Modules Cardiovasculaire complicaties en cardiovasculaire ziekten COVID-19

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Nederlandse Vereniging Voor Cardiologie (NVVC)

IN SAMENWERKING MET
Nederlandse Vereniging Voor Intensive Care Geneeskunde (NVIC)
Nederlandse Vereniging voor Thoraxchirurgie (NVT)
Nederlandse Vereniging van Artsen voor Longziekten en Tuberculose (NVALT) Nederlandse Internisten Vereniging (NIV)
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MET ONDERSTEUNING VAN
Kennisinstituut van de Federatie Medisch Specialisten

FINANCIERING
De ontwikkeling werd gefinancierd uit de Stichting Kwaliteitsgelden Medisch Specialisten (SKMS)

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Module 1 Omvang van cardiale schade bij in het ziekenhuis opgenomen COVID-19 patiënten

Clinical question

How often and in what extent do admitted COVID-19 patients have signs of cardiac injury as defined according to the Fourth Universal Definition of Myocardial Infarction? And if so, what is the outcome of the non-ischemic injury and ischemic (type 1 and 2) infarction patients?

Introduction

The paradigm that the presence of cardiovascular disease is a risk factor for severe COVID-19 and that COVID-19 can cause myocardial injury has recently been described. Questions remain whether and to what extent COVID-19 causes myocardial damage and whether myocardial injury is an important contributor of outcome with implications for management, like medication, imaging, long-term follow-up and perhaps situations were triaging patients is needed.

Search and select

A review of the literature was performed to answer the following question:

What is the occurrence, extent and outcome of cardiac injury and myocardial infarction in admitted patients with COVID-19?

P: Admitted COVID-19 patients

I: Presence of evidence of elevated cardiac troponin values (cTn) **– either cTnT or cTnI –** with at least 1 valueabove the 99th percentile upper reference limit (URL).

C: Admitted COVID-19 patients without cardiac injury

O: Mortality, revascularization, IC-admission, days on ventilation, hospital duration, intervention (PCI, CABG, ICD implantation, Left and/or Right Ventricle Assist Device support), VA-ECLS, VV-ECLS.

Relevant outcome measures

Mortality and revascularization were considered as crucial outcome measures and IC-admission, days on ventilation, hospital duration, intervention (PCI, CABG, ICD implantation, Left and/or Right Ventricle Assist Device support), VA-ECLS, VV-ECLS important outcomes.

Search and select (Methods)

The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms until July 6th 2020. The systematic literature search resulted in 484 hits. See search strategy for detail.

120 Studies were initially included based on title and abstract screening. After a second assessment in which the titles and abstracts of the 120 studies were assessed for inclusion based on the PICO, 26 studies were selected. Studies that described the underlying mechanism, described the wrong outcome, did not define the intervention in the right way, did not contain original data or were literature reviews but not systematic reviews were excluded. After reading the full text six papers were included (1 systematic review, 5 single studies). Since the search of the systematic review was performed on March 29, all studies published before that date were excluded (1 study). In total 5 papers (1 systematic review, 4 single studies) were included.

Results

Five studies were included in the analysis of the literature. Important study characteristics and results are summarized in the evidence tables. The assessment of the risk of bias is summarized in the risk of bias table.

Summary of literature

Description of studies

The aim of the review of **Santoso (2020)** was to explore the association between cardiac injury and mortality, the need for intensive care unit (ICU) care, acute respiratory distress syndrome (ARDS), and severe coronavirus disease 2019 (COVID-19) in patients with COVID-19 pneumonia PubMed, SCOPUS, EuropePMC, ProQuest, and Cochrane Central Databases were searched. Search results were limited to 2020. All research articles in adult patients diagnosed with COVID-19 with information on cTnl, cardiac injury, and clinical grouping or outcome of the clinically validated definition of mortality, the need for ICU care, acute respiratory distress syndrome (ARDS), or severe COVID-19 were included. Articles other than original research (e.g., case report or series, review articles, letters to editor, editorials or commentaries), duplicate publication, and non-English articles were excluded. The search was finalized on March 29th 2020. A total of 13 studies were included. Four studies were not peer-reviewed. All studies were retrospective observational studies. Most of the included studies defined cardiac injury as cTnl above 99th percentile in which the troponine cut-off was different in the included studies. Some of the studies included in this review did not specify a definition for cardiac injury. Seven of the included studies reported on mortality and were included in a meta-analysis (Risk ratio M-H). Three studies were included in a meta-analysis considering the relation between cardiac injury and IC-admission (risk ration M-H).

Barman (2020) aimed to delineate the prognostic importance of presence of concomitant cardiac injury on admission in patients with COVID-19 in Turkey. In this multi-center retrospective observational study, data of consecutive patients who were treated for COVID19 between 20 March and 20 April 2020 were collected. Clinical characteristics, laboratory findings and outcomes data were obtained from electronic medical records. Acute cardiac injury was defined as high sensitivity cardiac troponin I serum levels above the 99th percentile upper reference limit, regardless of new abnormalities in ECG. In-hospital clinical outcome was compared between patients with and without cardiac injury. total of 607 hospitalized patients with COVID-19 were included in the study. **Kuno (2020)** aimed to investigate whether cardiovascular disease or cardiac injury increased the risk of mechanical ventilation or mortality using the electronic medical records of Mount Sinai Health System in New York City. Kuno retrospectively analyzed a cohort of 8438 COVID-19 patients seen between March 1 and April 22, 2020. Mount Sinai health system combines 7 hospitals with more than 3800 beds and more that 410 ambulatory practices across metropolitan New York. Among 8438 patients, 54.7% of patients (N = 4616) were admitted to these hospitals. Analysis was performed on April 30th, 2020, which included patients who remained in the hospitals. Cardiac injury was defined as troponin I elevation which was defined as 99th percentile upper reference limit.

Lorente-Ros (2020) studied the effect of myocardial injury assessment on risk stratification of COVID-19 patients. In this observational study, a matched cohort of 112 patients was developed. After matching, an adequate comparability was shown by a decrease of the standardized differences to less than 20% for all covariates. Mortality was compared between patients with and without cardiac injury. Cardiac injury was defined as cTnI levels greater than the 99th percentile of a healthy population.

Wei (2020) sought to characterize the prevalence and clinical implications of acute myocardial injury in a large cohort of patients with laboratory-confirmed COVID-19. Data of 103 consecutive patients with laboratory-confirmed SARS-CoV-2 infection admitted to the Public Health Clinical Centre of Chengdu and West China Hospital, Sichuan University, was collected between 16 January and 10 March 2020. Acute myocardial injury was defined by an cTnT value greater than the institutional upper limit of normal (14pg/mL). Outcomes of interest included death, admission to an intensive care unit (ICU), need for mechanical ventilation, treatment with vasoactive agents and classification of disease severity.

Table 1.1 describes the characteristics of the included studies.

Table 1.1 Study characteristics of included studies. It should be noted that the cardiac troponins (cTn) assays used in these studies differ in analytical characteristics, including their assessment of the upper reference limits, thereby limiting the direct comparability between studies.

Study	Study type	N	Country	Cardiac injury definition	Method	Outcome
Santoso, 2020	Systematic review	2389 (13 studies) Mortality: N= 1550 (7 studies) IC admission N=524 (3 studies)	Not reported except 'Most of the studies are from China'	highly sensitive cardiac troponin I (cTnI) above 99th percentile upper reference limit Moment of measurement: not reported	Odds ration meta-analysis (Mantel-Haenszel)	Mortality, IC admission
Barman,2020	multi-center retrospective study	607	Turkey	high sensitivity cardiac troponin I serum levels above the 99th percentile upper reference limit, regardless of new abnormalities in ECG Moment of measurement: at hospital admission	Chi-square test was used to assess differences in categorical variables between groups. Student's t-test or Mann–Whitney U test was used to compare unpaired samples as needed. Cox regression model	Mortality, IC admission, hospital duration
Kuno, 2020	Retrospective study	8438 5320 in which troponin was measured	US	Cardiac injury was defined as troponin I elevation which was defined as 99th percentile upper reference limitMoment of measurement: not reported	RR, stratification for age groups	Mortality
Lorente-Ros, 2020	Matched retrospective cohort. After matching, an adequate comparability was shown by a decrease of the standardized differences to less than 20% for all covariates	707	Spain	cTnI levels greater than the 99th percentile upper reference limit Moment of measurement: at hospital admission	Multivariate Cox proportional hazards regression models	Mortality, IC admission, hospital duration
Wei, 2020	Prospective assessment of medical records	101	China	Acute myocardial injury was defined by an cTnT value greater than the institutional upper limit of normal (14pg/mL) Moment of measurement: at hospital admission	Student t-test or the Mann-Whitney U test to compare death for elevated cTn levels, Chi-square	Mortality, IC admission

Results

The included studies solely reported mortality (Santoso, Barman, Kuno, Lorente-Ros, Wei), IC-admission (Santoso, Barman, Lorente-Ros, Wei) and hospital duration (Barman, Lorente-Ros). Ventilation was also an outcome in some studies (Kuno, Lorente-Ros, Wei) but was not defined as days on ventilation but if ventilation was necessary. Therefore, this literature overview only reports on mortality, IC-admission and hospital duration.

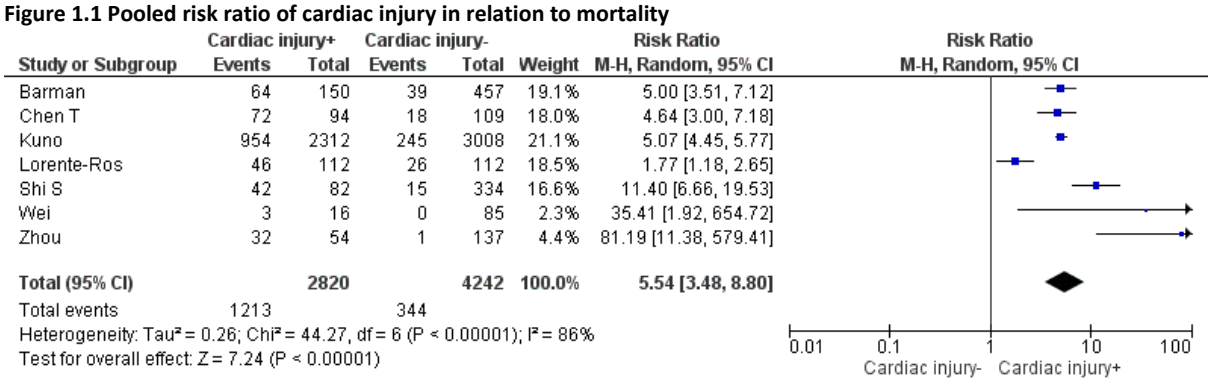
1. Mortality

The systematic review of Santoso (2020) described 7 studies (of which 4 not peer reviewed) in which the outcome mortality was studied. The meta-analysis of Santoso calculated a pooled risk ratio of 7.95 (95% CI 5.12-12.34). The heterogeneity (I^2) was 65%, meaning this may represent substantial heterogeneity. Barman (2020), Kuno (2020), Lorente-Ros (2020) and Wei (2020) also studied the outcome mortality in relation to cardiac injury. Barman (2020) and Lorente-Ros (2020) performed a univariate and multivariate regression analysis. In the study of Barman (2020) the univariate analysis (30 days) resulted in odds ratio (OR) of 7.97 (95% CI 5.03-12.64; P<0.001). The multivariable regression model (30 day) resulted in OR 10.58 (95% CI 2.42-46.27; P<0.001). In the multivariate model age, sex, hypertension, diabetes mellitus, CAD, smoking, COPD, creatinine, glucose, CRP and D-dimer ≥500 were taken into account in addition to cardiac injury. In the study of Lorente-Ros (2020) in the matched cohort all-cause mortality within 30 days was higher in those with cTnI elevation (41.1% vs. 23.2%; p = 0.005). The univariable regression model (30 days) resulted in Hazard Ratio (HR) of 4.355 (95% CI 3.112–6.093; P<0.001). The Multivariable regression model (30 days) resulted in HR 1.716 (95% CI 1.182–2.492; P=0.005). In the multivariable model sex, age, hypertension, RAAS inhibitors use, hematocrit, creatinine, D-Dimer, C-reactive protein and CCI were taken into account in addition to cardiac injury.

The study of Kuno (2020) resulted in an RR of 5.07 (95% CI 4.45-5.76) for mortality and the study of Wei (2020) calculated the difference between patients with and without cardiac injury that died. Patients with acute myocardial injury were older, with a higher prevalence of pre-existing cardiovascular disease and more likely to require ICU admission (62.5% vs 24.7%, p=0.003), mechanical ventilation (43.5% vs 4.7%, p<0.001) and treatment with vasoactive agents (31.2% vs 0%, p<0.001). Log cTnT was associated with disease severity (OR 6.63, 95% CI 2.24 to 19.65), and all of the three deaths occurred in patients with acute myocardial injury.

A pooled risk ratio was calculated in which only the peer reviewed studies from the systematic review of Santoso (2020) and the results of Barman (2020), Kuno (2020), Lorente-Ros (2020) and Wei (2020) were included (figure 1.1). The pooled risk ratio of COVID-19 patients with cardiac injury in relation to mortality was 5.54 (95% CI 3.48 – 8.80). This means that COVID-19 patients with cardiac injury had a 5 times higher chance on mortality in comparison to a COVID-19 patient without cardiac injury. The I^2 was 86%, indicating that these studies might represented substantial heterogeneity.

Figure 1.1 Pooled risk ratio of cardiac injury in relation to mortality



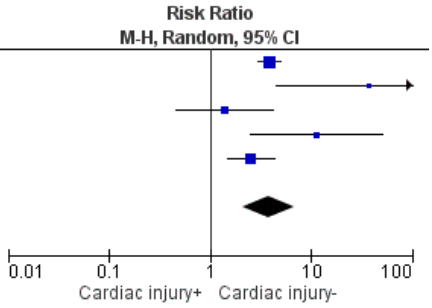
2. IC admission (important outcome)
In the systematic review of Santoso (2020) three studies assessed the outcome IC admission and were included in a meta-analysis. Of the individual studies Barman (2020), Lorente-Ros (2020) and Wei (2020) assessed IC admission.
For IC admission the systematic review of Santoso shows a Pooled Risk Ratio (RR) of 7.94 (95% CI 1.51-41.78), meaning that cardiac injury was associated with a higher need for IC admission in COVID-19 patients. The studies of Barman, Lorente-Ros and Wei compared the number of IC admission for COVID-19 patients with and without cardiac injury. The studies of Barman (72% vs 19%; P<0.001) and Wei (62.5% vs 24.7%; P=0.003) showed a significant difference between both groups. Lorente-Ros concluded that there was no significant difference between both groups (6.3% and 4.3%; P=0.527). However, the number of patients requiring IC admission in this study were very small (7 and 5) what might have influenced the effect.

A pooled RR was calculated including only the peer reviewed studies from the systematic review of Santoso (2020) and the individual studies that assessed IC admission (figure 1.2). The pooled RR of COVID-19 patients with cardiac injury in relation to IC admission was 3.78 (95% CI 2.07-6.89). This means that COVID-19 patients with cardiac injury had a 3.8 times higher change of IC admission. The I^2 was 66%, indicating that these studies might represented substantial heterogeneity.

Figure 1.2 Pooled risk ratio of cardiac injury in relation to IC admission

	Cardiac injury+		Cardiac injury-			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
Barman	64	94	70	397	36.0%	3.86 [3.00, 4.98]
Huang	4	19	1	179	6.5%	37.68 [4.44, 320.19]
Lorente-Ros	7	112	5	112	16.5%	1.40 [0.46, 4.28]
Wang D	8	36	2	102	11.3%	11.33 [2.52, 50.90]
Wei	10	16	21	85	29.6%	2.53 [1.49, 4.30]
Total (95% CI)		**277**		**875**	**100.0%**	**3.78 [2.07, 6.89]**
Total events	93		99			

Heterogeneity: Tau² = 0.24; Chi² = 11.63, df = 4 (P = 0.02); I² = 66%
Test for overall effect: Z = 4.34 (P < 0.0001)



3. Hospital duration (important outcome)
Barman (2020) reported a significant difference between patient with cardiac injury and without cardiac injury for hospital duration (Cardiac injury: 12 (5–14) days, no cardiac injury–: 9 (4–12) days; P<0.001). Lorente-Ros (2020) reported no significant difference between patient with cardiac injury and without cardiac injury for hospital duration (Cardiac injury: 11 (6 to 17) days, no cardiac injury: 9 (5 to 13) days; P=0.934).

<u>Level of evidence of the literature</u>
The level of evidence was assessed according to the GRADE methodology (GRADE: Grading Recommendations Assessment, Development and Evaluation, http://www.gradeworkinggroup.org/).

Mortality (crucial outcome)
Starting with a high level of evidence for prognostic studies, the level of evidence regarding the outcome measure mortality was downgraded by 2 levels because of risk of bias (retrospective design, correction for confounders often not applied) to 'low'.

IC admission (important outcome)
Starting with high level of evidence for observational studies in a prognostic studies, the level of evidence regarding the outcome measure IC admission was downgraded by 2 levels because of risk of bias (retrospective design, correction for confounders often not applied), by 1 level for indirectness (none of the studies are performed in the Netherlands and each country can have

different criteria for IC admission and IC admission may depend on IC capacity) by 1 level because of imprecision (wide confidence interval in study Santoso, few events in study of Lorente-Ros) to 'very low'.

Hospital duration (important outcome)
Starting with high level of evidence for prognostic studies, the level of evidence regarding the outcome measure hospital duration was downgraded with 1 level for inconsistency (both studies assessing hospital duration come to a different conclusion), 1 level for indirectness (the studies are performed in other European countries and each country may have their own criteria for hospital discharge), and 1 level for imprecision (only two studies included, low number of patients and follow up duration and number of patients lost to follow up unclear) to 'very low'.

Conclusions
Mortality (crucial)

Low GRADE	Cardiac injury, defined as cTn elevation greater than 99th percentile, in COVID-19 patients could be associated with a higher risk of mortality. *Sources: Santoso, Lorente-Ros, Barman, Wei*

IC admission (important)

Very low GRADE	We are unsure if cardiac injury, defined as cTn elevation greater then 99th percentile, in COVID-19 patients is associated with IC admission. *Sources: Santoso, Lorente-Ros, Barman, Wei*

Hospital duration (important)

Very low GRADE	We are unsure if cardiac injury, defined as cTn elevation greater then 99th percentile, in COVID-19 patients is associated with the number of days of admission in the hospital. *Sources: Barman, Lorente-Ros*

Overwegingen – van bewijs naar aanbeveling
Voor- en nadelen van de interventie en de kwaliteit van het bewijs
De kwaliteit van het bewijs van de geïncludeerde studies is overwegend laag tot zeer laag. De GRADE systematiek is gevolgd om de kwaliteit van het bewijs te beoordelen. Deze is hier dan ook gevolgd. In een nieuwe situatie (zoals COVID) is het logisch dat de meeste studies nog niet kunnen voldoen aan de strenge eisen die aan studies van hoge kwaliteit worden gesteld. De GRADE methodiek zet de kwaliteit van het bewijs echter af tegen de best mogelijke kwaliteit en niet tegen de best mogelijke kwaliteit in de huidige situatie. De GRADE systematiek geeft het vertrouwen weer in de schatting van het effect van een interventie. Wanneer de modules en de search worden geüpdate zijn er hopelijk studies van betere kwaliteit beschikbaar en kan het niveau van de kwaliteit van het bewijs hierop worden aangepast.

De aanwezigheid van myocardiale schade varieerde in de verschillende studies tussen 9,6% en 46,3%. Van alle geïncludeerde patiënten in de pooled risk ratio van cardiale schade in relatie tot mortaliteit had 40% myocardiale schade. In de pooled risk ratio in relatie tot IC opname had 25% myocardiale schade. Grofweg kan gesteld worden dat minimaal een kwart van de patiënten met COVID-19 die opgenomen moeten worden in het ziekenhuis myocardiale schade heeft. Patiënten met myocardiale schade hebben een hogere mortaliteit en moeten vaker op de IC worden opgenomen. Dit is een klinisch relevant effect voor een grote patiëntenpopulatie.
Slechts 2 van de geïncludeerde studies beschreven opname duur als uitkomstmaat, een studie vond

een significant verschil tussen patiënten met en zonder myocardiale schade, de andere studie vond geen significant verschil. Op basis van deze resultaten kan hierover dan ook geen conclusie getrokken worden.
De bewijskracht uit de literatuur search is laag tot zeer laag. Dit komt o.a. door het retrospectieve design van de geïncludeerde studies en de mate van heterogeniteit. Echter laten wel alle geïncludeerde studies, evenals de pooled risk ratios, het positieve effect van myocardiale schade op mortaliteit en IC opname zien. Daarnaast is het belangrijk te realiseren dat het literatuuronderzoek is uitgevoerd met de op 6 juli 2020 beschikbare gegevens. Na deze datum zijn er onderzoeken gepubliceerd die helaas niet meer konden worden meegenomen in de analyse. Studies van latere datum met gegevens uit Azië en Europa ondersteunen ook de bevinding van het positieve effect van myocardiale schade op mortaliteit en IC opname, zoals onder andere blijkt uit studies van Cao (2020) en Stefanini (2020).
De conclusies van het literatuur onderzoek en ook recentere literatuur maken het daarom aannemelijk dat myocardiale schade een ongunstig effect heeft op het beloop van COVID-19 patiënten. Echter om dit met meer zekerheid te kunnen stellen is een grote prospectieve studie nodig.
Het meten van myocardiale schade door middel van laboratoriumdiagnostiek (cardiaal troponine) heeft geen nadelige effecten voor de patiënten aangezien dit meegenomen kan worden in het routinematige laboratoriumonderzoek dat gedurende een ziekenhuis opname plaats vindt.
De meeste data uit de literatuur search komt uit ziekenhuizen buiten Europa, meestal uit China, en vanuit regio's die zwaar getroffen zijn door de pandemie. Dit zou effect gehad kunnen hebben op de mate van myocardiale schade. Het is dan ook de vraag of de resultaten uit de literatuur search ook volledig van toepassing zijn op de Nederlandse populatie. In de meeste geïncludeerde studies zijn de troponine waardes alleen bij opname bepaald. Hierdoor zijn mogelijk ook patiënten met een chronisch verhoogd troponine meegenomen. Onder andere bij patiënten met chronisch hartfalen, diabetes mellitus, pulmonale hypertensie en chronische nierziekten kan het troponine chronisch verhoogd zijn. Deze chronische comorbiditeiten zijn echter ook bekende risicofactoren voor een gecompliceerd beloop van COVID-19. Het is dan ook de vraag of in deze groep de hogere mortaliteit en IC opnames volledig kan worden toegeschreven aan nieuwe myocardiale schade door COVID-19 of dat de verhoogde troponine waardes het resultaat zijn deze chronische comorbiditeiten. Om onderscheid te kunnen maken tussen deze 2 patiëntgroepen is het van belang het troponine gedurende de opname te vervolgen om een rise and fall te kunnen detecteren.
Evenwel is het belangrijk om onderscheid te maken tussen ischemische (type 1 en type 2 myocardinfarct) en non-ischemische myocard schade (acute en chronische myocard schade tgv myocarditis, hartfalen en/of nierinsufficientie). Vanuit dat oogpunt is bij aanwezigheid van verhoogde troponine waardes het afnemen van een specifieke cardiale anamnese, het verrichten van ECG's en cardiale beeldvorming belangrijk om tot een specifiekere diagnose te komen.

<u>CAPACITY</u>
CAPACITY is een internationale registratie van patiënten met COVID-19 op basis van het ISARIC WHO CRF, aangevuld met informatie over specifieke cardiovasculaire parameters (https://capacity-covid.eu/). CAPACITY is in het voorjaar van 2020 gestart en bevat gegevens van 13034 patiënten uit 13 landen, afkomstig van 79 registrerende centra. CAPACITY bevat omvangrijke informatie over patiënten met COVID, omdat ongeveer 40% van de in Nederland opgenomen COVID19 patiënten in de registratie is opgenomen (n = 5524).
De peer-reviewed publicatie van CAPACITY over het onderwerp van deze module is momenteel in voorbereiding. De resultaten van CAPACITY kunnen daarom kunnen nog niet worden meegenomen bij het literatuuronderzoek, maar bij de overwegingen worden wel de voorlopige resultaten van CAPACITY meegenomen. De peer-reviewed publicatie over het onderwerp van deze module wordt binnenkort verwacht en bij een update van de module zal de publicatie in het literatuuronderzoek worden meegenomen.

In het prospectief opgezette CAPACITY II multicenter cohort onderzoek zal nader onderzoek verricht worden naar het optreden van cardiovasculaire complicaties bij COVID-19 en wat de korte en lange termijn gevolgen zijn. Vierhonderd COVID-19 patiënten met minimaal 4x UNL gestegen positieve troponine en/of nieuwe pathologische ECG afwijkingen en/of verdenking op cardiale aandoening binnen 24 uur na opname worden geïncludeerd en volgens de 'Aanbeveling voor vroege detectie cardiale schade bij COVI-19 infectie' van de NVVC vervolgd. Naast deze 400 patiënten met aanwijsbare cardiale betrokkenheid, worden ook 100 COVID-19 patiënten gevolgd die geen cardiale betrokkenheid hebben. Dit cohort dient als een controle groep. De follow-up beloopt maximaal 10 jaar.

Waarden en voorkeuren van patiënten (en evt. hun verzorgers)

Patiënten met COVID-19 worden geadviseerd om, tijdens of na ziekenhuisopname, aanvullende cardiale diagnostiek zoals ECG en troponine bepaling te laten verrichten indien daar aanleiding toe is. Patiënten die opgenomen zijn geweest met COVID-19 dienen alert te zijn op klachten zoals symptomen van hartfalen die kunnen wijzen op cardiale restschade en die te bespreken met hun huisarts of medisch specialist.

Kosten (middelenbeslag)

De kosten van een troponine bepaling zijn zeer laag, € <10 (NZa, 2020). Daar tegenover staat dat het waardevolle informatie over de prognose van een patiënt kan geven, waardoor hoog risicopatiënten eerder opgespoord kunnen worden. De troponine waardes zouden gebruikt kunnen worden in risico stratificatie modellen voor triage van hoog risicopatiënten die bijvoorbeeld baat zouden kunnen hebben van vroege medicatie toediening. Dit zou op de langere termijn juist kosten kunnen besparen als dit tot kortere ziekenhuisopname zou leiden. Om hierin meer inzicht te verkrijgen is echter wel aanvullend onderzoek nodig.
Er is nog veel onduidelijkheid t.a.v. het onderliggende mechanisme van de myocardiale schade. Dit zou kunnen berusten op non-ischemische oorzaken zoals virale myocarditis dan wel ischemische schade o.b.v. zowel een type I als II myocardinfarct. Om bij deze patiënten de juiste therapie in te kunnen zetten is aanvullende diagnostiek in de vorm van specifieke cardiale anamnese, ECG's en cardiale beeldvorming (echocardiografie, cardiale MRI en zo nodig coronair angiografie) nodig. Het standaard bepalen van troponine bij COVID-19 patiënten zal dan ook leiden tot een toename van aanvullende diagnostiek gedurende de opname. Dit geeft hogere kosten, echter als hierdoor eerder gestart kan worden met een geschikte interventie zoals een revascularisatie of het opstarten van hartfalen medicatie brengt dit uiteindelijk ook weer gezondheidswinst met zich mee.

Aanvaardbaarheid, haalbaarheid en implementatie

Er is geen kwantitatief of kwalitatief onderzoek gedaan naar de aanvaardbaarheid en haalbaarheid van de interventie. Echter het bepalen van cardiaal troponine kan routinematig worden meegenomen in de laboratoriumdiagnostiek gedurende de opname en brengt zeer lage kosten met zich mee. Dit zou daarom ook geen belemmering moeten vormen. Een nadeel zou echter kunnen zijn dat aan een verhoogd troponine ook consequenties gebonden moeten worden en aanvullend een cardiale anamnese, ECG en cardiale beeldvorming nodig is om het onderliggend mechanisme (myocarditis dan wel myocardiale ischemie) in specifieke patiënten te achterhalen om tijdig met een geschikte interventie te starten. Dit brengt hogere zorgkosten met zich mee en zou gevolgen kunnen hebben voor de wachtlijsten voor de betreffende beeldvorming in een ziekenhuis.
Om meer inzicht te verkrijgen in de onderliggende mechanismes van myocardiale schade is aanvullend prospectief onderzoek nodig waarbij standaard cardiale anamnese, ECG's en aanvullende cardiale beeldvorming wordt verricht bij COVID-19 patiënten met verhoogde troponine waarde. Dit kan helpen in de besluitvorming om aanvullende diagnostiek in te zetten bij patiënten met COVID-19 en myocardiale schade.
Vanuit patiënt oogpunt zijn er voor het bepalen van troponine geen bezwaren te verwachten. Indien

aanvullende beeldvorming noodzakelijk is zijn hier natuurlijk wel de risico's van het betreffende onderzoek aan verbonden en moet hiervoor informed consent aan de patiënt gevraagd worden. Er is geen bezwaar in het kader van gezondsheidsgelijkheid, de betreffende onderzoeken/interventies zijn voor iedereen beschikbaar.

Aanbevelingen

Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies

Ondanks de lage bewijskracht van de literatuur search, laten alle geïncludeerde studies een slechtere uitkomst zien bij patiënten met COVID-19 en myocardiale schade. Mede gezien de lage kosten van een troponine bepaling en het feit dat dit gemakkelijk meegenomen kan worden in het routinematig laboratoriumonderzoek tijdens een ziekenhuisopname, adviseren wij om te overwegen bij iedere patiënt die wordt opgenomen met COVID-19 standaard troponine bepalingen te verrichten. Het is belangrijk om het troponine gedurende de opname op te volgen om een rise-and-fall te kunnen detecteren om onderscheid te kunnen maken met patiënten met een chronisch verhoogd troponine. Op deze manier kunnen hoog risicopatiënten tijdig worden opgespoord en kan triage plaats vinden van patiënten die mogelijk baat hebben bij vroegtijdig starten van therapie. Het bepalen van troponine heeft tot gevolg dat bij een verhoogde waarde ook meer aanvullende cardiale diagnostiek noodzakelijk is. Dit brengt hogere zorgkosten en belasting voor de wachtlijsten met zich mee. Echter het vroegtijdig opsporen van hoog risicopatiënten en het onderliggende mechanisme van myocardiale schade maakte het mogelijk om eerder met een geschikte therapie te starten wat uiteindelijk ook weer gezondheidswinst op zou kunnen leveren.

Overweeg cardiale markers (troponine) te bepalen bij opname van een COVID-19 patiënt en indien afwijkend deze te vervolgen conform de 'Aanbeveling voor vroege detectie cardiale schade bij COVID-19 infectie' van de NVVC.

Verricht afhankelijk van het biochemische verloop aanvullende cardiale diagnostiek (anamnese, ECG en beeldvorming) tijdens opname of daarna.

Kennislacunes

- What is the most common underlying mechanism of myocardial injury in COVID-19 patients?
- Has standardized cardiac imaging with echocardiography, cardiac MRI or coronary angiography therapeutic consequences in this patient group?
- What is the prognostic impact of myocardial injury on the short (days-weeks) and long-term (month-years) outcome of COVID-19 patients?

Literatuur

Barman, H. A., Atici, A., Sahin, I., Alici, G., Tekin, E. A., Baycan, Ö. F., ... & Celik, F. B. (2020). Prognostic significance of cardiac injury in COVID-19 patients with and without coronary artery disease. Coronary artery disease.

Cao J, Zheng Y, Luo Z, et al. Myocardial injury and COVID-19: Serum hs-cTnI level in risk stratification and the prediction of 30-day fatality in COVID-19 patients with no prior cardiovascular disease. Theranostics 2020; 10: 9663-9673.

Kuno, T., Takahashi, M., Obata, R., & Maeda, T. (2020). Cardiovascular comorbidities, cardiac injury and prognosis of COVID-19 in New York City. American Heart Journal.

Lorente-Ros, A., Ruiz, J. M. M., Rincón, L. M., Pérez, R. O., Rivas, S., Martínez-Moya, R., ... & Zamorano, J. L. (2020). Myocardial injury determination improves risk stratification and predicts mortality in COVID-19 patients. Cardiology Journal.

Santoso, A., Pranata, R., Wibowo, A., Al-Farabi, M. J., Huang, I., & Antariksa, B. (2020). Cardiac injury is associated with mortality and critically ill pneumonia in COVID-19: a meta-analysis. The American Journal of Emergency Medicine.

Stefanini GG, Chiarito M, Ferrante G, et al. Early detection of elevated cardiac biomarkers to optimise risk stratification in patients with COVID-19. Heart 2020; 106: 1512-1518.
Wei, J. F., Huang, F. Y., Xiong, T. Y., Liu, Q., Chen, H., Wang, H., ... & Peng, Y. (2020). Acute myocardial injury is common in patients with covid-19 and impairs their prognosis. Heart.
NVVC. Aanbeveling voor vroege detectie cardiale schade bij COVID-19 infectie. https://netwerk.nvvc.nl/manual/covid-19 of kwaliteit@nvvc.nl.

Bijlagen bij module 1

Evidence tables

Evidence table systematic reviews

Study reference	Study characteristics	Patient characteristics	Prognostic factor (cardiac injury definition)	Follow-up	Outcome measures and effect size	Comments
Santoso, 2020	SR and meta-analysis of cohort studies *Literature search up to 29 March 2020* **A**: Chen T, 2020 (mortality) **B**: Li K, 2020 (mortality) [not peer reviewed] **C**: Luo XM, 2020 (mortality) [not peer reviewed] **D**: Shi S, 2020 (mortality) **E**: Wu C, 2020 (mortality, IC admission) [not peer reviewed] **F**: Zhang F, 2020 (mortality) [not peer reviewed] **G**: Zhou 2020 (mortality) **H**:Wang D, 2020 (IC admission) **I**: Huang, 2020 (IC admission) **J**: Hu L, 2020 **K**: Hu B, 2020 **L**: Zhao W, 2020 **M**: Zhang Guqin, 2020 <u>Study design</u>: all studies are observational retrospective studies	Inclusion criteria SR: all research articles in adult patients diagnosed with COVID-19 with information on cTnI, cardiac injury, and clinical grouping or outcome of the clinically validated definition of mortality, the need for ICU care, acute respiratory distress syndrome (ARDS), or severe COVID-19 Exclusion criteria SR: articles other than original research (e.g., case report or series, review articles, letters to editor, editorials or commentaries), duplicate publication, and non-English articles. *13 studies included (7 report on mortality and 3 on IC admission)* <u>Important patient characteristics at baseline</u>: <u>N, mean age deceased vs mean age survivors</u> **A**: N=799, analysis based on N=274, 68y(†) vs 51y **B:** N=32, 69y(†) vs 51y **C**: N=403, 71y(†) vs 59y **D**: N=416, N/A **E**: N=188, N/A **F**: N=48, 78.65y(†) vs 66.16y **G**: N=191, 69y(†) vs 52y **H**: N=138, 66y (†) vs 51y **I**: N=41, 49y(†) vs 49y **J**: N=323, 65y(†) vs 56y	**A**: cTnI above 99th percentile **B**: Unspecified **C**: Unspecified **D**:cTnI above 99th percentile **E**: Unspecified **F**: cTnI above 99th percentile **G**:cTnI above 99th percentile **H**: cTnI above 99th percentile **I**: cTnI above 99th percentile **J**: Unspecified **K**: Unspecified **L**: Unspecified **M**: cTnI above 99th percentile	<u>End-point of follow-up</u>: **A**: Max 46 days (patients admitted from 13 January 020 to 28 February 2020) **B**: Max 34 days (Patients admitted from January 31 to March 5, 2020) **C**: Max 26 days (patients admitted from Jan 30 to Feb 25, 2020) **D**: Max 26 days (patients admitted from January 20, 2020, to February 10th, final date of follow up February 15, 2020) **E**: Max 48 days (patients admitted from December 25, 2019 to January 27, 2020 follow-up complete on February 11) **F**: Max 52 days (patients admitted from 25th December, 2019 to 15th February, 2020) **G**: Max 33 days (patients admitted between Dec 29 and Jan 31, 2020) **H**: Max 33 days (patients admitted from January 1 to	<u>Outcome measure Mortality</u> Effect measure: RR [95% CI] **A**: 4.64 [3.00, 7.18] **B**: 6.69 [2.61, 17.17] [not peer reviewed] **C**: 10.94 [6.83, 17.52] [not peer reviewed] **D**: 11.40 [6.66, 19.53] **E**: 5.25 [2.90, 9.50] [not peer reviewed] **F**: 6.08 [1.93, 19.13] [not peer reviewed] **G**: 81.19 [11.38, 579.41] Pooled risk ratio 7.95 [5.12 – 12.34] Heterogeneity (I^2): 65% <u>Outcome measure IC admission</u> Effect measure: RR [95% CI]	<u>Facultative</u>: Most of the included studies are from China, are pre-prints and have a small number of included participants. Patients are included in the early days of the COVID pandemic (most of them enrolled in January and February 2020). Patients that deceased are older and more frequently male then the survivors. The effect is measured in RR, so a correction for this confounding factors was not performed.

	Setting and Country: Not available per study, most of the studies are from China Source of funding: Not reported	**K**: N=36, 66.5y(†) vs 56y **L**: N=78, 69y(†) vs 45y **M**: N=221, 62(†) vs 51y *Sex (% male, deceased vs survivors):* **A**: 73%(†) vs 55% **B**: 73%(†) vs 22% **C**: 57%(†) vs 44.9% **D**: N/A **E**: N/A **F**: 70.6%(†) vs 67.7% **G**: 70%(†) vs 59% **H**: 61.1%(†) vs 52% **I**: 85%(†) vs 68% **J**: 52.9%(†) vs 49.7% **K**: 68.8%(†) vs 65% **L**: 55%(†) vs 40.4% **M**: 63.6%(†) vs 44% Groups comparable at baseline Patients that deceased are older and more frequently male then the survivors.		January 28, 2020, follow up until February 3rd) **I**: N/A (patients admitted from Dec 16, 2019, to Jan 2, 2020) **J**: average observation period 28 days (20-47 days) (patients enrolled from January 8 to February 20, 2020, follow up until 10 March 2020) **K**: N/A (patients admitted from January 8 to February 9, 2020) **L**: Max 39 days (patients admitted from 21st January to 8th February 2020, follow up until February 29) **M**: Max 44 days (patients admitted from January 2 2020 to February 10 2020, follow up until February 15 2020) For how many participants were no complete outcome data available? **A: 525** **B**: 5 **C**: 0 **D**: N/A **E**: 0 **F**: 2 **G**: 0 **H**: 0 **I**: 0 J: 0 K: 14 L: 41 M: 168	**E**: 2.39 [1.50, 3.80] [not peer reviewed] **H**: 11.33 [2.52, 50.90] **I**: 37.68 [4.44, 320.19] Pooled risk ratio 7.94 [1.51 – 41.78] Heterogeneity (I^2): 79%	A sensitivity analysis by leave-one-out was performed to single out heterogeneity. Sensitivity analysis showed that heterogeneity for mortality outcomes could be reduced by removal of G: Zhou 2014 et al. study (RR 7.22 [4.97, 10.47], p < 0.001: I^2: 54%, p = 0.05). The removal of E: Wu et al. reduced heterogeneity for the need for ICU care (RR 16.85 [4.93, 57.62], p < 0.001; I^2: 0%, p = 0.36)

Evidence table individual studies

Study reference	Study characteristics	Patient characteristics	Prognostic factor(s)	Follow-up	Outcome	Comments
Barman, 2020	Type of study: multi-center retrospective study Setting: COVID-19 patients who were hospitalized in three government hospitals Country: Turkey Source of funding: N/A	Inclusion criteria: consecutive COVID-19 patients who were hospitalized in three government hospitals in Istanbul, Turkey between 20 March 2020 and 20 April 2020 Exclusion criteria: Patients < 18 y, with concurrent ST-segment elevation myocardial infarction, with history of advanced kidney failure [estimated glomerular filtration rate (eGFR) <30 ml/min] or hemodialysis and patients with missing laboratory parameters on admission including cTnI, and creatine kinase myocardial band (CK-MB) N= 607 Cardiac injury N= 150 No Cardiac injury N = 457 Mean age ± SD: Cardiac injury: 66.0y ± 14.5 No Cardiac injury: 55.3y ± 15.2 Sex(%male): Cardiac injury: 54% No Cardiac injury: 52%	high sensitivity cardiac troponin I serum levels above the 99th percentile upper reference limit, regardless of new abnormalities in ECG Moment of measurement: at hospital admission	patients were hospitalized between 20 March 2020 and 20 April 2020, follow up until 20 April 2020 For how many participants were no complete outcome data available? N (%): N/A Reasons for incomplete outcome data described? No	*Mortality* Cardiac injury = 64 (42%) No Cardiac injury– = 39 (8%) P<0.001 Univariable regression model (30 days) OR 7.97 [5.03–12.64] P <0.001 Multivariable regression model (30 days) OR 10.58 [2.42–46.27] P<0.001 Cardiac injury was found to be a predictor of mortality. Sugbroup analysis When patients with previous CAD were excluded from analyses, presence of cardiac injury was still an independent predictor of mortaliy (OR 2.52, 95% CI 1.17–5.45; P = 0.018) *IC admission* Cardiac injury N= 108 (72%) No Cardiac injury N= 87 (19%) P<0.001 Patients with cardiac injury were more frequently admitted to the IC then patients without cardiac injury. *Hospital duration (days)* Cardiac injury: 12 (5–14) days No Cardiac injury: 9 (4–12) days P<0.001	Student's t-test or Mann–Whitney U test, Cox regression model

					Patients with cardiac injury spent more days in the hospital then patients without cardiac injury.	
Kuno, 2020	Type of study: Retrospective cohort Setting:7 hospitals with more than 3800 beds and more that 410 ambulatory practices across metropolitan New York Country: US Source of funding: No extramural funding	Inclusion criteria: N/A Exclusion criteria: N/A N= 8438, 5320 used for analysis (troponin measured) Median age ± SD: 59 [43, 71] Sex: 53.9% male	Cardiac injury was defined as troponin I elevation which was defined as 99th percentile upper reference limit Moment of measurement: not reported	Endpoint of follow-up: Patients admitted from March 1 to April 22, 2020, follow up until April 30th For how many participants were no complete outcome data available? N (%): N/A Reasons for incomplete outcome data described? No	*Mortality* Cardiac injury: 41.3% (954/2312) No Cardiac injury : 8.1% (245/3008) RR 5.07 (4.45-5.76) Patients with cardiac injury have an increased risk of mortality	RR
Lorente-Ros, 2020	Type of study: Matched retrospective cohort Setting: a large tertiary hospital Country: Spain Source of funding: N/A	Inclusion criteria: patients aged 18 years and older admitted to a large tertiary hospital with COVID-19 infection were retrospectively included with prospective follow-up. Exclusion criteria: primary cardiac presentation, i.e. type 1 myocardial infarction N=707 Cardiac injury n = 112 No Cardiac injury- n=112 Mean age ± SD: 66.76 ± 15.7 years Sex: 63% male	cTnI levels greater than the 99th percentile of a healthy population Moment of measurement: at hospital admission	Endpoint of follow-up: Patients admitted from March 18 to March 23, 2020 All patients were followed for 1 month For how many participants were no complete outcome data available? For the total group the outcome data of 66 (out of 707) remained hospitalized after 1 month. For the matched cohort the information is not available. Reasons for incomplete outcome data described? N/A	*Mortality* Cardiac injury N= 46 (41.1%) No Cardiac injury N= 26 (23.2%) P=0.005 All-cause mortality within 30 days was higher in those with cTnI elevation Univariable regression model (30 days) Hazard Ratio 4.355 (3.112–6.093) P< 0.001 Multivariable regression model (30 days) Hazard Ratio 1.716 (1.182–2.492) P= 0.005 cTnI elevation was independently associated with a higher risk of all-cause mortality within 30 days. Age, CRP and creatinine on admission were also independent prognostic factors. *IC admission* Cardiac injury N=7 (6.3%)	Multivariate Cox proportional hazards regression models, comparing means

					No Cardiac injury N= 5 (4.5%) P= 0.527 There is no difference in patient with and without cardiac injury regarding IC-admission *Hospital duration (median days)* Cardiac injury: 11 (6 to 17) days No Cardiac injury: 9 (5 to 13) days P= 0.934 There is no difference in patients with and without cardiac injury regarding hospital duration.	
Wei, 2020	Type of study: Propspective assessment of medical records Setting: laboratory-confirmed SARS-CoV-2 infection admitted to the Public Health Clinical Centre of Chengdu and West China Hospital, Sichuan University Country: China Source of funding: none declared	Inclusion criteria: N/A Exclusion criteria: N/A N=101 cTnT≤14pg/mL n=85 cTnT>14pg/mL n=16 Mean age ± SD: Total 49 (34–62)y cTnT≤14pg/mL: 47 (33–55)y cTnT>14pg/mL : 67 (61.0–80.5)y P<0.001 Sex: % M Total: 53.5% male cTnT≤14pg/mL: 55.3% male cTnT>14pg/mL : 43.8% male P= 0.401	Acute myocardial injury was defined by an cTnT value greater than the institutional upper limit of normal (14pg/mL) Moment of measurement: at hospital admission	Endpoint of follow-up: Patients admitted between between 16 January and 10 March 2020 For how many participants were no complete outcome data available? N/A Reasons for incomplete outcome data described? N/A	*Mortality* cTnT≤14pg/mL 0 death (0%) cTnT>14pg/mL 3 death (18.8%) P<0.001 *IC admission* cTnT≤14pg/mL 21 IC admissions (24.7%) cTnT>14pg/mL 10 IC admissions (62.5%) P=0.003 Patients with acute myocardial injury were more likely to require admission to ICU	Multivariate analysis

Table of quality assessment – prognostic factor (PF) studies

Based on: QUIPS[A] (Haydn, 2006; Haydn 2013)

Study reference (first author, year of publication)	**Study participation[1]** Study sample represents the population of interest on key characteristics? (high/moderate/low risk of selection bias)	**Study Attrition[2]** Loss to follow-up not associated with key characteristics (i.e., the study data adequately represent the sample)? (high/moderate/low risk of attrition bias)	**Prognostic factor measurement[3]** Was the PF of interest defined and adequately measured? (high/moderate/low risk of measurement bias related to PF)	**Outcome measurement[3]** Was the outcome of interest defined and adequately measured? (high/moderate/low risk of measurement bias related to outcome)	**Study confounding[4]** Important potential confounders are appropriately accounted for? (high/moderate/low risk of bias due to confounding)	**Statistical Analysis and Reporting[5]** Statistical analysis appropriate for the design of the study? (high/moderate/low risk of bias due to statistical analysis)
Santoso, 2020	Low risk	Moderate (information on number of patients still in the hospital when follow up ended unavailable)	Low, definition matches PICO	Low Ic admission: moderate	High (correction for confounders not applied)	Low
Barman, 2020	Low (in- and exclusion criteria defined)	Moderate (information on number of patients still in the hospital when follow up ended unavailable)	Low, definition matches PICO	Low Ic admission : moderate	Low, correction for confounders was performed	Low
Kuno, 2020	Low	Moderate (information on number of patients still in the hospital when follow up ended unavailable)	Low, definition matches PICO	Low	High (correction for confounders not applied)	Low
Lorente-Ros 2020	Moderate (matched cohort was develop but selection not transparent)	Moderate (unclear if patients that have not died or been discharged from the hospital are included in the matched cohort)	Low, definition matches PICO	Low Ic admission : moderate	Low, correction for confounders was performed	low
Wei, 2020	Low	Moderate (information on number of patients still in the hospital when follow up ended unavailable)	Low, definition matches PICO	Low	High (correction for confounders not applied)	Moderate (for the outcome mortality the number of patients is so low that a comparison between both groups may not be appropriate)

A

[1] Adequate description of: source population or population of interest, sampling and recruitment, period and place of recruitment, in- and exclusion criteria, study participation, baseline characteristics.

[2] Adequate response rate, information on drop-outs and loss to follow-up, no differences between participants who completed the study and those lost to follow-up.

[3] Method of measurement is valid, reliable, setting of measurement is the same for all participants.

[4] Important confounders are listed (including treatments), method of measurement is valid, reliable, setting of measurement is the same for all participants, important confounders are accounted for in the design (matching, stratification, initial assembly of comparable groups), or analysis (appropriate adjustment)

[5] Enough data are presented to assess adequacy of the analysis, strategy of model building is appropriate and based on conceptual framework, no selective reporting.

Table of quality assessment – prognostic factor (PF) studies (studies included in review Santoso)
*Based on: QUIPS[A] (Haydn, 2006; Haydn 2013)*Research question:

Study reference (first author, year of publication)	**Study participation[1]** Study sample represents the population of interest on key characteristics? (high/moderate/low risk of selection bias)	**Study Attrition[2]** Loss to follow-up not associated with key characteristics (i.e., the study data adequately represent the sample)? (high/moderate/low risk of attrition bias)	**Prognostic factor measurement[3]** Was the PF of interest defined and adequately measured? (high/moderate/low risk of measurement bias related to PF)	**Outcome measurement[3]** Was the outcome of interest defined and adequately measured? (high/moderate/low risk of measurement bias related to outcome)	**Study confounding[4]** Important potential confounders are appropriately accounted for? (high/moderate/low risk of bias due to confounding)	**Statistical Analysis and Reporting[5]** Statistical analysis appropriate for the design of the study? (high/moderate/low risk of bias due to statistical analysis)	**Peer reviewed**
A: Chen T, 2020	Low (all patients diagnosed with Covid-19)	Low (for the analysis only the data of patients that died or were discharged from the hospital were included)	Moderate risk (cTnI>15.6 pg/mL)	low	x	low	Yes
B: Li K, 2020 (mortality)	Low (all patients diagnosed with Covid-19)	Moderate (5 patients were still hospitalized at the moment of analysis)	Low risk (cTnI 34.2pg/mL)	low	x	low	No
C: Luo XM, 2020 (mortality)	Low (all patients diagnosed with Covid-19)	Low (for the analysis data of patients that died or were discharged from the hospital were included)	Low risk (-cTnI>40 pg/mL)	low	x	low	No Santoso also included incorrect results from this study. Should be: Mortality cardiac injury+ 47/96 (49.0%) recovered: CI+ 18/208
D: Shi S, 2020 (mortality)	Low (all patients diagnosed with Covid-19)	Moderate (319 patients remained in the hospital at the time of analysis)	Low risk (Cardiac injury was defined as blood levels of cardiac biomarkers (cTNI) above the 99thpercentile upper reference limit, regardless of new abnormalities in electrocardiography and echocardiography)	low	x	low	Yes
E: Wu C, 2020 (mortality, IC admission)	Low (all patients diagnosed with Covid-19)	Low (all patients died or were discharged at the moment of analysis)	High risk (cTnI≥ 6.126 pg/mL)	low	x	low	No

F: Zhang F, 2020 (mortality)	low (patients were diagnosed or suspected of Covid-19)	Low (all patients died or were discharged at the moment of analysis)	Low risk (cTnI) were above the 99th percentile upper reference limit (0.026ug/L)	low	x	low	No
G: Zhou 2020(mortality)	Low (all patients diagnosed with Covid-19)	Low (all patients died or were discharged at the moment of analysis)	Low (Acute cardiac injury was diagnosed if serum levels of cardiac biomarkers (eg, highsensitivity cardiac troponin I) were above the 99th percentile upper reference limit, (≥28 pg/mL) or if new abnormalities were shown in electrocardiography and echocardiography)	Low	X	low	Yes
H:Wang D, 2020 (IC admission)	Low (all patients diagnosed with Covid-19)	Moderate (some patients remained hospitalized at the moment of analysis, number is unknown)	Low (cTn were above the 99th percentile upper reference limit ≥26.2 pg/mL or new abnormalities were shown in electrocardiography and echocardiography)	low	X	low	Yes
I: Huang, 2020 (IC admission)	Low (all patients diagnosed with Covid-19)	Moderate (7 patients still hospitalized at the time of analysis)	Low (cardiac injury was diagnosed if serum levels of cardiac biomarkers (eg, troponin I) were above the 99th percentile upper reference limit >28 pg/mL, or new abnormalities were shown in electrocardiography and echocardiography)	Low	x	low	yes

[A] https://methods.cochrane.org/sites/methods.cochrane.org.prognosis/files/public/uploads/QUIPS%20tool.pdf

[1] Adequate description of: source population or population of interest, sampling and recruitment, period and place of recruitment, in- and exclusion criteria, study participation, baseline characteristics.

[2] Adequate response rate, information on drop-outs and loss to follow-up, no differences between participants who completed the study and those lost to follow-up.

[3] Method of measurement is valid, reliable, setting of measurement is the same for all participants.

[4] Important confounders are listed (including treatments), method of measurement is valid, reliable, setting of measurement is the same for all participants, important confounders are accounted for in the design (matching, stratification, initial assembly of comparable groups), or analysis (appropriate adjustment)

[5] Enough data are presented to assess adequacy of the analysis, strategy of model building is appropriate and based on conceptual framework, no selective reporting.

Table of excluded studies

Author and year	Reason for exclusion
Toraih, 2020	Bijlage 1 Wrong study design: cardiac biomarkers as predictor of cardiac injury, poor prognosis, severity, ICU admission and mortality
Parohan, 2020	Bijlage 2 Cardiac injury is assessed by serum analysis (lactate dehydrogenase, cardiac troponin I, creatine kinase and myoglobin)
Aikawa, 2020	Systematic review but described in a letter to the editor. Important information is missing (for example excluded papers and reason for exclusion)
Li, X, 2020	
Li, B, 2020	Wrong outcome: severe vs mild COVID-19
Li, J, 2020	Studies the association of severity of COVID with cardiac injury
Huang, 2020	Wrong comparison: not focused on cardiac injury, comparing clinical characteristics of severe and non-severe patients
Aboughdir, 2020	No systematic review
Alexander, 2020	No original data
Ammirati, 2020	No original data
Ashraf, 2020	Wrong P, wrong I, no original data
Benett, 2020	No original data, commentary
Bangalore, 2020	wrong I, Wrong C
Bansal, 2020	No comparison, wrong O, merely a description
Bonow, 2020	No original data
Cappannoli, 2020	Is not a comparison between covid patients with and without cardiac injury
Chapman, 2020	Opinion, describes potential mechanisms
Cheng, 2020	Focuses on potential mechanisms, no comparison
Dong, 2020	Case study of 4 patients
Fried, 2020	Case study of 4 cases
Giustino, 2020	Wrong comparison, wrong I
Guo, 2020	This paper was excluded because it was published during the search period of the included systematic review Santoso
Jaffe, 2020	Describes possible mechanisms, no comparison
Kang, 2020	No comparison, no I, focuses on mechanisms
Kollias, Kyriakoulis, 2020	Wrong I, not systematic review
Kollias, Anastasios, 2020	No original data, letter to the editor
Lala, 2020	Wrong I: Troponin not defined as elevated or not but the absolute value is used in the analysis
Larson, 2020	Not right comparison, wrong O
Lazaridis, 2020	wrong comparison,
Li, 2020	Wrong O
Lim, 2020	No systematic literature overview. The 2 studies described here are also included in our set
Madjid, 2020	Wrong comparison, Wrong I
Si, 2020	Wrong I: Troponin not defined as elevated or not but the absolute value is used in the analysis
Su, 2020	No comparison between patients with and without cardiac injury
Tahir, 2020	No comparison, merely a description of cardiac manifestations
Tersalvi, 2020	Focuses on the potential mechanism behind cardiac injury in COVID-19 patients
Zeng, 2020	No original data
Zhou, 2020	Wrong O: severe COVID-19
Zhu, 2020	No original data, focuses on underlying mechanism, no comparison

Literature search strategy

Ovid/Medline

1 exp Myocardial Ischemia/ or ((cardia* or heart or myocard* or coronary or endocard* or subendocard*) adj3 (attack or infarction or ischemi* or ischaemi* or anoxia or hypoxia or lesion or injury or damage or trauma)).ti,ab,kf. (535266)

2 ((exp Coronavirus/ or Coronavirus Infections/ or pneumonia virus*.ti,ab,kf. or cov.ti,ab,kf.) and ((outbreak or wuhan).ti,ab,kf. or novel.af. or '19'.ti,ab,kf. or '2019'.ti,ab,kf. or epidem*.af. or epidemy.af. or epidemic*.af. or pandem*.af. or new.ti,ab,kf.)) or (coronavirus* or 'corona virus*' or ncov or '2019ncov' or 'covid19' or "covid 19" or "sars cov 2" or 'sars2' or "ncov 2019" or "sars coronavirus 2" or "sars corona virus 2" or "severe acute respiratory syndrome cov 2" or "severe acute respiratory syndrome cov2" or "severe acute respiratory syndrome cov*").ti,ab,kf. (43132)

3 limit 2 to yr="2019 -Current" (31021)

4 1 and 3 (414)

5 4 not ((exp animals/ or exp models, animal/) not humans/) not (letter/ or comment/ or editorial/) (356)

6 (meta-analysis/ or meta-analysis as topic/ or (meta adj analy$).tw. or (systematic*or literature adj2 review$1).tw. or (systematic adj overview$1).tw. or exp "Review Literature as Topic"/ or cochrane.ab. or cochrane.jw. or embase.ab. or medline.ab. or (psychlit or psyclit).ab. or (cinahl or cinhal).ab. or cancerlit.ab. or ((selection criteria or data extraction).ab. and "review"/)) not (Comment/ or Editorial/ or Letter/ or (animals/ not humans/)) (293781)

7 5 and 6 (14) SR

8 4 not 7 (400) Overige

Embase

No.	Query	Results
#7	#3 NOT #6 Overige	**305**
#6	#4 AND #5 SR	**19**
#5	('meta analysis'/de OR 'meta analysis (topic)'/exp OR cochrane:ab OR embase:ab OR psycinfo:ab OR cinahl:ab OR medline:ab OR ((systematic NEAR/1 (review OR overview)):ab,ti) OR ((meta NEAR/1 analy*):ab,ti) OR metaanalys*:ab,ti OR 'data extraction':ab OR cochrane:jt OR 'systematic review'/de) NOT (('animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	**524957**
#4	#3 NOT ('conference abstract'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it) NOT (('animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	**324**
#3	#1 AND #2	**392**
#2	('coronavirus disease 2019'/exp OR (('coronavirinae'/exp OR 'coronavirus infection'/de OR coronavirus*:ti,ab,kw OR 'corona virus*':ti,ab,kw OR 'pneumonia virus*':ti,ab,kw OR cov:ti,ab,kw OR ncov:ti,ab,kw) AND (outbreak:ti,ab,kw OR wuhan:ti,ab,kw)) OR covid19:ti,ab,kw OR 'covid 19':ti,ab,kw OR ((coronavirus*:ti,ab,kw OR 'corona virus*':ti,ab,kw) AND 2019:ti,ab,kw) OR 'sars cov 2':ti,ab,kw OR sars2:ti,ab,kw OR 'coronavirus*':ti,ab,kw OR 'corona virus*':ti,ab,kw OR 'ncov 2019':ti,ab,kw OR ncov:ti,ab,kw OR 'sars coronavirus 2':ti,ab,kw OR 'sars corona virus 2':ti,ab,kw OR 'severe acute respiratory syndrome cov 2':ti,ab,kw OR 'severe acute respiratory syndrome cov2':ti,ab,kw) AND [2019-2020]/py	**24590**
#1	'heart muscle injury'/exp OR 'heart muscle ischemia'/exp OR 'heart infarction'/exp OR (((cardia* OR heart OR myocard* OR coronary OR endocard* OR subendocard*) NEAR/3 (attack OR infarction OR ischemi* OR ischaemi* OR anoxia OR hypoxia OR lesion OR injury OR damage OR trauma)):ti,ab,kw)	**601459**

Module 2 Prognostische factoren voor uitkomst bij COVID-19 patiënten met cardiovasculaire risicofactoren of cardiale ziekte

Clinical question

In which proven COVID-19 patients with cardiovascular risk factors or underlying cardiovascular disease should one be alert to a poor outcome?

Inleiding

De COVID-19 pandemie roept wereldwijd diverse vragen op bij zorgverleners, onderzoekers en patiënten. Patiënten met cardiovasculaire risicofactoren en/of cardiovasculaire aandoeningen zijn een kwetsbare groep op het gebied van infectieziekten. Dit is onder meer te verklaren door de effecten van de diverse cardiovasculaire risicofactoren op de immunologische functie en de betrokkenheid van het immuunsysteem bij het ontstaan van cardiovasculaire aandoeningen. Kennis over het risico op een ernstig ziektebeloop en overlijden bij deze groep patiënten is van belang voor een passende response op het gebied van voorzorgsmaatregelen, monitoring en therapie. Het tempo waarin de pandemie zich voltrekt, de globale verschillen in opname criteria, het ontbreken van voldoende testcapaciteiten en het ontbreken van systematische datacollectie zijn van invloed op de beschikbaarheid en kwaliteit van wetenschappelijke literatuur die inzicht kan verschaffen in de prevalentie van cardiovasculaire risicofactoren en cardiovasculaire aandoeningen bij COVID-19 patiënten. Gegeven het hiervoor genoemde is het zinvol om met regelmaat een kritische selectie te maken van beschikbare literatuur over de voorspellende waarde van cardiovasculaire risicofactoren en cardiovasculaire aandoeningen op het ziektebeloop en mortaliteit van COVID-19 patiënten en door middel van passende analyse modellen de data te doorgronden.

Search and select

A review of the literature was performed to answer the following question:

Which independent prognostic factors (cardiovascular risk factors or cardiovascular disease) strongly predict a poor outcome of COVID-19 infection, independent of other factors?

P: All proven COVID-19 patients

I: Presence of one of the following prognostic factors: cardiovascular risk factors such as smoking, obesity, hypercholesterolemia, hypertension, diabetes (insulin resistance, non-alcoholic steatohepatitis), cardiovascular disease, cardiovascular history (arrhythmias, coronary artery disease, heart failure, valvular heart disease)

C: absence of the prognostic factors

O: mortality (crucial), IC-admission (crucial), hospital admission, length of stay, thromboembolic complications (pulmonary embolism, stroke, transient ischemic attack)

T: admission to hospital, admission to ICU, during hospital stay, at home

S: in-hospital, pre-hospital

Confounder: age

<u>Relevant outcome measures</u>

Mortality and IC-admission were considered as critical outcome measures for decision making and the other outcomes as important outcomes for decision making.

A priori, the working group did not define the outcome measures listed above, but used the definitions used in the studies.

A priori, the working group did not define minimal clinically relevant differences for the outcome measures.

Prognostic research: Study design and hierarchy

For this research question, it is aimed to investigate multiple cardiovascular factors that might predict disease severity and mortality in patients with COVID-19. To investigate whether factors are predictive, a longitudinal relation between candidate prognostic factors (measured at T0) and outcome (measured at T1) has to be investigated. Often, prognostic factors are correlated with other factors (Foroutan, 2020). To describe the effect of single prognostic factors, these should be measured in relation to its confounders. Mostly, important confounders can be predefined. Only models including all predefined confounders and measuring longitudinal associations between candidate predictors and outcome can be taken into account. When multiple factors are investigated, multivariable models predicting outcome are developed and will be used as a tool for clinical decision making.

When reviewing literature, there is a hierarchy in quality of individual studies. Preferably, models for clinical decision making show the efficacy of using multivariable models in healthcare. In this way, they are most helpful to decide which factors should be used in clinical practice. Differences in clinical decision making according to the developed model and the effect on patient related outcome should be measured after sufficient follow-up periods (Moons, 2008). If such studies are not available, studies validating the effects of developed prognostic multivariable models in other samples of the target population (external validation) are preferred as there is more confidence in the results of these studies compared to not externally validated studies. Most samples do not completely reflect the characteristics of the total population, resulting in deviated associations, possibly having consequences for conclusions. Studies validating prognostic multivariable models internally (e.g. bootstrapping or cross validation) or studies reporting unvalidated prognostic multivariable models can be used to answer the research question as well, but downgrading the level of evidence is obvious due to risk of bias and/or indirectness as it is not clear whether models perform sufficient in target populations. Due to the low confidence in the results of externally unvalidated models, specific results regarding factors of interest reported in such models will be described only if factors have been used in at least two multivariable models/studies. Univariable prognostic models (or multivariable prognostic models not taking confounders into account) cannot be graded as confidence in these models is too low.

<u>Search and select (Methods)</u>

The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms until 9-6-2020. The systematic literature search resulted in 567 hits. See search strategy for detail. No studies investigating the impact of a multivariable cardiovascular prognostic model on healthcare regarding mortality, IC-admission, hospital admission, length of stay and/or thromboembolic complications were found. Studies developing and/or validating a multivariable prognostic model were selected based on the following criteria: systematic reviews, randomized controlled trials (RCTs) and observational studies (cohort studies) assessing the longitudinal relation between cardiovascular risk factors (smoking, obesity, hypercholesterolemia, hypertension, diabetes), cardiovascular disease and cardiovascular history (measured at hospital admission/during hospital stay), with mortality, IC-admission, hospital admission, length of stay, thromboembolic complications (measured at endpoint) in proven COVID-19 patients. Age was considered as confounder that had to be included in the multivariable models.

45 studies were initially selected based on title and abstract screening. After reading the full text, 37 studies were excluded (see the table with reasons for exclusion under the tab Methods), and 8 studies were included.

Some systematic reviews evaluated the association between cerebrovascular, cardiovascular disease, diabetes mellitus or hypertension and poor outcome in patients with COVID-19, for example

Huang (2020), Li (2020), Lippi (2020), Pranata (2020a), Pranata (2020b) and Zheng (2020). These systematic reviews were not included, because associations were calculated without taking any confounders into account.

Results

Eight studies were included in the analysis of the literature. Important study characteristics and results are summarized in the evidence tables. The assessment of the risk of bias is summarized in the risk of bias table.

Summary of literature

Description of studies

Chen (2020), Giacomelli (2020) and Wang (2020) measured candidate factors during hospital stay and measured mortality outcome as endpoint. Cummings (2020), Gao (2020), Klang (2020) and Palaiodimos (2020) measured candidate factors during hospital stay and measured in-hospital mortality as endpoint. Petrilli (2020) measured candidate factors during hospital stay and measured discharge to hospice or death among those admitted to hospital as endpoint. Multivariable models showing associations between predefined candidate prognostic factors and outcome were reported. One study (Chen, 2020) internally validated the risk factors by establishing a nomogram based on the results of the multivariate analysis. It was decided to include unvalidated studies in the literature review for this outcome as well, as risk of bias of Chen (2020) was moderate.

A brief overview of study characteristics of the included studies is reported in table 2.1. Extended information about risk of bias is included in the and risk of bias table. It should be noted that populations, measurement of factors and selection methods of factors were not well reported in many studies.

Table 2.1 Study characteristics of included studies

Study	Population	N	Age Median (IQR)	Inclusion period	Follow-up	Method	Outcome
Chen, 2020	Hospitalized COVID-19 patients, from 575 hospitals; China	1590	Not reported	Admission to hospital until January 31, 2020 (startpoint of admission to hospital not reported)	Not reported	Multivariate Cox regression; included prognostic factors were selected based on univariable analyses; nomogram developed based on backward stepdown selection	Mortality
Cummings, 2020	Hospitalized COVID-19 patients ≥18 y, critically ill with acute hypoxaemic respiratory failure, 2 hospitals, USA	257	62 y (51-72)	Admission to hospitals between March 2 to April 1, 2020; Candidate factors were measured during hospital stay (collected from medical records)	April 28, 2020	Multivariate Cox regression; included prognostic factors were considered relevant to in-hospital mortality by the authors.	In-hospital mortality
Gao, 2020	Hospitalized COVID-19 patients, 1 hospital, China	2877	Not reported for total group	Admission to hospital between February 5 to March 15, 2020; Candidate factors were measured during hospital stay (collected from medical records)	April 1, 2020	Multivariable Cox proportional hazards model; reason of selection of included prognostic factors in multivariable model not described.	In-hospital mortality
Giacomelli, 2020	Hospitalized COVID-19 patients ≥18 y, 1 hospital, Italy	233	61 y (50-72)	Admission to hospital between February 21 and March 19, 2020; Candidate factors were measured during hospital stay (collected from medical records)	April 20, 2020	Multivariable Cox proportional hazard models; included prognostic factors were selected based on univariable analyses.	Mortality
Klang, 2020	Hospitalized COVID-19 patients ≥18 y, 5 hospitals, USA	3406	Not reported for total group	Admission to hospital between March 1 and May 17, 2020; Candidate factors were measured during hospital stay (collected from medical records)	Not reported	Multivariable logistic regression models; adjusted for age decile, male sex, CAD, CHF, HTN, DM, hyperlipidemia, CKD, history of cancer, smoking (past or present), BMI 30 – 40 kg/m2, BMI ≥ 40 kg/m2 and race; included prognostic factors were selected based on univariable analyses; no validation reported	In-hospital mortality
Palaiodimos, 2020	Hospitalized COVID-19 patients, 1 hospital, USA	200	64 y (50-73.5)	Admission to hospital between March 9 to March 22, 2020; Candidate factors were measured during	3-weeks follow-up:	Multivariate logistic regression model; 3 models used (model 1: BMI and age; model 2: all the variables	In-hospital mortality

				hospital stay (collected from medical records)	April 12, 2020	with significant univariate associations; model 3: variables of model 2 in addition to clinically significant variables which did not show a significant univariate association); no validation reported	
Petrilli, 2020	Admitted and not admitted to hospital COVID-19 patients, >260 outpatients office sites and 4 acute care hospitals, USA	5279 (2441 were admitted to the hospital)	Tested population: 54 y (38-66) Admitted population: 63 y (51-74)	Patients tested between March 1 and April 8, 2020; Candidate factors were measured during hospital stay (collected from medical records)	May 5, 2020	Multivariable logistic regression models; predictors selected based on previous published literature and clinical experience of authors of patients with COVID-19.	Inpatient hospital admission, discharge to hospice or death among those admitted to hospital
Wang, 2020	Hospitalized COVID-19 patients >60 y, 1 hospital, China	339	69 y (65-76)	Admission to hospital between January 1 and February 6, 2020; Candidate factors were measured during hospital stay (collected from medical records)	4 weeks from the last admission	Multivariate Cox regressions; included prognostic factors were selected based on univariable analyses; no validation reported	Mortality

Results of graded studies

All studies reported models predicting mortality and Petrilli (2020) reported a model predicting hospital admission. Table 2.2 shows the reported model design.

Table 2.2 Reported prognostic models for mortality

Study	Mortality n/N (%)	Outcome(s)	Included prognostic factors
Chen, 2020	50/1590 (3.1%)	Mortality	Age; Coronary heart disease; Cerebrovascular disease; Dyspnea; Procalcitonin; Aspartate aminotransferase; Total bilirubin; Creatinine
Cummings, 2020	101/257 (39.0%)	Time to in-hospital mortality from hospital admission	Age; Sex; Symptom duration before hospital presentation; Hypertension; Chronic cardiac disease; COPD; Diabetes; IL-6 concentrations; D-dimer concentrations
Gao, 2020	56/2877 (1.9%)	All-cause mortality during hospitalization	Hypertension; Age; Sex, Diabetes; Myocardial infarction; Treatment by percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG); Renal failure; Chronic heart failure; Asthma; COPD; Stroke
Giacomelli, 2020	48/233 (20.6%)	Mortality (censoring date April 20, 2020)	Age; Sex; Obesity; being treated with ≥1 anti-hypertensive agent; Disease severity; Presence of anemia; Lymphocyte count; D-dimer; C-reactive protein; Creatinine; Creatinine kinase
Klang, 2020	1136/3406 (33.4%)	In-hospital mortality	Age; Sex; Comorbidities (CAD, CHF, HTN, DM, hyperlipidemia, CKD, cancer); Obesity; Smoking status
Paladaiomidos, 2020	48/200 (24%)	In-hospital mortality	Age; BMI; Heart failure; Coronary artery disease; Diabetes; Chronic kidney disease or end-stage renal disease; COPD; current or former smoker
Petrilli, 2020	665/2741 (24.3%)	1) Admission to hospital 2) Mortality (only admitted patients in analysis)	Age; BMI; Sex; Week; Ethnicity; Smoking status; Coronary artery disease; Heart failure; Hypertension; Diabetes; Asthma or COPD; Chronic kidney disease; Cancer
Wang, 2020	65/339 (19.2%)	Mortality	Age; Cardiovascular disease; Cerebrovascular disease; COPD

Abbreviations: CAD, Coronary artery disease; CHF, Congestive heart failure; CKD, Chronic kidney disease; HTN, hypertension; DM, Diabetes mellitus; BMI, Body mass index.

Mortality predicted by prognostic factors measured during hospital stay

As reported models had different outcome measures and included factors were different, results could not be pooled. Because models were unvalidated, only results regarding factors that were included in at least two studies will be discussed. Table 2.3 shows relevance of reported associations for mortality.

Table 2.3 Relevance of prognostic factors for mortality

	Statistically significant								
	Chen	**Cummings**	**Gao**	**Giacomelli**	**Klang Age≤50 y**	**Klang Age>50 y**	**Palaiodimos**	**Petrilli**	**Wang**
Predictor	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**HR (95% CI)**	**HR 95% CI)**
Age	**Yes** <65y: ref 65-74: 3.43 (1.24-9.5) ≥75: 7.86 (2.44-25.35)	**Yes** Per 10y: 1.39 (1.29-1.57)	**Yes** Per year: 1.06 (1.04-1.09)	**Yes** Per 10y: 2.08 (1.48-2.92)	**Yes** Per 10y: 3.0 (1.9-4.8)	**Yes** Decile: 1.7 (1.6-1.8)	**Yes** Quartiles: 1.73 (1.13-2.63)	**Yes** 19-44y: ref 45-54: 1.12 (0.80-1.60) 55-64: 2.04 (1.50-2.80) 65-74: 2.88 (2.46-4.80) ≥75: 3.46 (2.46-4.80))	**Yes** 1.86 (1.06-3.26)
BMI (kg/m^2)	-	No <40: ref ≥40: 0.76 (0.4-1.47)	-	**Yes** <30: ref ≥30: 3.04 (1.42-6.49)	**Yes** <30: ref 30-40: 1.1 (0.5-2.3) ≥40: 5.1 (2.3-11.1)	**Yes** >30: ref 30-40: 1.1 (0.9-1.3) ≥40: 1.6 (1.2-2.3)	**Yes** 25-34: ref <25: 1.37 (0.52-3.64) ≥35: 3.78 (1.45-9.83)	**Yes** <25: ref 25-30: 0.91 (0.74-1.11) 30-40: 1.02 (0.82-1.27) ≥40: 1.41 (0.98-3.02) Unknown: 1.85 (1.13-3.02)	-
Smoking	-	-	-	-	No 1.7 (0.8-3.8)	No 1.0 (0.8-1.2)	No 0.83 (0.37-1.87)	**Yes** Never: ref Former: 1.13 (0.93-1.37) Current: 0.90 (0.61-1.31) Unknown: 1.56 (1.26-1.93)	-
Hypertension (yes/no)	-	No 1.58 (0.89-2.81)	**Yes** 2.00 (1.13-3.54)	-	No 0.5 (0.2-1.1)	No 1.1 (0.9-1.3)		No 0.94 (0.76-1.16)	-
Diabetes (yes/no)	-	No 1.31 (0.81-2.10)	-	-	No 1.3 (0.7-2.6)	**Yes** 1.4 (1.2-1.7)	No 1.16 (0.55-2.44)	No 1.10 (0.93-1.31)	-
Coronary artery disease or congestive heart failure (yes/no)	-	**Yes** 1.76 (1.08-2.86)	-	-	-	-	-	-	-
Coronary artery disease (yes/no)	**Yes** 4.28 (1.14-16.13)	-	-	-	No 0.6 (0.2-2.1)	**Yes** 1.3 (1.1-1.6)	No 1.53 (0.54-4.34)	No 1.12 (0.92-1.36)	-
Cerebrovascular disease (yes/no)	**Yes** 3.1 (1.07-8.94)	-	-	-	-	-	-	-	No 1.38 (0.65-2.93)
Heart failure (yes/no)	-	-	**Yes** 3.3 (1.33-8.19)	-	**Yes** 4.0 (1.6-10.4)	No 1.0 (0.8-1.3)	No 1.43 (0.50-4.06)	**Yes** 1.77 (1.43-2.20)	-

Hospital admission predicted by prognostic factors measured during hospital stay
Hospital admission was only reported in the study of Petrilli (2020). Because the model was unvalidated and was included in only one study, the results regarding prognostic factors for hospital admission will not be discussed.

Level of evidence of the literature
The level of evidence was assessed according to the GRADE methodology (GRADE: Grading Recommendations Assessment, Development and Evaluation, http://www.gradeworkinggroup.org/).

Mortality predicted by prognostic factors
Body Mass Index (BMI)
Starting with a high level of evidence for prognostic studies, the level of evidence regarding the outcome measure mortality was downgraded by 1 level because of risk of bias (some patients were still under treatment at the end of the study) and by 1 level because of indirectness (studies are not validated) and 1 level for imprecision (wide confidence intervals, one included in the confidence interval) to 'very low'.

Smoking
Starting with a high level of evidence for prognostic studies, the level of evidence regarding the outcome measure mortality was downgraded by 1 level because of risk of bias (some patients were still under treatment at the end of the study) and by 1 level because of indirectness (studies are not validated) and 1 level for imprecision (wide confidence intervals, one included in the confidence interval) to 'very low'.

Hypertension
Starting with a high level of evidence for prognostic studies, the level of evidence regarding the outcome measure mortality was downgraded by 1 level because of risk of bias (some patients were still under treatment at the end of the study) and by 1 level because of indirectness (studies are not validated) and 1 level for imprecision (wide confidence intervals, too many prognostic factors included in relation to number of events) to 'very low'.

Diabetes
Starting with a high level of evidence for prognostic studies, the level of evidence regarding the outcome measure mortality was downgraded by 1 level because of risk of bias (some patients were still under treatment at the end of the study) and by 1 level because of indirectness (studies are not validated)) and 1 level for imprecision (wide confidence intervals and one included in the confidence interval) to 'very low'.

Coronary artery disease or congestive heart failure
Starting with a high level of evidence for prognostic studies, the level of evidence regarding the outcome measure mortality was downgraded by 1 level because of risk of bias (some patients were still under treatment at the end of the study), by 1 level because of indirectness (studies are not validated) and by 1 level because of inconsistency of results to 'very low'.

Cerebrovascular disease
Starting with a high level of evidence for prognostic studies, the level of evidence regarding the outcome measure mortality was downgraded by 1 level because of risk of bias (some patients were still under treatment at the end of the study), by 1 levels because of indirectness (studies are not

validated), by 1 level because of inconsistency of results and by 1 level because of number of included patients (imprecision) to ‘very low’.

Heart failure
Starting with a high level of evidence for prognostic studies, the level of evidence regarding the outcome measure mortality was downgraded by 1 level because of risk of bias (some patients were still under treatment at the end of the study), by 1 levels because of indirectness (studies are not validated), by 1 level because of inconsistency of results and by 1 level because of number of included patients (imprecision) to ‘very low’.

Conclusions

Mortality predicted by prognostic factors measured during hospital stay

Very low GRADE	We are unsure whether Body Mass Index is a predictor of mortality in COVID-19 patients admitted to hospital, adjusted for age. *Sources: Cummings, 2020; Giacomelli, 2020; Klang, 2020; Palaiodimos, 2020; Petrilli, 2020*

Very low GRADE	We are unsure whether smoking is a predictor of mortality in COVID-19 patients admitted to hospital, adjusted for age. *Sources: Klang, 2020; Palaiodimos, 2020; Petrilli, 2020*

Very low GRADE	We are unsure whether hypertension is a predictor of mortality in COVID-19 patients admitted to hospital, adjusted for age. *Sources: Cummings, 2020; Gao, 2020; Klang, 2020; Petrilli, 2020*

Very low GRADE	We are unsure whether diabetes is a predictor of mortality in COVID-19 patients admitted to hospital, adjusted for age. *Sources: Cummings, 2020; Klang, 2020; Palaiodimos, 2020; Petrilli, 2020*

Very low GRADE	We are unsure whether coronary artery disease or congestive heart failure is a predictor of mortality in COVID-19 patients admitted to hospital, adjusted for age. *Sources: Chen, 2020; Cummings, 2020; Klang, 2020; Palaiodimos, 2020; Petrilli, 2020*

Very low GRADE	We are unsure whether cerebrovascular disease is a predictor of mortality in COVID-19 patients admitted to hospital, adjusted for age. *Sources: Chen, 2020; Wang, 2020*

Very low GRADE	We are unsure whether heart failure is a predictor of mortality in COVID-19 patients admitted to hospital, adjusted for age. *Sources: Klang, 2020; Palaiodimos, 2020; Petrilli, 2020*

- **GRADE**	We cannot conclude which other cardiovascular risk factors, cardiovascular disease or cardiovascular history can predict mortality in COVID-19 patients due to lack of studies testing multivariable models taking age into account.

Hospital admission predicted by prognostic factors measured during hospital stay

- **GRADE**	We cannot conclude which cardiovascular risk factors, cardiovascular disease or cardiovascular history can predict hospital admission in COVID-19 patients due to lack of studies testing multivariable models taking age into account.

Overwegingen – van bewijs naar aanbeveling

Voor- en nadelen van de interventie en de kwaliteit van het bewijs

De kwaliteit van het bewijs van de geïncludeerde studies is overwegend laag tot zeer laag. De GRADE systematiek is gevolgd om de kwaliteit van het bewijs te beoordelen. Deze is hier dan ook gevolgd. In een nieuwe situatie (zoals COVID) is het logisch dat de meeste studies nog niet kunnen voldoen aan de strenge eisen die aan studies van hoge kwaliteit worden gesteld. De GRADE methodiek zet de kwaliteit van het bewijs echter af tegen de best mogelijke kwaliteit en niet tegen de best mogelijke kwaliteit in de huidige situatie. De GRADE systematiek geeft het vertrouwen weer in de schatting van het effect van een interventie. Wanneer de modules en de search worden geüpdate zijn er hopelijk studies van betere kwaliteit beschikbaar en kan het niveau van de kwaliteit van het bewijs hierop worden aangepast.

Op basis van de huidige literatuursamenvatting kunnen alleen conclusies worden getrokken waarin weinig vertrouwen wordt gegeven aan de correctheid van de schatting van het prognostisch effect van cardiovasculaire risico factoren of cardiovasculaire aandoeningen op mortaliteit. Hoewel op basis van de resultaten van de gerapporteerde modellen geconcludeerd zou kunnen worden dat BMI (gecorrigeerd voor leeftijd) statistisch gezien (klinische relevantie onbekend) een voorspeller zou kunnen zijn van mortaliteit, kan deze conclusie op dit moment niet worden ondersteund met bewijskracht vanuit de geselecteerde literatuur. De bewijskracht van de gevonden studies is zeer laag, onder andere door beperkingen in de methodologische opzet van de gevonden studies. Er is behoefte aan kwalitatief goed opgezette studies, welke gemaakte voorspellende modellen valideren in een Westerse populatie. In de literatuur werd daarom geen bewijs gevonden voor voorspellers die een rol zouden kunnen spelen bij mortaliteit in patiënten met COVID-19, wanneer wordt gecorrigeerd voor leeftijd.

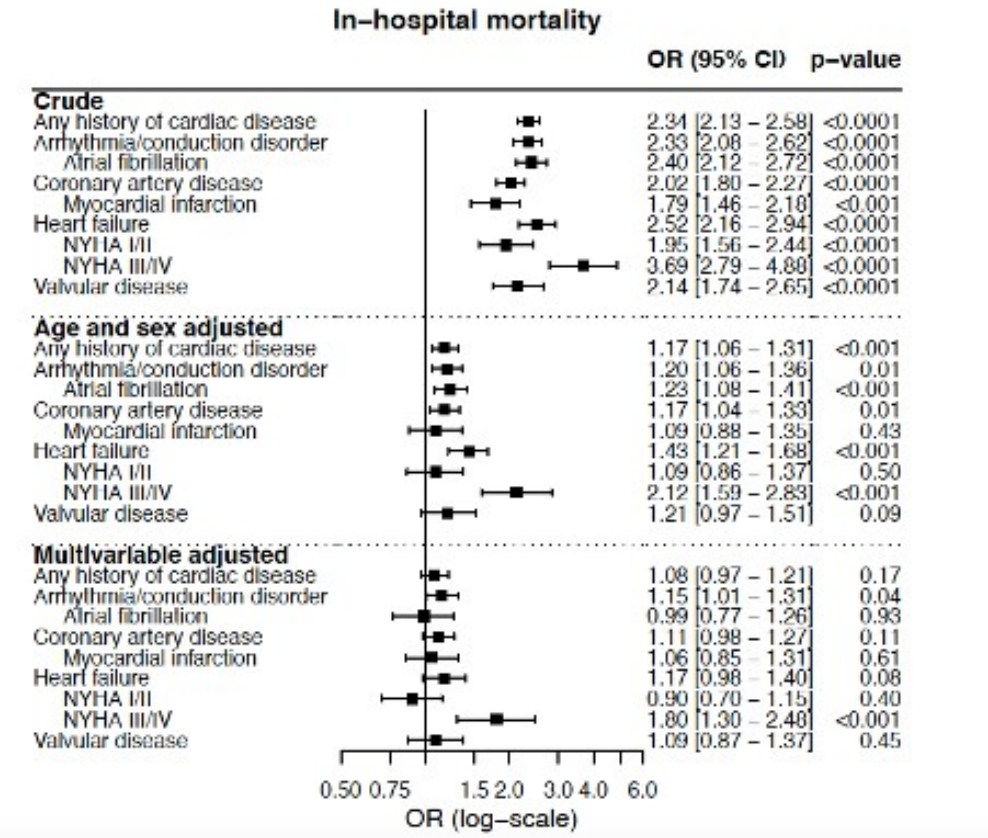
Wanneer prognostische factoren kunnen worden vastgesteld, en deze gebruikt wensen te worden ten behoeve van klinische besluitvorming, maakt men gebruik van een beoordelingsmodel. Het is verstandig de voorspellende waarde van het te ontwikkelen beoordelingsmodel te optimaliseren door het te ontwikkelen model intern en extern te valideren en waar nodig te verbeteren. De effectiviteit van de toepassing van het ontwikkelde model wordt bij voorkeur getest in de praktijk door het effect op patiënt gerelateerde uitkomstmaten te meten alvorens het als standaard beoordelingsmiddel wordt ingezet.

CAPACITY

CAPACITY is een internationale registratie van patiënten met COVID-19 op basis van het ISARIC WHO CRF, aangevuld met informatie over specifieke cardiovasculaire parameters (https://capacity-covid.eu/). CAPACITY is in het voorjaar van 2020 gestart en bevat gegevens van 13034 patiënten uit 13 landen, afkomstig van 79 registrerende centra. CAPACITY bevat omvangrijke informatie over patiënten met COVID, omdat ongeveer 40% van de in Nederland opgenomen COVID19 patiënten in de registratie is opgenomen (n = 5524).

De peer-reviewed publicatie van CAPACITY over het onderwerp van deze module is momenteel in voorbereiding. De resultaten van CAPACITY kunnen daarom kunnen nog niet worden meegenomen bij het literatuuronderzoek, maar bij de overwegingen worden wel de voorlopige resultaten van CAPACITY meegenomen. De peer-reviewed publicatie over het onderwerp van deze module wordt binnenkort verwacht en bij een update van de module zal de publicatie in het literatuuronderzoek worden meegenomen.

Figuur 1.1 Associaties tussen cardiale voorgeschiedenis en in-hospital mortaliteit uit de CAPACITY registry en data uit de LEOSS registry gezamenlijk (n=10712)



Een vergelijking van de basale kenmerken tussen patiënten met een cardiale voorgeschiedenis en patiënten zonder cardiale voorgeschiedenis laat zien dat patiënten met een cardiale voorgeschiedenis ouder zijn en meer cardiale risicofactoren en co-morbiditeit hebben.
De opnameduur op de Intensive Care en in het ziekenhuis zijn voor beide groepen vergelijkbaar. Patiënten met een cardiale voorgeschiedenis ontwikkelen vaker een acute nierinsufficiëntie tijdens de ziekenhuis opname en hebben vaker nierfunctiestoornissen in de voorgeschiedenis. In de vergelijking valt op dat een groter deel van de patiënten met een cardiale voorgeschiedenis komt te overlijden tijdens een ziekenhuisopname vanwege COVID-19 infectie.

Leeftijd, geslacht en algemene “frailty” lijken een belangrijke voorspellende waarde te hebben.

Preliminaire resultaten van Nederlandse data uit de CAPACITY registry geven aan dat bij patiënten met een cardiale co-morbiditeit, hartfalen geassocieerd lijkt te zijn met een verhoogd risico op op mortaliteit gedurende de opname. Analyse van gecombineerde data (n= 10712) uit de CAPACITY registry en data uit de LEOSS registry (Lean Europeaan Open Survey on SARS-CoV-2 infected patients; dit is een multicenter prospectieve cohort studie met als primaire doel het identificeren

van onafhankelijke predictoren voor uitkomst bij patiënten gediagnostificeerd met SARS-CoV2) laat zien dat er bij patiënten met een cardiale co-morbiditeit, na adjusteren voor leeftijd, geslacht, BMI, hypertensie, CKD, COPD en diabetes, een significante associatie bestaat tussen NYHA III/IV hartfalen en in-hospital mortaliteit.

Waarden en voorkeuren van patiënten (en evt. hun verzorgers)
Aan patiënten met cardiovasculaire risicofactoren en/of cardiovasculaire aandoeningen kan meegegeven worden dat zij in de COVID-pandemie de aanwijzingen vanuit de overheid, zorgverleners en zorginstituten over preventieve maatregelen en testindicaties volgen die betrekking hebben op de risicogroepen.

Kosten (middelenbeslag)
Niet van toepassing

Aanvaardbaarheid, haalbaarheid en implementatie
De aanbeveling is aanvaardbaar en haalbaar aangezien de COVID-infectie nadrukkelijk aandacht heeft en krijgt vanuit de overheid en zorgverleners. In de landelijke adviezen wordt expliciet aandacht besteedt aan de risicogroepen.

Aanbeveling
Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies
Patiënten met cardiovasculaire risicofactoren en/of cardiovasculaire aandoeningen zijn een kwetsbare groep op het gebied van infectieziekten. Er zijn geen aanwijzingen gevonden dat dit in de COVID-epidemie anders ligt. Overtuigende bewijskracht voor het effect van cardiovasculaire risicofactoren en/of cardiovasculaire aandoeningen op mortaliteit en ernst van het ziektebeloop bij COVID-19 infectie ontbreekt in de samengevatte literatuur. Echter, de aanwijzingen uit de CAPACITY registry dat patiënten met een cardiale voorgeschiedenis ouder zijn en meer co-morbiditeit hebben, dat leeftijd en frailty belangrijke voorspellers van mortaliteit zijn en dat meer patiënten met een cardiale voorgeschiedenis overlijden aan COVID-19 dan patiënten zonder cardiale voorgeschiedenis, worden als belangrijk gezien in het identificeren van deze patiëntengroep als een risicogroep. Derhalve wordt geadviseerd om de patiënten met cardiovasculaire risicofactoren en/of cardiovasculaire aandoeningen in de COVID-epidemie te beschouwen als risicogroep en de daarvoor vigerende adviezen en preventiemaatregelen te volgen. Bij patiënten met cardiale co-morbiditeit lijkt vooral hartfalen (NYHA III/IV) geassocieerd met mortaliteit. Er zijn momenteel echter onvoldoende aanwijzingen gevonden die voor specifieke risicofactoren of aandoeningen aanzetten tot extra maatregelen bovenop de hiervoor genoemde.

Beschouw patiënten met cardiovasculaire risicofactoren en/of cardiovasculaire aandoeningen in de COVID pandemie als een risicogroep; patiënten met hartfalen hebben hierbinnen mogelijk een groter risico op overlijden. Zorgverleners en patiënten volgen in de vigerende adviezen en preventiemaatregelen vanuit de overheid en zorginstituten de aanwijzingen voor de risicogroepen.

Kennislacunes
Is heartfailure in proven COVID-19 patients with cardiovascular risk factors or underlying cardiovascular disease associated with a poor outcome?

Literatuur
Chen, R., Liang, W., Jiang, M., Guan, W., Zhan, C., Wang, T., ... & Hu, Y. (2020). Risk factors of fatal outcome in hospitalized subjects with coronavirus disease 2019 from a nationwide analysis in China. Chest.

Cummings, M. J., Baldwin, M. R., Abrams, D., Jacobson, S. D., Meyer, B. J., Balough, E. M., ... & Hochman, B. R. (2020). Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in New York City: a prospective cohort study. The Lancet.

Gao, C., Cai, Y., Zhang, K., Zhou, L., Zhang, Y., Zhang, X., ... & Zhao, Y. (2020). Association of hypertension and antihypertensive treatment with COVID-19 mortality: a retrospective observational study. European Heart Journal, 41(22), 2058-2066.

Giacomelli, A., Ridolfo, A. L., Milazzo, L., Oreni, L., Bernacchia, D., Siano, M., ... & Piscaglia, M. (2020). 30-day mortality in patients hospitalized with COVID-19 during the first wave of the Italian epidemic: a prospective cohort study. Pharmacological Research, 104931.

Klang, E., Kassim, G., Soffer, S., Freeman, R., Levin, M. A., & Reich, D. L. (2020). Morbid Obesity as an Independent Risk Factor for COVID-19 Mortality in Hospitalized Patients Younger than 50. Obesity.

Palaiodimos, L., Kokkinidis, D. G., Li, W., Karamanis, D., Ognibene, J., Arora, S., ... & Mantzoros, C. S. (2020). Severe obesity, increasing age and male sex are independently associated with worse in-hospital outcomes, and higher in-hospital mortality, in a cohort of patients with COVID-19 in the Bronx, New York. Metabolism, 108, 154262.

Petrilli, C. M., Jones, S. A., Yang, J., Rajagopalan, H., O'Donnell, L., Chernyak, Y., ... & Horwitz, L. I. (2020). Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: prospective cohort study. bmj, 369.

Wang, L., He, W., Yu, X., Hu, D., Bao, M., Liu, H., ... & Jiang, H. (2020). Coronavirus disease 2019 in elderly patients: Characteristics and prognostic factors based on 4-week follow-up. Journal of Infection.

Bijlagen bij module 2

Evidence tables

Table of quality assessment – Prognostic factor (PF) studies

Based on: QUIPS[A] (Haydn, 2006; Haydn 2013)

Study reference (first author, year of publication)	**Study participation[1]** Study sample represents the population of interest on key characteristics? (high/moderate/low risk of selection bias)	**Study Attrition[2]** Loss to follow-up not associated with key characteristics (i.e., the study data adequately represent the sample)? (high/moderate/low risk of attrition bias)	**Prognostic factor measurement[3]** Was the PF of interest defined and adequately measured? (high/moderate/low risk of measurement bias related to PF)	**Outcome measurement[3]** Was the outcome of interest defined and adequately measured? (high/moderate/low risk of measurement bias related to outcome)	**Study confounding[4]** Important potential confounders are appropriately accounted for? (high/moderate/low risk of bias due to confounding)	**Statistical Analysis and Reporting[5]** Statistical analysis appropriate for the design of the study? (high/moderate/low risk of bias due to statistical analysis)	**Overall judgment** *High risk of bias: at least one domain judged to be at high risk of bias.* *Model development only: high risk of bias.* Risk of bias: low/moderate/high/unclear
Chen, 2020	Unclear (inclusion criteria not clearly described)	Moderate (21% excluded because of incomplete medical records: differences not described)	Unclear (assessment not well described)	High (endpoint for mortality not described: patients could be still under treatment at endpoint of the study)	Low (accounted for age)	Moderate (reason for selection of factors is unclear)	Moderate
Cummings, 2020	High (only COVID-19 patients included who were critically ill with acute hypoxaemic respiratory failure)	Unclear (loss to follow-up not described)	Low	High (some patients were still under treatment at endpoint of the study)	Low (accounted for age)	Moderate (independent variables included in multivariable Cox model considered relevant to in-hospital mortality by the authors.	High
Gao, 2020	Low	Unclear (loss to follow-up not described)	Low	High (patients could be still under treatment at endpoint of the study: not described)	Low (accounted for age)	Unclear (reason of selection of included prognostic factors in multivariable model not described)	Moderate
Giacomelli, 2020	Low	Unclear (loss to follow-up not described)	Low	High (some patients, 10%, were still under treatment at endpoint of the study)	Low (accounted for age)	Low (significant factors univariate analysis included in multivariable analysis)	Moderate
Klang, 2020	Low	High (patients who were still hospitalized during the study period and/or with missing BMI were excluded)	Low	High (22% were still hospitalized at endpoint of the study and were excluded)	Low (accounted for age)	Moderate (all factors included in the multivariate model)	High
Palaiodimos, 2020	Low	Unclear (loss to follow-up not described)	Low	Low	Low (accounted for age)	Low (3 models developed, BMI and age, all the	Low

						variables with significant univariate associations and addition of clinically significant variables)	
Petrilli, 2020	Low	High (patients who were still hospitalized during the study period were censored)	Low	High (mortality after discharge was not measured unless patients was readmitted to the system)	Low (accounted for age)	Low (included all selected predictors based on a priori clinical significance after testing for collinearity using the variance inflation factor)	High
Wang, 2020	Low	Unclear (loss to follow-up not described)	Low	High (54% was still hospitalized at endpoint of the study)	Low (accounted for age)	Low (significant factors univariate analysis included in multivariable analysis)	High

Table of excluded studies

Author and year	Reason for exclusion
Aggarwal 2020	Wrong comparison: mortality in patients with severe COVID-19 disease and pre-existing history of CVD. Only 3 studies
Alqahtani 2020	Wrong comparison: prevalence of chronic diseases (COPD), no multilevel analysis
Cecconi 2020	Wrong outcome: composite outcome (ICU transfer or death)
Galloway 2020	Wrong outcome: composite outcome (transfer to a critical care unit bed or death)
Guan 2020	Wrong outcome: Only composite endpoint used in multivariate analysis. Same cohort as Chen (2020).
Hamer 2020	Wrong comparison: lifestyle risk factors
Hu 2020	Wrong outcome: composite outcome
Huang 2020	Wrong study design: associations between diabetes and composite outcome composite poor outcome, including mortality, severe COVID-19, ARDS, need for ICU care, and disease progression, no predictive value (no adjustments performed)
Imam 2020	Wrong comparison: imaging findings, medication, laboratory values
Jain 2020	Wrong study design: sample size <200 included
Kumar 2020	Wrong outcome: composite outcome (severe clinical course)
Li 2020a	Wrong study design: associations between CVD, hypertension and myocardial injury and mortality, no predictive value (no adjustments performed)
Li 2020b	Wrong outcome: severe covid-19
Lippi 2020	Wrong study design: associations between hypertension and disease severity and mortality, no predictive value (no adjustments performed)
Liu 2020	Wrong outcome: composite outcome (disease severity)
Luo 2020	Article in Chinese
Nikpouraghdam 2020	Wrong comparison: comorbidity as predicting factor (no separate diseases)
Parohan 2020	Wrong study design: associations between comorbidities and mortality, no predictive value (no adjustments performed)
Pranata 2020a	Wrong study design: associations between CVD and mortality/poor composite outcome, no predictive value (no adjustments performed)
Pranata 2020b	Wrong study design: associations between hypertension and mortality, no predictive value (no adjustments performed)
Roncon 2020	Not searched in Medline. Searched on Diabetes Mellitus
Santoso 2020	Wrong outcome: prognostic effect troponin on outcomes
Shi 2020	Small sample (N<200)
Shi 2020a	Wrong comparison: cardiac biomarkers (troponin, CK-MB, MYO)
Shi 2020b	Wrong comparison: cardiac injury biomarkers
Tamara 2020	Wrong outcome: severe covid-19
Tian 2020	Wrong study design: no multilevel analysis
Wang 2020a	Wrong outcome: COVID-19
Wang 2020b	Wrong comparison: predictive laboratory model compared to clinical model (age, hypertension, CHD)
Zhang 2020a	Wrong outcome: recovery of patients during follow-up
Zhang 2020b	Wrong comparison: mortality in hypertensive patients, no prognostic factor (no adjustments performed)
Zhang 2020c	Wrong outcome: COVID-19 severity
Zhao 2020	Wrong outcome: severe covid-19
Zheng 2020	Wrong study design: associations between hypertension, CVD, diabetes and non-critical/critical or mortality, no predictive value (no adjustments performed)
Zuin 2020	Commentary article

Literature search strategy

Ovid/Medline

1 ((exp Coronavirus/ or Coronavirus Infections/ or pneumonia virus*.ti,ab,kf. or cov.ti,ab,kf.) and ((outbreak or wuhan).ti,ab,kf. or novel.af. or '19'.ti,ab,kf. or '2019'.ti,ab,kf. or epidem*.af. or epidemy.af. or epidemic*.af. or pandem*.af. or new.ti,ab,kf.)) or (coronavirus* or 'corona virus*' or ncov or '2019ncov' or 'covid19' or "covid 19" or "sars cov 2" or 'sars2' or "ncov 2019" or "sars coronavirus 2" or "sars corona virus 2" or "severe acute respiratory syndrome cov 2" or "severe acute respiratory syndrome cov2" or "severe acute respiratory syndrome cov*").ti,ab,kf. (34799)

2 limit 1 to dt="20191201-20220101" (22129)

3 exp Cardiovascular Diseases/ or angiocardiopathy.ti,ab,kf. or angiocardiovascular disease.ti,ab,kf. or hypovolemia.ti,ab,kf. or ((cardiovascular or heart or cardiac or coronary) adj3 (complication* or disorder* or disturbance* or lesion* or syndrome* or event* or risk* or history or failure or overload or dysfunction or arrest or aneurysm* or anomal* or atheroscleros* or calcification* or constriction* or dissection or obstruction or occlusion or perforation or thrombos*)).ti,ab,kf. or exp Smoking/ or smoking.ti,ab,kf. or exp Obesity/ or adipose tissue hyperplasia.ti,ab,kf. or adipositas.ti,ab,kf. or adiposity.ti,ab,kf. or corpulency.ti,ab,kf. or fat overload syndrome.ti,ab,kf. or obesitas.ti,ab,kf. or obesity.ti,ab,kf. or overweight.ti,ab,kf. or obese.ti,ab,kf. or exp hypercholesterolemia/ or cholesteremia.ti,ab,kf. or cholesterinemia.ti,ab,kf. or cholesterolemia.ti,ab,kf. or hypercholesteremia.ti,ab,kf. or hypercholesterinaemia.ti,ab,kf. or hypercholesterinemia.ti,ab,kf. or hypercholesterolaemia.ti,ab,kf. or hypercholesterolemia.ti,ab,kf. or exp Hypertension/ or high blood pressure.ti,ab,kf. or hypertens*.ti,ab,kf. or exp Diabetes mellitus/ or diabetes.ti,ab,kf. or diabetic.ti,ab,kf. or insulin resistanc*.ti,ab,kf. or exp Non-alcoholic fatty liver disease/ or non alcoholic steato-hepatitis.ti,ab,kf. or non-alcoholic steatohepatitis.ti,ab,kf. or non-alcoholic steatosis hepatitis.ti,ab,kf. or non-alcoholic steatotic hepatitis.ti,ab,kf. or nonalcoholic fatty liver inflammation.ti,ab,kf. or nonalcoholic steato-hepatitis.ti,ab,kf. or nonalcoholic steatohepatitis.ti,ab,kf. or nonalcoholic steatosis hepatitis.ti,ab,kf. or nonalcoholic steatotic hepatitis.ti,ab,kf. or exp Arrhythmias, Cardiac/ or arrhythmia.ti,ab,kf. or ectopic heart rhythm.ti,ab,kf. or ectopic rhythm.ti,ab,kf. or heart aberrant conduction.ti,ab,kf. or arrhytmia.ti,ab,kf. or arrythmia.ti,ab,kf. or dysrhythmia.ti,ab,kf. or heart ectopic beat.ti,ab,kf. or heart ectopic ventricle contraction.ti,ab,kf. or heart rhythm disorder.ti,ab,kf. or atrioventricular junction arrhythmia.ti,ab,kf. or bradycardia.ti,ab,kf. or cardiac channelopath*.ti,ab,kf. or cardiopulmonary arrest*.ti,ab,kf. or commotio cordis.ti,ab,kf. or heart fibrillation.ti,ab,kf. or heart muscle conduction disturbance.ti,ab,kf. or heart palpitation.ti,ab,kf. or heart preexcitation.ti,ab,kf. or heart proarrhythmia.ti,ab,kf. or pacemaker failure*.ti,ab,kf. or parasystole.ti,ab,kf. or tachycardia.ti,ab,kf. or acute coronary syndrome.ti,ab,kf. or cardiac allograft vasculopathy.ti,ab,kf. or coronary bifurcation lesion.ti,ab,kf. or coronary subclavian steal syndrome.ti,ab,kf. or kounis syndrome.ti,ab,kf. or no reflow phenomenon.ti,ab,kf. (3642523)

4 2 and 3 (1382)

5 4 not ((exp animals/ or exp models, animal/) not humans/) not (letter/ or comment/ or editorial/) (1091)

6 (meta-analysis/ or meta-analysis as topic/ or (meta adj analy$).tw. or ((systematic* or literature) adj2 review$1).tw. or (systematic adj overview$1).tw. or exp "Review Literature as Topic"/ or cochrane.ab. or cochrane.jw. or embase.ab. or medline.ab. or (psychlit or psyclit).ab. or (cinahl or cinhal).ab. or cancerlit.ab. or ((selection criteria or data extraction).ab. and "review"/)) not (Comment/ or Editorial/ or Letter/ or (animals/ not humans/)) (449490)

7 (exp clinical trial/ or randomized controlled trial/ or exp clinical trials as topic/ or randomized controlled trials as topic/ or Random Allocation/ or Double-Blind Method/ or Single-Blind Method/ or (clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or randomized controlled trial or multicenter study or clinical trial).pt. or random*.ti,ab. or (clinic* adj trial*).tw. or ((singl* or doubl* or treb* or tripl*) adj (blind$3 or mask$3)).tw. or Placebos/ or placebo*.tw.) not (animals/ not humans/) (1990319)

8 Epidemiologic studies/ or case control studies/ or exp cohort studies/ or Controlled Before-After Studies/ or Case control.tw. or (cohort adj (study or studies)).tw. or Cohort analy$.tw. or (Follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or Longitudinal.tw. or Retrospective*.tw. or prospective*.tw. or consecutive*.tw. or Cross sectional.tw. or Cross-sectional studies/ or historically controlled study/ or interrupted time series analysis/ [Onder exp cohort studies vallen ook longitudinale, prospectieve en retrospectieve studies] (3449163)

9 5 and 6 (67)**Systematic reviews**

10 5 and 7 (78)

11 5 and 8 (205)

12 10 not 9 (60) **RCT's**

13 11 not 10 not 9 (169) **Observationeel**

Embase Session Results (9 Jun 2020)

No.	Query	Results
#27	#20 NOT #19 NOT #18 **Observationeel (P AND I)**	**282**
#26	#19 NOT #18 **RCT's (P AND I)**	**113**
#20	#4 AND #12	**381**
#19	#4 AND #11	**132**
#18	#4 AND #5 **Systematic reviews (P AND I)**	**94**
#17	#15 NOT #14 NOT #13 Observationeel (P AND I AND O)	**195**
#16	#14 NOT #13 RCT (P AND I AND O)	**84**
#15	#9 AND #12	**268**
#14	#9 AND #11	**99**
#13	#9 AND #10 SR (P AND I AND O)	**68**
#12	'major clinical study'/de OR 'clinical study'/de OR 'case control study'/de OR 'family study'/de OR 'longitudinal study'/de OR 'retrospective study'/de OR 'prospective study'/de OR 'comparative study'/de OR 'cohort analysis'/de OR ((cohort NEAR/1 (study OR studies)):ab,ti) OR (('case control' NEAR/1 (study OR studies)):ab,ti) OR (('follow up' NEAR/1 (study OR studies)):ab,ti) OR (observational NEAR/1 (study OR studies)) OR ((epidemiologic NEAR/1 (study OR studies)):ab,ti) OR (('cross sectional' NEAR/1 (study OR studies)):ab,ti)	**5969696**
#11	('clinical trial'/exp OR 'randomization'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp OR 'placebo'/exp OR 'prospective study'/exp OR rct:ab,ti OR random*:ab,ti OR 'single blind':ab,ti OR 'randomised controlled trial':ab,ti OR 'randomized controlled trial'/exp OR placebo*:ab,ti) NOT 'conference abstract':it	**2399535**
#10	('meta analysis'/de OR cochrane:ab OR embase:ab OR psycinfo:ab OR cinahl:ab OR medline:ab OR ((systematic NEAR/1 (review OR overview)):ab,ti) OR ((meta NEAR/1 analy*):ab,ti) OR metaanalys*:ab,ti OR 'data extraction':ab OR cochrane:jt OR 'systematic review'/de) NOT (('animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	**497183**
#9	#8 NOT ('conference abstract'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it) NOT (('animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	**1027**
#8	#3 AND #7	**1310**
#7	'mortality'/exp OR 'mortality':ti,ab OR death*:ti,ab OR fatal*:ti,ab OR 'hospital admission'/exp OR 'hospital admission':ti,ab OR 'hospital admittance':ti,ab OR 'patient admission':ti,ab OR 'intensive care'/exp OR 'critical care':ti,ab OR 'intensive care':ti,ab OR 'intensive therapy':ti,ab OR 'length of stay'/exp OR 'length of stay':ti,ab OR 'infarction'/exp OR 'bloodless':ti,ab OR 'infarct*':ti,ab OR 'thromboembolic accident':ti,ab OR 'thromboembolism'/exp OR thromboembolism*:ti,ab OR 'lung embolism*':ti,ab OR 'pulmonary embolism*':ti,ab OR 'cerebrovascular accident'/exp OR cva:ti,ab OR 'cerebrovascular accident':ti,ab OR 'transient ischemic attack'/exp OR tia:ti,ab OR 'transient ischemic attack':ti,ab OR 'poor outcome':ti,ab	**4177433**
#6	#4 AND #5	**94**
#5	('meta analysis'/de OR cochrane:ab OR embase:ab OR psycinfo:ab OR cinahl:ab OR medline:ab OR ((systematic NEAR/1 (review OR overview)):ab,ti) OR ((meta NEAR/1 analy*):ab,ti) OR metaanalys*:ab,ti OR 'data extraction':ab OR cochrane:jt OR 'systematic review'/de) NOT (('animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	**497183**
#4	#3 NOT ('conference abstract'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it) NOT (('animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	**1767**
#3	#1 AND #2	**2228**
#2	'cardiovascular risk'/exp OR 'cardiovascular disease'/exp OR 'angiocardiopathy':ti,ab OR 'angiocardiovascular disease':ti,ab OR hypovolemia:ti,ab OR (((cardiovascular OR heart OR cardiac OR coronary) NEAR/3	**5896926**

No.	Query	Results
	(complication* OR disorder* OR disturbance* OR lesion* OR syndrome* OR event* OR risk* OR history OR failure OR overload OR dysfunction OR arrest OR aneurysm* OR anomal* OR atherosclerosis* OR calcification* OR constriction* OR dissection OR obstruction OR occlusion OR perforation OR thrombos*)):ti,ab) OR 'smoking'/exp OR smoking:ti,ab OR 'obesity'/exp OR 'adipose tissue hyperplasia':ti,ab OR 'adipositas':ti,ab OR 'adiposity':ti,ab OR 'corpulency':ti,ab OR 'fat overload syndrome':ti,ab OR 'obesitas':ti,ab OR 'obesity':ti,ab OR 'overweight':ti,ab OR 'obese patient'/exp OR 'obese':ti,ab OR 'hypercholesterolemia'/exp OR 'cholesteremia':ti,ab OR 'cholesterinemia':ti,ab OR 'cholesterolemia':ti,ab OR 'hypercholesteremia':ti,ab OR 'hypercholesterinaemia':ti,ab OR 'hypercholesterinemia':ti,ab OR 'hypercholesterolaemia':ti,ab OR 'hypercholesterolemia':ti,ab OR 'hypertension'/exp OR 'high blood pressure':ti,ab OR hypertens*:ti,ab OR 'diabetes mellitus'/exp OR 'diabetes':ti,ab OR 'diabetic':ti,ab OR 'insulin resistance'/exp OR 'insulin resistance':ti,ab OR 'nonalcoholic steatohepatitis'/exp OR 'nash (nonalcoholic steatohepatitis)':ti,ab OR 'non alcoholic steato-hepatitis':ti,ab OR 'non-alcoholic steatohepatitis':ti,ab OR 'non-alcoholic steatosis hepatitis':ti,ab OR 'non-alcoholic steatotic hepatitis':ti,ab OR 'nonalcoholic fatty liver inflammation':ti,ab OR 'nonalcoholic steato-hepatitis':ti,ab OR 'nonalcoholic steatohepatitis':ti,ab OR 'nonalcoholic steatosis hepatitis':ti,ab OR 'nonalcoholic steatotic hepatitis':ti,ab OR 'heart arrhythmia'/exp OR 'arrhythmia':ti,ab OR 'ectopic heart rhythm':ti,ab OR 'ectopic rhythm':ti,ab OR 'heart aberrant conduction':ti,ab OR 'arrhytmia':ti,ab OR 'arrythmia':ti,ab OR 'dysrhythmia':ti,ab OR 'heart ectopic beat':ti,ab OR 'heart ectopic ventricle contraction':ti,ab OR 'heart rhythm disorder':ti,ab OR 'atrioventricular junction arrhythmia':ti,ab OR bradycardia:ti,ab OR 'cardiac channelopath*':ti,ab OR 'cardiopulmonary arrest*':ti,ab OR 'commotio cordis':ti,ab OR 'heart fibrillation':ti,ab OR 'heart muscle conduction disturbance':ti,ab OR 'heart palpitation':ti,ab OR 'heart preexcitation':ti,ab OR 'heart proarrhythmia':ti,ab OR 'pacemaker failure*':ti,ab OR parasystole:ti,ab OR tachycardia:ti,ab OR 'acute coronary syndrome':ti,ab OR 'cardiac allograft vasculopathy':ti,ab OR 'coronary bifurcation lesion':ti,ab OR 'coronary subclavian steal syndrome':ti,ab OR 'kounis syndrome':ti,ab OR 'no reflow phenomenon':ti,ab	
#1	(('coronavirinae'/exp OR 'coronavirus infection'/de OR coronavirus*:ti,ab,kw OR 'corona virus*':ti,ab,kw OR 'pneumonia virus*':ti,ab,kw OR cov:ti,ab,kw OR ncov:ti,ab,kw) AND (outbreak:ti,ab,kw OR wuhan:ti,ab,kw) OR covid19:ti,ab,kw OR 'covid 19':ti,ab,kw OR ((coronavirus*:ti,ab,kw OR 'corona virus*':ti,ab,kw) AND 2019:ti,ab,kw) OR 'sars cov 2':ti,ab,kw OR sars2:ti,ab,kw OR 'coronavirus*':ti,ab,kw OR 'corona virus*':ti,ab,kw OR 'ncov 2019':ti,ab,kw OR ncov:ti,ab,kw OR 'sars coronavirus 2':ti,ab,kw OR 'sars corona virus 2':ti,ab,kw OR 'severe acute respiratory syndrome cov 2':ti,ab,kw OR 'severe acute respiratory syndrome cov2':ti,ab,kw) AND [2019-2020]/py	**18864**

Module 3 Effect van medicatie die ACE-2 expressie beïnvloedt op uitkomst bij COVID-19 patiënten

Clinical question

What is the effect of medication that influence ACE-2 expression (ACEi, ARBs, NSAIDs and thiazolidinediones) on the outcomes of COVID-19?

Inleiding

COVID-19 gebruikt het ACE-2 om de cel te infecteren. Dit ACE-2 breekt angiotensine II af. Angiotensine II verhoogt de bloeddruk. Medicijnen die worden gegeven tegen te hoge bloeddruk zoals ACE remmers of ARBs kunnen het niveau van ACE-2 verhogen. Er werd aanvankelijk gedacht dat veel ACE-2 gevoeliger zou maken voor COVID-19 omdat het immers de 'poort' is voor het virus. Echter, ACE-2 lijkt ook te beschermen tegen teveel angiotensine II, en teveel angiotensine II komt vaak voor in de long bij een door COVID-19 veroorzaakte longontsteking. Het is dus onduidelijk of medicijnen die ACE-2 verhogen of juist verlagen kwaad kunnen.

Search and select

A review of the literature was performed to answer the following question:

What is the effect of using medication that influence ACE-2 expression (ACEi, ARBs, NSAIDs and thiazolidinediones) on the outcomes in patients with COVID-19?

P: All proven COVID-19 patients
I: Using medication before and during COVID-19 that influence ACE-2 expression: ACEi, ARBs, NSAIDs and thiazolidinediones
C: No use of medication that influence ACE-2 expression before and during COVID-19
O: Mortality, IC-admission, hospital admission, length of stay, thromboembolic complications (pulmonary embolism, stroke, transient ischemic attack), ventilation.

Relevant outcome measures

Mortality was considered as critical outcome measure for decision making and the other outcomes as important outcomes for decision making.
A priori, the working group did not define minimal clinically relevant differences for the outcome measures.

Search and select (Methods)

The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms until June 24th, 2020. The systematic literature search resulted in 567 hits. See search strategy for detail.
64 studies were initially selected based on title and abstract screening. After reading the full text, 56 studies were excluded (see the table with reasons for exclusion under the tab Methods), and nine studies were included.

Results

Nine studies were included in the analysis of the literature. Important study characteristics and results are summarized in the evidence tables. The assessment of the risk of bias is summarized in the risk of bias table.

Summary of literature

Description of studies

Zhang (2020) assessed the relationship between ACEI/ARB use and COVID-19 infection in a systematic review. A comprehensive search of the PubMed, Embase, and Cochrane Library databases was performed to identify all relevant articles published between Jan 1, 2020 and May 9, 2020. Observational studies that met all the following criteria were included:
(1) study design: case-control, case-crossover, self-controlled case series (SCCS) or cohort study; (2) antihypertensive treatment: ACEI/ARB use versus non-ACEI/ARB use; (3) outcomes: the incidence of COVID-19, critical cases, or death; (4) adequate data were used to extract the risk estimates if the adjusted data were not provided in the publication. Editorials, correspondences, conference abstracts and commentary articles were excluded. Twelve articles (case-control and cohort studies) involving more than 19,000 COVID-19 cases were included. Information on follow-up duration or the number of patients for whom no complete outcome data was available was not mentioned.

Mackay (2020) evaluated whether use of ACEIs or ARBs either increased risk for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection or was associated with worse COVID-19 disease outcomes, and the efficacy of these medications for COVID-19 treatment in a systematic review. MEDLINE (Ovid) and Cochrane Database of Systematic Reviews were searched from 2003 to 4 May 2020, with planned ongoing surveillance for 1 year; the World Health Organization database of COVID-19 publications and medRxiv.org through 17 April 2020; and ClinicalTrials.gov to 24 April 2020, with planned ongoing surveillance. Observational studies and trials in adults that examined associations and effects of ACEIs or ARBs on risk for SARS-CoV-2 infection and COVID-19 disease severity and mortality were included. Nineteen studies were included. Some of the included studies describe a composite outcome measure ‘severe COVID-19’.

Felice (2020) investigated the association between chronic use of angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs) and COVID-19 related outcomes in hypertensive patients. A single center study was conducted on 133 consecutive hypertensive subjects presenting to the Emergency Department with acute respiratory symptoms and/or fever who were diagnosed with COVID-19 infection between 9th and 31st March 2020. All patients were grouped according to their chronic antihypertensive medications (ACEIs, N=40; ARBs, N=42; not on RAAS inhibitors, N=51).

Gao (2020) investigated if treatment of hypertension, especially with RAAS inhibitors, had an impact on the mortality of patients with COVID-19. Consecutive patients admitted to Huo
Shen Shan Hospital (solely to the treatment of COVID-19, in Wuhan, China) from 5 February to 15 March 2020 were included. In total, 2877 consecutive hospitalized patients with confirmed COVID-19 were enrolled in the study. The median time from symptom onset to discharge (last follow-up) was 39 (30–50) days. There were 710/850 (83.5%) patients with hypertension taking antihypertensive medications. There were 183 (25.7%) patients treated with RAAS inhibitors and 527 (74.2%) treated with beta-blockers, CCBs, or diuretics (non-RAAS inhibitors). For the outcome measures of interest the group of 710 patients was used, meaning that hypertensive patients treated with RAAS inhibitors were compared to hypertensive patients on taking antihypertensive medications other than RAAS inhibitors. The medical history and blood pressure at admission did not differ significantly between the RAAS inhibitor-treated [RAASi (+)] and non-RAAS inhibitor-treated patients [RAASi (–)]. There were 14 patients who reported shivering at admission in the RAASi (–) cohort, compared with none in the RAASi (+) cohort. There were 183 (25.7%) patients treated with RAAS inhibitors and 527 (74.2%) with beta-blockers, CCBs, or diuretics (non-RAAS inhibitors).

Jung (2020) aimed to assess the associations between prior use of RAAS inhibitors and clinical outcomes among Korean patients with coronavirus 2019 (COVID-19). Among 5179 confirmed COVID-19 cases, 762 patients were RAAS inhibitor users and 4417 patients were nonusers. Relative to nonusers, RAAS inhibitor users were more likely to be older, male, and have comorbidities. Among 1954 hospitalized patients with COVID-19, 377 patients were RAAS inhibitor users and 1577 patients were nonusers.

López-Otero (2020) performed a single-center, retrospective, observational cohort study on 965 patients diagnosed with COVID-19 from 10 March to 6 April 2020. In total, 210 patients were under ACEI or ARB treatment at the time of diagnosis. 165 (78.57%) were taking them for more than 1 year. During the study period, 38 patients died (3.94%), of whom 35 (3.6%) had heart failure. The cohort of patients under ACEI/ARB was older (72.1 ± 13.2 vs 56.0 ± 20.5; P<0.01) and had more cardiovascular risk factors (hypertension, diabetes, smoking, and dyslipidemia) and cardiovascular comorbidities (coronary artery diseases and ventricular dysfunction) than the cohort without ACEI/ARB. There were fewer women in the ACEI/ARB group (43.8% vs 59.5%; P<0.01). Renal impairment and peripheral vasculopathy were also more prevalent in patients taking ACEI/ARB.

Selçuk (2020) aimed to determine the relation between the use of angiotensin converting enzyme inhibitors (ACE inh) and angiotensinogen receptor blockers (ARBs) and in-hospital mortality of hypertensive patients diagnosed with COVID-19 pneumonia. All patients were on ACE inh/ARBs or other antihypertensive therapy. In total, 113 hypertensive COVID-19 patients were included, of them 74 patients were using ACE inh/ARBs. During in-hospital follow up, 30.9% (n = 35 patients) of patients died.

Imam (2020) evaluated mortality predictors of COVID-19 in a large cohort of hospitalized patients in the US. Retrospective, multicenter cohort of inpatients diagnosed with COVID-19 by RT-PCR from March 1-April 1,2020 was performed, and outcome data evaluated from March 1-April 17, 2020. Measures included demographics, comorbidities, clinical presentation, laboratory values, and imaging on admission. Primary outcome was mortality. Secondary outcomes included length of stay, time to death, and development of acute kidney injury in the first 48-hours. 1305 patients were hospitalized during the evaluation period. Mean age was 61.0±16.3, 53.8% were male and 66.1% was African-American. Mean BMI was 33.2±8.8 kg/m^2. Median Charlson Comorbidity Index (CCI) was 2 (1-4), 72.6% of patients had at least one comorbidity, with hypertension (56.2%) and diabetes mellitus (30.1%) being the most prevalent. ACE-I/ARB use and NSAIDs use were widely prevalent (43.3% and 35.7% respectively). Mortality occurred in 200 (15.3%) of patients with median time of 10 (6-14) days.

Zhou (2020) aimed to explore the clinical characteristics of COVID-19 complicated by hypertension. A retrospective, single-center study was conducted in which 110 discharged patients with COVID-19 at Wuhan Fourth Hospital in Wuhan, China, from January 25 to February 20, 2020 were included. All study cases were grouped according to whether they had a history of hypertension. Then, a subgroup analysis for all hypertensive patients was carried out based on whether to take ACEI or ARB drugs. The mean age of 110 patients was 57.7 years (range, 25–86 years), of which 60 (54.5%) were male patients. The main underlying diseases included hypertension [36 (32.7%)] and diabetes [11 (10.0%)].

Table 3.1 General study characteristics

Author (year)	Study type	Comments	N	Country	Outcome
Zhang (2020)	Systematic review and meta-analysis			Multiple	*Mortality*
Mackay (2020)	Systematic review	There is overlap between studies included in Zhang and Mackay. Mackay included two studies for mortality that are not included in Zhang. One of those papers is not peer-reviewed and the other is in Chinese so both cannot be used.		Multiple	*Mortality was assessed but not used, see comments,* *IC admission* *Hospital admission*
Felice, (2020)	Observational study		133	Italy	*Mortality, IC admission, Hospital admission, Ventilation*
Gao (2020)	Observational study		2877	China	*Mortality, Ventilation*
Imam (2020)	Observational study		1305	US	*Mortality*
Jung (2020)	Observational study		5179	Korea	*Mortality, Ventilation, Thromboembolic complications*
López-Otero (2020)	Observational study		965	Spain	*Mortality, IC admission, Hospital admission, Thromboembolic complications*
Selçuk (2020)	Observational study		113	Turkey	*Mortality, IC admission, Hospital admission, Ventilation, Length of stay*
Zhou (2020)	Observational study		110 (36 of which were used for the analysis of interest)	China	*Mortality, length of stay*

Results

The results were described for two different groups, an overall group in which all users were compared with non-users and a group in which only hypertensive patients were included. Within each group a distinction was made between results for ACEi/ARBS use, ACEi use, ARBS use or NSAID use.

1. Mortality

1.1 Overall

1.1.1ACEI/ARBS

We were unable to provide a pooled estimate for mortality since some studies did not provide the absolute number of events or used a composite outcome measure. Therefore, the results of each of the studies were described separately.

Zhang (2020) performed a meta-analysis to study the relation between ACEI/ARBS use and mortality. In this meta-analysis, all studies that assessed this relation were included, irrespective of the type of patients in the intervention (all patients using ACEI/ARBS or only hypertensive patients) and control group (all COVID-19 patients not on ACEI/ARBS, hypertensive patients not on ACEI/ARBS but on other or no blood pressure lowering medication). Overall, the risk of mortality in ACEI/ARB-exposed was similar to non-ACEI/ARB exposed COVID-19 patients (pooled OR 0.73; 95% CI 0.5-1.07; P=0.11) (figure 3.1).

Imam (2020) and López-Otero (2020) also studied the relation between ACEI/ARBS use and mortality between users of ACEI/ARBS) and non-users. In a multivariate analysis both Imam and López-Otero reported no statistical significant difference in mortality between users of ACEI/ARBS and non-users (López-Otero (8 out of 78 ACEI/ARBS users died): OR, 0.62; 95%CI, 0.17-2.26; P =0.486, Imam: adjusted OR 1.20; 95%CI 0.86-1.68; P=0.278). López-Otero found that the absence of an impact on mortality remained both in the multivariate analysis and in the propensity score model, including in the evaluation of treatment taken for more than 1 year.
Reynolds (2020) (included in the review of Mackay) studied the relation between ACEi or ARBS use and the composite outcome 'severe COVID-19', defined as ICU admission, use of noninvasive or mechanical ventilation, or death. The mean difference between users and non-users of this medication was −0.1 (95%CI −3.7 to 3.5) meaning that there was no statistically significant difference between both groups.
None of the studies showed a statistically significant difference between ACEI or ARBS use and non-users with regard to mortality (or a composite outcome including mortality).

1.1.2 ARBS
Reynolds (2020) (included in the review of Mackay) studied the relation between ARBS and the composite outcome 'severe COVID-19', defined as ICU admission, use of noninvasive or mechanical ventilation, or death. The mean difference between users and non-users of this medication was −1.4 (95%CI −6.1 to 3.3) meaning that there was no statistically significant difference between both groups.
Mancia (2020) (included in the review of Mackay) studied the relation between ARBS and the composite outcome 'severe COVID-19' defined as assisted ventilation or death. The adjusted OR was 0.83 (95% CI 0.63–1.10).
Jung (2020) studied the relation between ACEI/ARBS use (N=377) and mortality. Since most of the included patients only used ARBS the results of this paper are used for the ARBS only category. In a multivariate analysis (adjusted for age, sex, Charlson Comorbidity Index, immunosuppression, and hospital type) Jung found no statistical significant difference in mortality between users and non-users (adjusted OR, 0.88 ; 95% CI 0.53–1.44; p=0.60).
In the study of López-Otero (2020) 6 out of 50 ACEI users died. López-Otero found no statistically significant difference in a multivariate analysis (analysis adjusted for arterial oxygen saturation <95%, diabetes mellitus, hypoxemia, hypercapnia, lymphocytes, creatinine, elevated troponin, ferritin, C-reactive protein, interleukin-6))(OR 1.54; 95%CI 0.42-5.59).
Mehra (2020) (included in the review of Zhang) studied the relation between ARBS use and mortality and found an OR of 1.23 (95%CI 0.87-1.74).
None of the studies showed a statistically significant difference between ARBS use and non-users with regard to mortality (or a composite outcome including mortality).

1.1.3 ACEI
Reynolds (2020) (included in the review of Mackay) studied the relation between ACEI and the composite outcome 'severe COVID-19', defined as ICU admission, use of noninvasive or mechanical ventilation, or death. The mean difference between users and non-users of this medication was −1.9 (95%CI −6.6 to 2.8) meaning that there was no statistically significant difference between both groups.
Bean (2020) (included in the review of Mackay) found and adjusted OR for the composite outcome 'mortality and transfer to critical care within 7 days of symptom onset' of 0.29 (95%CI: 0.10–0.75) for ACEi use vs non-users. This paper was not peer-reviewed.

Mancia (2020) (included in the review of Mackay) studied the relation between ACEI and the composite outcome 'severe COVID-19' defined as assisted ventilation or death. The adjusted OR was 0.91 (95% CI 0.69–1.21).
In the study of López-Otero (2020) 2 out of 29 ACEI users died. López-Otero found no statistically significant difference in a multivariate analysis adjusted for arterial oxygen saturation <95%, diabetes mellitus, hypoxemia, hypercapnia, lymphocytes, creatinine, elevated troponin, ferritin, C-reactive protein, interleukin-6) (OR 0.14; 95% CI 0.01-1.57).
Mehra (2020) (included in the review of Zhang) studied the relation between ACEI use and mortality and found an OR of 0.33 (95% CI 0.20-0.54).
Three studies showed no statistically significant difference between ACEI use and non-users with regard to mortality (or a composite outcome including mortality). Two studies (one not peer reviewed and assessed mortality within 7 days of symptom onset) showed a statically significant difference.

1.1.4 NSAID
For NSAID use, Imam (2020) found that NSAID users had a statistical significant lower risk of mortality compared to non NSAID users in a multivariate analysis (adjusted for age, Initial Serum Creatinine, CCI, NSAID, HTN, ACE-I/ARB use, CKD) (OR 0.57; 95%CI 0.40-0.82; P=0.002).

1.1.5 Thiazolidinediones
Reynolds (2020) studied the relation between thiazide diuretics and the composite outcome 'severe COVID-19', defined as ICU admission, use of noninvasive or mechanical ventilation, or death. The mean difference between users and non-users of this medication was −3.4 (95% CI −8.3 to 1.6).

1.2 Hypertensive patients
1.2.1 ACEI/ARBS
We were unable to provide a pooled estimate for mortality since some studies did not provide the absolute number of events or used a composite outcome measure. Therefore, the results of each of the studies were described separately.
Zhang (2020) performed a meta-analysis of seven studies in which hypertensive ACEI/ARB users were compared with hypertensive patients on other blood pressure lowering medication or no medication. In this meta-analysis Zhang observed no statistically significant difference in risk of mortality among those who used ACEI/ARB (OR 0.62; 95% CI 0.38-1.02; P=0.059, I^2=74.8%) (figure 3.2).
Zhang (2020) found in meta-analysis of four studies that ACEI/ARB use in hypertensive patients was associated with a lower risk of mortality compared to those on non-ACEI/ARB antihypertensive drugs (OR 0.48, 95% CI 0.29-0.81; P=0.006; I^2 0%).

Selçuk (2020) found that ACEI/ARBs use was associated with a higher risk of mortality (adjusted OR 3.66; 95%CI 1.11-18.18; P=0.032). The Kaplan-Meir curve analysis displayed that patients on ACE inh/ ARBs therapy had a higher incidence of in-hospital death than those who were not (log rank test p value <.001).
Felice (2020) found no statistically significant association between ACEI/ARB use in hypertensive patients in a multivariate analysis (OR 0.56; 95% CI 0.17-1.83; P=0.341).
Gao (2020) found no statistically significant association between ACEI/ARB use in hypertensive patients in a multivariate analysis (adjusted OR 0.85;95% CI 0.28-2.58; P=0.774).
Zhou (2020) found no statistically significant difference in mortality between ACEI/ARB use (N= in hypertensive patients using Student's unpaired t-test. We calculated the OR which was 0.49 (95% CI 0.082-2.966).

Reynolds (2020) (included in the review of Mackay) studied the relation between ACEi or ARBS use in hypertensive patients and the composite outcome 'severe COVID-19', defined as ICU admission, use of noninvasive or mechanical ventilation, or death. The mean difference between users and non-users of this medication was −0.5 (95%CI −4.3 to 3.2).
Most of the studies showed no statistically significant difference between ACEI/ARBS use in hypertensive patients and non-users with regard to mortality (or a composite outcome including mortality). In the sub-analysis of Zhang (included only hypertensive patients on other than ACEI/ARBS drugs in the control group, so did not include hypertensive patients on no medication) and Selçuk a significant difference was found.

1.2.2 ARBS
Reynolds (2020) (included in the review of Mackay) studied the relation between ARBS use in hypertensive patients and the composite outcome 'severe COVID-19', defined as ICU admission, use of noninvasive or mechanical ventilation, or death. The mean difference between users and non-users of this medication was 0.1 (95% CI −4.8 to 4.9).
Jung (2020) studied the relation between hypertensive ACEI/ARB users and hypertensive patients on other blood pressure lowering medication or no medication. Since most of the included patients only used ARBS the results of this paper are used for the ARBS only category. Jung found that RAAS inhibitor use was not independently associated with a higher risk of mortality among hypertensive COVID-19 patients (adjusted OR 0.71; 95% CI 0.40-1.26; P=0.25) adjusted for age, sex, Charlson Comorbidity Index, immunosuppression, and hospital type.
Mehra (included in the review of Zhang) studied the relation between ARBS use and mortality. Mehra found an OR of 1.233 (95% CI 0.87-1.74).
None of the studies showed a statistically significant difference between ARBS use in hypertensive patients and non-users with regard to mortality (or a composite outcome including mortality).

1.2.3 ACEI
Reynolds (2020) (included in the review of Mackay) studied the relation between ACEI use in hypertensive patients and the composite outcome 'severe COVID-19', defined as ICU admission, use of noninvasive or mechanical ventilation, or death. The mean difference between users and non-users of this medication was −3.3 (−8.2 to 1.7).
Mehra (included in the review of Zhang) studied the relation between ACEI use and mortality. Mehra found an OR of 0.33 (95% CI 0.20-0.54).
The study showed no statistically significant difference between ACEI use in hypertensive patients and non-users with regard to mortality (or a composite outcome including mortality) and one study found a statistically significant difference.

1.2.4 Thiazolidinediones
Reynolds (2020) studied the relation between thiazide diuretics and the composite outcome 'severe COVID-19', defined as ICU admission, use of noninvasive or mechanical ventilation, or death. The mean difference between users and non-users of this medication was 0.6 (95% CI −4.5 to 5.7).

2. IC-admission
2.1 Overall
2.1.1 ACEI/ARBS
In the review of Mackay (2020) two studies assessed the relationship between ACEI/ARBs use and IC-admission (Rentsch and Reynolds). Rentsch (2020) found that admission to the IC was more likely to occur in patients using ACEI/ARBS compared to non-users (adjusted OR 1.69; 95% CI 1.01-2.84). This study was not peer-reviewed.
Reynolds (2020) studied the relation between ACEi or ARBS use and the composite outcome 'severe COVID-19', defined as ICU admission, use of noninvasive or mechanical ventilation, or death. The

mean difference between users and non-users of this medication was −0.1 (95%CI −3.7 to 3.5) meaning that there was no statistically significant difference between both groups.
López-Otero (2020) found no statistically significant difference in a multivariate analysis (adjusted for arterial oxygen saturation <95%, diabetes mellitus, hypoxemia, hypercapnia, lymphocytes, creatinine, elevated troponin, ferritin, C-reactive protein, interleukin-6)(OR 0.87; 95% CI 0.30-2.50; P=0.798).

Two studies showed no statistically significant difference and one study that was not peer reviewed showed a statistically significant difference.

2.1.2 ARBS
Reynolds (2020) (included in the review of Mackay) studied the relation between ARBS and the composite outcome 'severe COVID-19', defined as ICU admission, use of noninvasive or mechanical ventilation, or death. The mean difference between users and non-users of this medication was −1.4 (95%CI −6.1 to 3.3) meaning that there was no statistically significant difference between both groups.
López-Otero (2020) found that 7 ARBS users were admitted to the intensive care unit. López-Otero (2020) found no statistically significant difference in a multivariate analysis (adjusted for arterial oxygen saturation <95%, diabetes mellitus, hypoxemia, hypercapnia, lymphocytes, creatinine, elevated troponin, ferritin, C-reactive protein, interleukin-6)(OR 0.84; 95% CI 0.25-2.87 P=0.786).

2.1.3 ACEI
Bean (2020) (included in the review of Mackay) found and adjusted OR for the composite outcome 'mortality and transfer to critical care within 7 days of symptom onset' of 0.29 (95%CI: 0.10–0.75) for ACEi use vs non-users. This paper was not peer-reviewed.
Reynolds (2020) (included in the review of Mackay) studied the relation between ACEI and the composite outcome 'severe COVID-19', defined as ICU admission, use of noninvasive or mechanical ventilation, or death. The mean difference between users and non-users of this medication was −1.9 (95%CI −6.6 to 2.8) meaning that there was no statistical significant difference between both groups.
López-Otero (2020) found that 6 ACEI users were admitted to the intensive care unit. López-Otero (2020) found no statistically significant difference between ACEI users and non-users in a multivariate analysis (adjusted for arterial oxygen saturation <95%, diabetes mellitus, hypoxemia, hypercapnia, lymphocytes, creatinine, elevated troponin, ferritin, C-reactive protein, interleukin-6)(OR 0.97; 95% CI 0.22-4.16 P=0.962).

One study showed no statistically significant difference and one study that was not peer reviewed showed a statistically significant difference

Thiazolidinediones
Reynolds (2020) studied the relation between thiazide diuretics and the composite outcome 'severe COVID-19', defined as ICU admission, use of noninvasive or mechanical ventilation, or death. The mean difference between users and non-users of this medication was −3.4 (95% CI −8.3 to 1.6) meaning that there was no statistically significant difference between both groups.

2.2 Hypertensive patients
2.2.1 ACEI/ARBS
Felice (2020) found that admission to semi-intensive/intensive care units was less likely to occur in hypertensive patients using ARB or ACEI (adjusted OR 0.25 95% CI 0.09-0.66; P=0.006).

Selçuk (2020) found a statistically significant difference (P=0.001) between IC-admission for hypertensive ACEI/ARB users (50%) compared to hypertensive non-users (17.9%). No correction for confounders was applied.
Reynolds (2020) (included in the review of Mackay) studied the relation between ACEi or ARBS use in hypertensive patients and the composite outcome 'severe COVID-19', defined as ICU admission, use of noninvasive or mechanical ventilation, or death. The mean difference between users and non-users of this medication was −0.5 (95%CI −4.3 to 3.2).
One study found no statistically significant difference, one study found a statistically significant difference in favour of ARB/ACEI users and one study found a statistically significant difference in favour of non-users.

2.2.2 ARBS
Reynolds (2020) (included in the review of Mackay) studied the relation between ARBS use in hypertensive patients and the composite outcome 'severe COVID-19', defined as ICU admission, use of noninvasive or mechanical ventilation, or death. The mean difference between users and non-users of this medication was 0.1 (95% CI −4.8 to 4.9), meaning there was no statistically significant difference.

2.2.3 ACEI
Reynolds (2020) (included in the review of Mackay) studied the relation between ACEI use in hypertensive patients and the composite outcome 'severe COVID-19', defined as ICU admission, use of noninvasive or mechanical ventilation, or death. The mean difference between users and non-users of this medication was −3.3 (−8.2 to 1.7), meaning there was no statistically significant difference.

2.2.4 Thiazolidinediones
Reynolds (2020) studied the relation between thiazide diuretics and the composite outcome 'severe COVID-19', defined as ICU admission, use of noninvasive or mechanical ventilation, or death. The mean difference between users and non-users of this medication was 0.6 (95% CI −4.5 to 5.7), meaning there was no statistically significant difference

3. Hospital admission
3.1 Overall
3.1.1 ACEI/ARBS
López-Otero (2020) reported 731 patients admitted to the hospital (75.8%), of which 210 were ACEI/ARBS users. López-Otero concluded in a multivariate analysis (adjusted for days with symptoms, fever, arterial oxygen saturation, <95%, age, sex, health personnel, institutionalized, dependency status, dementia, hypertension, dyslipidemia, ventricular dysfunction, lung disease, previous cancer, hypothyroidism, antiplatelet therapy) that there was no statistically significant difference in hospital admission in ACEI/ARBS users vs non-users (OR 0.85; 95% CI 0.45-1.64; P=0.638.
Rentsch (2020) (included in the review of Mackay) found in a multivariate analysis that there was no statistically significant difference between hospital admission in ACEI/ARBS users vs non-users (adjusted OR 1.24; 95% CI 0.79-1.95). This study was not peer-reviewed.
Two studies found no statistically significant difference (one of those studies was not peer-reviewed).

3.1.2 ARBS
López-Otero (2020) concluded in a multivariate analysis (adjusted for days with symptoms, fever, arterial oxygen saturation <95%, age, sex, health personnel, institutionalized, dependency status,

dementia, hypertension, dyslipidemia, ventricular dysfunction, lung disease, previous cancer, hypothyroidism, antiplatelet therapy) that there was no statistically significant difference in hospital admission in ARBS users (n=50) vs non-users (n=134) (OR 1.10; 95% CI 0.59-2.04 P=0.757).

3.1.3 ACEI
Rossi (2020) (included in the review of Mackay) performed a multivariate analysis and found an adjusted HR with ACEI (adjusted for age, sex, and Charlson comorbidity score) of 1.13 (95%CI 1.1–1.5). When the analysis was restricted to patients with cardiovascular disease the aHR was 1.12 (95%CI 0.82–1.54; (adjusted for age, sex, and Charlson comorbidity score).
López-Otero (2020) concluded in a multivariate analysis (adjusted for days with symptoms, fever, arterial oxygen saturation <95%, age, sex, health personnel, institutionalized, dependency status, dementia, hypertension, dyslipidemia, ventricular dysfunction, lung disease, previous cancer, hypothyroidism, antiplatelet therapy) that there was no statistically significant difference in hospital admission in ACEI users (N=20) vs non-users (N=77) (OR 0.78; 95% CI 0.38-1.60 P=0.505).

3.2 Hypertensive patients
3.2.1 ACEI/ARBS
Felice (2020) concluded in a multivariate analysis (adjusted for gender, BMI, days with symptoms prior to admission, previous cardiovascular events, diabetes and cancer) that there was no statistically significant difference in hospital admission in hypertensive ACEI/ARBS users vs non-users OR 0.39 (95% CI 0.05-2.94; P=0.365).

4. Length of stay
4.2 Hypertensive patients
4.2.1 ACEI/ARBS
Selçuk (2020) assessed length of stay for hypertensive patients on ACEI/ARBS and hypertensive patients on other medication. There was no statistically significant difference between both groups ACE inh/ARBs users: 9 days ± 6, Non-user 8 days ± 4 (P=0.524).
Zhou (2020) found no statistically significant difference (P=0.405) in hospital length of stay in hypertensive patients using ACEI/ARB (mean 10.1 days, SD 5.2) and hypertensive patients using other antihypertensive drugs (mean 11.7, SD 6.0). We calculated the mean difference between the groups which was 1.60 (95% CI-2.31-5.51).
Two studies found no statistically significant difference.

5. Ventilation
Ventilation was defined differently in each of the studies. Jung assesses mechanical ventilation, Felice assesses oxygen therapy and non-invasive ventilation, Gao assesses invasive mechanical ventilation, Mancia assisted ventilation and Selçuk endotracheal intubation.

5.1 Overall
5.1.1 ACE/ARBS
Reynolds (2020) (included in the review of Mackay) studied the relation between ACEi or ARBS use and the composite outcome ‘severe COVID-19’, defined as ICU admission, use of noninvasive or mechanical ventilation, or death. The mean difference between users and non-users of this medication was −0.1 (95%CI −3.7 to 3.5) meaning that there was no statistically significant difference between both groups.

5.1.2 ARBs
Reynolds (2020) (included in the review of Mackay) studied the relation between ARBS and the composite outcome ‘severe COVID-19’, defined as ICU admission, use of noninvasive or mechanical

ventilation, or death. The mean difference between users and non-users of this medication was −1.9 (95%CI −6.6 to 2.8) meaning that there was no statistically significant difference between both groups.
Jung (2020) studied the relation between ACEI/ARBS use and ventilation (mechanical ventilation). Since most of the included patients only used ARBS the results of this paper were used for the ARBS only category. Jung calculated an adjusted OR of 1.03 (95% CI 0.50-2.13; P=0.93).
Mancia (2020) (included in the review of Mackay) studied the relation between ARBS and the composite outcome 'severe COVID-19' defined as assisted ventilation or death. The adjusted OR was 0.83 (95% CI 0.63–1.10).

Three studies found no statistically significant difference.

5.1.3 ACEI
Reynolds (2020) (included in the review of Mackay) studied the relation between ACEI and the composite outcome 'severe COVID-19', defined as ICU admission, use of noninvasive or mechanical ventilation, or death. The mean difference between users and non-users of this medication was −1.9 (95%CI −6.6 to 2.8) meaning that there was no statistically significant difference between both groups.
Mancia (2020) (included in the review of Mackay) studied the relation between ACEI and the composite outcome 'severe COVID-19' defined as assisted ventilation or death. The adjusted OR was 0.91 (95% CI 0.69–1.21).

Two studies found no statistically significant difference.

5.1.4 Thiazolidinediones
Reynolds (2020) studied the relation between thiazide diuretics and the composite outcome 'severe COVID-19', defined as ICU admission, use of noninvasive or mechanical ventilation, or death. The mean difference between users and non-users of this medication was −3.4 (95% CI −8.3 to 1.6) meaning that there was no statistically significant difference between both groups.

5.2 Hypertensive patients
5.2.1 ACEI/ARBS
Gao (2020) compared users of RAAS inhibitors (5;2.7%) with non-RAAS inhibitor users (25;4.7%) and found no statistically significant difference (P=0.292). Felice (2020) found an adjusted OR 0.58; 95%CI 0.21-1.60; P=0.296. Selçuk (2020) reported a statistically significant difference between ACEI/ARBS users (44.6% required ventilation) vs non-users (10.3% require ventilation) (P<0.001), however there was no correction for confounders performed.
Reynolds (2020) (included in the review of Mackay) studied the relation between ACEi or ARBS use in hypertensive patients and the composite outcome 'severe COVID-19', defined as ICU admission, use of noninvasive or mechanical ventilation, or death. The mean difference between users and non-users of this medication was −0.5 (95%CI −4.3 to 3.2).

5.2.2 ARBS
Reynolds (2020) (included in the review of Mackay) studied the relation between ARBS use in hypertensive patients and the composite outcome 'severe COVID-19', defined as ICU admission, use of noninvasive or mechanical ventilation, or death. The mean difference between users and non-users of this medication was 0.1 (95% CI −4.8 to 4.9) meaning that there was no statistically significant difference between both groups.

5.2.3 ACEI

Reynolds (2020) (included in the review of Mackay) studied the relation between ACEI use in hypertensive patients and the composite outcome 'severe COVID-19', defined as ICU admission, use of noninvasive or mechanical ventilation, or death. The mean difference between users and non-users of this medication was −3.3 (−8.2 to 1.7) meaning that there was no statistically significant difference between both groups.

5.2.4 Thiazolidinediones
Reynolds (2020) studied the relation between thiazide diuretics and the composite outcome 'severe COVID-19', defined as ICU admission, use of noninvasive or mechanical ventilation, or death. The mean difference between users and non-users of this medication was 0.6 (95% CI −4.5 to 5.7) meaning that there was no statistically significant difference between both groups.

6. Thromboembolic complications
6.1 Overall
6.1.1 ACEI/ARBS
López-Otero (2020) reported on heart failure (defined according to the European Society of Cardiology guidelines). In a multivariate analysis, there was no statistically significant difference between ACEI/ARBS users and non-users (OR 1.37; 95% CI 0.39-4.77; P=0.622). The absence of an impact on heart failure remained both in the multivariate analysis and in the propensity score model, including in the evaluation of treatment taken for more than 1 year.

6.1.2 ARBS
Jung (2020) reported on acute cardiac event defined as cardiac arrest, myocardial infarction or acute heart failure. Since most of the included patients only used ARBS the results of this paper are used for the ARBS only category. No statistically significant differences were observed between RAAS inhibitor users and nonusers in terms of acute cardiac injury (OR 0.88; 95% CI 0.59 1.31; P=0.53).
López-Otero (2020) reported on heart failure (defined according to the European Society of Cardiology guidelines). In a multivariate analysis, there was no statistically significant difference between ARBS users and non-users (OR 0.46; 95% CI 0.12-1.72 P=0.248).

6.1.3 ACEI
López-Otero (2020) reported on heart failure (defined according to the European Society of Cardiology guidelines). In a multivariate analysis, there was no statistically significant difference between ACEI users and non-users (OR 3.01 95%CI 0.89-10.16 P=0.076).

Level of Evidence
The level of evidence was assessed according to the GRADE methodology (GRADE: Grading Recommendations Assessment, Development and Evaluation, http://www.gradeworkinggroup.org/).

1. Mortality
1.1 Overall
ACEI/ARBS
Starting with a high level of evidence for observational studies (prognostic question), the level of evidence regarding the outcome measure mortality was downgraded by one level because of risk of bias (not all studies corrected for confounders, number of events sometimes not reported) to 'moderate'.

ARBS
Starting with a high level of evidence for observational studies (prognostic question), the level of evidence regarding the outcome measure mortality was downgraded by one level because of risk of bias (not all patients may have reached the outcome mortality yet and were still hospitalized at the moment of analysis) and one level for indirectness (two studies used a composite outcome measure) to 'low'.

ACEI
Starting with a high level of evidence for observational studies (prognostic question), the level of evidence regarding the outcome measure mortality was downgraded by one level because of risk of bias (one study not peer reviewed, not all patients may have reached the outcome mortality yet and were still hospitalized at the moment of analysis), one level because of indirectness (two studies used a composite outcome measure and one study assessed 7-day mortality) to 'low'.

NSAID
Starting with a high level of evidence for observational studies (prognostic question), the level of evidence regarding the outcome measure mortality was downgraded by one level because of risk of bias (unable to assess if the groups are comparable and information is unavailable on how many patients were still hospitalized at the moment of analysis) and two levels for imprecision (only one study available, small number of patients included) to 'very low'.

Thiazolidinediones
Starting with a high level of evidence for observational studies (prognostic question), the level of evidence regarding the outcome measure mortality was downgraded by one level because of risk of bias (some patients may not have reached the outcome yet by the date of analysis) and one level for indirectness (a composite outcome measure was used) to 'low'.

1.2 Hypertensive patients
ACE/ARBS
Starting with a high level of evidence for observational studies (prognostic question), the level of evidence regarding the outcome measure mortality was downgraded by one level because of risk of bias (number of events sometimes not reported but only ORs), and one level for imprecision (difference in effect size) to 'low'.

ARBS
Starting with a high level of evidence for observational studies (prognostic question), the level of evidence regarding the outcome measure mortality was downgraded by one level because of risk of bias (some patients may not have reached the outcome yet by the date of analysis), and one level because of indirectness (one study used a composite outcome measure) to 'low'.

ACEI
Starting with a high level of evidence for observational studies (prognostic question), the level of evidence regarding the outcome measure mortality was downgraded by one level because of risk of bias (some patients may not have reached the outcome yet by the date of analysis), one level for imprecision (some studies show a statistically significant difference and some do not) and one level because of indirectness (a composite outcome measure was used) to 'very low'.

Thiazolidinediones
Starting with a high level of evidence for observational studies (prognostic question), the level of evidence regarding the outcome measure mortality was downgraded by one level because of risk of

bias (some patients may not have reached the outcome yet by the date of analysis) and one level because of indirectness (a composite outcome measure was used) to ‘low’.

2. IC admission
2.1 Overall
ACE/ARBS
Starting with a high level of evidence for observational studies (prognostic question), the level of evidence regarding the outcome measure IC admission was downgraded by one level because of risk of bias (one study not peer reviewed, follow up duration unclear), one level because of imprecision (some studies show no effect, one study shows a significant effect) and one level because of indirectness (in one study a composite outcome measure was used) to ‘very low’.

ARBS
Starting with a high of evidence for observational studies (prognostic question), the level of evidence regarding the outcome measure IC admission was downgraded by 1 level because of risk of bias (some patients were still hospitalized at the moment of analysis and still could be admitted to the IC at a later moment), one level for indirectness (one study used a composite outcome measure) and one level for imprecision (small number of events) to ‘very low’.

ACE
Starting with a high of evidence for observational studies (prognostic question), the level of evidence regarding the outcome measure IC admission was downgraded by 1 level because of risk of bias (some patients were still hospitalized at the moment of analysis and still could be admitted to the IC at a later moment), one level for indirectness (one study used a composite outcome measure) and one level because of imprecision (low number of events) to ‘very low’.

Thiazolidinedione
Starting with a high level of evidence for observational studies (prognostic question), the level of evidence regarding the outcome measure IC admission was downgraded by one level because of risk of bias (some patients may not have reached the outcome yet by the date of analysis) and one level because of indirectness (a composite outcome measure was used) to ‘low’.

2.2 Hypertensive patients
ACEI/ARBS
Starting with a high level of evidence for observational studies (prognostic question), the level of evidence regarding the outcome measure IC admission was downgraded by one level because of risk of bias and one level for imprecision (wide range of effects) and one level because of indirectness (a composite outcome measure was used in one study and in one study the outcome was semi intensive care or intensive care) to ‘very low’.

ARBS
Starting with a high level of evidence for observational studies (prognostic question), the level of evidence regarding the outcome measure IC admission was downgraded by one level because of risk of bias (some patients may not have reached the outcome yet by the date of analysis) and one level because of indirectness (a composite outcome measure was used) to ‘low’.

ACEI
Starting with a high level of evidence for observational studies (prognostic question), the level of evidence regarding the outcome measure IC admission was downgraded by one level because of risk

of bias (some patients may not have reached the outcome yet by the date of analysis) and one level because of indirectness (a composite outcome measure was used) to ‘low’.

Thiazolidinedione
Starting with a high level of evidence for observational studies (prognostic question), the level of evidence regarding the outcome measure IC admission was downgraded by one level because of risk of bias (some patients may not have reached the outcome yet by the date of analysis) and one level because of indirectness (a composite outcome measure was used) to ‘low’.

3. Hospital admission
3.1 Overall
ACE/ARBS
Starting with a high level of evidence for observational studies (prognostic question), the level of evidence regarding the outcome measure hospital admission was downgraded by two levels because of risk of bias (one study not peer reviewed, follow up duration unclear to ‘low’.

ARBS
Starting with a high level of evidence for observational studies (prognostic question), the level of evidence regarding the outcome measure hospital admission was downgraded by one level because of risk of bias (follow up duration unclear), one level for imprecision (small number of events) to ‘low’.

ACEI
Starting with a high level of evidence for observational studies (prognostic question), the level of evidence regarding the outcome measure hospital admission was downgraded by one level because of risk of bias (follow up duration unclear), one level for imprecision (small number of events, one study shows a statistically significant, the other does not) to ‘low’.

3.2 Hypertensive patients
ACE/ARBS
Starting with a high level of evidence for observational studies (prognostic question), the level of evidence regarding the outcome measure hospital admission was downgraded by one level because of risk of bias (the study only included hypertensive subjects who presented to the emergency department with acute respiratory symptoms/fever), and two levels because of imprecision (small sample size, wide CI) to ‘very low’.

4. Length of stay
4.2 Hypertensive patients

ACEI/ARBS
Starting with a high level of evidence for observational studies (prognostic question), the level of evidence regarding the outcome measure length of stay was downgraded by two level because of risk of bias (no correction for confounders, in one study follow up duration unclear) and one level because of imprecision (small number of included patients) to ‘very low’.

5. Ventilation

5.1 Overall
ACE/ARBS

Starting with a high level of evidence for observational studies (prognostic question), the level of evidence regarding the outcome measure ventilation was downgraded by one level because of risk of bias (some patients may not have reached the outcome yet by the date of analysis) and one level because of indirectness (a composite outcome measure was used) to ‘low’.

ARBS
Starting with a high level of evidence for observational studies (prognostic question), the level of evidence regarding the outcome measure ventilation was downgraded by one level because of risk of bias (some patients may not have reached the outcome yet by the date of analysis), one level for imprecision (wide confidence interval) and one level because of indirectness (a composite outcome measure was used in two studies) to ‘very low’.

ACEI
Starting with a high level of evidence for observational studies (prognostic question), the level of evidence regarding the outcome measure ventilation was downgraded by one level because of risk of bias (some patients may not have reached the outcome yet by the date of analysis), one level for imprecision (wide confidence interval) and one level because of indirectness (a composite outcome measure was used in two studies) to ‘very low’.

Thiazolidinediones
Starting with a high level of evidence for observational studies (prognostic question), the level of evidence regarding the outcome measure ventilation was downgraded by one level because of risk of bias (some patients may not have reached the outcome yet by the date of analysis) and one level because of indirectness (a composite outcome measure was used) to ‘low’.

5.2 Hypertensive patients
ACEI/ARBS
Starting with a high level of evidence for observational studies (prognostic question), the level of evidence regarding the outcome measure ventilation was downgraded by one level because of risk of bias (some studies did not correct for confounding), one level for imprecision (some studies describe a significant difference, some studies found no significant difference) and one level because of indirectness (composite outcome measure, different definitions of ventilation) to ‘very low’.

ARBS
Starting with a high level of evidence for observational studies (prognostic question), the level of evidence regarding the outcome measure ventilation was downgraded by one level because of risk of bias (some patients may not have reached the outcome yet by the date of analysis) and one level because of indirectness (a composite outcome measure was used) to ‘low’.

ACEI
Starting with a high level of evidence for observational studies (prognostic question), the level of evidence regarding the outcome measure ventilation was downgraded by one level because of risk of bias (some patients may not have reached the outcome yet by the date of analysis) and one level because of indirectness (a composite outcome measure was used) to ‘low’.

Thiazolidinediones
Starting with a high level of evidence for observational studies (prognostic question), the level of evidence regarding the outcome measure ventilation was downgraded by one level because of risk of bias (some patients may not have reached the outcome yet by the date of analysis) and one level because of indirectness (a composite outcome measure was used) to ‘low’.

6. Tromboembolic complications
6.1 Overall
ACEI/ARBS
Starting with a high level of evidence for observational studies (prognostic question), the level of evidence regarding the outcome measure thromboembolic complications was downgraded by 1 level because of risk of bias (some patients were still hospitalized at the moment of analysis and still could develop thromboembolic complications), one level because of indirectness (thromboembolic complications was defined as hear failure) and one level because of imprecision (small number of events) to 'very low'.

ARBS
Starting with a high level of evidence for observational studies (prognostic question), the level of evidence regarding the outcome measure thromboembolic complications was downgraded by 1 level because of risk of bias (some patients were still hospitalized at the moment of analysis and still could develop thromboembolic complications), one level because of indirectness (thromboembolic complications was defined as hear failure in one study and in one study a small number of patients in the I group were using ACEI) and one level because of imprecision (small number of events) to 'very low'.

ACEI
Starting with a high level of evidence for observational studies (prognostic question), the level of evidence regarding the outcome measure thromboembolic complications was downgraded by 1 level because of risk of bias (some patients were still hospitalized at the moment of analysis and still could develop thromboembolic complications), one level because of indirectness (thromboembolic complications was defined as hear failure) and one level because of imprecision (wide confidence interval) to 'very low'.

Conclusions
1. Mortality
1.1 Overall

Moderate GRADE	ACEI/ARBS use probably does not increase mortality. *Sources: Zhang (2020), Imam (2020), López-Otero (2020), Reynolds (2020)*

Low GRADE	The evidence suggests that ARBS use does not increase mortality. *Sources: Reynolds (2020), Mancia (2020) , Jung (2020) , Mehra (2020)*

Low GRADE	The evidence is uncertain about the effect of ACEI use on mortality. *Sources: Mancia (2020), Reynolds (2020), Bean (2020), Mehra (2020)*

Low GRADE	The evidence suggests that thiazolidinediones use does not increase mortality. *Sources: Reynolds (2020)*

Very low GRADE	The evidence is very uncertain about the effect of NSAIDS use on mortality. *Sources: Imam (2020)*

1.2 Hypertensive patients

Very low GRADE	ACEI/ARBS use may not increase mortality, but the evidence is very uncertain *Sources: Zhang (2020), Felice (2020), Gao (2020), Zhou (2020), Reynolds (2020), Selçuk (2020)*

Low GRADE	The evidence suggests that ARBS or thiazolidinediones use does not increase mortality. *Sources: Reynolds (2020), Mehra (2020)*

Very low GRADE	The evidence is very uncertain about the effect of ACEI use on mortality. *Sources: Reynolds (2020), Mehra (2020)*

2. IC admission

2.1 Overall

Very low GRADE	The evidence is very uncertain about the effect of ACEI/ARBS or ACEI use on IC admission. *Sources: Reynolds (2020), López-Otero (2020), Bean (2020), Rentsch (2020)*

Very low GRADE	ARBS use may have no effect on IC admission, but the evidence is very uncertain. *Sources: Reynolds (2020), López-Otero (2020*

Low GRADE	The evidence suggests that thiazolidinediones use does not increase IC admission. *Sources: Reynolds (2020)*

2.2 Hypertensive patients

Very low GRADE	The evidence is very uncertain about the effect of ACEI/ARBS on IC admission *Sources: Reynolds (2020), Felice (2020), Selçuk (2020)*

Low GRADE	The evidence suggests that ARBS use, ACEI use, or thiazolidinediones use does not increase IC admission. *Sources: Reynolds (2020)*

3. Hospital admission

3.1 Overall

Low GRADE	The evidence suggests that ACEI/ARBS use, ARBS use, or ACEI use does not increase hospital admission. *Sources: López-Otero (2020), Rentsch (2020), Rossi (2020)*

3.2 *Hypertensive patients*

Very Low GRADE	ACEI/ARBS use may have no effect on hospital admission, but the evidence is very uncertain. *Sources: Felice (2020)*

4. Length of stay

4.2 Hypertensive patients

Very low GRADE	ACEI/ARBS may have no effect on length of stay, but the evidence is very uncertain. *Sources: Selçuk (2020), Zhou (2020)*

5. Ventilation

5.1 Overall

Low GRADE	The evidence suggests that ACEI/ARBS use, ACEI use or thiazolidinediones use does not increase ventilation. Sources: Reynolds (2020), Jung (2020), Mancia (2020)

Very Low GRADE	ARBS use may have no effect on ventilation, but the evidence is very uncertain. *Sources: Reynolds (2020), Mancia (2020), Jung (2020)*

5.2 Hypertensive patients

Very low GRADE	The evidence is very uncertain about the effect of ACEI/ARBS use on ventilation. *Sources: Gao (2020), Reynolds (2020), Felice (2020), Selçuk (2020)*

Low GRADE	The evidence suggests that ARBS use, ACEI use or thiazolidinediones use does not increase ventilation. *Sources: Reynolds (2020)*

6. Tromboembolic complications

6.1 Overall

Very low GRADE	ACE/ARBS use, ARBS use or ACEI use may have no effect on tromboembolic complications, but the evidence is very uncertain. *Sources: López-Otero, Jung*

Overwegingen – van bewijs naar aanbeveling

Voor- en nadelen van de interventie en de kwaliteit van het bewijs

De kwaliteit van het bewijs van de geïncludeerde studies is overwegend laag tot zeer laag. De GRADE systematiek is gevolgd om de kwaliteit van het bewijs te beoordelen. Deze is hier dan ook gevolgd. In een nieuwe situatie (zoals COVID) is het logisch dat de meeste studies nog niet kunnen voldoen aan de strenge eisen die aan studies van hoge kwaliteit worden gesteld. De GRADE methodiek zet de

kwaliteit van het bewijs echter af tegen de best mogelijke kwaliteit en niet tegen de best mogelijke kwaliteit in de huidige situatie. De GRADE systematiek geeft het vertrouwen weer in de schatting van het effect van een interventie. Wanneer de modules en de search worden geüpdate zijn er hopelijk studies van betere kwaliteit beschikbaar en kan het niveau van de kwaliteit van het bewijs hierop worden aangepast.
In deze literatuursamenvatting is het effect van het gebruik van ACEI, ARBS, NSAIDS en thiazolidinediones van COVID-19 patiënten onderzocht op de uitkomstmaten mortaliteit, ic opname, ziekenhuisopname, verblijfsduur, ventilatie en tromboembolische complicaties. Mortaliteit was gedefinieerd als kritische uitkomstmaat. De literatuur laat zien dat er geen associatie is tussen gebruik van ACEI/ARBS (gecombineerd of los van elkaar) met mortaliteit voor zowel de overall groep (waarin gebruikers met niet gebruikers worden vergeleken) als de subgroep met alleen hypertensieve patiënten. De kwaliteit van het bewijs varieert van moderate (voor de overall groep waarin ACEI/ARBS gebruikers gecombineerd) tot zeer laag. Met betrekking tot NSAID gebruik is de kwaliteit van het wetenschappelijk bewijs zeer laag en kunnen geen conclusies voor de praktijk worden getrokken.
Voor de belangrijke uitkomstmaten was de kwaliteit van het bewijs laag tot zeer laag. Ook hier wijst het gebruik van het gebruik van ACEI, ARBS (zowel los als gecombineerd) en thiazolidinediones op geen of nauwelijks associatie met de belangrijke uitkomstmaten.
Er zijn nauwelijks studies waarin gebruik van ACEI, ARBs werd geassocieerd met hoger risico op slechte uitkomst, een van de weinige (Sulcuk et al) was een zeer kleine studie. Over het algemeen was er een zwakke associatie met betere uitkomsten bij gebruik van deze middelen (zie figuur 1 en 2) . Dit sluit nagenoeg uit dat deze middelen een negatief effect hebben op het beloop van een COVID-19 infectie. Het toont niet aan dat ze beschermend zijn, maar een beschermend effect kan niet worden uitgesloten. Herhaaldelijk uitsluiten van associatie met nadelige uitkomsten is wel in staat om de kans dat dat een dergelijk middel direct nadelige effecten heeft als zeer onwaarschijnlijk te beoordelen. Kortom, er is sterk bewijs voor de afwezigheid van een relatie tussen gebruik van ACEI, ARBs en slechtere uitkomsten. Er is geen sterk bewijs voor de beschermende effecten van deze middelen, maar dit kan ook niet worden uitgesloten.

<u>CAPACITY</u>
CAPACITY is een internationale registratie van patiënten met COVID-19 op basis van het ISARIC WHO CRF, aangevuld met informatie over specifieke cardiovasculaire parameters (https://capacity-covid.eu/). CAPACITY is in het voorjaar van 2020 gestart en bevat gegevens van 13034 patiënten uit 13 landen, afkomstig van 79 registrerende centra. CAPACITY bevat omvangrijke informatie over patiënten met COVID, omdat ongeveer 40% van de in Nederland opgenomen COVID19 patiënten in de registratie is opgenomen (n = 5524).
De peer-reviewed publicatie van CAPACITY over het onderwerp van deze module is momenteel in voorbereiding. De resultaten van CAPACITY kunnen daarom kunnen nog niet worden meegenomen bij het literatuuronderzoek, maar bij de overwegingen worden wel de voorlopige resultaten van CAPACITY meegenomen. De peer-reviewed publicatie over het onderwerp van deze module wordt binnenkort verwacht en bij een update van de module zal de publicatie in het literatuuronderzoek worden meegenomen.

De eerste analyses van de CAPACITY data zijn in lijn met bovengenoemde bevindingen. Daarbij lijken nog zeer voorlopige analyses te suggereren dat staken van juist meer krachtige ARBs geassocieerd is met slechtere uitkomsten ook na correctie voor confounders. Deze analyses moeten nog definitief worden bevestigd.

<u>Waarden en voorkeuren van patiënten (en evt. hun verzorgers)</u>

Patiënten die een behandeling met ACEI/ARBs krijgen vinden complete en eenduidige informatievoorziening belangrijk, o.a. over de veiligheid en risico's van de behandeling.

Kosten (middelenbeslag)
De genoemde middelen zijn veelal reeds uit patent en daarmee generiek verkrijgbaar en zeer goedkoop (<1 euro per dag). De aanbevelingen die hier gedaan worden hebben vrijwel geen effect op kosten.

Aanvaardbaarheid, haalbaarheid en implementatie
Continueren van antihypertensiva bij patiënten met een ernstig verlopende infectieziekte zal in de dagelijkse praktijk discussie kunnen geven gezien de zorg voor te veel effect op de bedreigde bloeddrukregulatie. Daarom is uitdrukkelijk het advies om per geval te beoordelen of deze middelen doorgegeven kunnen worden, waarbij we hier herhalen dat indien klinisch wordt ingeschat dat deze worden verdragen het aanbeveling verdient ze niet te staken.

Aanbeveling(en)
Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies
Er is geen relatie tussen gebruik ACEI en ARB en slechtere uitkomsten COVID-19 infectie. Dit is een sterk gegeven gezien meerdere studies deze associatie niet vinden op 1 kleine studie na. Eerder gebruik van ACE/ARBs lijkt geassocieerd met minder slechte uitkomsten van een ernstige COVID-19 infectie. Staken tijdens opname van ACE/ARBs in het kader van COVID-19 infectie is geassocieerd met slechtere uitkomsten. De gevonden associaties zijn zwak, echter met een redelijke effectgrootte. Het type bewijs is ook zwak (retrospectief).

Staak of ontraad ACEI/ARBs niet bij mensen die een COVID-19 infectie doormaken ongeacht ernst van de infectie, anders dan om acute hemodynamische redenen, acuut ernstig nierfunctieverlies of ernstige nierinsufficiëntie.

Kennislacunes
- Er is een kennislacune met betrekking tot de effecten van eerder gebruik van NSAIDs. Door een gebrek aan studies hierover kunnen daar nu geen aanbevelingen over geformuleerd worden.
- Er is geen formele studie gedaan naar het effect van doorgeven dan wel staken van ACEi/ARBs tijdens opname. Daarnaast wordt vaak niet gerapporteerd of ACEi/ARBs tijdens opname worden gecontinueerd of gestaakt.

Literatuur
Felice C., Nardin C., Di Tanna GL., Grossi U., Bernardi E., Scaldaferri L., …& Rattazzi M. (2020). Use of RAAS Inhibitors and Risk of Clinical Deterioration in COVID-19: Results From an Italian Cohort of 133 Hypertensives. Am J Hypertens. 2020 Oct 21;33(10):944-948.

Gao C., Cai Y., Zhang K., Zhou L., Zhang Y., Zhang X., …&Li F. (2020). Association of hypertension and antihypertensive treatment with COVID-19 mortality: a retrospective observational study. Eur Heart J. 2020 Jun 7;41(22):2058-2066.

Imam Z., Odish F., Gill I., O'Connor D., Armstrong J., Vanood A., …& Halalau A. (2020). Older age and comorbidity are independent mortality predictors in a large cohort of 1305 COVID-19 patients in Michigan, United States. J Intern Med. 2020 Oct;288(4):469-476.

Jung SY., Choi JC., You SH., Kim WY.(2020). Association of Renin-angiotensin-aldosterone System Inhibitors With Coronavirus Disease 2019 (COVID-19)- Related Outcomes in Korea: A Nationwide Population-based Cohort Study. Clin Infect Dis. 2020 Nov 19;71(16):2121-2128.

López-Otero D., López-Pais J., Cacho-Antonio CE., Antúnez-Muiños PJ., González-Ferrero T., Pérez-Poza M., …& González-Juanatey JR. (2020). Impact of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers on COVID-19 in a western population. CARDIOVID registry. Rev Esp Cardiol (Engl Ed). 2021 Feb;74(2):175-182.

Mackey K., King VJ., Gurley S., Kiefer M., Liederbauer E., Vela K., …& Kansagara D. (2020). Risks and Impact of Angiotensin-Converting Enzyme Inhibitors or Angiotensin-Receptor Blockers on SARS-CoV-2 Infection in Adults: A Living Systematic Review. Ann Intern Med. 2020 Aug 4;173(3):195-203.

Selçuk M., Çınar T., Keskin M., Çiçek V., Kılıç Ş., Kenan B., …& Orhan AL. (2020). Is the use of ACE inb/ARBs associated with higher in-hospital mortality in Covid-19 pneumonia patients? Clin Exp Hypertens. 2020 Nov 16;42(8):738-742.

Zhang X., Yu J., Pan LY., Jiang HY. (2020). ACEI/ARB use and risk of infection or severity or mortality of COVID-19: A systematic review and meta-analysis. Pharmacol Res. 2020 Aug;158:104927.

Zhou X., Zhu J., Xu T. (2020). Clinical characteristics of coronavirus disease 2019 (COVID-19) patients with hypertension on renin-angiotensin system inhibitors. Clin Exp Hypertens. 2020 Oct 2;42(7):656-660.

Bijlagen bij module 3

Evidence tables

Evidence table for systematic review of RCTs and observational studies (intervention studies)

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
Zhang, 2020	SR and meta-analysis of cohort and case-control studies *Literature search between Jan 1, 2020 and May 9, 2020* **A**: Feng, 2020 **B**: Li Juyi, 2020 **C**: Mancia, 2020 **D**: Meng, 2020 **E**: Reynolds, 2020 **F**: Tedeschi, 2020 **G**: Yang, 2020 **H**: Zhang, 2020 **I**: Mehra, 2020 **J**: Yu, 2020 **K**: Mehta, 2020 **L**: Li xiaochen et al, 2020 *Setting and country* **A**: China **B**: China **C**: Italy **D**: China **E**: USA	Inclusion criteria SR: (1) study design: case-control, case-crossover, self-controlled case series (SCCS) or cohort study; (2) antihypertensive treatment: ACEI/ARB use versus non-ACEI/ARB use; (3) outcomes: the incidence of COVID-19, critical cases, or death; (4) Exclusion criteria SR: editorials, correspondences, conference abstracts and commentary articles *12 studies included of which 8 report on mortality* <u>Important patient characteristics at baseline</u>: <u>N (ACE/ARB; Non ACE/ARB), mean age</u> **A**: N= 33; N=80, 53y **B**: N= 115; N=247, 66y **C**: N (ACEI) = 1502 (ARB)= 1394; N/A, 68y **D**: N= 17; N=25, 64y **E**: N= 091; N= 986, 64y	The dose, name and moment in time (before and during COVID-19) the medication is used is not described. The systematic review only describes the number of patients per study on ACEi/ARBs and number of patients not on an ACEi/ARBs <u>N of patients on patients on ACEi/ARBs</u> **A**: 33 **B**: 115 **C**: ACEI 1502, ARB 1394 **D**: 17 **E**: 1091 **F**: 165 **G**: 43 **H**: 188	For all studies the control group is defined as COVID-19 patients not on an ACEi/ARBs. <u>*No. of patients not on an ACEI/ARB*</u> **A**: 80 **B**: 247 **C**: NA **D**: 25 **E**: 986 **F**: 136 **G**: 83 **H**: 940 **I**: non-ACEI 8140, non-ARB 8354 **J**: 173 **K**: non-ACEI 1619, non-ARB 1637 **L**: 503	<u>End-point of follow-up</u>: **A-L**: Not available <u>*Study period*</u> **A:** Jan 1 to Feb 15 2020 **B**: Jan 15 to Mar 15 2020 **C**: Feb 21 to Mar 11 2020 **D**: Jan 11 to Feb 23 2020 **E**: Mar 1 to Apr 15 2020 **F**: Feb 1 to Apr 4 2020 **G**: Jan 5 to Feb 22 2020 **H**: Dec 31 2019 to Feb 20 2020 **I**: Dec 20 2019 to Mar 12 2020 **J**: Jan 17 to Feb 19 2020 **K**: Mar 8 to Apr 12 2020	*1. Mortality* No definition for mortality provided. **A-L:** NA Meta-analysis (**B, D, F, G, H, I, J, K**) Pooled OR = 0.73 [95 % CI 0.5–1.07] P = 0.11 Random effect analysis The risk of mortality in ACEI/ARB-exposed was similar to non-ACEI/ARB exposed COVID-19 patients Heterogenitiy (I^2): 70.7% P = 0.001 Sub analysis ACEI/ARB exposure and risk of mortality in COVID-19 patients with antihypertensive indication Pooled ES 0.62 [95%CI 0.38-1.02] P=0.059	The authors conclude that that ACEI/ARB use did not increase mortality risk among patients with COVID-19. However, patient exposure to ACEI/ARBs for the treatment of hypertension was associated with a lower risk of mortality. <u>*Personal remarks*</u>: <u>*Sensitivity analyses*</u> Adjusted vs unadjusted estimates no significant increase in the mortality risk of patients with ACEI/ARB exposure regardless of unadjusted OR = 0.66 [95 % CI, 0.38–1.12] P = 0.121 or adjusted estimates OR = 0.91 [95 % CI, 0.51–1.61] P = 0.87

	F: Italy **G**: China **H**: China **I**: Asia, Europe, and North America **J**: China **K**: USA **L**: China <u>Source of funding and conflicts of interest:</u> This review was supported by Zhejiang Provincial Natural Science Foundation of China Conflicts of interest: none declared	**F**: N= 165; N=136, 76y **G**: N= 43; N=48, 66y **H**: N= 188; N= 940, 64y **I**: N (ACEI) = 770 N (ARB)= 556; N (non-ACEI)=8140 N (nonARB)= 8354, 49y **J**: N= 103; N=173, 60y **K**: N (ACEI)= 116 N(ARB)=98; N(non-ACEI)= 1619 N(nonARB)= 1637, 49y **L**: N= 42; N= 503, 60y *<u>Sex (% males)</u>:* **A**: 57% **B**: 52% **C**: NA **D**: 57% **E**: 50% **F**: 72% **G**: 49% **H**: 53% **I**: 60% **J**: 53% **K**: 40% **L**: 51% Groups comparable at baseline? This information is not available *<u>Confounder adjustment</u>* **A**: No **B**: No **C**: No **D**: No **E**: No **F**: Age, gender, presence of CV comorbidities and COPD	**I**: ACEI 770, ARB 556 **J**: 103 **K**: ACEI 116, ARB 98 **L**: 42 *<u>Measurement of ACEI/ARB use</u>* **A**: Medical record review **B**: Medical record review **C**: Databases of health care use **D**: Medical record review **E**: Pharmacy fill records **F**: Medical record review **G**: Medical record review **H**: Medical record review **I**: Medical record review **J**: Medical record review **K**: Electronic medical records **L**: Medical record review		**L**: Jan 26 to Feb 5 2020 <u>For how many participants were no complete outcome data available?</u> (intervention/control) **A-L**: NA	Heterogenitiy (I^2): 74.8% *2. IC-admission* Not reported *3. Hospital admission* Not reported *4. Length of stay* Not reported *5. Ventilation* Not reported *6. Thromboembolic complications* Not reported	Studies grouped by study location There was a significantly lower mortality risk in studies from China OR=0.65 [95 % CI 0.46−0.91] P = 0.013. There were no significant increase in mortality risk in studies form other countries (OR = 0.88, 95 % CI, 0.48–1.62, P = 0.689). Analysis limited to studies that only included patients on ACEi/ARBs for antihypertensive indications A lower risk of mortality was observed among those who used ACEI/ARB OR = 0.62 [95 % CI 0.38–1.02] P = 0.059 Heterogenity (I^2): 74.85% P=0.001 After excluding studies that enrolled patients with hypertension not on antihypertensive treatment, a meta-analysis of four studies found that ACEI/ARB exposure was associated with a lower risk of mortality

		G: No **H**: Age, gender, comorbidities and in-hospital medications **I**: Age, race, coexisting conditions and medications **J**: Sex, age, smoking, symptom, diabetes, cardiovascular diseases, chronic liver disease, and other comorbidity **K**: Propensity score matched **L**: No					compared to those on non-ACEI/ARB antihypertensive drugs (OR = 0.48, 95 % CI, 0.29−0.81, P = 0.006; I^2 = 0%). *Heterogeneity:* The I^2 of 70.9% may represent substantial heterogeneity. The subgroup analysis described above does not explain the heterogeneity (unexplained). The heterogeneity may be explained by differences in the study populations (indication for ACEi/ARBs use, characteristics and comorbidities of the non-users, country), follow-up duration and completion of follow-up.
Mackay, 2020	SR of observational studies *Literature search MEDLINE (Ovid) and Cochrane Database of Systematic Reviews from 2003 to 4 May 2020, the World Health Organization database of COVID-19*	Inclusion criteria SR: observational studies of adults in any setting examining associations between use of ACEIs or ARBs and risks for acquiring SARS-CoV-2 and COVID-19, SARS, or MERS; observational studies of adults with COVID-19, SARS, or MERS, in any setting, examining associations between ACEI or	The dose, name and moment in time (before and during COVID-19) the medication is used is not described N of patients on patients on ACEi/ARBs	For all studies the control group is defined as COVID-19 patients not on an ACEi/ARBs. No further details are available. *No. of patients not on an ACEI/ARB* **A-N:** NA	Study period: **A**: 3/1/20–3/22/20 **B**: 1/1/20–2/15/20 **C**: /15/20–3/15/20 **D**: Time varied by site (range, 12/27/19–2/29/20); **E**: NA **F**: 12/20/19–3/15/20; **G**: 1/11/20–2/23/20 **H**: 2/8/20–3/30/20 **I**: 3/1/20–4/15/20	*1. Mortality* No definition for mortality provided. Unadjusted **A:** (Mortality and transfer to critical care within 7 d of symptom onset) ACEi OR 0.64 (0.28–1.43)	The authors conclude that no indication exists to prophylactically stop ACEI or ARB treatment because of concerns about COVID-19.

	publications and medRxiv.org through 17 April 2020; and ClinicalTrials.gov to 24 April 2020 **A**: Bean, 2020 (not peer reviewed) **B**: Feng, 2020 **C**: Li, 2020 **D**: Liu, 2020 **E**: Mancia, 2020 **F**: Mehra, 2020 **G**: Meng, 2020 **H**: Rentsch, 2020 (not peer reviewed) **I**: Reynolds, 2020 **J**: Rossi, 2020 **K**: Yang, 2020 **L**: Peng, 2020 **M:** Zeng, 2020 **N**: Zhang, 2020 *Setting and country* **A:** adults with COVID-19 admitted to 2 hospitals; United Kingdom **B:** adults with COVID-19 admitted to 3 hospitals; China **C:** adults with COVID-19 and HTN admitted to 1 hospital; China **D:** adults with COVID-19	ARB use and risks for a broad range of clinical outcomes, including death, severity of illness (mechanical ventilation, intensive care unit [ICU] admission, length of stay, need for non-invasive ventilation, hospitalization, organ dysfunction), cardiovascular events, and radiologic findings; and trials in adults with COVID-19, in any setting, comparing laboratory or clinical outcomes between patients treated with either ACEIs or ARBs and those receiving "usual care," placebo, or other treatments. Exclusion criteria SR: case reports and case series with fewer than 10 patients *19 studies included of which 6 report on mortality, 2 on hospitalization and 1 on IC-admission* <u>Important patient characteristics at baseline</u>: **A**: n = 205 Mean age: 63 y Male: 52% HTN: 51% Diabetes: 30% Heart disease: 15% **B**: n = 476 Median age: 53 y Male: 57%	NA (the SR describes the N of patients receiving ACEI or ARB with severe Illness (%), and non-severe illness (%) **A**: ACEI only: 9/53 (17); 37/152 (24) **B**: 2/124 (2); 29/352 (9) **C**: 57/173 (32.9); 58/189 (30.7) **D**: 4/28 (14.3); 8/18 (44.4) **E**: NA **F**: ACEI: 16/515 (3.1); 754/8395 (9.0) ARB: 38/515 (7.4); 518/8395 (6.2) **G**: 4/17 (23.5); 12/25 (48) **H**: Hospitalization: 147/297 (49.5) ICU admission: 69/122 (56.6) Not hospitalized: 108/288 (37.5) **I**: NA **J**: 501/1075 (46.6); 317/1578 (20.1 **K**: 15/50 (30.0); 28/76 (36.8)		**J**: 2/27/20–4/2/20 **K**: 1/5/20–2/22/20 **L**: 1/20/20–2/15/20 **M:** 1/5/20–3/8/20 **N**: 12/31/19–2/20/20 <u>For how many participants were no complete outcome data available?</u> (intervention/control) **A-N**: NA	ACEi aOR 0.29 (0.10–0.75) **C:** OR 0.76 [95%CI 0.43–1.33] **E:** Assisted ventilation or Death ACEI:aOR 0.91 (0.69–1.21) ARB: aOR 0.83 (0.63–1.10) **F**: ACEI OR 0.33 [95% CI 0.19–0.54] ARB OR 1.21 [95%CI 0.86–1.71] I: severe covid: ICU admission, use of noninvasive or mechanical ventilation, or death Overall ACEi (mean diff for severe covid) −1.9 (−6.6 to 2.8) ARB (mean diff) −1.4 (−6.1 to 3.3) ACEi or ARB mean diff −0.1 (−3.7 to 3.5) Thiazide diuretic (mean diff) −3.4 (−8.3 to 1.6) hypertensive patients ACE inhibitor (mean diff for severe covid) −3.3 (−8.2 to 1.7) ARB mean diff 0.1 (−4.8 to 4.9)	

	aged >65 y with preexisting HTN admitted to 3 hospitals; China **E:** Patients with COVID-19 aged >40 y; Lombardy, Italy **F:** patients with COVID-19 admitted to 169 hospitals in Asia, Europe, and North America with discharge status available in registry **G:** adults with COVID-19 and pre-existing HTN receiving medication and admitted to 1 hospital; China **H:** adults born 1945–1965 with positive COVID-19 test result; U.S. Veterans Health Administration **I:** patients with HTN and positive COVID-19 test result in 1 health system; United States **J:** patients with COVID-19; Reggio Emilia, Italy	HTN: 24% Diabetes: 10% Heart disease: 8% **C**: n = 362 Mean age: 66 y Male: 52% HTN: 100% Diabetes: 35% Heart disease: 17% **D**: n = 46 Age, sex, and comorbid conditions NR **E**: n = 6272 Mean age: 68 y Male: 63% HTN (receiving medication): 58% CVD: 30% **F**: n = 8910 Mean age: 49 y HTN: 26% Coronary artery disease: 11% Diabetes: 14% **G**: n = 42 Median age: 65 y Male: 57% HTN: 100% **H**: n = 585 Median age: 66 y Male: 95% HTN: 72% Diabetes: 44% Vascular disease: 28% **I**: n = 2573 (Demographics reported for patients with HTN tested for COVID-19) Median age: 64 y	**L**: 3/16 (18.6); 19/96 (19.8) **M:** 15/30 (50); 13/45 (29) **N**: NA			ACE inhibitor or ARB mean diff −0.5 (−4.3 to 3.2) Thiazide diuretic (mean diff) 0.6 (−4.5 to 5.7) **J**: HR for death with ACEI 0.8 [95%CI 0.50–1.3] **K**: OR 0.32 [95%CI 0.07–1.51] **M:** OR 0.65 [95%CI 0.12–3.58] **F**: Adjusted for severe illness ACEI OR 0.33 [95%CI 0.20–0.54] ARB OR 1.23 [95% CI 0.87–1.74] **N:** Adjusted HR (age, sex, comorbid conditions, and in-hospital medications) 0.42 [95%CI 0.19–0.92] *2. IC-admission* A: see mortality H: unadjusted OR 1.94 [95%CI 1.30–2.90] adjusted OR 1.69 [95%CI 1.01–2.84] I: see mortality *3. Hospital admission* **H:** unadjusted OR 1.63 [95%CI 1.17–2.27] Adjusted (age, race, comorbid conditions, and Veterans Aging Cohort Study index) aOR 1.24	

	K: adults with preexisting HTN at 1 hospital; Hubei, China L: adults with COVID-19 and preexisting CVD at 1 hospital; China **M:** adults with COVID-19 admitted to 1 hospital; China **N:** adults aged 18–74 y with COVID-19 admitted to 9 hospitals; China <u>Source of funding and conflicts of interest:</u> Authors did not receive funding for this study outside of salary support. No conflicts of interest were declared.	Male: 51% HTN: 100% Diabetes: 40% History of MI: 11% CKD: 25% **J**: n = 2653 Mean age: 63 y Male: 50% HTN: 18% Diabetes: 12% Heart failure: 6% **K**: n = 126 Median age: 66 y Male: 49% HTN: 100% Diabetes: 30% Heart disease: 18% **L**: n = 112 Patients with preexisting CVD Mean age: 62 y Male: 47% HTN: 82% Diabetes: 21% **M:** n = 75 Patients with COVID pneumonia and HTN Mean age: 67 y Male: 55% HTN: 100% Diabetes: 31% **N**: n = 1128 Mean age: 64 y Male: 53% HTN: 100% Groups comparable at baseline? This information is not available				[95%CI 0.79–1.95] **J**: aHR with ACEI (age, sex, and Charlson comorbidity score): 1.13 [95%CI 1.1–1.5] aHR (age, sex, and Charlson comorbidity score, and restricted to patients with CVD) with ACEI aHR 1.12 [95%CI 0.82–1.54] *4. Length of stay* Not reported *5. Ventilation* E: see mortality I: see mortality *6. Thromboembolic complications* Not reported	

1= Reported for hypertensive patients; 2= Calculated for 610 COVID 19 patients out of total of 49 277; 3 = Patients tested for COVID-19; 4= Patients aged over 35 years suspected of or diagnosed with COVID-19; 5= Not on any antihypertensive drug; 6= Before matching; 7= After matching; 8= Other regimens; 9 = Reported for COVID-19-positive patients (187 out of 288 suspected of or diagnosed patients)

Evidence table for intervention studies (randomized controlled trials and non-randomized *observational* studies [cohort studies, case-control studies, case series])[1]

This table is also suitable for diagnostic studies (screening studies) that compare the effectiveness of two or more tests. This only applies if the test is included as part of a test-and-treat strategy – otherwise the evidence table for studies of diagnostic test accuracy should be used.

Study reference	Study characteristics	Patient characteristics [2]	Intervention (I)	Comparison / control (C) [3]	Follow-up	Outcome measures and effect size [4]	Comments
Felice, (2020)	Type of study: retrospective observational study Setting and country: hypertensive patients who presented to the emergency department, Italy Funding and conflicts of interest: Funding not reported. No conflicts of interest declared.	Inclusion criteria: all consecutive hypertensive subjects who presented to the emergency department (ED) with acute respiratory symptoms/fever, and were diagnosed with COVID-19 infection Exclusion criteria: NA N total at baseline: 133 ACEI N=40 ARB N=42 Not on RAAS inhibitors N=51 Important prognostic factors[2]: *Mean age (SD):* *ACEI: 73.1 (11.5)* *ARB: 69.0 (13.4)* *Not on RAAS: 76.2 (11.9)* *Sex male (%):* *ACEI: 28 (70)*	Hypertensive patients on ACEI Patients on ACEI were chronically using ACEIs. 70% were taking ramipril. Hypertensive patients on ARB Patients on ARB were chronically using ARBs. Olmesartan was used in more than 50% of patients.	Hypertensive patients using other blood pressure lowering medications then ACEI or ARBs.	Length of follow-up: Mean 15.8 ± 8.6 days Loss-to-follow-up: NA Incomplete outcome data: No	*1. Mortality* OR of 0.41 (CI 95%, 0.18-0.92; P=0.030) aOR (gender, BMI, days with symptoms prior to admission, previous cardiovascular events, diabetes and cancer) OR 0.56, CI95% 0.17-1.83, P=0.341 *2. IC-admission (semi intensive care/ic)* OR 0.36 [95%CI 0.17-0.75] P=0.007 aOR (gender, BMI, days with symptoms prior to admission, previous cardiovascular events, diabetes and cancer) OR 0.25 [CI95% 0.09-0.66] P=0.006 Admission to semi-intensive/intensive care units, less likely to occur in hypertensive	

		ARB: 31 (74) *Not on RAAS 27 (53)* Groups comparable at baseline? No significant differences were observed for all demographics and clinical parameters, except for the history of chronic heart failure, which was more frequently observed in hypertensive patients not on RAAS inhibitors (31%; P=0.007).				patients using ARB or ACEI (significant). *3. Hospital admission* OR 0.45 [95%CI 0.09-2.24] P=0.327 aOR 0.39 [95%CI 0.05-2.94] P=0.365 *4. Length of stay* Not reported *5. Ventilation* Defined as Oxygen therapy OR 0.46 [95%CI 0.18-1.18] P=0.107 aOR 0.51 [95%CI 0.15-1.78] P=0.292 Defined as non-invasive ventilation OR 0.70 [95%CI 0.34-1.44] P=0.336 aOR 0.58[95%CI 0.21-1.60] P=0.296*6.* *6. Thromboembolic complications* Not reported	
Gao (2020)	Type of study: retrospective observational Setting and country: Covid patients admitted to the hospital, China (for our	Inclusion criteria: All patients admitted to Huo Shen Shan Hospital, Wuhan, China, from 5 February to 15 March 2020, with confirmed COVID-19 Exclusion criteria: NA	Hypertensive patients on ACEI and/or ARBs	Hypertensive patients not on RAAS (but on B blockers, antidiuretics etc)	Length of follow-up: median 21 (12–32) days Loss-to-follow-up: NA	*1. Mortality* RAASI: 4/183 (2.2%) Non-RAASI: 19/527 (3.6%) OR Unadjusted 0.60 (95% CI 0.20–1.76) P= 0.354 Adjusted (age, sex, medical history of diabetes, insulin-treated diabetes, myocardial infarction,	

	outcome measures only hypertensive patients) Funding and conflicts of interest: Not reported and no conflicts of interest declared.	Patients were confirmed or suspected COVID-19 patients <u>N total at baseline</u>: N total: 2877 N hypertensive patients on antihypertensive medication=710 (183 on RAAS inhibiter, 527 on non-RAAS inhibitor) <u>Important prognostic factors</u>[2]: *age ± SD:* *Non-RAAS inhibitor: 64.84 ± 11.19* *RAAS inhibitor: 62.64 ± 11)* *Sex (%male):* *Non-RAAS inhibitor: 266 (50.5%)* *RAAS inhibitor: 104 (56.8%)* Groups comparable at baseline? Yes, for all (symptoms at admission, blood pressure, medical history) except shivering			<u>Incomplete outcome data</u>: NA	underwent PCI/CABG, renal failure, stroke, heart failure, and COPD) ORa 0.85 [95% CI 0.28–2.58] P= 0.774 Propensity score adjusted 0.93 [95% CI 0.31–2.84] P=0.901 *2. IC-admission* Not reported *3. Hospital admission* Not reported *4. Length of stay* Not reported *5. Ventilation* Defined as invasive mechanical ventilation RAASI: 5 (2.7%) Non-RAASI: 25 (4.7%) P=0.292 There is no significant difference in mechanical ventilation between hypertensive patients on RAAS inhibitors and on non-Raas inhibitors. *6. Thromboembolic complications* Not reported	
Imam (2020)	Type of study: Retrospective, multicenter cohort	<u>Inclusion criteria</u>: patients hospitalized with SARS-CoV-2 infection demonstrated by a positive RT-PCR on nasopharyngeal swab per	NSAID use ACEI/ARBs use No further details available	patients hospitalized with SARS-CoV-2	<u>Length of follow-up</u>: NA	*1. Mortality* Univariate analysis NSAIDS use OR 0.55 [95% CI0.39-0.78] P=.001	

	Setting and country: patients hospitalized with COVID-19, US Funding and conflicts of interest: none and none declared	world health organization (WHO) guidance between March 1-April 1,2020 Exclusion criteria: NA N total at baseline: Total N=1305 ACEI or ARBs N=565 (43.3%) NSAIDS N= 466 (35.7%) Important prognostic factors[2]: Not available per group *age ± SD: 61.0 ±16.3* *Male Sex 702 (53.8%)* Groups comparable at baseline? NA because the groups are not defined as in the PICO			Loss-to-follow-up: NA Incomplete outcome data: NA	ACE-I/ARB use OR 1.55 [95% CI 1.15-2.10] P=.004 Multivariate analysis (Age, Initial Serum Creatinine, CCI, NSAID, HTN, ACE-I/ARB use, CKD) NSAID use OR 0.57 [95%CI 0.40-0.82] P=0.002 ACE-I/ARB use OR 1.20 [95%CI 0.86-1.68] P=0.278 *2. IC-admission* Not reported *3. Hospital admission* Not reported *4. Length of stay* Not reported *5. Ventilation* Not reported *6. Thromboembolic complications* Not reported	
Jung (2020)	Type of study: population based cohort using a database of de-identified COVID-19 patient data	Inclusion criteria: patients with COVID-19 who were ≥18 years old Exclusion criteria: NA N total at baseline: N total = 5179	RAAS inhibitor users were defined as patients with RAAS inhibitor use at 1–30 days before the index date	Patients who had never received RAAS inhibitors or had received them at 31–365 days before the index date. A prescription duration of ≥7	Length of follow-up: All patients were followed until the first instance of death or	*1. Mortality* Defined as in-hospital mortality Observed for 33/377 RAAS inhibitor users (9%) and for 51/1577 nonusers (3%) (p<0.001) Univariate analysis (total group) OR 3.88 [95%CI 2.48 6.05] P<0.001	

	Setting and country: patients admitted to the hospital and patients not admitted to the hospital, Korea Funding and conflicts of interest: No funding and no conflicts of interest declared.	N hospitalized (with clinical outcomes) = 1954 N (hospitalized RAASi users) = 377 N (hospitalized non RAASi users) = 1577 <u>Important prognostic factors for total</u>: *age ± SD:* *RAASi:62.5 ± 14.7* *Non-RAASI: 41.5 ± 16.6* *Sex (% male):* *RAASi: 400 (52)* Non-RAASi: *1895 (43)* Charlson comorbidity index (mean (SD)) RAASi: 3.3 (2.8) Non-RAASi: 1.2 (1.9) Groups comparable at baseline? No, there is a significant difference between the groups on all included factors (age, sex, comorbidities, Charlson comorbidity index, immunosuppression)		days was required to define drug use.	April 8, 2020 <u>Loss-to-follow-up</u>: NA <u>Incomplete outcome data</u>: NA	Multivariate analysis (total group, adjusted for age, sex, Charlson Comorbidity Index, immunosuppression, and hospital type)) adjusted OR, 0.88 [95% CI 0.53–1.44] p=0.60 RAAS inhibitor use was not independently associated with a higher risk of mortality among COVID-19 patients Multivariate analysis (adjusted for age, sex, Charlson Comorbidity Index, immunosuppression, and hospital type) <u>hypertensive</u> patients adjusted OR 0.71 [95% CI 0.40–1.26] p=0.25 RAAS inhibitor use was not independently associated with a higher risk of mortality among hypertensive COVID-19 patients. *2. IC-admission* Not reported *3. Hospital admission* Not reported *4. Length of stay* Not reported *5. Ventilation* Defined as mechanical ventilation) OR 3.74 [95% CI 1.91 7.34] P<0.001	

						Adjusted OR 1.03 [0.50 2.13] P=0.93 RAAS inhibitor use was not independently associated with a higher risk of mechanical ventilation *6. Thromboembolic complications* Defined as acute cardiac event OR 1.69 [95% CI 1.19 2.39] P= 0.003 Adjusted OR 0.88 [95% CI 0.59 1.31] P=0.53 RAAS inhibitor use was not independently associated with a higher risk of an acute cardiac event	
López-Otero (2020)	Type of study: Single-center, retrospective, observational cohort study Setting and country: Hospitalized and non-hospitalized patients, Spain Funding and conflicts of interest: Funding information NA, no conflict of interest declared.	Inclusion criteria: all cases of laboratory-confirmed SARS-CoV-2 infection in the area, Exclusion criteria: NA N total at baseline: Total N=965 ACEI/ARB N= 213 No ACEI/ARB N = 755 Important prognostic factors[2]: *age ± SD:* ACEI/ARB *: 72.1 ± 13.2* No ACEI/ARB*: 56.0 ± 20.5* *Sex (%female):*	Use of ACEI, ARB or both Of the COVID-19 patients, 210 (21.8%) were under ACEI or ARB treatment at the time of diagnosis; of these, 165 (78.57%) were taking them for more than 1 year.	No use of ACEI or ARB	Length of follow-up: Study period from 10 March to 6 April Loss-to-follow-up: NA Incomplete outcome data: NA	*1. Mortality* Univariate analysis OR 1.49 [95%CI 0.73-3.06] p=0.276 Multivariate analysis (adjusted for fever, oxygen saturation < 95%, age, sex, obesity, health personnel, dependency status, hypertension, diabetes mellitus, dyslipidemia, arterial disease, heart disease, atrial fibrillation, pneumonia, chronic renal disease, cerebrovascular disease, autoimmune disease, anticoagulation, beta-blockers) OR 0.62 [95%CI 0.17-2.26] P=0.468	Subgroup of patients requiring hospitalization, The absence of an impact on mortality and on heart failure remained both in the multivariate analysis and in the propensity score model, including in the evaluation of treatment taken for more than 1 year

		ACEI/ARB *: 43.8 59.5* No ACEI/ARB*: 59.5* Groups comparable at baseline? The cohort of patients under ACEI/ARB was older (72.1 ± 13.2 vs 56.0 ± 20.5; P < .01) and had more cardiovascular risk factors (hypertension, diabetes, smoking, and dyslipidemia) and cardiovascular comorbidities (coronary artery diseases and ventricular dysfunction) than the cohort without ACEI/ARB. There were fewer women in the ACEI/ARB group (43.8% vs 59.5%; P < .01). Renal impairment and peripheral vasculopathy were also more prevalent in patients taking ACEI/ARB.				Propensity score matching ACEI/ARBs OR 0.47 [95%CI 0.14-1.64] P=0.239 Previous treatment with ACEI/ARB (combined and individually) showed no impact on mortality. *2. IC-admission* Univariate analysis OR 1.36 [95%CI 0.64-2.90] P=0.427 Multivariate analysis (adjusted for arterial oxygen saturation < 95%, diabetes mellitus, hypoxemia, hypercapnia, lymphocytes, creatinine, elevated troponin, ferritin, C-reactive protein, interleukin-6) OR 0.87 [95%CI 0.30-2.50] P=0.798 Previous treatment with ACEI/ARB (combined and individually) showed no impact on IC admission *3. Hospital admission* Univariate analysis OR 2.27 [95% CI 1.63-3.16] P<.001 Multivariate analysis (adjusted for days with symptoms, fever, arterial oxygen saturation < 95%, age, sex,	

						health personnel, institutionalized, dependency status, dementia, hypertension, dyslipidemia, ventricular dysfunction, lung disease, previous cancer, hypothyroidism, antiplatelet therapy) OR 0.85 [95%CI 0.45-1.64] P=0.638 Previous treatment with ACEI/ARB (combined and individually) showed no impact on hospital admission. *4. Length of stay* Not reported *5. Ventilation* Not reported *6. Thromboembolic complications* Defined as heart failure Univariate analysis OR 2.20 [95%CI 1.09-4.44] P=0.028 Multivariate analysis (adjusted for fever, oxygen saturation < 95%, age, sex, obesity, health personnel, dependency status, hypertension, diabetes mellitus, dyslipidemia, arterial disease, heart disease, atrial fibrillation, pneumonia, chronic renal disease, cerebrovascular disease,	

						autoimmune disease, anticoagulation, beta-blockers) OR 1.37 [95%CI 0.39-4.77] P=0.622	
Selçuk (2020)	Type of study: observational Setting and country: hypertensive patients admitted due to Covid-19 infection, Turkey Funding and conflicts of interest: The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors. No conflicts of interest were declared.	Inclusion criteria: consecutive hypertensive patients admitted to our centers due to Covid- 19 infection Exclusion criteria: Patients with the absence of in-hospital clinical data, heart failure patients with hypertension were not included in the study N total at baseline: N total = 113 ACE inh/ARBs users N=74 Non-users N=39 Important prognostic factors[2]: *age ± SD:* ACE inh/ARBs users: 67 ± 11 Non-user: 58 ± 10 *Sex (N, % male):* ACE inh/ARBs users: 36 (48.6) Non-user: 23 (59.0) Groups comparable at baseline? The patients in the ACE inh/ARBs group were older. The frequency	Patients on ACEI and/or ARBs	All patients were on other than ACE inh/ARBs antihypertensive therapy unless no contraindication was present.	Length of follow-up: NA Loss-to-follow-up: INA Incomplete outcome data: NA	*1. Mortality* Univariate analysis OR 6.30 (95%CI 2.03–19.58) P0.001 Multivariate analysis (adjusted for age, coronary artery disease, ACE inh/ARBs use, D-dimer, WBC count, creatinine, plasma glucose, and lactate dehydrogenase) OR 3.66 (95%CI: 1.11–18.18) p= .032 ACEI/ARB use is an independent predictor of inhospital mortality. Kaplan-Meir curve analysis displayed that patients on ACE inh/ ARBs therapy had higher incidence of in-hospital death than those who were not [log rank test p value <.001 *2. IC-admission* ACE inh/ARBs users: 37 (50.0) Non-user: 7 (17.9)) P=.001 *3. Hospital admission* Not reported *4. Length of stay (days)* ACE inh/ARBs users: 9 ± 6 Non-user: 8 ± 4 P=0.524	

		of coronary artery disease was significantly higher in patients using an ACE inh/ARBs as anti-hypertensive treatment (p = .009). The other baseline features and medical treatments were indifferent between the groups. patients in the ACE inh/ARBs group had significantly higher white blood cell (WBC) and neutrophils count				*5. Ventilation* Defined as endotracheal intubation ACE inh/ARBs users: 33 (44.6) Non-user: 4 (10.3) P<0.001*6.* *6. Thromboembolic complications* Not reported	
Zhou (2020)	Type of study: Retrospective, single center cohort Setting and country: discharged patients with COVID-19, China Funding and conflicts of interest: not reported and none declared	Inclusion criteria: confirmed patients with COVID-19 at Wuhan Fourth Hospital discharged from January 25 to February 20, 2020. Exclusion criteria: NA N total at baseline: Total N=110 History of hypertension N=36 (32.7%) ACEI or ARBs N=15 (41.7%) (43.3%) Other antihypertensive drugs (control) N=21 (58.3%) Important prognostic factors[2]: *Age ± SD* ACEI/ARBs users: 58.5 ± 10.1 years Other: 69.2 ± 7.5 years	Patients taking ACEI/ARBs No further details available	Patients taking other antihypertensive drugs. No further details available	Length of follow-up: NA Loss-to-follow-up: NA Incomplete outcome data: NA	*1. Mortality* ACEI/ARBs users: 2 (13.3%) Non-user: 5 (23.8%) P<0.676. *2. IC-admission* Not reported *3. Hospital admission* Not reported *4. Length of stay* *Mean (SD)* *I: 10.1(5.2)* *C: 11.7(6.0)* *P=0.405* *5. Ventilation* Not reported *6. Thromboembolic complications* Not reported	

		Male Sex: N (%) ACEI/ARBs users: *9 (60%)* Other: 10 (47.6%) Groups comparable at baseline? Age was significant different (p=0.001) between groups. Other factors were comparable.					

Notes:

1. **Prognostic balance between treatment groups is usually guaranteed in randomized studies, but non-randomized (observational) studies require matching of patients between treatment groups (case-control studies) or multivariate adjustment for prognostic factors (confounders) (cohort studies); the evidence table should contain sufficient details on these procedures**
2. **Provide data per treatment group on the most important prognostic factors [(potential) confounders]**
3. **For case-control studies, provide sufficient detail on the procedure used to match cases and controls**
4. **For cohort studies, provide sufficient detail on the (multivariate) analyses used to adjust for (potential) confounders**

Table of quality assessment for systematic reviews of RCTs and observational studies

Based on AMSTAR checklist (Shea et al.; 2007, BMC Methodol 7: 10; doi:10.1186/1471-2288-7-10) and PRISMA checklist (Moher et al 2009, PLoS Med 6: e1000097; doi:10.1371/journal.pmed1000097)

1. **Research question (PICO) and inclusion criteria should be appropriate and predefined**
2. **Search period and strategy should be described; at least Medline searched; for pharmacological questions at least Medline + EMBASE searched**
3. **Potentially relevant studies that are excluded at final selection (after reading the full text) should be referenced with reasons**

Study **First author, year**	**Appropriate and clearly focused question?[1]** **Yes/no/unclear**	**Comprehensive and systematic literature search?[2]** **Yes/no/unclear**	**Description of included and excluded studies?[3]** **Yes/no/unclear**	**Description of relevant characteristics of included studies?[4]** **Yes/no/unclear**	**Appropriate adjustment for potential confounders in observational studies?[5]** **Yes/no/unclear/notapplicable**	**Assessment of scientific quality of included studies?[6]** **Yes/no/unclear**	**Enough similarities between studies to make combining them reasonable?[7]** **Yes/no/unclear**	**Potential risk of publication bias taken into account?[8]** **Yes/no/unclear**	**Potential conflicts of interest reported?[9]** **Yes/no/unclear**
Zhang, 2020	Yes	Yes	Yes	No (number of events not reported per study)	Unclear (some studies in the SR adjusted for counfounders but not all)	Yes	Yes (subgroup analysis were performed to make reasonable combining of studies)	Yes (publication bias could not be assessed because less than 10 studies were included in the meta-analysis)	No
Mackay, 2020	Yes	Yes	No (no exclusion reason were provided)	Yes	Unclear (some studies in the SR adjusted for counfounders but not all)	Yes	Yes (a meta-analysis might not be appropriate and was not performed)	No	No (not for included studies)

4. **Characteristics of individual studies relevant to research question (PICO), including potential confounders, should be reported**
5. **Results should be adequately controlled for potential confounders by multivariate analysis (not applicable for RCTs)**
6. **Quality of individual studies should be assessed using a quality scoring tool or checklist (Jadad score, Newcastle-Ottawa scale, risk of bias table etc.)**
7. **Clinical and statistical heterogeneity should be assessed; clinical: enough similarities in patient characteristics, intervention and definition of outcome measure to allow pooling? For pooled data: assessment of statistical heterogeneity using appropriate statistical tests (e.g. Chi-square, I^2)?**
8. **An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test, Hedges-Olken). Note: If no test values or funnel plot included, score "no". Score "yes" if mentions that publication bias could not be assessed because there were fewer than 10 included studies.**
9. **Sources of support (including commercial co-authorship) should be reported in both the systematic review and the included studies. Note: To get a "yes," source of funding or support must be indicated for the systematic review AND for each of the included studies.**

Risk of bias table for intervention studies (observational: non-randomized clinical trials, cohort and case-control studies)

Study reference (first author, year of publication)	**Bias due to a non-representative or ill-defined sample of patients?**[1] (unlikely/likely/unclear)	**Bias due to insufficiently long, or incomplete follow-up, or differences in follow-up between treatment groups?**[2] (unlikely/likely/unclear)	**Bias due to ill-defined or inadequately measured outcome ?**[3] (unlikely/likely/unclear)	**Bias due to inadequate adjustment for all important prognostic factors?**[4] (unlikely/likely/unclear)
Felice, (2020)	Unlikely (hypertensive confirmed covid patients)	unlikely	Mortality: Unlikely IC-admission: unclear (admitted to semi/ intensive care) Hospital admission: unclear (criteria not defined) Oxygen therapy: unlikely Non-invasive ventilation: unlikely	Mortality: Unlikely (adjusted for for gender, BMI, days with symptoms prior to admission, previous cardiovascular events, diabetes and cancer) IC admission: unlikely (adjusted for gender, BMI, days with symptoms prior to admission, previous cardiovascular events, diabetes and cancer) Hospital admission: unlikely (adjusted) *Oxygen therapy:* unlikely (adjusted) Non-invasive ventilation: unlikely (adjusted)
Gao (2020)	Unlikely (hypertensive confirmed or susptected covid patients)	Unlikely	Mortality: unlikely Invasive mechanical ventilation: unlikely	Mortality: Unlikely (age, sex, medical history of diabetes, insulin-treated diabetes, myocardial infarction, underwent PCI/CABG, renal failure, stroke, heart failure, and COPD) Invasive mechanical ventilation: likely (no correction for confounders)
Imam (2020)	Unclear (the groups are different then in the PICO so samples not possible to assess)	Unclear (information is missing on how many patients were still hospitalized at the moment of analysis)	Mortality: unlikely	Unlikely (multivariate analysis performed)
Jung (2020)	unlikely	Unclear (information is missing on how many patients were still hospitalized at the moment of analysis)	Mortality: unlikely Mechanical ventilation: unlikely Acute cardiac event: unlikely	Mortality: Unlikely (age, sex, Charlson Comorbidity Index, immunosuppression, and hospital type) Mechanical ventilation: unlikely (age, sex, Charlson Comorbidity Index, immunosuppression, and hospital type) Acute cardiac event: unlikely (adjusted for age, sex, Charlson Comorbidity Index, immunosuppression, and hospital type)

López-Otero (2020)	Unlikely (confirmed COVID patients)	Unclear (unclear how long the follow up duration was and how many patients are still hospitalized)	Mortality: unlikely IC admission: unclear Heart failure: according to the European Society of Cardiology guidelines	Unlikely (adjusted for days with symptoms, fever, arterial oxygen saturation < 95%, age, sex, health personnel, institutionalized, dependency status, dementia, hypertension, dyslipidemia, ventricular dysfunction, lung disease, previous cancer, hypothyroidism, antiplatelet therapy) Hospital admission: unlikely IC-admission: unlikely Heart failure: unlikely
Selçuk (2020)	Unlikely (hypertensive confirmed covid patients)	Unclear (there is no information available on follow-up duration)	Mortality: unlikely IC admission: unclear (criteria not described, may depend on capacity) Length of stay: unclear (discharge criteria not described, may depend on capacity) Ventilation: unlikely	Mortality: unlikely (adjusted for adjusted for age, coronary artery disease, ACE inh/ARBs use, D-dimer, WBC count, creatinine, plasma glucose, and lactate dehydrogenase) IC-admission: likely (no correction for confounders) Length of stay: likely (no correction for confounders) Ventilation: likely (no correction for confounders)
Zhou (2020)	Unlikely	Unlikely (all included patients have been discharged)	Mortality: unlikely Length of stay: unclear (discharge criteria not described, may depend on capacity)	Mortality: likely (no correction for confounders) Length of stay: likely (no correction for confounders)

1. **Failure to develop and apply appropriate eligibility criteria: a) case-control study: under- or over-matching in case-control studies; b) cohort study: selection of exposed and unexposed from different populations.**
2. **2 Bias is likely if: the percentage of patients lost to follow-up is large; or differs between treatment groups; or the reasons for loss to follow-up differ between treatment groups; or length of follow-up differs between treatment groups or is too short. The risk of bias is unclear if: the number of patients lost to follow-up; or the reasons why, are not reported.**
3. **Flawed measurement, or differences in measurement of outcome in treatment and control group; bias may also result from a lack of blinding of those assessing outcomes (detection or information bias). If a study has hard (objective) outcome measures, like death, blinding of outcome assessment is not necessary. If a study has "soft" (subjective) outcome measures, like the assessment of an X-ray, blinding of outcome assessment is necessary.**
4. **Failure to adequately measure all known prognostic factors and/or failure to adequately adjust for these factors in multivariate statistical analysis.**

Table of excluded studies

Author and year	Reason for exclusion
de Abajo (2020)	Wrong C: C are not COVID-19 patients
Grover (2020)	Search strategy unclear. The authors state a quality assessment was performed but the results are not available
Guo (2020)	This is a research letter not a research paper, does not describe methods or results very well. Info regarding the characteristics of included studies is missing
Iaccarino (2020)	The authors analyse in a multilevel model the associatoin with mortality, number of patients on ACE inhibitors not available.
Bean (2020)	Included in review Mackey
Cannata (2020)	Wrong comparison (continuation vs discontinuation), correspondence making it hard to assess methodology
Emilsson (2020)	Wrong O: outcome is serum level ace2
Guo (2020)	Wrong I: use of medication was not a factor, not described in paper. Wel opgenomen in een van de reviews
Huang (2020)	Wrong outcome
Khera (2020)	Wrong C: comparison of ACEi and ARBs users
Mancia (2020)	Included in review Mackay
Mehra (2020)	Included in review Zhang
Peng (2020)	Paper is in Chinese
Pirola (2020)	Wrong outcome: composite outcome (in-hospital death and/or severe illness)
Reynolds (2020)	Included in review Mackay
Tadic (2020)	Wrong study design: prevalence of hypertension and CVD. 2 studies included that match our PICO, but both these studies are already in the literature set.
Yang (2020)	Included in review Mackay
Zhang (2020)	Included in review Zhang
Johnson (2020)	Used publicly available country level data
Morales (2020)	Wrong comparison (no control group)
Spaak (2020)	Paper in Swedish
Zhang (2020)	Wrong intervention: statin with ACEI/ARB
Calò (2020)/Journal of hypertension	Is a correspondence, not a research paper including a method and result section.
Calò (2020)/Journal of medical virology	It is a letter to the editor not a research paper including a method and result section
Rauch (2020)	Wrong outcome and not a research paper including a method and result section, merely a discussion based on other (not necisarily covid) literature
Saber-Ayad (2020)	Description of literature on the topic but not systematic (no search strategy, no outcomes defined etc)
Sunden-Cullberg (2020)	This is a research letter not a research paper, does not describe methods or results very well
Tan (2020)	Wrong outcome (effects on the digestive system)
Bravi (2020)	Wrong outcome (severe COVID-19 and death is combined)
Timerbulatov (2020)	Paper not in English (Russian)
Li (2020)	Included in review Mackay
Talreja (2020)	This is a viewpoint that describes literature on the topic but is not a systematic literature overview (does not describe search strategy or or a systematic description of outcomes)
Amat-Santos (2020)	Wrong study design: non-pre-specified interim analysis, only 11 COVID19 patients included
Autor Anonymous (2020); Title EMA advice on renin-angiotensin system medicines during covid-19 pandemic	Wrong study design: no original study: summary of EMA advice
Chen (2020)	Wrong population: patients with diabetes and covid-19: focus on insulin, subgroup using ACE inhibitor (n=32)
Chodick (2020)	Wrong outcome: risk of COVID infection
de Abajo (2020)	same as rayyan-79961775
Feng (2020)	Wrong study design: description of characteristics
Feng (2020)	same as rayyan-79961796
Fosbol (2020)	Wrong outcome: risk of COVID infection

Gianfrancesco (2020)	Specifically focused on patients with reumatic disease
Kolin (2020)	Wrong outcome
Mehta (2020)	Wrong outcome: risk of Covid infection
Rico-Mesa (2020)	Not a systematic evaluation of literature. Outcomes not defined
Singh (2020)	Harm or benefit in COVID-19 patients receiving RASB has not been typically assessed in the included studiees yet. So intervention not present
Sriram (2020)	Wrong outcome: outcome in this study is ACE2 expression
Vaduganathan (2020)	No original data, no systematic review
Yang (2020)	Same as rayan 79962048
Yousefifard (2020)	Wrong P, not COVID-19 patients
Zhang (2020)	Same as Rayan 79962053
Zhou (2020)	Same as rayyan-79962061
Kim (2020)	wrong outcome and analysis based on big data
Arjomandi Rad (2020)	Wrong outcome: outcome is tromboembolic events
Bidulka (2020)	Wrong P: no patients with COVID, wrong O: staf. Aureus
Russo (2020)	Aim of this study is to describe the prevalence of pre-admission antithrombotic therapies
Stafford (2020)	Wrong P (not covid patients), wrong outcome (pulmonary adverse drug events)

Literature search strategy
OVID/Medline

1	exp angiotensin converting enzyme inhibitors/ or exp Anti-Inflammatory Agents, Non-Steroidal/ or exp Angiotensin Receptor Antagonists/ or exp Thiazolidinediones/ (265060)
2	(angiotensin ii receptor antagonist* or angiotensin ii receptor blocker* or angiotensin ii receptor blocking agent* or angiotensin receptor antagonist* or angiotensin receptor blocker* or angiotensin receptor blocking agent* or arb or nsaid* or thiazol* or ace inhibitor* or angiotensin converting enzyme inhibiting agent* or angiotensin converting enzyme inhibitor* or angiotensin i converting enzyme inhibitor* or dipeptidyl carboxypeptidase i inhibitor* or dipeptidyl carboxypeptidase inhibitor* or kininase ii inhibitor* or peptidyl dipeptidase inhibitor* or peptidyldipeptide hydrolase inhibitor* or acei).ti,ab,kf. (87285)
3	1 or 2 (304951)
4	((exp Coronavirus/ or Coronavirus Infections/ or pneumonia virus*.ti,ab,kf. or cov.ti,ab,kf.) and ((outbreak or wuhan).ti,ab,kf. or novel.af. or '19'.ti,ab,kf. or '2019'.ti,ab,kf. or epidem*.af. or epidemy.af. or epidemic*.af. or pandem*.af. or new.ti,ab,kf.)) or (coronavirus* or 'corona virus*' or ncov or '2019ncov' or 'covid19' or "covid 19" or "sars cov 2" or 'sars2' or "ncov 2019" or "sars coronavirus 2" or "sars corona virus 2" or "severe acute respiratory syndrome cov 2" or "severe acute respiratory syndrome cov2" or "severe acute respiratory syndrome cov*").ti,ab,kf. (40060)
5	3 and 4 (301)
6	limit 5 to dt="20191201-20220101" (276)
7	6 not ((exp animals/ or exp models, animal/) not humans/) not (letter/ or comment/ or editorial/) (213)

Embase

No.	Query	Results
#4	#3 NOT ('conference abstract'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it) NOT (('animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	**296**
#3	#1 AND #2	**427**
#2	'angiotensin receptor antagonist'/exp OR 'angiotensin ii receptor antagonist*':ti,ab,kw OR 'angiotensin ii receptor blocker*':ti,ab,kw OR 'angiotensin ii receptor blocking agent*':ti,ab,kw OR 'angiotensin receptor antagonist*':ti,ab,kw OR 'angiotensin receptor blocker*':ti,ab,kw OR 'angiotensin receptor blocking agent*':ti,ab,kw OR arb:ti,ab,kw OR 'nonsteroid antiinflammatory agent'/exp OR nsaid*:ti,ab,kw OR 'thiazolidine derivative'/exp OR 'thiazol*':ti,ab,kw OR 'dipeptidyl carboxypeptidase inhibitor'/exp OR 'ace inhibitor*':ti,ab,kw OR 'angiotensin converting enzyme inhibiting agent*':ti,ab,kw OR 'angiotensin converting enzyme inhibitor*':ti,ab,kw OR 'angiotensin i converting enzyme	**965640**

No.	Query	Results
	inhibitor*':ti,ab,kw OR 'dipeptidyl carboxypeptidase i inhibitor*':ti,ab,kw OR 'dipeptidyl carboxypeptidase inhibitor*':ti,ab,kw OR 'kininase ii inhibitor*':ti,ab,kw OR 'peptidyl dipeptidase inhibitor*':ti,ab,kw OR 'peptidyldipeptide hydrolase inhibitor*':ti,ab,kw OR acei:ti,ab,kw	
#1	('coronavirus disease 2019'/exp OR (('coronavirinae'/exp OR 'coronavirus infection'/de OR coronavirus*:ti,ab,kw OR 'corona virus*':ti,ab,kw OR 'pneumonia virus*':ti,ab,kw OR cov:ti,ab,kw OR ncov:ti,ab,kw) AND (outbreak:ti,ab,kw OR wuhan:ti,ab,kw)) OR covid19:ti,ab,kw OR 'covid 19':ti,ab,kw OR ((coronavirus*:ti,ab,kw OR 'corona virus*':ti,ab,kw) AND 2019:ti,ab,kw) OR 'sars cov 2':ti,ab,kw OR sars2:ti,ab,kw OR 'coronavirus*':ti,ab,kw OR 'corona virus*':ti,ab,kw OR 'ncov 2019':ti,ab,kw OR ncov:ti,ab,kw OR 'sars coronavirus 2':ti,ab,kw OR 'sars corona virus 2':ti,ab,kw OR 'severe acute respiratory syndrome cov 2':ti,ab,kw OR 'severe acute respiratory syndrome cov2':ti,ab,kw) AND [2019-2020]/py	**21099**

Module 4 Effect van anticoagulantie therapie op uitkomst bij COVID-19 patiënten

Clinical question

Should patients with COVID-19 be treated with prophylactic or therapeutic dose anticoagulation to prevent cardiovascular and thrombo-embolic complications and improve clinical outcome?

Introduction

Recently, in hospitalized COVID19 patients an increased incidence of thromboembolic events, pulmonary embolism, deep vein thrombosis and stroke has been reported. In some observational studies, the use of heparin was associated with lower mortality. Results of studies investigating whether systemic anticoagulation given to patients during mechanical ventilation results in better outcomes have however shown varying results. It is not known whether therapeutic anticoagulation in all hospitalized COVID19 patients improves outcome.

Search and select

A review of the literature was performed to answer the following question:

What is the effect of (prophylactic and therapeutic dose) anticoagulation therapy in COVID-19 patients on cardiovascular and thrombo-embolic complications and clinical outcome?

P: All proven COVID19 patients (subgroups: home, hospital, IC)
I: Use of vitamin K-antagonists, low-molecular weight heparin, unfractionated heparin, direct oral anticoagulants
C: No use of vitamin K-antagonists, low-molecular weight heparin, unfractionated heparin, direct oral anticoagulants
O: Mortality, IC-admission, length of stay, thromboembolic complications (pulmonary embolism, stroke, transient ischemic attack), ventilation, acute kidney injury, use of renal replacement therapy

Relevant outcome measures

Mortality (crucial), IC-admission, length of stay, thromboembolic complications (pulmonary embolism, stroke, transient ischemic attack), ventilation, acute kidney injury, use of renal replacement therapy.

Search and select (Methods)

The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms until 17 July 2020. The systematic literature search resulted in 567 hits. See search strategy for detail. Thirty-two studies were initially selected based on title and abstract screening. After reading the full text, 24 studies were excluded (see the table with reasons for exclusion under the tab Methods), and eight studies were included.

Summary of literature

Description of studies

The studies were grouped into 3 groups.

Group A: Anticoagulant drug use before hospital admission

Group A described studies in which COVID-19 patients using a therapeutic dose of anticoagulants before hospital admission were compared to patients not using anticoagulants or using a prophylactic dose (Group A: Anticoagulant use before hospital admission).

Group B: Prophylactic anticoagulant drug use start at hospital admission

Group B described studies in which COVID-19 patients received a prophylactic dose of anticoagulants at hospital admission were compared to patients not using anticoagulants.

Group C: Mixed or unclear start of anticoagulant therapy
Group C described studies in which COVID-19 patients using a therapeutic dose of anticoagulants were compared to patients not using anticoagulants or using a prophylactic dose. The patients that used therapeutic dose of anticoagulants was a mixed group of patients that already used anticoagulants before hospital admission or received it during hospital admission. In some studies the start moment of anticoagulant use was unclear and was therefore also included in group C.

Group A. Anticoagulant drug use before hospital admission
Klok (2020) performed an updated analysis of the incidence of the composite outcome of symptomatic acute pulmonary embolism (PE), deep-vein thrombosis, ischemic stroke, myocardial infarction and/or systemic arterial embolism in all COVID-19 patients admitted to the ICUs of two Dutch university hospitals and one Dutch teaching hospital from ICU admission to death, ICU discharge or April 22nd 2020. 184 ICU patients were included in the report. The median follow-up duration ranged from 7 to 14 days. All patients received pharmacological thromboprophylaxis and some full dose anticoagulation. This study is published as a research paper update.

Tremblay (2020) performed a retrospective analysis of patients with confirmed COVID-19, comparing outcomes among those who were and were not receiving anticoagulants for unrelated indications at the time of COVID-19 diagnosis. To adjust for bias due to non-random allocation of potential covariates among COVID-19 patients, propensity score-matching was performed. Propensity scores were calculated using a logistic regression model, adjusting for age, sex, race, Charlson Comorbidity Index and obesity. A total of 3772 patients were included of which 241 patients received AC, 672 received antiplatelet therapy, and 2859 patients not receiving AC or antiplatelet therapy at the time of COVID-19 diagnosis. This study is published as a letter to the editor.

Russo (2020) aimed to evaluate the prevalence of antithrombotic therapies at admission in patients with COVID-19 and the potential association between antithrombotic therapy and acute respiratory distress Syndrome (ARDS), as disease clinical presentation, or in-hospital mortality. 192 Consecutive patients with laboratory-confirmed COVID-19 admitted to emergency department of five Italian hospitals were included in the study. The study population was divided in two groups according to the evidence of ARDS at chest computed tomography at admission. Propensity score weighting adjusted regression analysis was performed to assess the risk ARDS at admission, and death during hospitalization, in patients treated or not with antiplatelet and anticoagulant agents.

Sivaloganathan (2020) studied the association between pre-admission antiplatelet/anticoagulant use and COVID-19 mortality. The study population comprised those patients with confirmed COVID-19 patients admitted as an inpatient in Brighton and Sussex University Hospitals NHS Trust between the 7 March and 9 April 2020. The case-control group was constructed at a ratio of 1:2 cases to controls matching for age and sex, selecting from this overall population. A case was defined as being on an anticoagulant or antiplatelet agent before admission. Controls were then selected from the study population with a limited propensity matching by age and sex to two controls who were not taking the medication of interest using a 'nearest neighbour' method. Thirty one cases and 62 controls were included. Data on patients' drug history were obtained using the Patient Administration System, which was also used to identify patient deaths up to 11 May 2020. This study is published as a correspondence.

Rossi (2020) aimed to assess if pharmacological cardio-active treatment reduced mortality risk in the setting of COVID-19 interstitial pneumonia. Rossi retrospectively enrolled 70 elderly patients affected by COVID-19 interstitial pneumonia between February 25, 2020, and April 20, 2020. All patients were affected by chronic heart disease (CHD) and they were followed in the divisional outpatient clinic of the Cardiology

Unit of the Policlinico of Modena Hospital. The follow-up ended on May 5, 2020. A total of 26/70 patients (37.1%) were treated with direct oral anticoagulants (DOAC) which underlying indication was pulmonary embolism (n = 7; 26.9%), deep vein thrombosis (n = 6; 23%) or atrial fibrillation (n = 13; 50%). The endpoint of the study was all-cause mortality. A multivariate analysis was performed to assess the relation between age, gender, direct anticoagulant intake and mortality. This study is published as a letter to the editor.

Group B: Prophylactic anticoagulant drug use start at hospital admission
Tang (2020) aimed to validate the usefulness of SIC score and other coagulation parameters, in screening out patients who can benefit from anticoagulant through retrospective analysis. Consecutive patients with severe COVID-19 admitted to Tongji Hospital of Huazhong University of Science and Technology in Wuhan from January 1 to February 13, 2020, were retrospectively enrolled. Exclusion criteria were a bleeding diathesis, hospital stay < 7 days, lack of information about coagulation parameters and medications, and age < 18 years. A retrospective review of the characteristics of these patients was performed through the electronic medical record system of the hospital, the medications and outcomes (28-day mortality) were monitored up to March 13, 2020. A total of 449 patients (181 females and 268 males) classified as severe COVID-19 were enrolled into the study. Two hundred and seventy-two (60.6%) patients had one or more chronic underlying diseases, mainly including hypertension (n = 177, 39.4%), diabetes (n = 93, 20.7%), and heart diseases (n = 41, 9.1%). Ninety-nine (22.0%) patients received heparin treatment for at least 7 days. A multivariate analysis was performed to assess the relation between anticoagulant intake and mortality.

Group C: Mixed or unclear start of anticoagulant therapy
Paranjpe (2020) assessed the association between administration of in-hospital anticoagulation (AC) and survival in a large cohort of hospitalized patients with COVID-19 and described this in a 'Letter'. Between March 14 and April 11, 2020, 2,773 patients were hospitalized with laboratory-confirmed COVID-19 within the Mount Sinai Health System in New York City. The authors used a Cox proportional hazards model to evaluate the effect of treatment-dose systemic AC (including oral, subcutaneous, or intravenous forms) on in-hospital mortality. The start moment of the AC is not described in the paper. The authors adjusted for age, sex, ethnicity, body mass index, history of hypertension, heart failure, atrial fibrillation, type 2 diabetes, AC use prior to hospitalization, and admission date. To adjust for differential length of stay and initiation of AC treatment, AC treatment duration was used as a covariate while intubation was treated as a time dependent variable. Among 2,773 hospitalized patients with COVID-19, 786 (28%) received systemic treatment-dose AC during their hospital course. This study is published as a letter.

Ljitos (2020) performed a systematic assessment of venous thromboembolism (VTE) using complete duplex ultrasound (CDU) in anticoagulated COVID-19 patients and described this in a 'brief report'. The authors performed a retrospective study in 2 French intensive care units (ICU) where CDU is performed as a standard of care. From March 19 to April 11, 2020, 26 consecutive patients with severe COVID-19 were screened for VTE. Seven patients used anticoagulants before hospital admission, eleven started anticoagulant use at hospital admission. Eight patients (31%) were treated with prophylactic anticoagulation, whereas 18 patients (69%) were treated with therapeutic anticoagulation. The overall rate of VTE in patients was 69%. All patients underwent mechanical ventilation, with prone positioning in 16 patients (62%). This study is published as a brief report.

The characteristics of the included studies were summarized in table 4.1.

Table 4.1 Overview of identified studies

Group	Author, year	Comparison	Start anticoagulants	Setting	Country	Study Design	Outcomes	Publication type
A. Anticoagulant drug use before hospital admission	Tremblay, 2020	Anticoagulant use at moment of infection (treatment dose) vs patients not using anticoagulants at moment of infection	Pre-admission	Hospitalized and ambulatory COVID-19 patients	US	retrospective observational	Mortality, hospital admission, mechanical ventilation Propensity matched analysis	To the editor
A. Anticoagulant drug use before hospital admission	Klok, 2020	Use of long-term therapeutic anticoagulation vs prophylactic dose	Pre-admission	Patients with proven COVID-19 pneumonia admitted to the ICU	Netherlands	Observational	Mortality (HR), a composite outcome (symptomatic acute pulmonary embolism (PE), deep-vein thrombosis, ischemic stroke, myocardial infarction and/or systemic arterial embolism) (corrected for competing risk of death)	Research paper update
A. Anticoagulant drug use before hospital admission	Russo, 2020	Pre-admission anticoagulant users vs non-users	Pre-admission	Emergency department	Italy	retrospective observational	Mortality Propensity score model	Research paper
A. Anticoagulant drug use before hospital admission	Sivaloganathan, 2020	pre-admission antiplatelet/anticoagulant use vs non users	Pre-admission	Hospitalized COVID-19 patients	UK	retrospective case control	Mortality (log rank, no correction for confounders) IC admission	Correspondence
A. Anticoagulant drug use before hospital admission	Rossi, 2020	Chronic anticoagulant users vs non-users	Pre-admission	Elderly COVID-19 patients with coronary heart disease followed in the outpatient clinic	Italy	retrospective observational	Mortality (corrected for age and gender)	Letter to the editor
B. Prophylactic anticoagulant drug use start at hospital admission	Tang, 2020	Prophylactic heparin vs non-users	Hospital admission	Hospitalized severe COVID-19 patients	China	retrospective observational	28-day mortality (adjusted for age, sex, underlying disease, platelet count, D-dimer)	Research paper
C. Mixed or unclear start of anticoagulant	Paranjpe, 2020	Treatment dose vs (prophylactic dose or non-users)	Unclear	Hospitalized COVID-19 patients	US	retrospective observational	Invasive mechanical ventilation (no correction for confounders),	Letter

							mortality ((no correction for confounders)	
C. Mixed or unclear start of anticoagulant	Llitjos, 2020	Patients using a therapeutic dose of anticoagulant vs patients using a prophylactic dose of anticoagulant	7 patients pre-admission, 11 patients at admission	COVID-19 patients admitted to the ICU	France	retrospective observational	Mortality, pulmonary embolism, acute kidney injury, (comparison between 2 groups, no correction for confounders), renal replacement therapy, VTE (including non-symptomatic VTE)	Brief report

Results

1. Mortality

Group A: Anticoagulant drug use before hospital admission

Klok (2020) studied 184 patients admitted to the ICU and compared patients on long-term therapeutic anti-coagulation with patients that received pharmacological thromboprophylaxis. The use of long-term therapeutic anticoagulation was not associated with all-cause death (HR 0.79, 95%CI 0.35–1.8).

Tremblay (2020) performed two types of analysis for mortality, a time-to-event analysis and event analysis. Overall, 15.0% of the patients died. Of the patients using anticoagulation 81 (33.6%) died, of the non-users 317 (11.1%) died. The time-to-event analysis (Kaplan-Meier) showed that there was no statistically significant difference in survival (P =0.367). The event analysis also showed no difference in mortality between the two groups HR 1.208; 95% CI 0.750-1.946.

Russo (2020) studied 192 COVID-19 patients. Thirty-five patients (18.5 %) died during the hospitalization. Russo found no statistically significant difference(P=0.678) between hospitalized COVID-19 patients on anticoagulant therapy with regard to survival (n=20, 12.7%) or non-survival (N=6, 17.1%). In a propensity score regression model the unadjusted RR for the risk of death was RR 1.42; 95%CI 0.53 – 2.47; P=0.493. In the adjusted model (adjusted for age, smoke, chronic obstructive pulmonary disease, hypertension, diabetes, coronary artery disease, heart failure, obesity, dyslipidemia) the RR for the risk of death was 1.15; 95%-CI 0.29 – 2.57; P=0.995. Antithrombotic therapy before admission did not influence the clinical presentation COVID-19 in terms in-hospital mortality.

Sivaloganathan (2020) found that using an anticoagulant agent before admission did not have a statistically significant effect on mortality in 31 patients with COVID-19 (P = 0.614) using the log-rank test, suggesting no protective effect. No correction for confounders was applied. However, the evident confounder in this analysis is the comorbidity of cardiovascular disease, itself an established risk factor for increased mortality in COVID-19, and thrombotic disorders.

Rossi (2020) studied 70 elderly patients affected by COVID-19 interstitial pneumonia. All patients were affected by chronic heart disease (CHD). In a multivariate analysis (adjusted for age and male gender) Rossi found an adjusted HR of 0.38; 95%CI 0.17 – 0.58; P=0.01 indicating that Chronic DOAC intake is an independent parameter associated with a decreased mortality risk for this patient group.

Group B: Prophylactic anticoagulant drug use start at hospital admission

Tang (2020) found no statistically significant difference on the 28-day mortality between prophylactic heparin users (n=30, 30.3%) and non-users (n=104, 29.7%) (P = 0.910) with severe COVID-19. The heparin treatment was associated with lower mortality in COVID-19 patients with Sepsis-Induced Coagulopathy (SIC) score ≥ 4 (40.0% vs 64.2%, P = .029), but not in those with SIC score < 4 (29.0% vs 22.6%, P = .419). In a multivariate analysis (adjusted for age, sex ratio, underlying disease, prothrombin time, platelet count, D-dimer) the adjusted OR for mortality was 1.647 (95%CI 0.929-2.921) P=0.088.

Group C: Mixed or unclear start of anticoagulant therapy

Paranjpe (2020) studied 2773 hospitalized COVID-19 patients of which 786 received anticoagulants (AC). In-hospital mortality for patients treated with AC was 22.5% (median survival 21 days). Of the patients that received a prophylactic dose of AC or no AC 22.8% died (median survival 14 days). In a multivariate proportional hazards model (adjusted for age, sex, ethnicity, body mass index, history of hypertension, heart failure, atrial fibrillation, type 2 diabetes, AC use prior to hospitalization, and admission date) , longer duration of AC treatment was associated with a reduced risk of mortality (adjusted HR of 0.86 per day; 95% confidence interval: 0.82 to 0.89; p < 0.001).

Llitjos (2020) studied 26 patients admitted to the ICU and compared patients on a treatment dose AC with patients that received a prohylactic dose AC or no AC. Three patients died of which 2 received treatment

dose AC (11%) and one received prophylactic dose AC or no AC (12%). The authors did not report if this was a statistically significant difference.

2. IC admission
Group A: Anticoagulant drug use before hospital admission
Sivaloganathan (2020) studied the relation between therapeutic anticoagulant use before hospital admission and IC admission. Of the patients using therapeutic anticoagulant drugs 5 (16.7%) required ICU admission, of the control group, 7 (11.3%). The chi-square test showed this was not a statistically significant difference (P=0.472). Correction for confounders was not applied.

Group B: Prophylactic anticoagulant drug use start at hospital admission
Not reported

Group C: Mixed or unclear start of anticoagulant therapy
Not reported

3. Length of stay
Group A-C: not reported

4. Thromboembolic complications
Group A: Anticoagulant drug use before hospital admission
Klok (2020) developed a composite outcome of symptomatic acute pulmonary embolism (PE), deep-vein thrombosis, ischemic stroke, myocardial infarction and/or systemic arterial embolism. The majority of thrombotic events were pulmonary embolism (65/75; 87%). The crude cumulative incidence of the composite outcome was 57% (95%CI 47–67%), and after adjustment for competing risk of death 49% (95%CI 41–57%). The incidence rate was 13/patient-year (95%CI 6.1–27).
In a competing risk model, chronic anticoagulation therapy at admission was associated with a lower risk of the composite outcome (HR 0.29; 95% CI 0.091–0.92).

Group B: Prophylactic anticoagulant drug use start at hospital admission
Not reported

Group C: Mixed or unclear start of anticoagulant therapy
Llitjos (2020) found that the overall rate of VTE was 69% of the 26 patients admitted to the ICU they studied. Pulmonary embolism was diagnosed in six patients (23%).The proportion of venous thromboembolic events was significantly higher in patients treated with prophylactic anticoagulation when compared with the therapeutic anticoagulation group (100% vs 56%, respectively; P=0.03). However, a high rate of thromboembolic events was found in COVID-19 patients treated with therapeutic anticoagulation, with 56% of venous thromboembolic events and six pulmonary embolisms.

5. Ventilation
Group A: Anticoagulant drug use before hospital admission
Tremblay (2020) performed two types of analysis for ventilation, a time-to-event analysis and event analysis. Overall, 13.8% required mechanical ventilation. The time-to-event analysis (Kaplan-Meier) showed that there was no statistically significant difference in ventilation (P=0.742). The event analysis also showed no difference in ventilation between the two groups HR 0.905; 95% CI, 0.571-1.435.

Group B: Prophylactic anticoagulant drug use start at hospital admission
Not reported

Group C: Mixed or unclear start of anticoagulant therapy
Paranjpe (2020) found that patients who received treatment-dose AC were more likely to require invasive mechanical ventilation (29.8% vs 8.1%; p < 0.001) as compared to those who received prophylactic dose AC or did not receive AC.
Llitjos (2020) reported that all included patients in both groups needed mechanical ventilation. However, all patients included in this study were admitted to the ICU.

6. Acute kidney injury therapy
Group A-B:
Not reported

Group C: Mixed or unclear start of anticoagulant therapy
Llitjos (2020) found that of the eight patients using prophylactic anticoagulation, 2 (25%) developed acute kidney injury. Of the 18 patients using therapeutic anticoagulation, 7 (39%) developed acute kidney injury. The authors did not report if this was a statistically significant difference.

7. Renal replacement therapy
Group A: Anticoagulant drug use before hospital admission
Tremblay (2020) found that of the patients that underwent renal replacement therapy 7 (2.9%) were on anticoagulant drugs versus 91 (3.2%) of the patients not on anticoagulant drugs or antiplatelets (P=0.051).

Group B: Prophylactic anticoagulant drug use start at hospital admission:
Not reported

Group C: Mixed or unclear start of anticoagulant therapy
Llitjos (2020) found that of the patients that received a therapeutic dose of anticoagulation, 4 (22 %) underwent renal replacement therapy. Of the patients on a prophylactic dose of anticoagulation 0 (0%) underwent renal replacement therapy. The authors did not report if this was a statistically significant difference.

Level of evidence of the literature
The level of evidence was assessed according to the GRADE methodology (GRADE: Grading Recommendations Assessment, Development and Evaluation, http://www.gradeworkinggroup.org/).

1. Mortality
Group A: Anticoagulant drug use before hospital admission
Starting with a high of evidence for observational studies (prognostic question), the level of evidence regarding the outcome mortality was downgraded by 2 levels because of risk of bias (not all studies correct for confounders, one study very specific patient group, studies described in correspondence or letter to the editor so very few information on methodology, patient characteristics and outcomes) to ‘low’.

Group B: Prophylactic anticoagulant drug use start at hospital admission
Starting with a high of evidence for observational studies (prognostic question), the level of evidence regarding the outcome mortality was downgraded by 1 level because of risk of bias (patient characteristics of the two groups not described) and 2 levels because of imprecision (only one study available, small number of patients and very low number of events) to ‘very low’.

Group C: Mixed or unclear start of anticoagulant therapy
Starting with a high of evidence for observational studies (prognostic question), the level of evidence regarding the outcome mortality was downgraded by 2 levels because of risk of bias (patient groups not well described, follow up not complete, one study described in letter so very few information on patients,

methods and results available), and 1 level because of imprecision (small number of patients and low number of events) to ‘very low’.

2. IC admission

Group A: Anticoagulant drug use before hospital admission

Starting with a high of evidence for observational studies (prognostic question), the level of evidence regarding the outcome IC admission was downgraded by 2 levels because of risk of bias (no information on patient characteristics, no correction for important confounders) and 1 level because of imprecision (small study population) to ‘very low’.

3. Length of stay

Not reported

4. *Thromboembolic complications*

Group A: Anticoagulant drug use before hospital admission

Starting with a high of evidence for observational studies (prognostic question), the level of evidence regarding the outcome measure thromboembolic complications was downgraded by 1 level because of risk of bias (absolute number of thromboembolic complication events unknown) and 1 level because of imprecision (low number of events) to ‘low’.

Group C: Mixed or unclear start of anticoagulant therapy

Starting with a high of evidence for observational studies (prognostic question), the level of evidence regarding the outcome measure thromboembolic complications was downgraded by 1 level because of risk of bias (no correction for confounders), 1 level for indirectness (the study only included severe Covid-19 patients admitted to the ICU) and 1 level for imprecision (very small sample size) to ‘very low’.

5. Ventilation

Group A: Anticoagulant drug use before hospital admission

Starting with a high of evidence for observational studies (prognostic question), the level of evidence regarding the outcome ventilation was downgraded by 1 level because of risk of bias (no correction for confounders) and 1 level for imprecision (very few events) to ‘low’.

Group C: Mixed or unclear start of anticoagulant therapy

Starting with a high of evidence for observational studies (prognostic question), the level of evidence regarding the outcome ventilation was downgraded by 1 level because of risk of bias (no correction for confounders), 1 level because of imprecision (both studies report different results), and 1 level because of indirectness (specific patient group in 1 study) to ‘very low’.

6. Acute kidney injury

Group C: Mixed or unclear start of anticoagulant therapy

Starting with a high of evidence for observational studies (prognostic question), the level of evidence regarding the outcome acute kidney injury was downgraded by 1 level because of risk of bias (no correction for confounders) and 2 levels because of imprecision (very small sample size of only 1 study) to ‘very low’.

7. Renal replacement therapy

Group A: Anticoagulant drug use before hospital admission

Starting with a high of evidence for observational studies (prognostic question), the level of evidence regarding the outcome acute kidney injury was downgraded by 1 level because of risk of bias (no correction for confounders) and 2 levels because of imprecision (only one study available, low number of events) to ‘very low’.

Group C: Mixed or unclear start of anticoagulant therapy
Starting with a high of evidence for observational studies (prognostic question), the level of evidence regarding the outcome acute kidney injury was downgraded by 1 level because of risk of bias (no correction for confounders) and 2 levels because of imprecision (very small sample size of only 1 study) to 'very low'.

Conclusions

1. Mortality

Group A: Anticoagulant drug use before hospital admission

Low **GRADE**	The evidence suggests that anticoagulation therapy does not affect mortality. *Sources: Klok (2020), Tremblay (2020), Russo (2020), Sivaloganathan (2020), Rossi (2020)*

Group B: Anticoagulant drug use start at hospital admission

Very Low **GRADE**	Prophylactic anticoagulation therapy may have little to no effect on mortality but the evidence is very uncertain. *Sources: Tang (2020)*

Group C: Mixed or unclear start of anticoagulant therapy

Very Low **GRADE**	Anticoagulation therapy may have little to no effect on mortality but the evidence is very uncertain. *Sources: Llitjos (2020), Paranjpe (2020)*

2. IC admission

Very low **GRADE**	Anticoagulation therapy (before hospital admission) may have little to no effect on IC-admission but the evidence is very uncertain. *Sources: Sivaloganathan (2020)*

3. Length of stay

Not reported

4. Thromboembolic complications

Group A: Anticoagulant drug use before hospital admission

Low **GRADE**	Anticoagulant drug use may result in a slight reduction in thromboembolic complications *Sources: Klok (2020)*

Group C: Mixed or unclear start of anticoagulant therapy

Very low **GRADE**	Anticoagulation therapy may reduce thromboembolic complications but the evidence is very uncertain *Sources: Llitjos (2020)*

5. Ventilation

Group A: Anticoagulant drug use before hospital admission

Very low **GRADE**	Anticoagulation therapy may have little to no effect on ventilation but the evidence is very uncertain *Sources: Tremblay (2020)*

Group C: Mixed or unclear start of anticoagulant therapy

Very low **GRADE**	The evidence is very uncertain about the effect of anticoagulation therapy on ventilation *Sources:* Paranjpe (2020), *Llitjos (2020)*

6. Acute kidney injury

Group C: Mixed or unclear start of anticoagulant therapy

Very low **GRADE**	The evidence is very uncertain about the effect of anticoagulation therapy on acute kidney injury *Sources: Llitjos (2020)*

7. Renal replacement therapy

Group A: Anticoagulant drug use before hospital admission

Very low **GRADE**	The evidence is very uncertain about the effect of anticoagulation therapy on renal replacement therapy *Sources: Tremblay (2020)*

Group C: Mixed or unclear start of anticoagulant therapy

Very low **GRADE**	The evidence is very uncertain about the effect of anticoagulation therapy on renal replacement therapy *Sources: Llitjos (2020)*

Overwegingen

Voor- en nadelen van de interventie en de kwaliteit van het bewijs

De kwaliteit van het bewijs van de geïncludeerde studies is overwegend laag tot zeer laag. De GRADE systematiek is gevolgd om de kwaliteit van het bewijs te beoordelen. Deze is hier dan ook gevolgd. In een nieuwe situatie (zoals COVID) is het logisch dat de meeste studies nog niet kunnen voldoen aan de strenge eisen die aan studies van hoge kwaliteit worden gesteld. De GRADE methodiek zet de kwaliteit van het bewijs echter af tegen de best mogelijke kwaliteit en niet tegen de best mogelijke kwaliteit in de huidige situatie. De GRADE systematiek geeft het vertrouwen weer in de schatting van het effect van een interventie. Wanneer de modules en de search worden geüpdate zijn er hopelijk studies van betere kwaliteit beschikbaar en kan het niveau van de kwaliteit van het bewijs hierop worden aangepast.
Hoewel er sterke aanwijzingen zijn dat een COVID19 infectie geassocieerd is met het verhoogd optreden van trombo-embolische complicaties, is er nog onvoldoende bewijs dat therapeutische antistolling de uitkomsten van COVID19 patiënten kan verbeteren. De bewijskracht van de geëvalueerde studies varieert van ‘laag’ tot ‘zeer laag’, met name gebaseerd op de beperkte studie grootte en matige wetenschappelijke kwaliteit van de studies. Geen van de studies laat een positief resultaat zien op mortaliteit, op één zeer kleine Italiaanse studie na, die 26 patiënten op een DOAC vergeleek met 44 patiënten zonder antistolling. De kwaliteit van het bewijs op andere uitkomsten, zoals IC opname, opname duur, trombo-embolische complicaties, beademingsbehoefte, nierfalen en dialyse behoefte wordt ook gewaardeerd als ‘zeer laag’.

Er zijn geen publicaties die een overtuigend positief effect van therapeutische antistolling in COVID19 laten zien, afgezien van 2 studies die een associatie laten zien tussen antistolling en het minder vaak optreden van longembolie.

CAPACITY
CAPACITY is een internationale registratie van patiënten met COVID-19 op basis van het ISARIC WHO CRF, aangevuld met informatie over specifieke cardiovasculaire parameters (https://capacity-covid.eu/). CAPACITY is in het voorjaar van 2020 gestart en bevat gegevens van 13034 patiënten uit 13 landen, afkomstig van 79 registrerende centra. CAPACITY bevat omvangrijke informatie over patiënten met COVID, omdat ongeveer 40% van de in Nederland opgenomen COVID19 patiënten in de registratie is opgenomen (n = 5524).
De peer-reviewed publicatie van CAPACITY over het onderwerp van deze module is momenteel in voorbereiding. De resultaten van CAPACITY kunnen daarom kunnen nog niet worden meegenomen bij het literatuuronderzoek, maar bij de overwegingen worden wel de voorlopige resultaten van CAPACITY meegenomen. De peer-reviewed publicatie over het onderwerp van deze module wordt binnenkort verwacht en bij een update van de module zal de publicatie in het literatuuronderzoek worden meegenomen.

Binnen de nog ongepubliceerde CAPACITY registratie zijn 694 patiënten met een indicatie voor therapeutische antistolling op grond van pre-existente aandoeningen, vergeleken met 4227 patiënten zonder antistollingsindicatie. Ook in deze analyse is er na correctie voor een verschil in baseline variabelen geen verschil in mortaliteit aantoonbaar. Wel is het gebruik van therapeutische antistolling voor opname geassocieerd met een 76% verminderd voorkomen van longembolieën.

Waarden en voorkeuren van patiënten (en evt. hun verzorgers)
Patiënten die een behandeling met medicijnen voor antistolling krijgen vinden complete en eenduidige informatievoorziening belangrijk, o.a. over de indicatie en de veiligheid en risico's van de behandeling (onderwerpen die van belang zijn in de communicatie met patiënten zijn terug te vinden zijn in de Landelijke Transmurale Afspraak antistollingszorg (https://lta-antistollingszorg.nl/communicatie-met-patienten). Daarom zijn de volgende aanbevelingen van belang:

- Patiënten met COVID-19 die met antistolling behandeld worden vanwege reeds aanwezige aandoeningen dienen deze door te gebruiken.
- Hoewel er duidelijk meer longembolieën voorkomen bij patiënten met COVID-19, is er tot op heden geen bewijs voor het voorschrijven en gebruiken van therapeutische dosis antistolling ter verbetering van de uitkomsten in deze patiëntengroep.

Kosten (middelenbeslag)
De huidige literatuurstudie geeft geen aanleiding tot verandering in het gangbare beleid. Er zijn daarom geen extra kosten of opbrengsten gemoeid met de huidige aanbevelingen
Aanvaardbaarheid, haalbaarheid en implementatie
De huidige literatuurstudie geeft geen aanleiding tot verandering in het gangbare beleid. Er zijn daarom geen problemen mbt aanvaardbaarheid, haalbaarheid en implementatie.

Aanbevelingen
Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies
Op grond van de huidige literatuur en de recente analyse van de CAPACITY data is er geen reden om de aanbevelingen aan te passen, zoals genoemd in de Leidraad COVID-19 Coagulopathie (https://www.demedischspecialist.nl/sites/default/files/Leidraad%20COVID-19%20coagulopathie.pdf). De auteurs van de richtlijn zijn bewust van berichten in de pers en op social media waarin er uitspraken worden gedaan over de uitkomst van enkele gerandomiseerde studies die verschillende doses antistolling hebben getest in opgenomen COVID-19 patiënten. Het standpunt van de auteurs is echter dat geen rekening gehouden kan worden met deze studieresultaten zolang er geen goed zicht is op belangrijke

details als karakteristieken van de bestudeerde patiënten, de gebruikte statistische analyses en het voorkomen van eindpunten, bijvoorbeeld in de vorm van een peer-reviewed publicatie of het vrijgeven van de database. Bij het finaliseren van deze module waren deze details niet beschikbaar.
In afwachting hiervan blijven de aanbevelingen daarom vooralsnog:

- Geef tromboseprofylaxe aan alle patiënten opgenomen met een COVID-19 infectie, ongeacht de Padua score (Barber 2010).
- Er is op dit moment nog geen goed advies te geven over de hoogte van de dosering; zowel de lage als de hoge dosis tromboseprofylaxe kan worden voorgeschreven aan op de gewone afdeling opgenomen patiënten.
- Geef aan COVID-19 patiënten op de ICU een verdubbeling van de standaard tromboseprofylaxe
- Geef (in de afwezigheid van pre-existente indicaties) geen therapeutische antistolling als er geen trombotische complicaties zijn vastgesteld.
- Zodra er overtuigend bewijs is voor een aanpassing van bovenstaand beleid, dan zal dit verwerkt worden in de multidisciplinaire richtlijn antitrombotisch beleid (https://richtlijnendatabase.nl/richtlijn/antitrombotisch_beleid/antitrombotisch_beleid_-_korte_beschrijving.html).

Kennislacunes

Gezien het feit dat gerandomiseerde studies ontbreken en de overige studies een lage bewijskracht hebben kan de oorspronkelijke onderzoeksvraag niet beantwoord worden. De vraag blijft dan ook: “Hebben COVID-19 patiënten baat bij het gebruik van profylactische en therapeutische dosis antistolling ter voorkoming van trombo-embolische complicaties en verbetering van de mortaliteit?”

Literatuur

Barbar S, Noventa F, Rossetto V, Ferrari A, Brandolin B, Perlati M, *et al.*A risk assessment model for the identification of hospitalized medical patients at risk for venous thromboembolism: the Padua Prediction Score. J Thromb Haemost, 8 (2010), pp. 2450-2457

Klok, F. A., Kruip, M. J. H. A., Van Der Meer, N. J. M., Arbous, M. S., Gommers, D. A. M. P. J., Kant, K. M., ... & Endeman, H. (2020). Confirmation of the high cumulative incidence of thrombotic complications in critically ill ICU patients with COVID-19: an updated analysis. Thrombosis research.

Llitjos, J. F., Leclerc, M., Chochois, C., Monsallier, J. M., Ramakers, M., Auvray, M., & Merouani, K. (2020). High incidence of venous thromboembolic events in anticoagulated severe COVID-19 patients. Journal of Thrombosis and Haemostasis.

Paranjpe, I., Fuster, V., Lala, A., Russak, A. J., Glicksberg, B. S., Levin, M. A., ... & Zhao, S. (2020). Association of treatment dose anticoagulation with in-hospital survival among hospitalized patients with COVID-19. Journal of the American College of Cardiology, 76(1), 122-124.

Rossi, R., Coppi, F., Talarico, M., & Boriani, G. (2020). PROTECTIVE ROLE OF CHRONIC TREATMENT WITH DIRECT ORAL ANTICOAGULANTS IN ELDERLY PATIENTS AFFECTED BY INTERSTITIAL PNEUMONIA IN COVID-19 ERA. European Journal of Internal Medicine.

Russo, V., Di Maio, M., Attena, E., Silverio, A., Scudiero, F., Celentani, D., ... & Di Micco, P. (2020). Clinical impact of pre-admission antithrombotic therapy in hospitalized patients with COVID-19: a multicenter observational study. Pharmacological Research, 104965.

Sivaloganathan, H., Ladikou, E. E., & Chevassut, T. (2020). COVID-19 mortality in patients on anticoagulants and antiplatelet agents. British Journal of Haematology, 190(4), e192-e195.

Tang, N., Bai, H., Chen, X., Gong, J., Li, D., & Sun, Z. (2020). Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. Journal of thrombosis and haemostasis, 18(5), 1094-1099.

Tremblay, D., van Gerwen, M., Alsen, M., Thibaud, S., Kessler, A., Venugopal, S., ... & Bhalla, S. (2020). Impact of anticoagulation prior to COVID-19 infection: a propensity score–matched cohort study. Blood, The Journal of the American Society of Hematology, 136(1), 144-147.

Bijlagen bij module 4

Evidence tables

Evidence table for intervention studies (randomized controlled trials and non-randomized *observational* studies [cohort studies, case-control studies, case series])[1]

This table is also suitable for diagnostic studies (screening studies) that compare the effectiveness of two or more tests. This only applies if the test is included as part of a test-and-treat strategy – otherwise the evidence table for studies of diagnostic test accuracy should be used.

Study reference	Study characteristics	Patient characteristics [2]	Intervention (I)	Comparison / control (C) [3]	Follow-up	Outcome measures and effect size [4]	Comments
Paranjpe, 2020	Type of study: retrospective observational Setting and country: hospitalized patients with COVID-19, US Funding and conflicts of interest: study supported by U54 TR001433-05, National Center for Advancing Translational Sciences, National Institutes of Health. Some of the authors received funding from (pharmaceutical) companies, NA	Inclusion criteria: NA Exclusion criteria: N N total at baseline: 2773 Intervention: 786 Control: 1987 Important prognostic factors[2]: *NA* Groups comparable at baseline? There is no information available on patient characteristics in both groups	Median time from admission to AC initiation was 2 days (IQR: 0 to 5 days). Median duration of AC treatment was 3 days (IQR: 2 to 7 days).	Prophylactic dose AC or no AC	Length of follow-up: NA Loss-to-follow-up: NA Incomplete outcome data: NA	*1. Mortality* In-hospital mortality for patients treated with AC: 22.5%, median survival 21 days No treatment dose: 22.8%, median survival 14 days Multivariate proportional hazards model (adjusted for age, sex, ethnicity, body mass index, history of hypertension, heart failure, atrial fibrillation, type 2 diabetes, AC use prior to hospitalization, and admission date) , longer duration of AC treatment was associated with a reduced risk of mortality (adjusted HR of 0.86 per day; 95% confidence interval: 0.82 to 0.89; $p < 0.001$). *2. IC admission* Not reported *3. Length of stay* Not reported	1. Mortality, 2. IC-admission, 3. length of stay, 4. thromboembolic complications (pulmonary embolism, stroke, transient ischemic attack), 5. ventilation, 6. acute kidney injury(AKI) (volgens KDIGO criteria), 7. use of renal replacement therapy

						4. Thromboembolic complications Not reported *5. Ventilation* Defined as invasive mechanical ventilation. Patients who received treatment-dose AC were more likely to require invasive mechanical ventilation (29.8% vs 8.1%; p < 0.001) *6. Acute kidney injury* Not reported *7. Renal replacement Therapy* Not reported	
Tremblay, 2020	Type of study: retrospective observational Setting and country: hospitalized patients with COVID-19, US Funding and conflicts of interest: NA, NA	Inclusion criteria: consecutive patients with laboratory confirmed COVID-19 between 1 March 2020 and 1 April 2020 Exclusion criteria: younger than 18 years of age and/or insufficient clinical documentation because they had been diagnosed at a rapid testing center N total at baseline: 3772	Patients who were on AC prior to COVID-19 infection	Patients who were not on AC or antiplatelet therapy	Length of follow-up: not reported Loss-to-follow-up: not reported Incomplete outcome data: not reported	*1. Mortality* HR 1.208 (95% CI, 0.750-1.946), *2. IC admission* Not reported *3. Length of stay* Not reported *4. Thromboembolic complications* Defined as overt thrombosis I: 3 (1.2%) C: 29 (1.0%) P=0.076 Defined as major bleeding I: 3 (1.2%) C: 11 (0.4%)	

		Intervention: 241 Control: 2859 Propensity matching yielded 139 patients who received AC and 417 patients who did not receive treatment <u>Important prognostic factors[2]</u>: *Age, mean (SD)* *I: 73.25 (13.6) year* *C: 52.36 (17.6) year* Sex (N, % males) I: 133 (55.2) C: 1533 (53.6) Groups comparable at baseline? Yes After propensity matching				P=0.007 *5. Ventilation* Defined as Intubation-mechanical Ventilation HR 0.905 (95% CI, 0.571-1.435), *6. Acute kidney injury* Not reported *7. Renal replacement Therapy* Defined as new RRT (of total group) I: 7 (2.9%) C: 91 (3.2%) P=0.051	
Klok, 2020	Type of study: Retrospective observational Setting and country: COVID-19 patients admitted to the ICUs, Netherlands Funding and conflicts of interest: funding outside the submitted work, no conflicts of interest declared	<u>Inclusion criteria</u>: <u>Exclusion criteria</u>: <u>N total at baseline</u>: 184 Intervention: 17 Control: 167 <u>Important prognostic factors[2]</u>: *NA* Groups comparable at baseline? NA	Patients on long-term therapeutic anticoagulation for various reasons, continued at ICU admission	Pharmacological thromboprophylaxis according to local hospital protocols	<u>Length of follow-up</u>: Patients were censored upon ICU discharge, when they died, or at April 22nd 2020, whichever came first. <u>Loss-to-follow-up</u>: NA	*1. Mortality* Use of long-term therapeutic anticoagulation was not associated with all-cause death (HR 0.79, 95%CI 0.35–1.8). *2. IC admission* Not reported *3. Length of stay* Not reported *4. Thromboembolic complications* In the competing risk model, the hazard ratio (HR) for the	

					Incomplete outcome data: NA	composite outcome (of symptomatic acute pulmonary embolism (PE), deep-vein thrombosis, ischemic stroke, myocardial infarction and/or systemic arterial embolism) associated with long-term therapeutic anticoagulation was 0.29 (95%CI 0.091–0.92). *5. Ventilation* Not reported *6. Acute kidney injury* Not reported *7. Renal replacement Therapy* Not reported	
Llitjos, 2020	Type of study: retrospective observational Setting and country: COVID-19 patients admitted to the ICU Funding and conflicts of interest: NA, no conflicts of interest declared.	Inclusion criteria: NA Exclusion criteria: NA N total at baseline: 26 Intervention: 8 Control: 18 Important prognostic factors[2] (total group): *Age* *I: 67.5 (53.5-76.2)* *C: 68 (45-72.7)* *Sex (male:* *I: 14 (78%)* *C: 6 (75%)*	Therapeutic anticoagulation Dose: left to the discretion of the treating physician. Patients treated with therapeutic anticoagulation received either low molecular weight heparin or unfractionated heparin with anti-Xa monitoring, with therapeutic levels of 0.3 to 0.7 U/mL of anti-Xa activity	Prophylactic anticoagulation	Length of follow-up: March 19 to April 11, 2020 Loss-to-follow-up: 16 patients were discharged from the ICU, and seven continued to receive mechanical ventilation Incomplete outcome data: Intervention: 0	*1. Mortality* I: 2 (11%) C: 1 (12%) NS, no P value reported *2. IC admission* Not reported *3. Length of stay* Not reported *4. Thromboembolic complications* Defined as pulmonary embolism I:6 (33%) C: 0 (0%) NS, no P value reported *5. Ventilation*	

		Groups comparable at baseline? Yes, based on age, sex and chronic medical condition			Control: 0	Defined as mechanical ventilation *I: 18 (100%)* *C: 8 (100%)* NS, no P value reported *6. Acute kidney injury* I:7 (39%) C:2 (25%) NS, no P value reported *7. Renal replacement Therapy* Defined as use of renal replacement therapy I: 4 (22%) C: 0 (0%) NS, no P value reported	
Tang, 2020	Type of study: Retrospective observational Setting and country: Patients classified as having severe COVID-19 in Tongji hospital, China Funding and conflicts of interest: National Mega Project on Major infectious Disease Prevention of China, no conflicts of interest declared	Inclusion criteria: Consecutive patients with severe COVID-19 admitted to Tongji Hospital of Huazhong University of Science and Technology in Wuhan from January 1 to February 13, 2020 Exclusion criteria: bleeding diathesis, hospital stay < 7 days, lack of information about coagulation parameters and medications, and age < 18 years	Patients receiving unfractionated heparin or low molecular weight heparin (LMWH) for 7 days or longer N = 94 received LMWH (40-60 mg enoxaparin/d) and five received unfractionated heparin (10 000-15 000 U/d), no anticoagulants other than heparin had been used for 7 days or longer in our patients	Patients not receiving heparin (not further defined)	Length of follow-up: 28 days Loss-to-follow-up: 0 Incomplete outcome data: NA	*1. Mortality* 28 day mortality I: N= 30 C: N=104 No difference on the 28-day mortality was found between heparin users and nonusers (30.3% vs 29.7%, P = .910). The heparin treatment was associated with lower mortality in patients with sepsis-induced coagulopathy SIC score ≥ 4 (40.0% vs 64.2%, P = .029), but not in those with SIC score < 4 (29.0% vs 22.6%, P = .419). Multivariate analysis (adjusted for age, sex ratio, underlying	

		N total at baseline: 449 Intervention: 99 Control: 350 Important prognostic factors[2]: The paper compares survivors vs nonsurvivors Total age: 65.1 ± 12.0 Sex ratio male/female: 268/181 Underlying disease: 272 (60.6%) Groups comparable at baseline? Not able to assess because the paper compares survivors with nonsurvivors				disease, prothrombin time, platelet count, D-dimer) aOR 1.647 (95%CI 0.929-2.921) P=.088 *2. IC admission* Not reported *3. Length of stay* Not reported *4. Thromboembolic complications* Not reported *5. Ventilation* Not reported *6. Acute kidney injury* Not reported *7. Renal replacement Therapy* Not reported	
Russo, 2020	Type of study: Retrospective observational Setting and country: COVID-19 patients admitted to emergency department of five Italian hospitals, Italy Funding and conflicts of interest: None, none declared	Inclusion criteria: confirmed COVID-19 patients patients admitted from February 2020 to April 2020 for fever and dyspnea to Emergency Department (ED) of five Italian Hospitals (Humanitas Hospital of Milan, Fatebenefratelli Hospital of Naples, Bergamo Hospital, Rivoli Hospital of Turin, Health Authority	18 (9.4 %) were taking non-vitamin K oral anticoagulant (NOAC) and 8 (4.2 %) patients were on well-controlled vitamin K oral anticoagulant (VKA) before admission	Patients not using anticoagulants before admission	Length of follow-up: patients admitted from February 2020 to April 2020 Loss-to-follow-up: NA Incomplete outcome data: It is unclear when the analysis was performed and how many	*1. Mortality* I: 20 (12.7%) C: 6 (17.1%) P=0.678 Propensity score regression model Unadjusted RR 1.42 (95%CI 0.53 – 2.47) P=0.493 Adjusted (age, smoke, chronic obstructive pulmonary disease (COPD), hypertension, diabetes, coronary artery disease (CAD), heart failure, obesity, dyslipidemia, stroke, and chronic kidney disease (CKD))	

		Bergamo East) <u>Exclusion criteria</u>: Discontinuation of antithrombotic therapy during hospitalization <u>N total at baseline</u>: 192 Intervention: 26 Control: 166 <u>Important prognostic factors</u>[2]: *Age* *I: 77.81±9.46 vs ;* *C:66.07±15.35* *P<0.001* *Sex* *I: NA* *C: NA* Groups comparable at baseline? No. Patients on anticoagulants had older age, higher prevalence of hypertension (80.8 % vs 54.2 %; P=0.02), atrial fibrillation (84.6 % vs 1.2 %; P<0.001), heart failure (30.8 % vs 7.2 %; P = 0.001), CKD (19.2 % vs 1.2 %; P = 0.012), previous stroke (23.1 % vs 6.0 %; P = 0.011) and CAD (30.8 % vs 10.8 %; P= 0.009)			patients were still hospitalized at the time of the analysis	aRR 1.15 (95%CI 0.29 – 2.57) P=0.995 *2. IC admission* Not reported *3. Length of stay* Not reported *4. Thromboembolic complications* Not reported *5. Ventilation* Not reported *6. Acute kidney injury* Not reported *7. Renal replacement Therapy* Not reported	

Sivaloganathan, 2020	Type of study: Case control propensity matched Setting and country: admitted COVID-19 patients, UK Funding and conflicts of interest: funded by the National Institute for Health Research (NIHR), no conflicts of interest declared	Inclusion criteria: patients while admitted as an inpatient in Brighton and Sussex University Hospitals NHS Trust between the 7 March and 9 April 2020 Exclusion criteria: N total at baseline: Intervention: 31 Control: 62 Important prognostic factors[2]: *Age (mean)* *I: 80.5 y* *C: 80.2 y* Groups comparable at baseline? Controls were selected from the study population with a limited propensity matching by age and sex to two controls who were not taking the medication of interest using a 'nearest neighbour' method. There was no information available on other prognostic factors.	Patients who took anticoagulants before admission, of which 23% (n = 7) were on warfarin, 39% (n = 12) apixaban, 3% (n = 1) dabigatran, 6% LMWH (n = 2), and 29% (n = 9) rivaroxaban	Controls were selected from the study population with a limited propensity matching by age and sex to two controls who were not taking the medication of interest using a 'nearest neighbour' method.	Length of follow-up: Patients admitted between the 7 March and 9 April 2020. Mortality followed up to 11 May 2020 Loss-to-follow-up: NA Incomplete outcome data: NA	*1. Mortality* *Log rank test* Being on an anticoagulant agent before admission did not have a statistically significant effect on mortality in patients with COVID-19 (P = 0.614) *2. IC admission* I: 16.7% C: 11.3% Chi-square: P=0.472 There was no statistically significant difference in the percentage of patients admitted to the intensive care unit *3. Length of stay* Not reported *4. Thromboembolic complications* Not reported *5. Ventilation* Not reported *6. Acute kidney injury* Not reported *7. Renal replacement Therapy* Not reported	

Rossi, 2020	Type of study: Retrospective observational Setting and country: elderly COVID-19 patients with chronic heart disease, Italy Funding and conflicts of interest: NA, no conflicts of interest declared	Inclusion criteria: elderly patients affected by COVID-19 interstitial pneumonia between February 25, 2020, and April 20, 2020. All the patients had chronic heart disease and were followed in the divisional outpatient clinic of the Cardiology Unit of the Policlinico of Modena Hospital. Exclusion criteria: NA N total at baseline: 70 Intervention: 26 Control: 44 Important prognostic factors[2]: *Age (median total group):* 79 years; range: 70–92) Groups comparable at baseline? NA	Chronic intake of anticoagulants 26/70 patients (37.1%) were treated with direct oral anticoagulants (DOAC) which underlying indication was pulmonary embolism (n = 7; 26.9%), deep vein thrombosis (n = 6; 23%) or atrial fibrillation (n = 13; 50%). The majority of patients received rivaroxaban (n = 11; 42.3%); followed by apixaban (n = 9; 34.6%), edoxaban (n = 4; 15.4%), and dabigatran (n = 2; 7.7%).	Elderly COVID-19 patients with chronic heart disease not on chronic intake of anticoagulants	Length of follow-up: patients affected by COVID-19 interstitial pneumonia between February 25, 2020, and April 20, 2020 The follow-up ended on May 5, 2020 Loss-to-follow-up: NA Incomplete outcome data: NA	*1. Mortality* Log-Rank (Mantel-Cox) = 9.767 P=0.01 Multivariate analysis (adjusted for age and male gender) aHR 0.38; 95%CI 0.17 – 0.58; P=0.01 Chronic DOAC intake is an independent parameter associated with a decreased mortality risk *2. IC admission* Not reported *3. Length of stay* Not reported *4. Thromboembolic complications* Not reported *5. Ventilation* Not reported *6. Acute kidney injury* Not reported *7. Renal replacement Therapy* Not reported	

Notes:

5. Prognostic balance between treatment groups is usually guaranteed in randomized studies, but non-randomized (observational) studies require matching of patients between treatment groups (case-control studies) or multivariate adjustment for prognostic factors (confounders) (cohort studies); the evidence table should contain sufficient details on these procedures

6. Provide data per treatment group on the most important prognostic factors [(potential) confounders]

7. **For case-control studies, provide sufficient detail on the procedure used to match cases and controls**
8. **For cohort studies, provide sufficient detail on the (multivariate) analyses used to adjust for (potential) confounders**

Risk of bias table for intervention studies (observational: non-randomized clinical trials, cohort and case-control studies)

Study reference (first author, year of publication)	Bias due to a non-representative or ill-defined sample of patients?[1] (unlikely/likely/unclear)	Bias due to insufficiently long, or incomplete follow-up, or differences in follow-up between treatment groups?[2] (unlikely/likely/unclear)	Bias due to ill-defined or inadequately measured outcome ?[3] (unlikely/likely/unclear)	Bias due to inadequate adjustment for all important prognostic factors?[4] (unlikely/likely/unclear)
Paranjpe 2020	Likely (Characteristics of groups are not described)	Unclear (no information available)	Unlikely	Mortality (unlikely) Ventilation : likely (no correction for confounders)
Llitjos 2020	unlikely	Likely (for mortality, some patients are still hospitalized at the time of the analysis)	Unlikely	Likely (no correction for confounders but groups seemed comparable)
Klok 2020	unlikely	Unclear (for mortality, some patients still at the ic)	Unlikely	Unlikely
Tremblay 2020	Unclear (unclear if patients received prophylactic AC in the hospital, the no of patients receiving it not mentioned)	Unclear (information NA)	Unlikely	Mortality: unlikely Ventilation: likely (no correction for confounders) Renal replacement therapy: likely (no correction for confounders)
Tang, 2020	Unclear (comparison in the study is between survivors and nonsurvivors)	unlikely	unlikely	Unlikely
Russo, 2020	unlikely	unlikely	unlikely	Unlikely (propensity score matched)
Sivaloganathan, 2020	Likely (there is no information on the patient characteristics except age)	unlikely	unlikely	Likely (propensity score matching was applied but only for age and gender)
Rossi, 2020	Likely (elderly COVID-19 patients with chronic heart disease)	Unclear (no information available)	Unlikely	Likely (only adjusted for age and male gender)

1. **Failure to develop and apply appropriate eligibility criteria: a) case-control study: under- or over-matching in case-control studies; b) cohort study: selection of exposed and unexposed from different populations.**
2. **2 Bias is likely if: the percentage of patients lost to follow-up is large; or differs between treatment groups; or the reasons for loss to follow-up differ between treatment groups; or length of follow-up differs between treatment groups or is too short. The risk of bias is unclear if: the number of patients lost to follow-up; or the reasons why, are not reported.**
3. **Flawed measurement, or differences in measurement of outcome in treatment and control group; bias may also result from a lack of blinding of those assessing outcomes (detection or information bias). If a study has hard (objective) outcome measures, like death, blinding of outcome assessment is not necessary. If a study has "soft" (subjective) outcome measures, like the assessment of an X-ray, blinding of outcome assessment is necessary.**
4. **Failure to adequately measure all known prognostic factors and/or failure to adequately adjust for these factors in multivariate statistical analysis.**

Table of excluded studies

Author and year	Reason for exclusion
Maldonado (2020)	No comparison between patients on anticoagulants and not on anticoagulants. There are 3 studies included in a qualitative analysis (1 is included in our set, 1 has no comparison, 1 is case study of 1 or 2 patients)
Fauvel (2020)	Wrong I/C: study compares patients with pulmonary embolism with patients without pulmonary embolisme
Tremblay (2020)	Same as rayyan-90706111
Al-Samkari (2020)	Wrong C: the study compares coagulation and inflammatory parameters. Not the use of anticoagulantia. : Coagulation and inflammatory parameters were compared between patients with and without coagulation-associated complications. Exclude want parameters (niet use zelf) vgl met complications
Cummings (2020)	No comparison between patients on anticoagulants and not on anticoagulants
Helms (2020)	Wrong C: the study compares covid and non covid patients on Thrombotic and ischemic complications
Liu (2020)	Proof-of-concept trial
Viecca (2020)	Proof-of-concept study, wrong I (antiplatelet), wrong O (hypoxemia)
Lodigiani (2020)	Study does not compare patients on anticoagulants with patiens not on anticoagulants but tromboembolytic events in patients admitted to IC and to ward
Porfidia (2020)	Does not include original data, is a comment on the paper of Tang
Aghamohammadi (2020)	No original data
Rossi (2020)	Same as rayyan-90706105
Pierce-Williams (2020)	Pregnant women, wrong outcome (severe vs critical)
Somani (2020)	Pre-print, not peer reviewed
Trigonis (2020)	Wrong C: all patients were using prophylactic Anticoagulants so wrong comparison
Zeng (2020)	Wrong I/C: high Padua prediction score vs low PPS
Secco (2020)	Wrong C: death vs survivor in stead of
Aghamohammadi (2020)	same as rayyan-88799905
Coto-Hernández (2020)	No original ata, comment on the paper of Tang
Doganci (2020)	No original data
Kow (2020)	No oiginal data
Menezes-Rodrigues (2020)	No original data
Sivaloganathan (2020)	Same as rayyan-90528100
Ayerbe (2020)	No information on dosage and start moment of anticoagulant drugs

Literature search strategy
OVID/Medline

1	((exp Coronavirus/ or Coronavirus Infections/ or pneumonia virus*.ti,ab,kf. or cov.ti,ab,kf.) and ((outbreak or wuhan).ti,ab,kf. or novel.af. or '19'.ti,ab,kf. or '2019'.ti,ab,kf. or epidem*.af. or epidemy.af. or epidemic*.af. or pandem*.af. or new.ti,ab,kf.)) or (coronavirus* or 'corona virus*' or ncov or '2019ncov' or 'covid19' or "covid 19" or "sars cov 2" or 'sars2' or "ncov 2019" or "sars coronavirus 2" or "sars corona virus 2" or "severe acute respiratory syndrome cov 2" or "severe acute respiratory syndrome cov2" or "severe acute respiratory syndrome cov*").ti,ab,kf. (46908)
2	limit 1 to dt="20191201-20220101" (34250)
5	letter/ (1089279)
7	(anti coagulant* or anticoagulant* or anticoagulat* or anit coagulat* or antivitamin k or vitamin k antagonist* or choay or depolymerized heparin or low molecular heparin or low molecular weight heparin or traxyparine or unfractionated heparin).ti. (37017)
8	2 and 7 (24)
9	from 8 keep 1-24 (24)

Embase

No.	Query	Results
#15	#4 AND #13 AND #14	**8**
#14	'anti coagulant*':ti OR 'anticoagulant*':ti OR 'antithrombotic*':ti OR anticoagulat*:ti	**52776**
#13	'letter'/it	**1108495**
#4	('coronavirus disease 2019'/exp OR (('coronavirinae'/exp OR 'coronavirus infection'/de OR coronavirus*:ti,ab,kw OR 'corona virus*':ti,ab,kw OR 'pneumonia virus*':ti,ab,kw OR cov:ti,ab,kw OR ncov:ti,ab,kw) AND (outbreak:ti,ab,kw OR wuhan:ti,ab,kw)) OR covid19:ti,ab,kw OR 'covid 19':ti,ab,kw OR ((coronavirus*:ti,ab,kw OR 'corona virus*':ti,ab,kw) AND 2019:ti,ab,kw) OR 'sars cov 2':ti,ab,kw OR sars2:ti,ab,kw OR 'coronavirus*':ti,ab,kw OR 'corona virus*':ti,ab,kw OR 'ncov 2019':ti,ab,kw OR ncov:ti,ab,kw OR 'sars coronavirus 2':ti,ab,kw OR 'sars corona virus 2':ti,ab,kw OR 'severe acute respiratory syndrome cov 2':ti,ab,kw OR 'severe acute respiratory syndrome cov2':ti,ab,kw) AND [2019-2020]/py	**25663**

Versiebeheer

Versie	Wijzigingen
Februari 2021	Eerste oplevering
29/03/2021	- Toevoeging aan titel tabel 1.1 (It should be noted that the cardiac troponins (cTn) assays used in these studies differ in analytical characteristics, including their assessment of the upper reference limits, thereby limiting the direct comparability between studies.) - Literatuurlijst aan module 3 toegevoegd - Afvaardiging NVIC bijgewerkt - De volgende zinsdelen zijn toegevoegd aan 'waarden en voorkeuren van de patiënt' module 1 ivm nog niet verwerkt commentaar …aanvullende cardiale diagnostiek zoals ECG en troponine bepaling te laten verrichten ….. … op klachten, zoals symptomen van hartfalen' - Figuren module 3 verwijderd ivm copyright - Titel aangepast ivm beter dekken van de inhoud van het document: cardiovasculaire ziekten toegevoegd
22/04/21	- NIV heeft de modules geautoriseerd, daardoor de zinsnede verwijderd die aangaf dat NIV het document had ontvangen maar nog niet geautoriseerd - Verwijzing Morgot Habets aangepast