COVID-19 and the cardiovascular system - special focus on thromboembolic events

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COVID-19 and cardiovascular diseases: special focus on thromboembolic events

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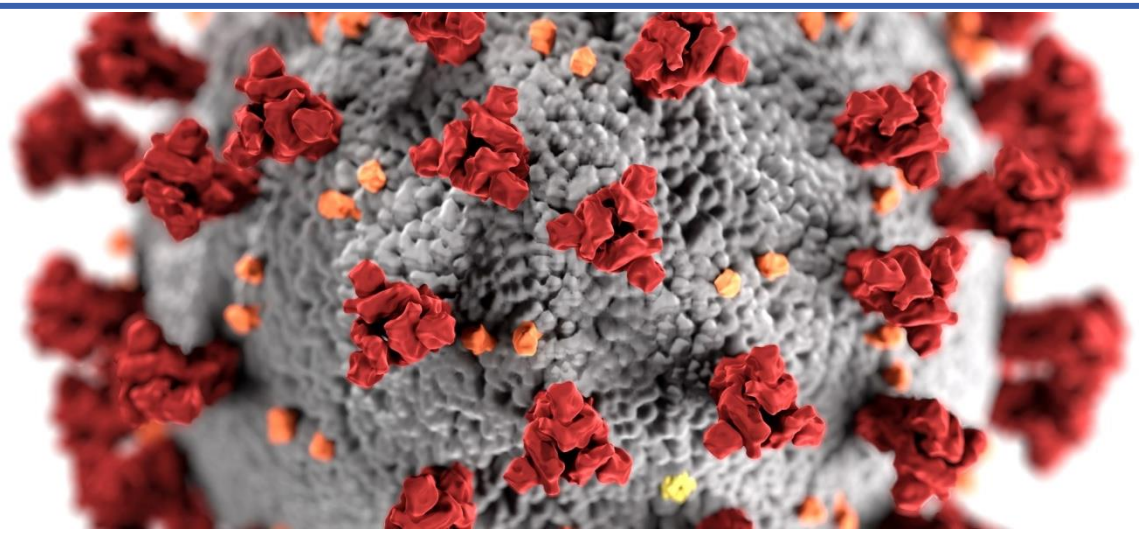
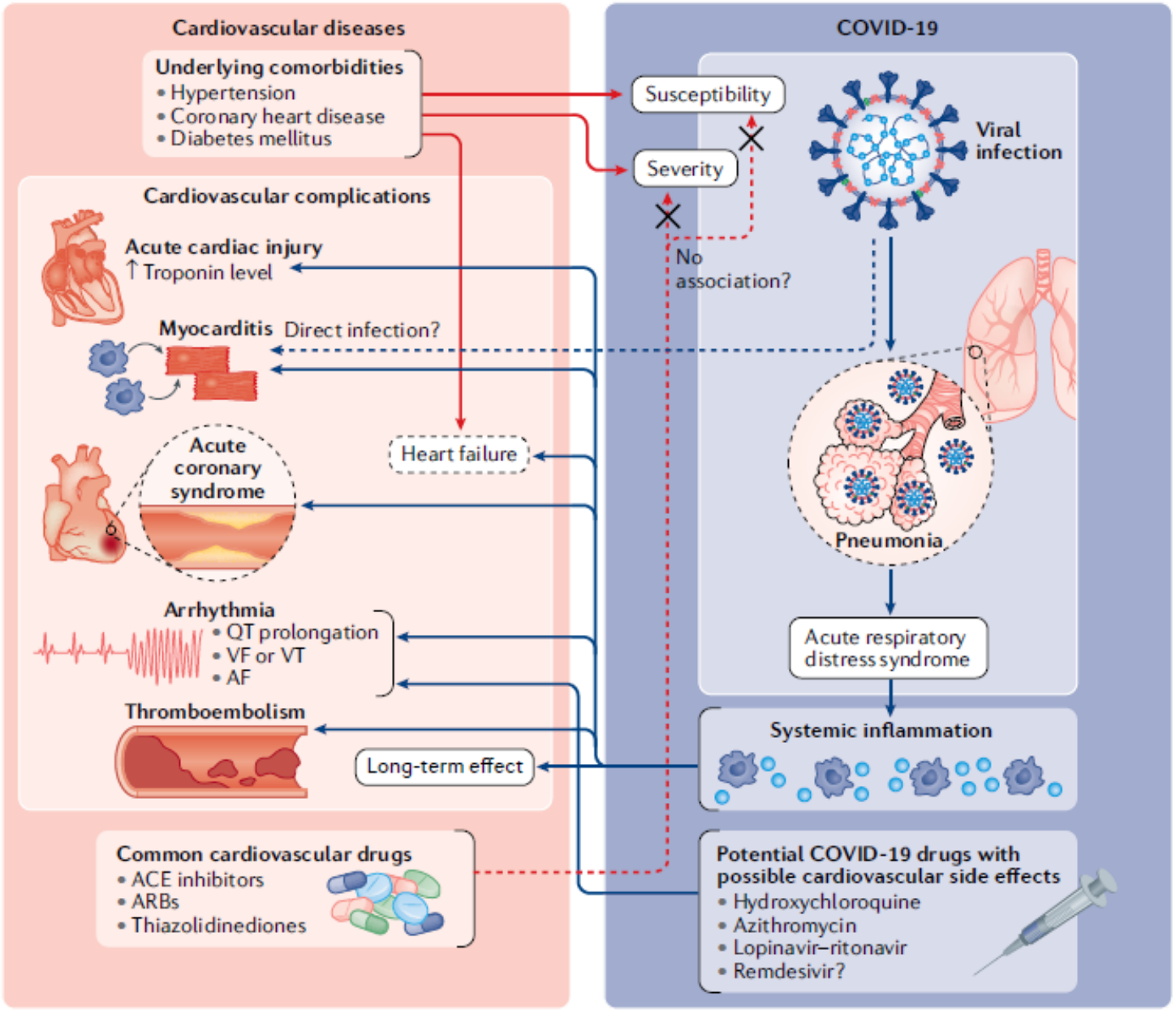
Rijeka, April 8, 2021

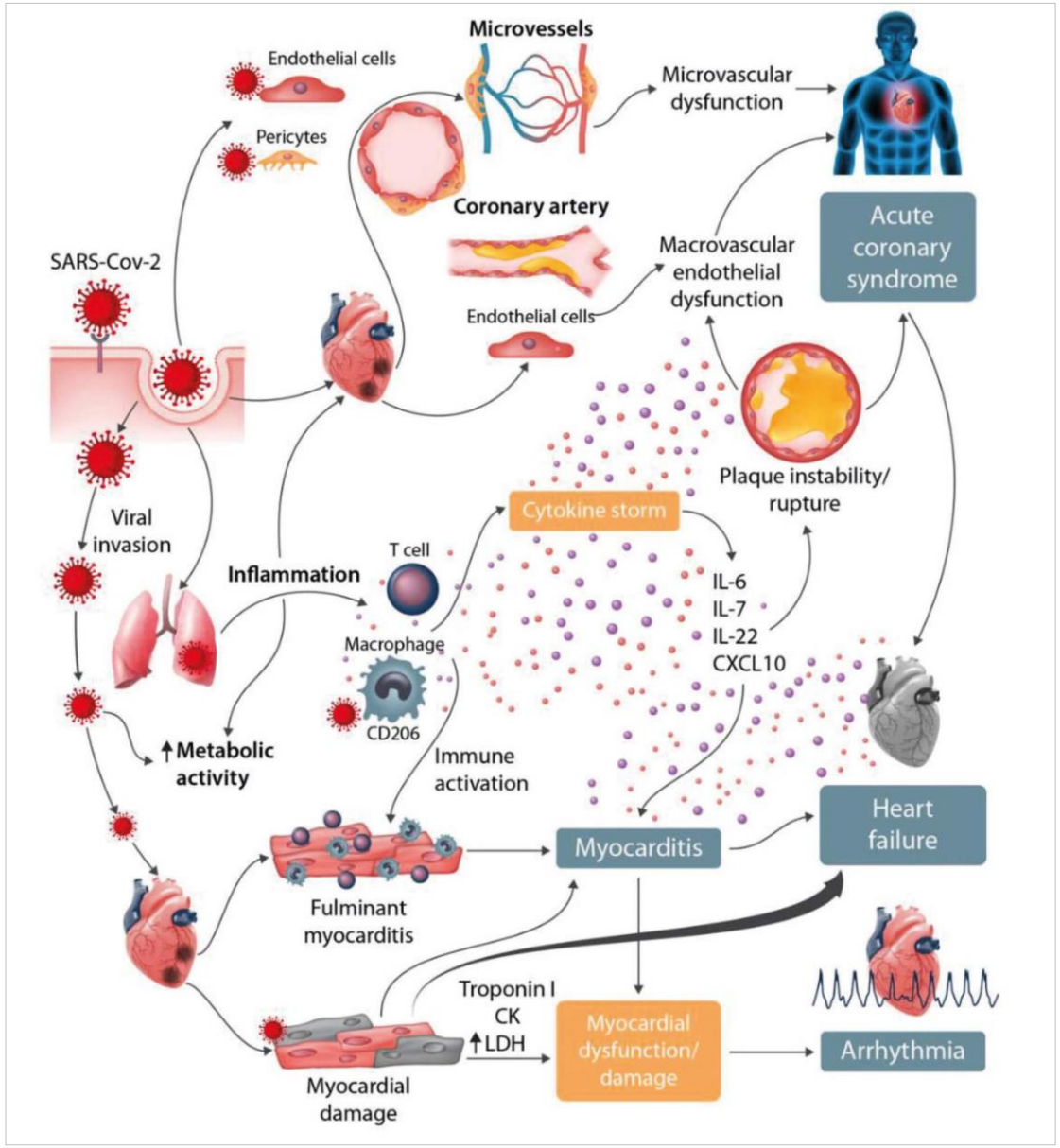


Bidirectional interaction between CV diseases and COVID-19



Nishiga M et al.
Nature Reviews Cardiology, 2020

Cardiovascular involvement in COVID-19: key manifestations and hypothetical mechanisms



Guzik TJ et al. Cardiovasc Res., 2020

What does ‘Patient Protection’ mean in the COVID-19 pandemic?

Contemporary Challenges During the COVID-19 Pandemic

Coagulopathies in patients with COVID-19

Diagnosis of venous thromboembolism in patients with COVID-19 is challenging and incidence is high[1,2]

Health system capacity challenges

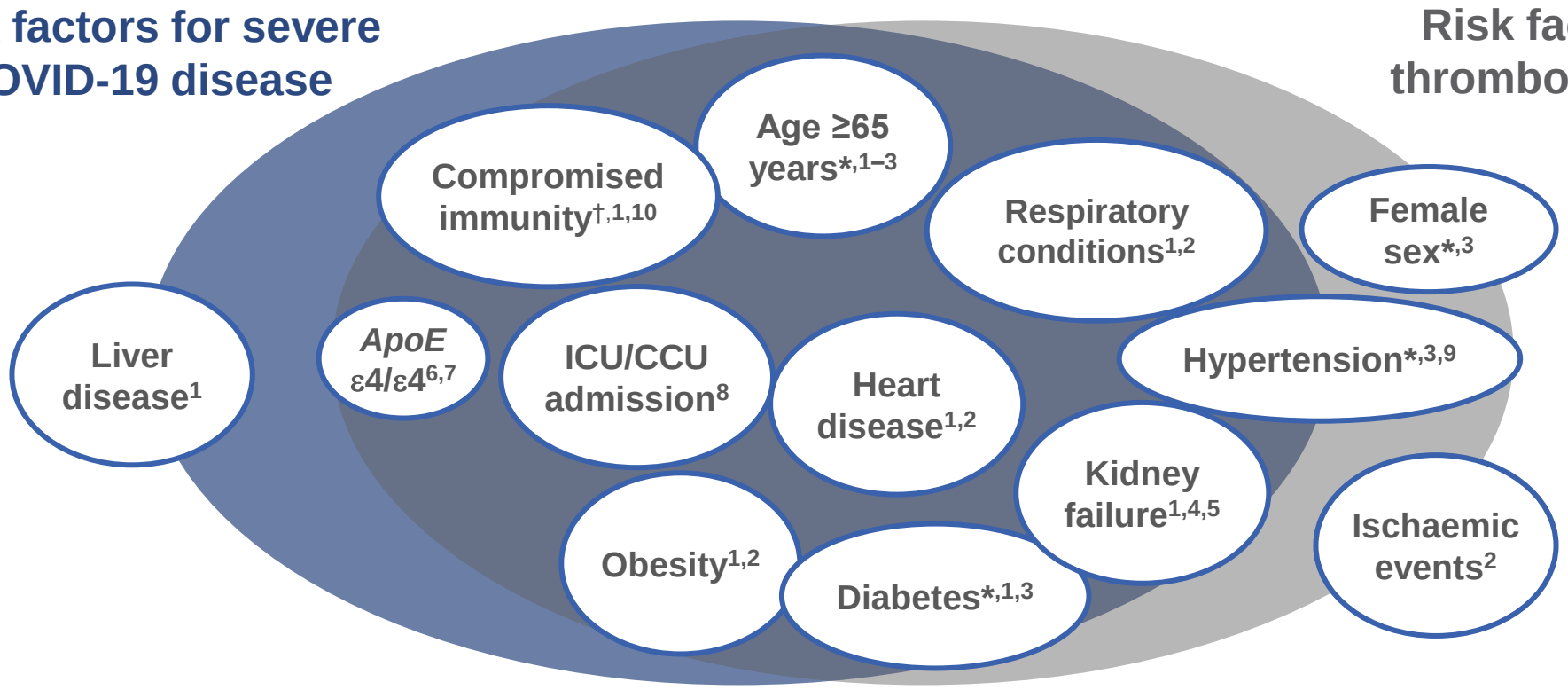
High priority given to patients with COVID-19 may compromise rapid triage (and treatment) of non-COVID-19 patients with acute cardiovascular disease[3]

Increased risk for vulnerable patients/ isolation policies

Continuity of medical care required for vulnerable patients during self-isolation and social distancing, but need to minimize person-to-person exposure risk for patients needing INR tests[4]

1. Spyropoulos AC et al. *J Thromb Haemost* 2020;10.1111/jth.14929; 2. Llitjos J-F et al. *J Thromb Haemost* 2020;10.1111/jth.14869; 3. ESC 2020; https://www.escardio.org/Education/COVID-19-and-Cardiology/ESC-COVID-19-Guidance [accessed 15 June 2020]; 4. Barnes GD et al. *J Thromb Thrombol* 2020;50:72–81.

Risk factors for severe COVID-19 disease overlap with risk factors for thromboembolic events



Additionally, people who live in a nursing home or care facility, and who therefore may be less mobile, are at increased risk of severe COVID-19 disease[1]

*Risk factors of thromboembolism for patients with AF.[3] †Including patients receiving cancer treatment.[1]

1. Centers for Disease Control and Prevention. People who are at higher risk for severe illness. Available at: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-at-higher-risk.html [accessed 11 June 2020]; 2. Barbar S et al. *J Thromb Haemost* 2010;8:2450–2457; 3. Lip GY et al. *Chest* 2010;137:263–272; 4. Ocak J et al. *J Thromb Haemost* 2013;11:627–633; 5. Fox KA et al. *Eur Heart J* 2011;32:2387–94; 6. Bennet AM et al. *JAMA* 2007;298:1300–1311; 7. Kuo C-L et al. *J Gerontol A Biol Sci Med Sci* 2020;glaa131; 8. Spyropoulos AC et al. *J Thromb Haemost* 2020;10.1111/jth.14929; 9. ESC 2020; https://www.escardio.org/Education/COVID-19-and-Cardiology/ESC-COVID-19-Guidance [accessed 22 June 2020]; 10. Zöller B et al. *Am J Cardiovasc Dis* 2012;2:171–183.

Correlation between older age, atrial fibrilation and COVID-19

- Incidence of atrial fibrillation is rising in the older age[1-3]
- Risk of stroke in patients with atrial fibrillation is substantially higher in the elderly[4]

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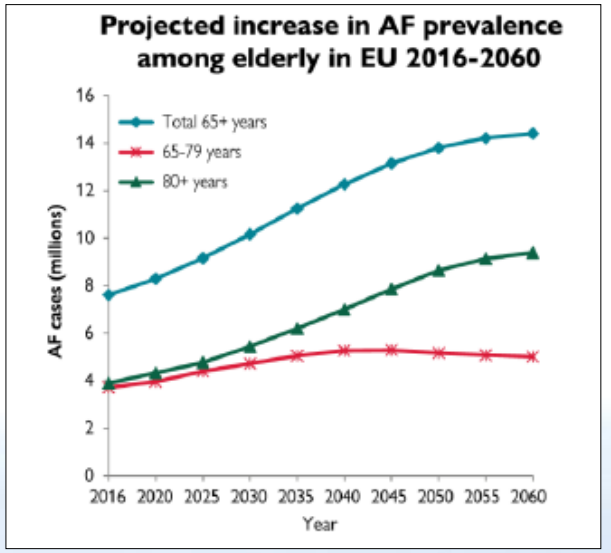
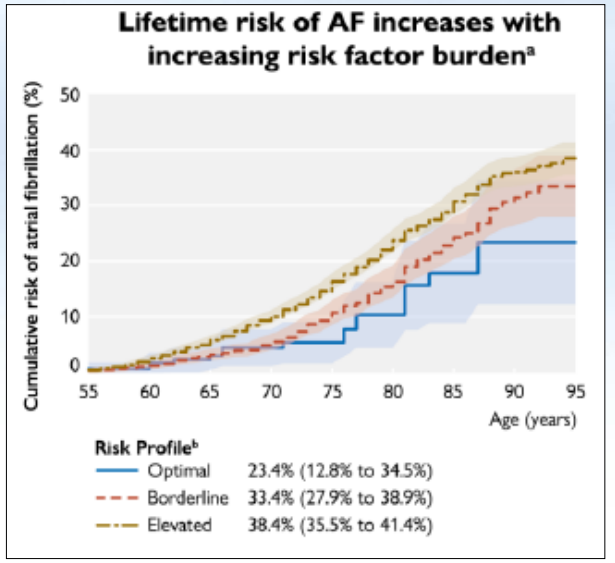
From the new ESC recommedations[5]:

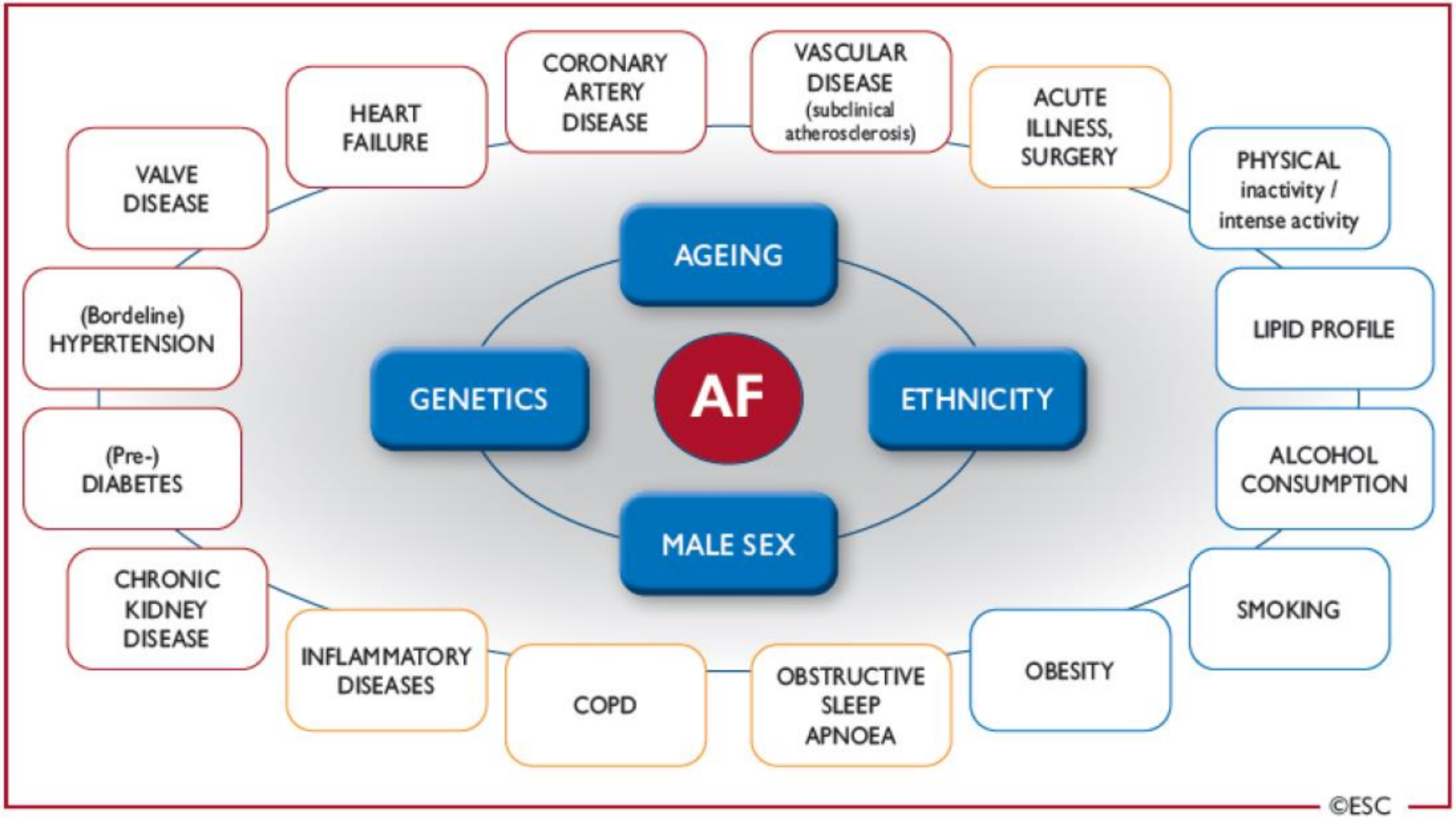
- *De novo* or reccurrent AF may be triggered by COVID-19 (fever, hypoxia, elevated sympathetic tone)
- In patients with severe pneumonia, acute respiratory distress syndrome (ARDS) and sepsis, incidence of AF during hospitalization is high





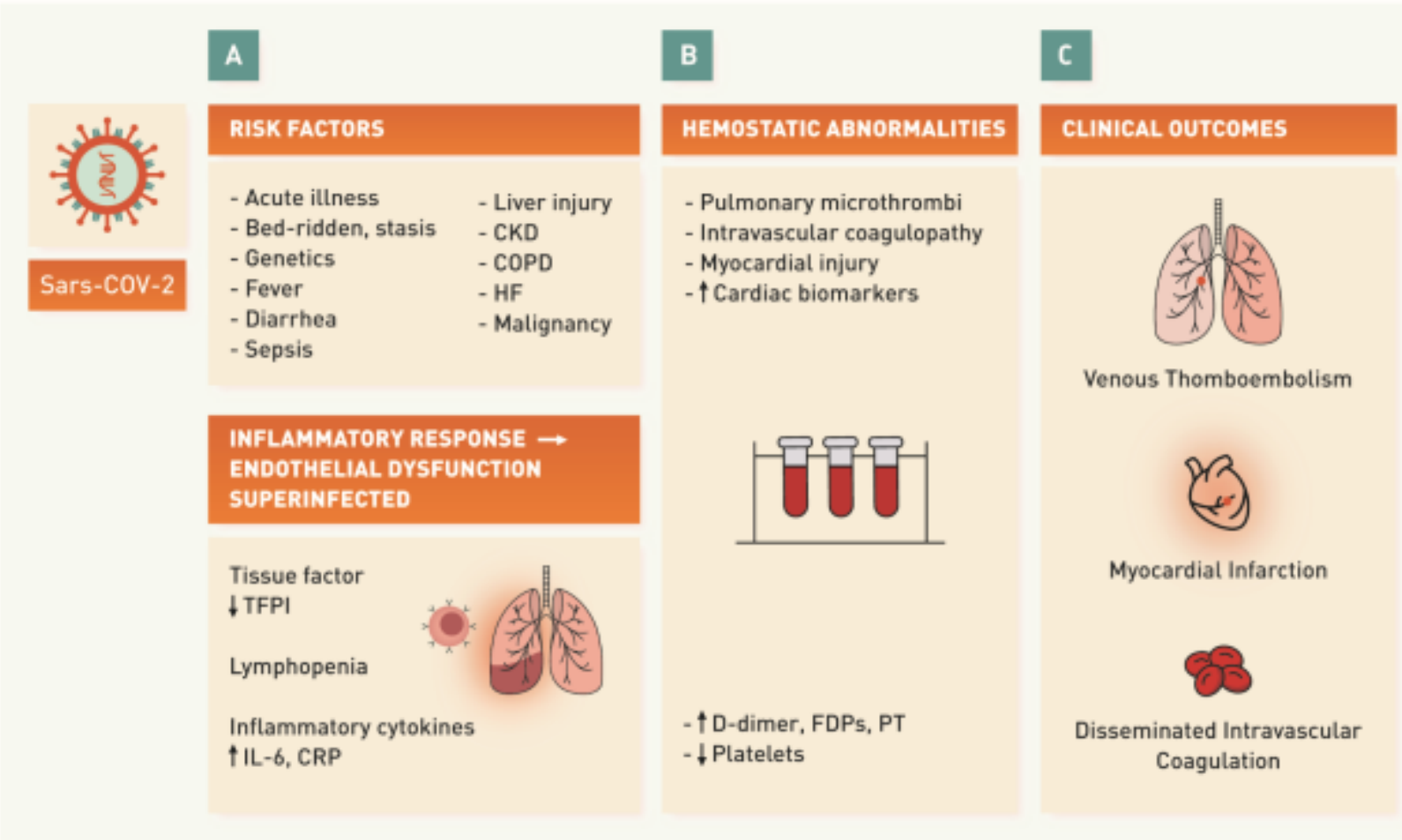
1.Miyasaka Y et al. Circulation. 2006;114:119-125
2.Lloyd-Jones DM, et al. Circulation 2004;110:1042-6.;
3.Ball J et al. Int J Cardiol 2013;167:1807-1824.;
4.Marinigh et al. Age as a risk factor for stroke in atrial fibrillation patients: implications for thromboprophylaxis. J Am Coll Cardiol. 2010 Sep 7;56(11):827-37.;
5.ESC Guidance for the Diagnosis and Management of CV Disease during the COVID-19 Pandemic
Available at: https://www.escardio.org/Education/COVID-19-and-Cardiology/ESC-COVID-19-Guidance#p11

Summary of risk factors for incident atrial fibrillation



2020 ESC Guidelines for the diagnosis and management of atrial fibrillation
Eur Heart J 2020 doi/10.1093/eurheartj/ehaa612

Venous thromboembolism (VTE)
Deep venous thrombosis/Pulmonary embolism (DVT/PE) and COVID-19



Bikdeli B, et al. *COVID-19 and Thrombotic or Thromboembolic Disease: Implications for Prevention, Antithrombotic Therapy, and Follow up.* JACC, Apr 2020.

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European Heart Journal (2019) **00**, 1–61
doi:10.1093/eurheartj/ehz405

ESC GUIDELINES

2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS)

The Task Force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC)

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European Society of Cardiology

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

9.8. Acute Pulmonary Embolism – Prevention and Diagnosis

Pulmonary embolism (PE) and COVID-19

- Although solid evidence is unavailable to date, a number of case reports suggest that the incidence of PE in patients with COVID-19 infection may be high.
- Taking this into account, together with COVID-19-associated systemic inflammation, coagulation activation, hypoxaemia and immobilization, anticoagulation at standard prophylactic doses should be considered for all patients admitted to the hospital with COVID-19 infection.
- Patients with COVID-19 infection often present with respiratory symptoms and may also report chest pain and haemoptysis. These symptoms largely overlap with the presentation of acute PE which may cause underdiagnosis of this relevant complication.
- Unexpected respiratory worsening, new/unexplained tachycardia, a fall in BP not attributable to tachyarrhythmia, hypovolaemia or sepsis, (new-onset) ECG changes suggestive of PE, and signs of DVT of the extremities should trigger a suspicion of PE.

ESC Guidance for the Diagnosis and Management of CV Disease during the COVID-19 Pandemic Dostupno na: https://www.escardio.org/Education/COVID-19-and-Cardiology/ESC-COVID-19-Guidance#p11

Diagnosis of PE in the COVID-19 pandemic

- It is recommended to only order diagnostic tests for PE when it is clinically suspected, although it is recommended to keep a low threshold of suspicion.
- The specificity of D-dimer tests may be lower in patients with COVID-19 compared to other clinical settings. Even so, it is still advised to follow diagnostic algorithms starting with pre-test probability and D-dimer testing, especially when pre-test probability dependent D-dimer thresholds are being used.
- This may help to rationalize the deployment of resources and personnel for transporting a patient to the radiology department with all the associated isolation precautions.
- In the clinical scenario of a patient with COVID-19, who has just undergone CT of the lungs but the findings cannot explain the severity of respiratory failure, CT pulmonary angiography may [or should] be considered before leaving the radiology department.

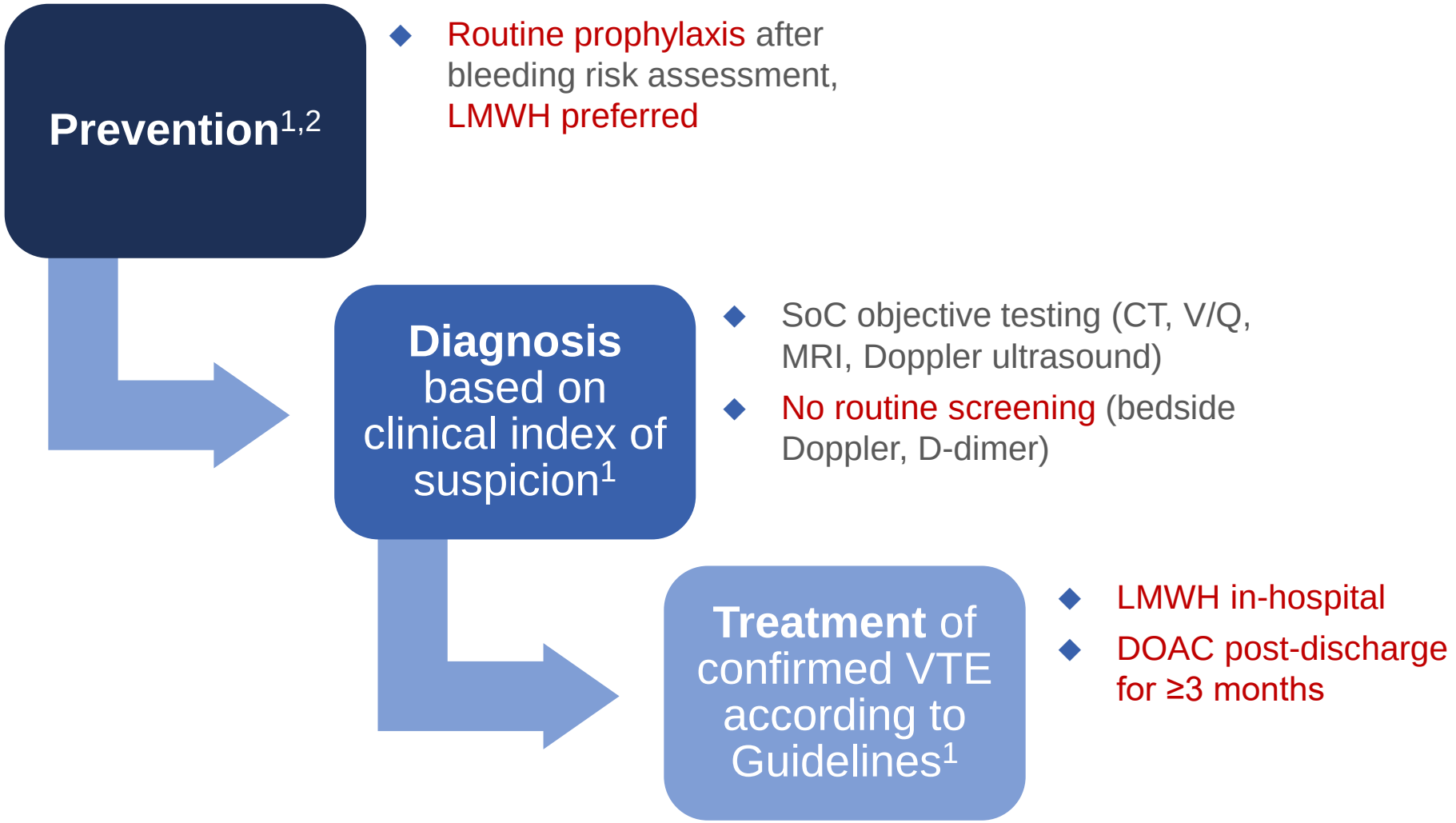
ESC Guidance for the Diagnosis and Management of CV Disease during the COVID-19 Pandemic Dostupno na: https://www.escardio.org/Education/COVID-19-and-Cardiology/ESC-COVID-19-Guidance#p11

Treatment of PE in the COVID-19 era

- When acute PE is confirmed, treatment should be guided by risk stratification in accordance with the current ESC guidelines.
- Patients in shock should receive immediate reperfusion therapy.
- Haemodynamically stable patients may be treated with UFH, LMWH or a DOAC (NOAC), depending on the possibility of oral treatment, renal function and other circumstances.
- When choosing the appropriate drug and regimen (parenteral versus oral) for initial, in-hospital anticoagulation, the possibility of rapid cardiorespiratory deterioration due to COVID-19 should be taken into account.
- Of note, some of the investigational drugs for COVID-19 may have relevant interactions with DOACs. In particular, this may be the case for lopinavir/ritonavir via Cytochrome P450 3A4 (CYP3A4) and/or P-glycoprotein (P-gp) inhibition. In such cases, the bleeding risk may be elevated and NOACs should be avoided.
- Chloroquine, a drug with a long half-life of approximately 2 weeks, has been associated with a mild inhibitive effect on P-gp, which may lower the plasma levels of the NOACs when combined; the clinical relevance of this interaction is unknown.
- Because close monitoring is necessary which may contribute to spreading of the infection, vitamin K antagonists (VKAs) should only be considered in special circumstances such as the presence of mechanical prosthetic valves or the antiphospholipid syndrome.

ESC Guidance for the Diagnosis and Management of CV Disease during the COVID-19 Pandemic Dostupno na: https://www.escardio.org/Education/COVID-19-and-Cardiology/ESC-COVID-19-Guidance#p11

Guidance for preventing, diagnosing and treating VTE in hospitalized patients with COVID-19



1. Spyropoulos AC et al. *J Thromb Haemost* 2020;10.1111/jth.14929; 2. Barnes GD et al. *J Thromb Thrombol* 2020;50:72–81.

How can we continue to protect vulnerable CV patients?

"Past experience has shown that patients will die from non-COVID-19 related illnesses in addition to COVID-19 itself as we divert all of our health care resources towards it"[1]

Royal College of General Practitioners

Patients still need protection against thrombosis

Desirable characteristics for anticoagulation therapy[2]

- A good balance of efficacy and safety
- Fast onset and offset of action
- Fixed oral dosing regimen
- Wide therapeutic window
- Low risk of food and drug interactions
- No need for routine coagulation monitoring

1. Royal College of General Practitioners. Royal College of General Practitioners Guidance on workload prioritisation during COVID-19. Available at: https://www.rcgp.org.uk/-/media/Files/Policy/A-Z-policy/2020/covid19/RCGP%20guidance/202003233RCGPGuidanceprioritisationroutineworkduringCovidFINAL [accessed 6 April 2020]; 2. Figure adapted from Ahmad Y and Lip GYH. *Curr Cardiol Rev* 2012;8:290–301.

Considerations for patients with non-valvular atrial fibrillation (AF)[1-3]

Switching to a DOAC for patients with non-valvular AF*

DOACs are recommended over VKAs for appropriate patients with non-valvular AF[1-3]


European Heart Journal
doi:10.1093/eurheartj/ehw210

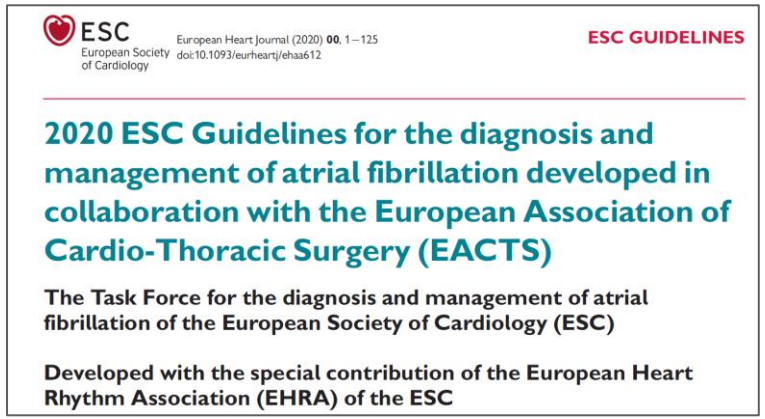
ESC GUIDELINES

2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS

The Task Force for the management of atrial fibrillation of the European Society of Cardiology (ESC)

Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC

Endorsed by the European Stroke Organisation (ESO)


ESC European Society of Cardiology

European Heart Journal (2020) 00, 1–125
doi:10.1093/eurheartj/ehaa612

ESC GUIDELINES

2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association of Cardio-Thoracic Surgery (EACTS)

The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC)

Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC

Recommendations	Class	Level
For stroke prevention in AF patients who are eligible for OAC, NOACs are recommended in preference to VKAs (excluding patients with mechanical heart valves or moderate-to-severe mitral stenosis).	I	A

*Those without mechanical heart valves or moderate or severe mitral stenosis

1. Kirchhof P et al. *Eur J Cardiothorac Surg* 2016;50:e1–e88; 2. Kirchhof P *et al*, *Eur Heart J* 2016; doi:10.1093/eurheartj/ehw210; 3. Hindricks G *et al*. *Eur Heart J* 2020; doi: 10.1093/eurheartj/ehaa612

Professional societies recommend specific actions to protect vulnerable CV patients

European Society of Cardiology[1]

- CV patients should be always protected from exposure to SARS-CoV-2 infection, in particular because of the worse outcome for this patient group
- The use of telemedicine is “highly desirable” to minimize infection risk

British Society for Haematology[2]

- To help minimise the number of patient visits, consider whether a DOAC that does not require monitoring can be used instead of warfarin

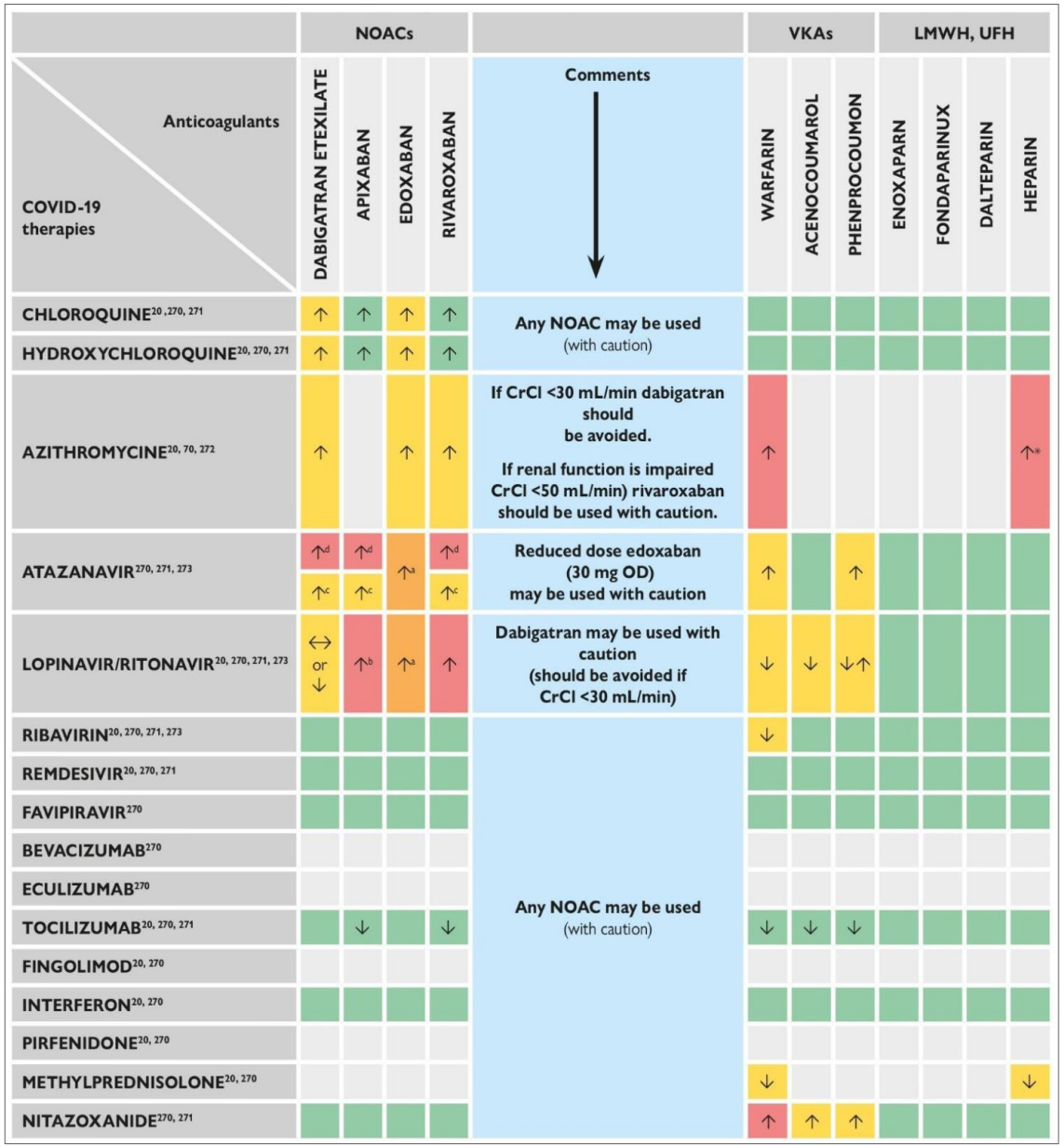
Royal College of General Practitioners[3]

- For patients on warfarin, consider switching to treatment with a DOAC if appropriate

“DOACs provide advantages over VKAs such as warfarin due to the lack of the need for routine monitoring and subsequent minimization of patient contact with the healthcare environment.”[4]

1. ESC 2020; https://www.escardio.org/Education/COVID-19-and-Cardiology/ESC-COVID-19-Guidance [accessed 16 June 2020]; 2. British Society for Haematology. INR testing for out-patients on warfarin during COVID-19 restrictions. Available at: https://b-s-h.org.uk/media/18162/inr-testing-for-out-patients-on-warfarin-during-covid-19-restrictions_23-03-2020.pdf [accessed 6 April 2020]; 3. Royal College of General Practitioners. Royal College of General Practitioners Guidance on workload prioritisation during COVID-19. Available at: https://www.rcgp.org.uk/-/media/Files/Policy/A-Z-policy/2020/covid19/RCGP%20guidance/202003233RCGPGuidanceprioritisationroutineworkduringCovidFINAL [accessed 6 April 2020]; 4. Spyropoulos AC et al. *J Thromb Haemost* 2020;10.1111/jth.14929.

Interaction of anticoagulant drugs with COVID-19 therapies



	NOACs					VKAs			LMWH, UFH			
Anticoagulants / COVID-19 therapies	DABIGATRAN ETEXILATE	APIXABAN	EDOXABAN	RIVAROXABAN	Comments	WARFARIN	ACENOCOUMAROL	PHENPROCOUMON	ENOXAPARN	FONDAPARINUX	DALTEPARIN	HEPARIN
CHLOROQUINE[20, 270, 271]	↑	↑	↑	↑	Any NOAC may be used (with caution)							
HYDROXYCHLOROQUINE[20, 270, 271]	↑	↑	↑	↑								
AZITHROMYCINE[20, 70, 272]	↑		↑	↑	If CrCl <30 mL/min dabigatran should be avoided. If renal function is impaired CrCl <50 mL/min) rivaroxaban should be used with caution.	↑						↑*
ATAZANAVIR[270, 271, 273]	↑[d] ↑[c]	↑[d] ↑[c]	↑[a]	↑[d] ↑[c]	Reduced dose edoxaban (30 mg OD) may be used with caution	↑		↑				
LOPINAVIR/RITONAVIR[20, 270, 271, 273]	↔ or ↓	↑[b]	↑[a]	↑	Dabigatran may be used with caution (should be avoided if CrCl <30 mL/min)	↓	↓	↓↑				
RIBAVIRIN[20, 270, 271, 273]					Any NOAC may be used (with caution)	↓						
REMDESIVIR[20, 270, 271]												
FAVIPIRAVIR[270]												
BEVACIZUMAB[270]												
ECULIZUMAB[270]												
TOCILIZUMAB[20, 270, 271]		↓		↓		↓	↓	↓				
FINGOLIMOD[20, 270]												
INTERFERON[20, 270]												
PIRFENIDONE[20, 270]												
METHYLPREDNISOLONE[20, 270]						↓						↓
NITAZOXANIDE[270, 271]						↑	↑	↑				

ESC Guidance for the Diagnosis and Management of CV Disease during the COVID-19 Pandemic Dostupno na: https://www.escardio.org/Education/COVID-19-and-Cardiology/ESC-COVID-19-Guidance#p11

Key points

- Consider anticoagulation at standard prophylactic doses in all patients admitted with COVID-19 infection.
- Consider the presence of acute PE in patients with COVID-19 infection in the setting of unexpected respiratory worsening, new/unexplained tachycardia, a fall in BP not attributable to tachyarrhythmia, hypovolaemia or sepsis, (new-onset) ECG changes suggestive of PE, and signs of deep vein thrombosis of the extremities.
- When acute PE is confirmed, treatment should be guided by risk stratification in accordance with the current ESC guidelines.
- DOACs may have interactions with some of the investigational drugs for COVID-19, notably lopinavir/ritonavir. In such cases, DOACs should be avoided. No major interactions have been reported between investigational drugs for COVID-19 and heparin anticoagulation.

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Important limitations of the ESC Guide

- The document is not a guideline but rather a guidance document. The recommendations are the result of observations and personal experience from health care providers at the forefront of the COVID-19 pandemic.

- Current evidence related to SARS-CoV-2 and its disease manifestations is observational and prospectively designed interventions are missing to form the basis for evidence-based recommendations.

- This guidance document does not replace any of the official ESC guidelines and is valid only as long as the pandemic status is maintained by the World Health Organization (WHO).

Thank you for your attention and interest
in this important topic!

Protecting patients in the COVID-19 era