Morning Brief : Scientific Review

15 April 2020

The purpose of the Morning Brief is to **summarize** and present key information, research articles and other relevant publications pertaining to critical care and COVID-19. We aim to prioritise information, articles and publications released in the preceding 24-48hours.

Stellenbosch University Research Response Team

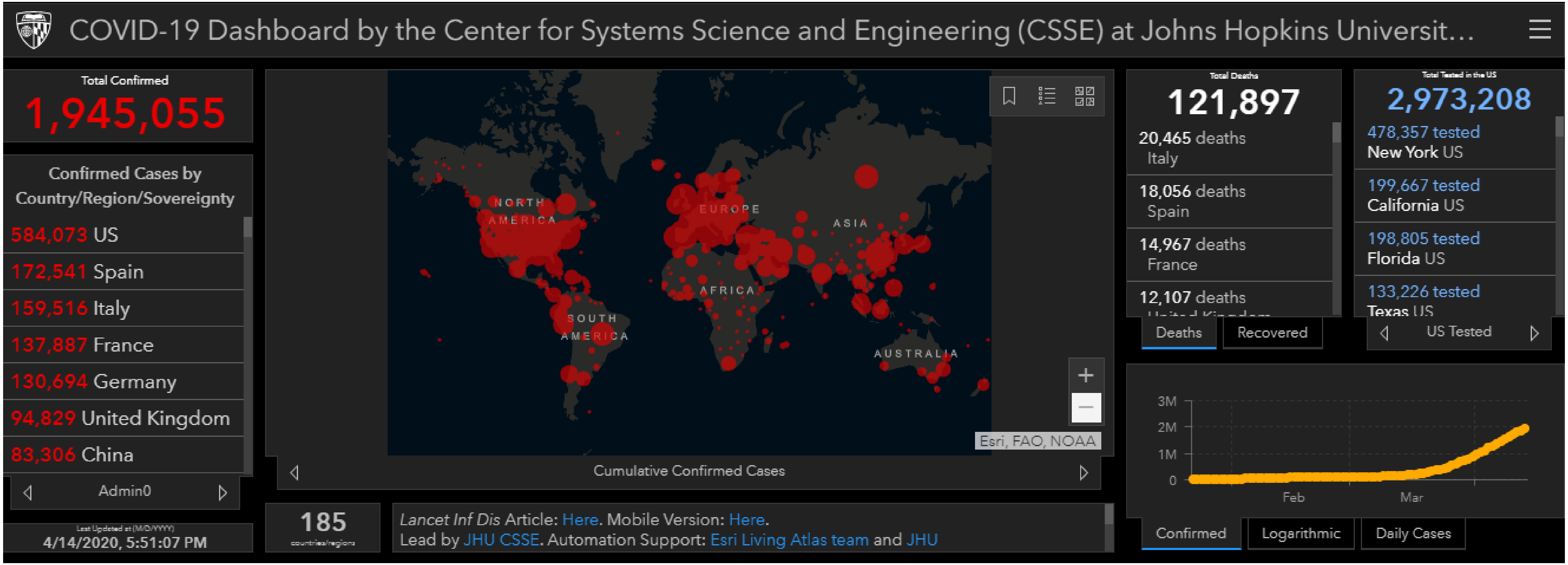
Content

- **Global Update**
- **South African Update**

Topic:

- **ACE2 and COVID-19**
- **Two reports on autopsies of COVID-19 patients**

Global Update



Accessed at 19:00 on 14 April 2020
Source: https://coronavirus.jhu.edu/map.html

South African Update

Currently, there are 35 people who tested COVID-19 positive being treated in hospitals in the Western Cape.
Of these patients, 18 of them are in intensive care

The provincial breakdown is as follows:

GAUTENG	909
WESTERN CAPE	643
KWAZULU – NATAL	489
EASTERN CAPE	174
FREE STATE	98
LIMPOPO	24
MPUMALANGA	22
NORTH WEST	22
NORTHERN CAPE	16
UNALLOCATED	18

COVID-19 Statistics in South Africa

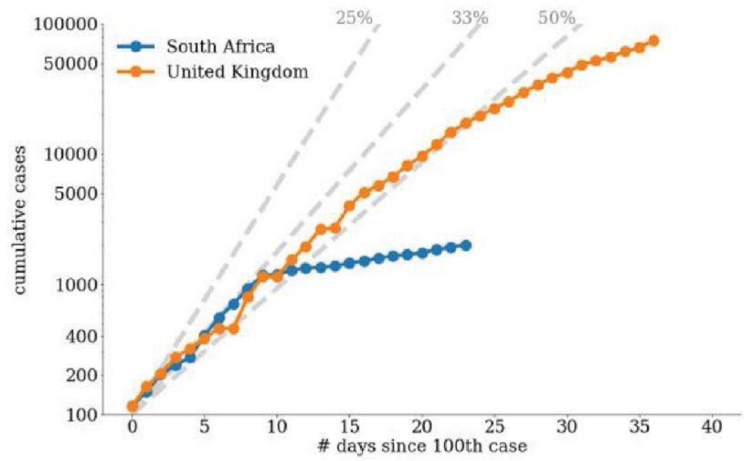
87022	2415	410	27
Tests Conducted	Positive Cases Identified	Recoveries	Deaths

Accessed at 19:10 on 14 April 2020
Source: https://sacoronavirus.co.za/
https://www.westerncape.gov.za/department-of-health/news/update-premier-alan-winde-coronavirus-14-april

In the initial period of infection, both South Africa and the United Kingdom had similar trajectories in the rate of infection. However, after South Africa implemented the national lockdown, its trajectory changed drastically as compared to the UK.

Covid-19 cases - SA vs UK

SA's expected vs actual trajectory



Learn more to Be READY for #COVID19:
www.sacoronavirus.co.za

NICD Hotline: 0800 029 999
WhatsApp 'Hi' to 0600 123 456

THIS IS AN IMPORTANT WEEK

10-16 April

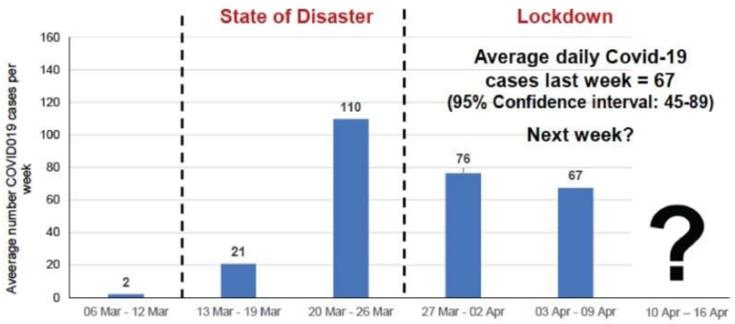
If we reach more than 90 new cases per day, lockdown will continue.

(Average new daily cases last week was 67)

STAY HOME
SAVE SOUTH AFRICA
TOGETHER WE CAN BEAT THE CORONAVIRUS

What should we do this week?

Follow the lockdown rules and monitor community transmission by average daily cases & community positivity/screened



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Source: https://sacoronavirus.co.za/2020/04/14/this-is-an-important-week-flattenthecurve/

Articles of Interest

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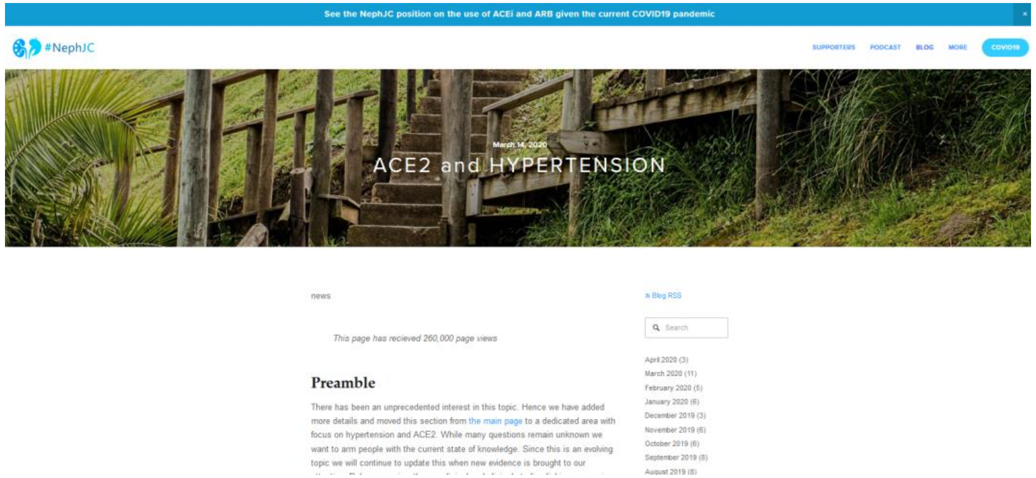
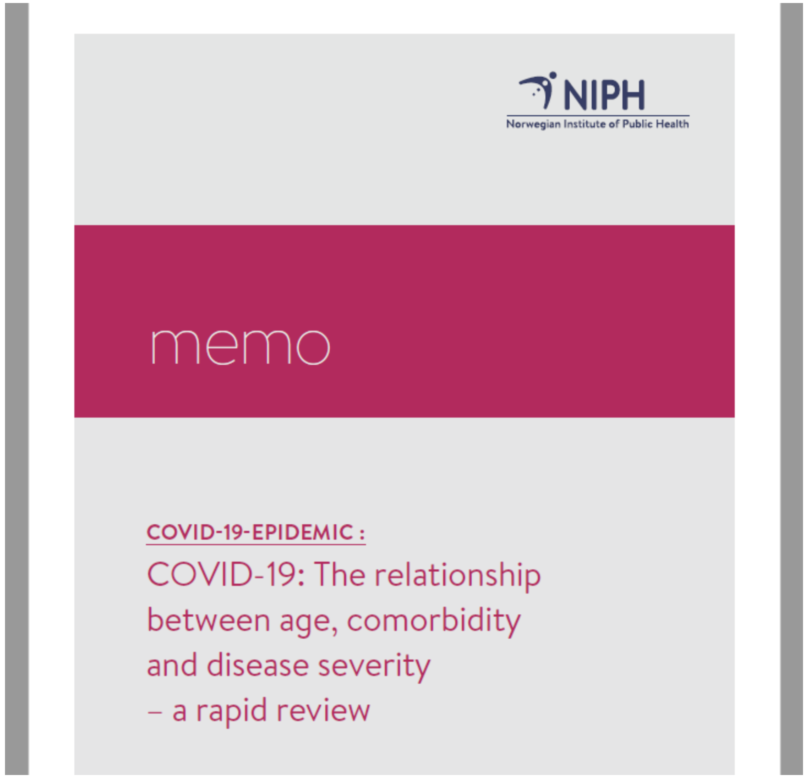


NephJC is a group of nephrologists and others who maintain a dedicated page on publications emerging on COVID19 and ACE inhibitors/ARBs, updated frequently.
http://www.nephjc.com/news/covidace2



The Norwegian Institute for Public Health conducts frequent literature searches and maps new papers into specific categories for easy access to information on COVID19. They also conduct rapid reviews of specific topics to summarise the currently available evidence.

"A rapid review is a form of knowledge synthesis that accelerates the process of conducting a traditional systematic review through streamlining or omitting specific methods to produce evidence for stakeholders in a resource-efficient manner."

Notes on the methods used in the literature included in this brief:

Sparks et al. is an editorial paper, taking the form of a narrative review.
The NephJC website is a curated list and discussion of published papers relevant to COVID-19 and ACE2.
Brurberg et al. is a rapid review for which Pubmed and Embase were searched with a comprehensive search strategy and two authors reviewed and summarised results from most included papers individually with limited duplicate review and data extraction.
Barton et al. and Fox et al., are descriptive case reports of autopsies.

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What is the link between ACE2 and COVID-19?

The SARS-CoV-2 spike protein gains entry into cells by binding ACE2 and type 2 transmembrane serine proteases. (SARS also uses ACE2)

ACE2 = enzyme in the renin angiotensin system, regulates vasoconstriction amongst other things.
Occurs in soluble and membrane-bound form.

ACE2 is expressed in alveolar epithelial cells, endothelial cells of veins and arteries of many tissues, squamous epithelium of nasopharynx, also in small intestine, kidney and other tissues.

ACE2 has not been shown to be found in B and T lymphocytes or macrophages.

Link: Does the inhibition of ACE by ARBs/ACEi lead to increased ACE2 expression and does this change viral entry?

- Animal studies: evidence for both increase and no increase in ACE2 after Rx with ACEis or ARBs.
- Humans: evidence only of soluble ACE2, none for membrane-bound. Inconclusive.
- No studies on whether increased ACE2 expression promotes viral entry or progression to severe disease.

Hypotheses both for risk and benefit of ACEis and ARBs in COVID-19, but no published evidence currently.

Refs: Sparks MA, Hiremath S et al. "The Coronavirus Conundrum: ACE2 and Hypertension Edition" NephJC http://www.nephjc.com/news/covidace2 *accessed 13 April 2020*
Sparks, MA et al. Sound Science before Quick Judgement Regarding RAS Blockade in COVID-19, CJASN Vol 15 May 2020, https://doi.org/10.2215/CJN.03530320,
Hamming, I, et al., Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesisJ Pathol 2004; 203: 631–637

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Are patients with comorbidities at greater risk of getting COVID-19, developing severe disease or dying?

Information from observational studies

Comparison of raw proportions:

$$\frac{\text{patients with comorbidities}}{\text{severe disease or deaths}} \quad \text{vs} \quad \frac{\text{patients with comorbidities}}{\text{mild disease or survivors}}$$

Most of these studies did not adjust for age. As age and cardiovascular comorbidities, hypertension, diabetes etc. are also correlated, the risk that can be attributed to age, and the risk attributed to comorbidities is hard to unravel with the current data.

It seems likely that age and comorbidities are independent risk factors for severe disease and there is probably no harm in monitoring both older patients, and those with comorbidities like hypertension, cardiovascular disease, COPD and diabetes more closely, as there are currently no proven beneficial interventions to prevent severe disease in high risk groups.

Refs: Sparks MA, Hiremath S et al. "The Coronavirus Conundrum: ACE2 and Hypertension Edition" NephJC http://www.nephjc.com/news/covidace2 *accessed 13 April 2020*
Sparks, MA et al. Sound Science before Quick Judgement Regarding RAS Blockade in COVID-19, CJASN Vol 15 May 2020, https://doi.org/10.2215/CJN.03530320,
Brurberg K, Fretheim A. COVID-19: The relationship between age, comorbidity and disease severity – a rapid review. Oslo: Norwegian Institute of Public Health, 2020.

Are patients on ACE inhibitors/ARBs at increased risk of infection or severity of disease?

Data on chronic medication use in COVID-19 patients are very rare and any existing comparisons are from small numbers of patients – not sufficient evidence for conclusions on medications as risk factors for COVID-19.

Working group of nephrologists tracking evidence on ACE inhibitors and Angiotensin II receptor blockers in COVID-19. http://www.nephjc.com/news/covidace2

List 13 statements released by hypertension, cardiovascular, nephrology and other societies, between 12 March and 29 March, all stating that currently there is not enough evidence to support stopping ACE inhibitors or Angiotensin II receptor blockers to prevent transmission or severe COVID-19 disease.

Several clinical trials are planned or ongoing to investigate risks and benefits of ACEis/ARBs in COVID-19 and will provide additional information when their results are available.

Refs: Sparks MA, Hiremath S et al. "The Coronavirus Conundrum: ACE2 and Hypertension Edition" NephJC http://www.nephjc.com/news/covidace2 *accessed 13 April 2020*
Sparks, MA et al. Sound Science before Quick Judgement Regarding RAS Blockade in COVID-19, CJASN Vol 15 May 2020, https://doi.org/10.2215/CJN.03530320

Two autopsies in Oklahoma, US

- 77 y
- History of hypertension, previous dvt, splenectomy for an unspecified genetic disease, pancreatitis, total knee replacement and previous positive antinuclear antibody serology
- 6 day history of fever and chills, no cough, no test and no treatment
- Sudden deterioration with weakness and shortness of breath
- Cardiac arrest in ambulance, resuscitation failed, died
- BMI 31
- PCR pos
- Findings:
- Lungs heavy, dark red colour, edematous parenchyma, no mucus plugging, diffuse alveolar damage, numerous hyaline membranes, thrombi in a few small pulmonary artery branches, congestion of alveolar septal capillaries, oedema in the airspaces, mucosal oedema in bronchial mucosa, no eosinophils, no neutrophils, CD4 positive and CD8 positive T-cells, few macrophages. No evidence of myocarditis.

42 y
Known with myotonic muscular dystrophy, and limited mobility
Cause of death acute bacterial bronchopneumonia due to aspiration, no evidence of diffuse alveolar damage, PCR pos

Refs: Barton, LM, et al., COVID-19 Autopsies, Oklahoma, USA, Am J Clin Pathol 2020;XX:1-9, DOI: 10.1093/ajcp/aqaa062

Four autopsies, New Orleans, US

Pre-print, not peer reviewed
Report on first 4 of twelve autopsies

4 autopsies, 44 – 76 years
All obese with hypertension, 3 with insulin dependent type 2 diabetes, 2 with chronic kidney disease
1 taking methotrexate (indication not stated)

3 Day history of mild cough and fever
Sudden respiratory decompensation and transport to emergency rooms
Worsening clinical picture of ARDS, intubated and ventilated in ICU
Rx: vancomycin, azithromycin, 1 on dexamethasone
Labs: PCR pos, elevated ferritin, fibrinogen, PT,
increase neutrophils and lymphopenia,
D-dimer high in 2

Refs: Fox, SE, et al., Pulmonary and Cardiac Pathology in Covid-19: The First Autopsy Series from New Orleans, medRxiv preprint doi: https://doi.org/10.1101/2020.04.06.20050575

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Four autopsies, New Orleans, US

Pre-print, not peer reviewed
Report on first 4 of twelve autopsies

Findings:
Heavy lungs, 3 with pink froth in airways, 1 with thick white mucus
Mild clear pericardial and pleural effusions
Diffuse parenchymal oedema, consolidation, dark red haemorrhage with focal demarcation in 3
Focal consolidation only in patient on immune-suppressor
Bilateral diffuse alveolar damage, moderate lymphocytic infiltrates (CD4 and CD8)
Thrombi in small vessels
Desquamated type 2 pneumocytes with apparent viral cytopathic effects
Hyalin membranes, fibrin deposits
Fibrin thrombi in alveolar capillaries, surrounded by oedema
Notable CD61 pos megakaryocytes, possibly representing resident pulmonary megakaryocytes, in alveolar capillaries and associated with platelets
Entrapment of neutrophils by fibrin and platelets
Signs of possible secondary infection in the case on immunosuppressor

Cardiac
Cardiomegaly and RV dilatation
No typical signs of viral myocarditis, but scattered individual myocyte necrosis was seen
They note that direct viral infection of myocytes not ruled out by their examination

Their summary:
“The dominant process in all cases was consistent with diffuse alveolar damage, with a mild to moderate mononuclear response consisting of notable CD4+ aggregates around thrombosed small vessels, and significant associated hemorrhage. Important additional mechanisms that may have contributed to death in this initial series of autopsies include a thrombotic microangiopathy that was restricted to the lungs. This process may involve activation of megakaryocytes, possibly those native to the lung, with platelet aggregation and platelet-rich clot formation, in addition to fibrin deposition. Small vessel thrombus formation in the lung periphery was in many cases associated with foci of alveolar hemorrhage.”

They speculate about the potential of SARS-CoV2 to infect megakaryocytes directly, because of previous speculation about SARS infecting megakaryocytes. But in vitro, it could not be shown that SARS could infect megakaryocytes.

Refs: Fox, SE, et al., Pulmonary and Cardiac Pathology in Covid-19: The First Autopsy Series from New Orleans, medRxiv preprint doi: https://doi.org/10.1101/2020.04.06.20050575
Yang M, Ng MH, Li CK, et al. Thrombopoietin levels increased in patients with severe acute respiratory syndrome. *Thromb Res*. 2008;122(4):473–477. doi:10.1016/j.thromres.2007.12.021

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This summary was prepared by
Dr E Maasdorp at Stellenbosch University as part of the daily brief to the TBH ICU team

If you want to know more about Rapid reviews:
https://www.who.int/alliance-hpsr/resources/publications/rapid-review-guide/en/
https://covidrapidreviews.cochrane.org/resources