



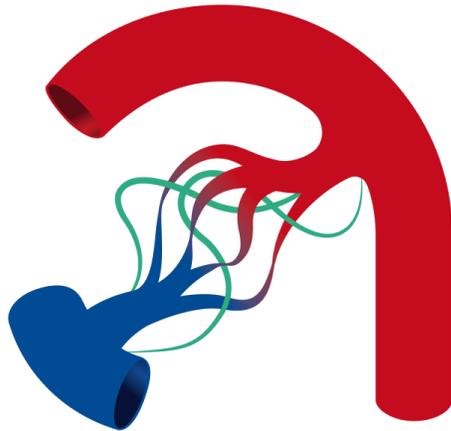
**European  
Reference  
Network**

for rare or low prevalence  
complex diseases



**Network**

Vascular Diseases  
(VASCERN)



# VASCERN Webinar: Heritable Thoracic Aortic Diseases (HTAD) and COVID-19 – Q&A Session

# VASCERN: The ERN on Rare Multisystemic Vascular Diseases

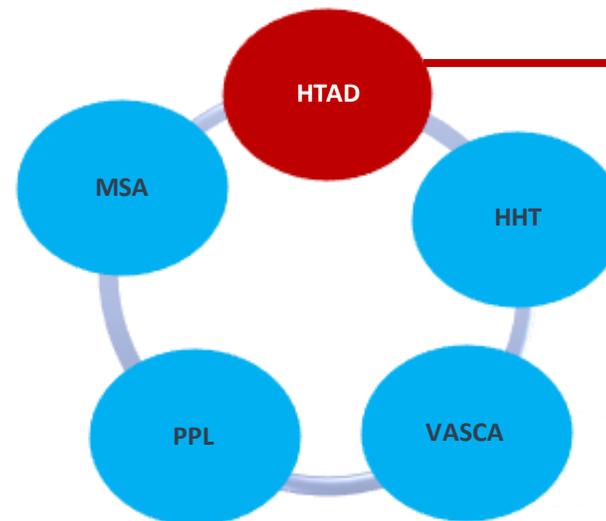


Gathers 30 Healthcare providers (HCP) full members plus 7 Affiliated Partners, coming from 17 EU countries

+ 70 Patient Organisations from all across Europe



More information available at:  
<https://vascern.eu>



5 Rare Disease Working Groups

**Heritable Thoracic Aortic Diseases (HTAD) Working Group**

- Marfan syndrome, Loeys-Dietz syndrome, Arterial Tortuosity Syndrome, Familial Thoracic Aortic Aneurysm and Aortic Dissection (TAAD), Familial Bicuspid Aortic Valve (BAV) etc...

# ePAG patient advocates of the HTAD WG



**Elena DE MOYA RUBIO**

**ePAG Co-Chair for HTAD**

Marfan Hilfe (Deutschland) e.V.

Germany



**Françoise STEINBACH**

**ePAG Deputy Co-Chair of HTAD**

Association Marfans

France



**+ other HTAD ePAG Patient Advocates and ePAG Patient Organisations from >14 other European countries!**

Full list here: <https://vascern.eu/expertise/epag/#1561643556720-6652f29e-7270>



# Professor Guillaume Jondeau



Cardiologist

Special interest in aortic diseases and Marfan syndrome

Reference Center for Marfan Syndrome and related disorders, department of cardiology at **AP-HP, Hôpital Bichat-Claude Bernard, Paris, France**

Co-Chair of VASCERN's Heritable Thoracic Aortic Diseases working group (HTAD WG) and coordinator of VASCERN.



# Professor Julie De Backer



Cardiologist and Clinical Geneticist

Special interest in Adult Congenital Heart Disease and Marfan syndrome

Department of Cardiology and Center for Medical Genetics at **Ghent University Hospital**, in **Belgium**

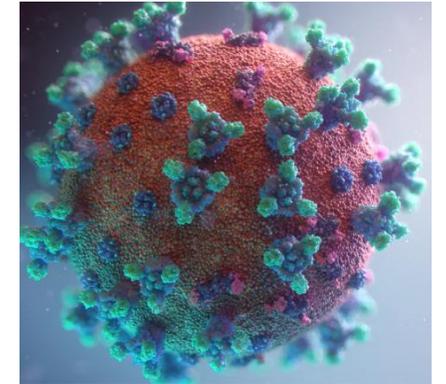
Chair of VASCERN's Heritable Thoracic Aortic Diseases working group (HTAD WG)

# Disease = COVID-19

## COVID-19 is caused by coronavirus Sars-CoV-2



- Stage I
  - early viral infection
  - associated constitutional symptoms
- Stage II
  - direct viral cytotoxicity (leading to cell death) of the pulmonary system with associated inflammatory activation
  - prominent respiratory system compromise, associated with dyspnea (shortness of breath) and ultimately acute respiratory distress syndrome (ARDS) and hypoxia
  - if the host is unable to clear the virus
- Stage III
  - Hyper-inflammatory state associated with profound elevations in inflammatory biomarkers
  - severe COVID-19 manifestations with multi-organ dysfunction and cytokine storm.
- Stage IV
  - delayed immune response: myocarditis, pseudo Kawasaki,...
- Stage V
  - Sequelae (consequences of COVID-19 disease)





# Toxicity of the disease

## 2 mechanisms for toxicity

### 1) direct effect of the virus

- HTAD : No decrease in efficiency of body for fighting the virus

### 2) hyper-immune reaction

- HTAD : No alteration in the immune system

## Disease more dangerous if patient fragile

- Is a patient with HTAD a fragile patient? The mutation itself does not weaken
- Previous and/or concomitant medical problem may weaken



# Fighting the disease COVID-19:

## 1) fighting coronavirus Sars-CoV-2

- *Nucleotide Analogs - Inhibitors of Viral Genome Replication*
  - Remdesivir functions as a chain terminator of RNA replication, initially designed for use against Ebola
  - favipiravir, which has investigational approval in several countries
  - Additional agents that are under study include emtricitabine/tenofovir and ribavirin
- *Protease Inhibitors - Inhibitors of Nonstructural Protein Generation*
  - Lopinavir, ritonavir combination in HIV,
  - Danoprevir, new specifically designed
- *Chloroquine...*
  - Thought to limit endosomal maturation
- *Antibodies from patients or synthetic antibodies*

# Fighting the disease COVID-19:



## 2) Immunomodulators

- Anti-inflammatories
  - Corticoids, IL6 inhibitors (tocilizimab, siltuximab)
  - Azithromycin (antibiotic) + chloroquine
  - JAK2 inhibitors (baricitinib)
  - Anti IL1, interferon gamma, colchicine
- 
- Vaccines
    - 6 currently being tested in humans, 82 in development



# Risks



- **of infection by COVID-19**
  - Immune suppression (not everybody will be infected, risk is not equal: true for all infectious diseases)
- **of occurrence of severe course**
  - Effect of the virus: immune suppression (eliminate more or less rapidly)
  - Effect of the immune reaction: (inappropriate, excessive reaction). No risk marker
- **in case of severe course**
  - **Severe course**
    - more dangerous for everyone,
    - more severe if previous damage weakens the body or the organ
  - **Complications of**
    - severe pneumopathy (ventilation, escarres...)
    - severe infection on all organs: renal failure (septic shock), hepatic necrosis (septic shock), cardiac failure (increased cardiac output)
- **in various organs : Effect of both the virus and the immune reaction**
  - Lungs: almost everybody
  - Heart (myocarditis): acute phase infection, later immune response
  - Vessels: acute phase thrombosis (pulmonary embolism, leg ischemia), later immune response
  - Gastro intestinal: direct virus (mostly acute phase)
  - Cutaneous: immune response ?
  - Kidney
  - ...
- **of long-term damage**
  - Long term consequences of acute alteration of organs

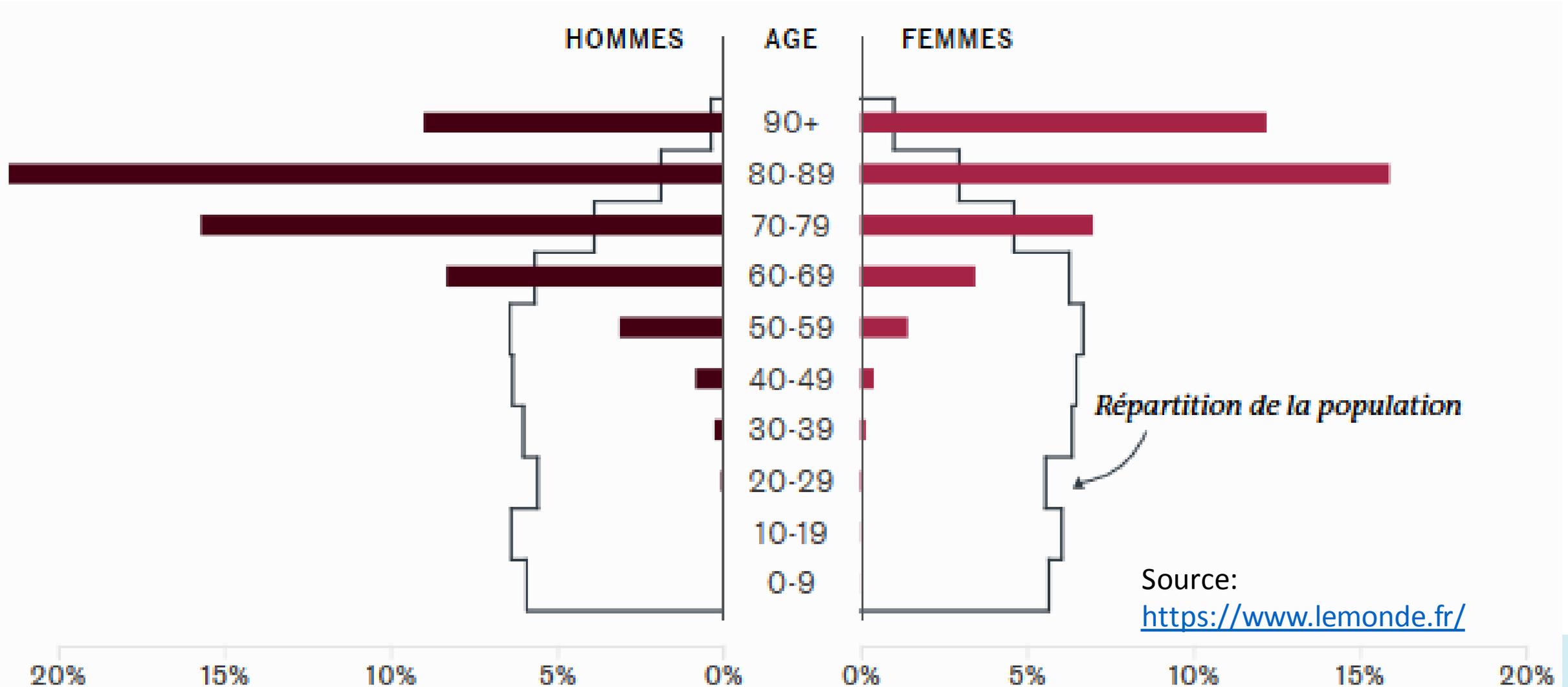
# Latest Research: N Engl J Med May 2020 Epub (Mehta M)



- 8910 pts COVID-19,
  - 11 countries
  - between Dec 20th 2019 and March 15 2020
- Multivariate logistic regression analysis found greater risk of death in:
  - Males
  - >65 years of age,
  - Coronary artery disease
  - Congestive heart failure
  - Previous cardiac arrhythmias,
  - Chronic obstructive pulmonary disease (COPD)
  - Current smokers
- No effect of angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs)/sartans

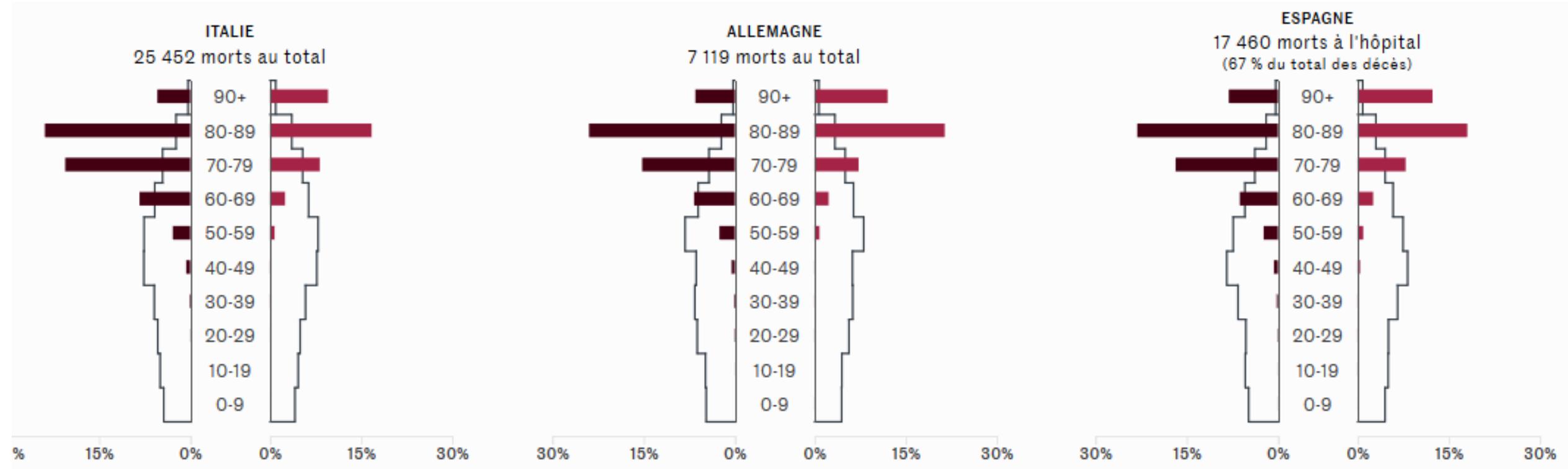


# Number of deaths by age/sex





# Number of deaths by age/sex in 3 countries



Source: <https://www.lemonde.fr/>



# Questions – ... and some answers



Questions from the Patient Community  
have been collected by VASCERN's HTAD ePAG advocates



# 3 Key Messages

1. HTAD Patient A  $\neq$  HTAD Patient B
2. Country A  $\neq$  Country B
3. COVID-19 = New Disease!





# General questions

## 1. Are patients which are recommended to get the flu vaccination also a COVID -19 high risk group?

Flu vaccination recommendations vary across countries – e.g

- US: *“The CDC recommends annual influenza vaccinations for everyone age 6 months or older.”*
- UK: *risk groups* (also includes those aged <10y)
- France: *people aged >6 months with underlying health conditions*

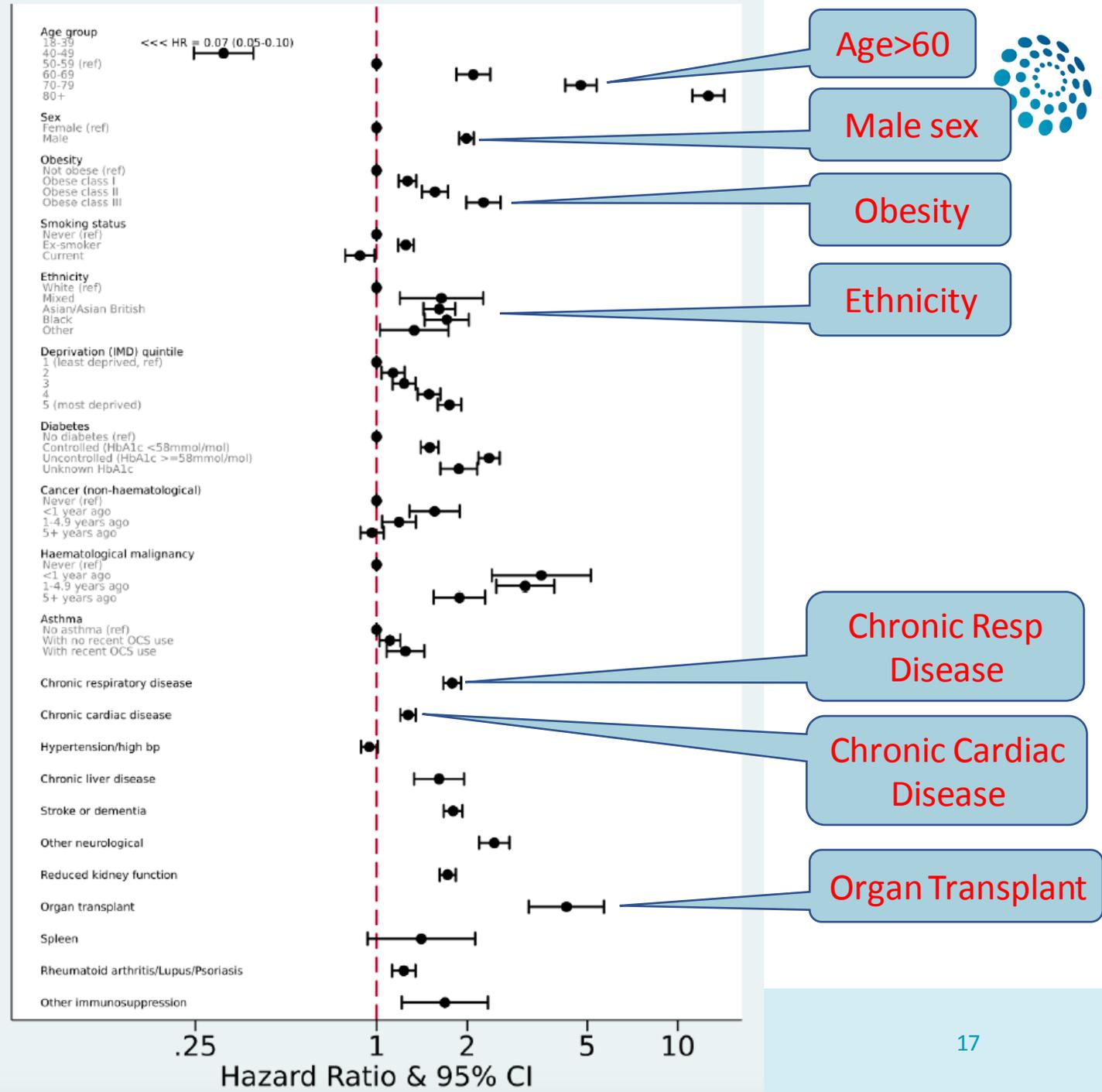
→ flu vaccination groups ≠ high risk groups

# General question

1. Are patients which are recommended to get the flu vaccination also a COVID-19 high risk group?

*OpenSAFELY: factors associated with COVID-19-related hospital death in the linked electronic health records of 17 million adult NHS patients.*

*medRxiv preprint doi: <https://doi.org/10.1101/2020.05.06.20092999>*

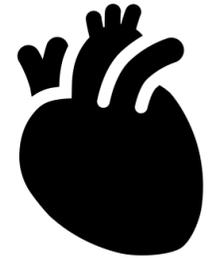




# General questions

## 2. What is a cardiovascular condition? Mitral valve prolapse? Previous aortic surgery (already repaired) Aneurysm, Dissection?

- Higher risk cardiovascular conditions include patients with:
  - Heart failure
  - Cardiomyopathy
  - Significant valve regurgitation
  - Patients with congenital cyanotic heart disease



[https://www.escardio.org/static\\_file/Escardio/Education-General/Topic%20pages/Covid-19/Patient%20Q\\_A-BD%20-%202023%2004%202020.pdf](https://www.escardio.org/static_file/Escardio/Education-General/Topic%20pages/Covid-19/Patient%20Q_A-BD%20-%202023%2004%202020.pdf)

- Mitral Valve Prolapse: No
- Previous aortic surgery: No
- Aortic aneurysm/dissection: No



# General questions

3. Are there any known cases of Marfan patients with COVID-19? And how is their healing process going?
- Some cases are known
    - None requiring hospitalisation
    - Recovery in all



# General questions

4. Should I postpone my aorta surgery/follow-up appointment because of COVID-19? Is this wise??

What should I do if my follow-up appointment is cancelled (no elective medicine)?

Is it safe not to go to the hospital, if we have an unusual issue not COVID-19 related?



Regulations on outpatient clinics/interventions differ across nations/regions



Surgery/FU appointments should be scheduled in agreement with your doctor

If you have a medical condition requiring attention **YOU SHOULD SEE YOUR GP/THE HOSPITAL** – as you would do in “normal times”



# General questions

## 5. Are blood pressure lowering medications working against COVID-19 too? (Valsartan )

*Reynolds et al, NEJM May 1st*



The NEW ENGLAND  
JOURNAL of MEDICINE

*Jarcho et al, NEJM May 1<sup>st</sup> (editorial,*



### CONCLUSIONS

We found no substantial increase in the likelihood of a positive test for COVID-19 or in the risk of severe COVID-19 among patients who tested positive in association with five common classes of antihypertensive medications.

Professional scientific societies and experts have spoken with one voice in advising that patients should not discontinue ACE inhibitor or ARB therapy out of a concern that they are at increased risk for infection, severe illness, or death during the COVID-19 pandemic. The data from these three studies support those recommendations.



# Specific questions

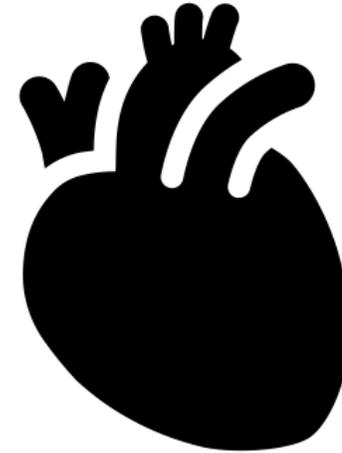
1. Is the risk of myocarditis\* increased for HTAD patients?

No – risk similar to general population

\*Myocarditis=inflammatory disease of the heart muscle

Infectious – virus

Immune - reaction

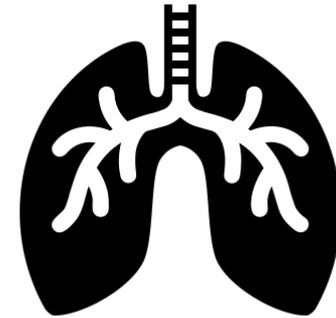




# Specific Questions

## 2. Pulmonary risk/complications with COVID-19 infection

- COVID-19 = Respiratory disease!
- Underlying pulmonary disease = higher risk
  - Emphysema (= “alveoli weakness”)
  - Severe asthma
  - Restrictive lung disease: complicated pneumothorax/severe pectus excavatum





# Specific Questions

3. Even if you have not had pneumothorax so far, are you at higher risk of it, if you need to get ventilation?
- Ventilation in COVID-19 patients often requires higher air pressure and holds a risk for pneumothorax (in everyone)– this needs to be taken into account in patients with HTAD but is not a contra-indication!



# Specific Questions

4. Is wearing a mask safe for people with Marfan in general or who have an aorta dissection (operated or not)? And if they normally have fatigue and air-hunger? Is the risk of hypercapnia higher?

In general for patients with HTAD: safe!



# Specific questions

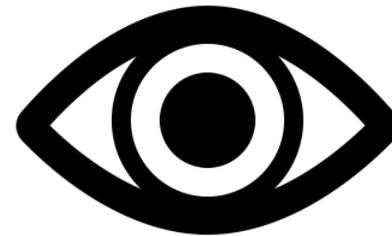
5. It seems that the virus can attack blood vessels in all organs, are we at higher risk here? And are people under AVK protected then? Clots
- Endothelial dysfunction: no evidence for patients with HTAD
  - Increased venous thrombosis risk similar as in general population – patients under anticoagulants possibly better outcome?
  - Kawasaki in children: no increased risk in HTAD



# Specific questions

## 6. What about ophthalmological complications?

- Ophthalmological manifestations of COVID-19: uncommon
- No data on increased risk





# General

## Follow the general hygiene rules!

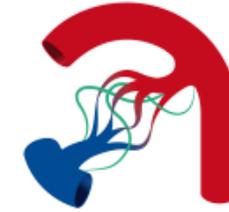
- Avoid people who are sick.
- Keep a two-metre distance from other individuals whenever possible.
- Wash hands thoroughly with soap and warm water for at least 20 seconds.
- Cover your mouth with a tissue when you cough or cough into the inside of your elbow.
- Cover your nose with a tissue when you sneeze or use the inside of your elbow.
- Avoid touching your eyes, nose and mouth.
- Clean often touched surfaces like doorknobs, handles, steering wheels, or light switches, with a disinfectant to remove the virus.
- Stay at home as much as possible, including working from home if this is feasible.
- If you have symptoms of fever (a temperature of 37.8°C or above), cough or a chest infection you should self-isolate.
- In some countries you may be asked to follow a stricter isolation (such as is the case with Italy, France, Spain, Belgium).



European  
Reference  
Network

VASCERN

Gathering the best expertise in Europe  
to provide accessible cross-border healthcare  
to patients with rare vascular diseases



VASCERN, the European Reference Network on Rare Multisystemic Vascular Diseases, is dedicated to gathering the best expertise in Europe in order to provide accessible cross-border healthcare to patients with rare vascular diseases (an estimated 1.3 million concerned). These include arterial disease (affecting aorta to small arteries), arterio-venous anomalies, venous malformations, and lymphatic diseases.

VASCERN currently consists of 35 expert teams from 30 highly specialised multidisciplinary Healthcare Providers (HCPs) plus 7 Affiliated Partner centers, coming from 17 EU Member States and of various European Patient Organisations and is coordinated in Paris, France.

Through our 5 Rare Disease Working Groups (RDWGs) as well as several thematic WGs and the ePAG – European Patient Advocacy Group, we aim to improve care, promote best practices and guidelines, reinforce research, empower patients, provide training for healthcare professionals and realise the full potential of European cooperation for specialised healthcare by exploiting the latest innovations in medical science and health technologies.

More information available at: <https://vascern.eu>

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