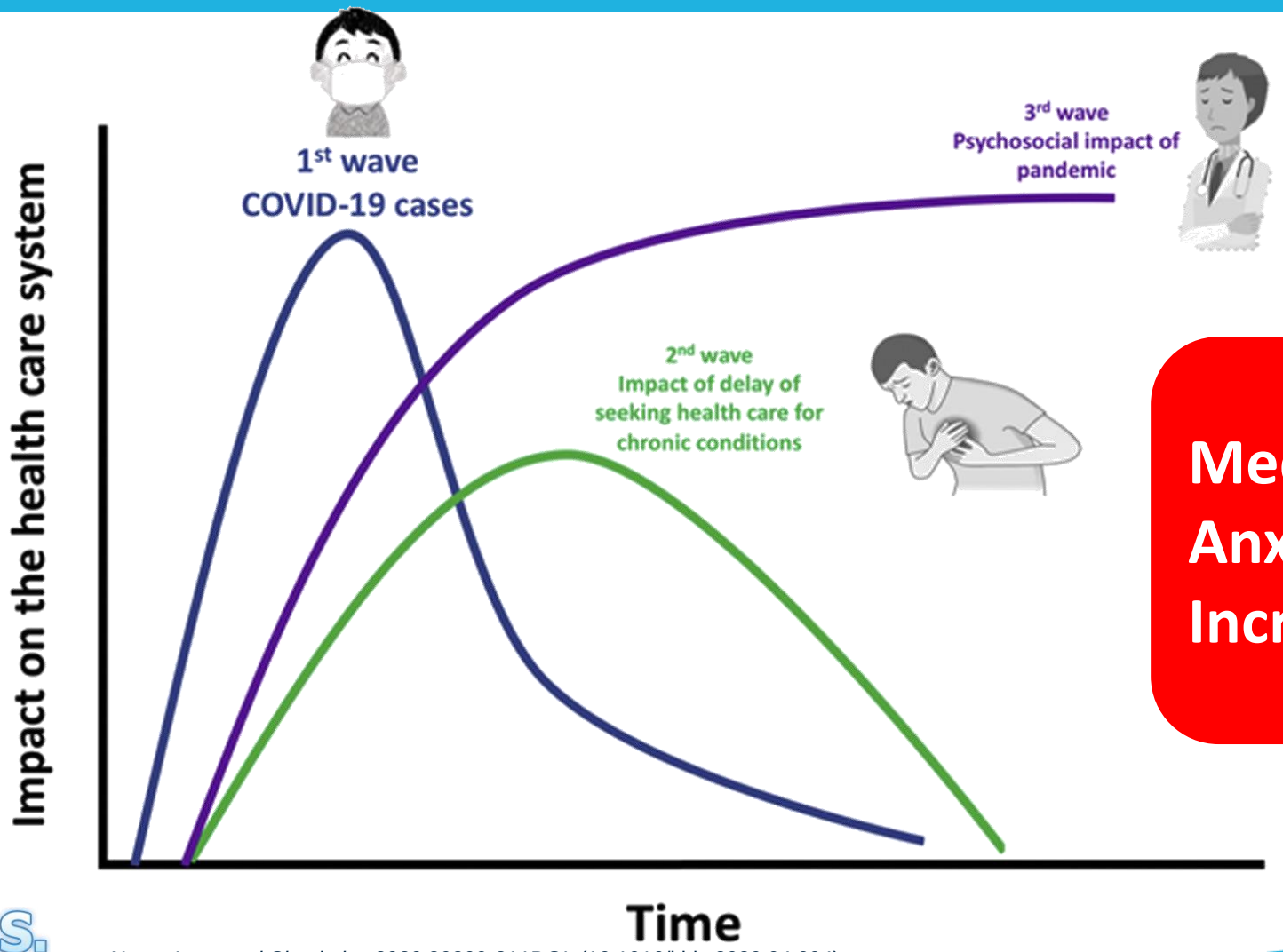

Medical care avoidance
Anxiety
Increased CV risk

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Heart, Lung and Circulation 2020 29809-811DOI: (10.1016/j.hlc.2020.04.004)

Conclusion:

- COVID-19 increases risk in patients with ASVD
- Drug interactions should be taken into account
- Collateral damage due to pandemic will affect ASVD prevalance unfavourably