

High Dose Vitamin D for the treatment of COVID-19

Rolling Collaborative Review of the European Network for Health Technology Assessment (EUnetHTA)



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Introduction:

The aim of this **EUnetHTA Rolling Collaborative Review** was to inform health policy at an early stage in the life cycle of therapies and to monitor ongoing studies and their results in the format of a Living Document.

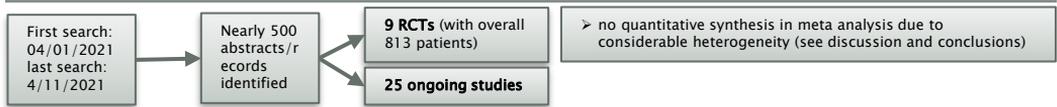
Methods:

- This Rolling Collaborative Review** was produced following the EUnetHTA **methodological framework** developed within the EUnetHTA response to COVID-19. We assessed high dose vitamin D in the treatment of COVID-19 doing (bi-)monthly updates from February 2021 up to November 2021.
- Systematic literature search:** Medline, Pubmed, medRxiv, bioRxiv, arXivso, Cochrane COVID-19 Study Register, ClinicalTrials.gov, ISRCTN Registry, EU Clinical Trials Register
- Date of search:** First search in January 2021, last search in November 2021
- Inclusion criteria:** English and German papers fulfilling PICOS criteria
- Screening, risk of bias, certainty of evidence:** Two reviewers independently screened search results and assessed risk of bias using the Cochrane RoB tool v2.0 and certainty of evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.
- Data extraction:** One reviewer extracted study data, checked by another.

PICOS:

Population	asymptomatic or pre-symptomatic SARS-CoV-2 infection, mild, moderate, severe or critical COVID-19 disease
Intervention	Vitamin D2 (ergocalciferol), vitamin D3 (cholecalciferol) with dosing above 4,000 IU per day, their metabolites ercalcidiol, calcifediol, calcitriol and ercalcitriol, alone or as adjunct treatment
Comparator	Any active treatment, placebo, or standard of care
Outcomes	All-cause mortality, hospital length of stay, viral burden (SARS-CoV-2 negativity), clinical progression (WHO Clinical Progression Scale), rates of hospitalization and of patients entering intensive care unit (ICU), (duration of) mechanical ventilation, quality of life, adverse and severe adverse events (AEs), withdrawals due to AEs
Study design	Randomised controlled trials (RCTs)

Results:



Outcome	Number of studies	Form	Relative effects	Certainty of evidence
All-cause mortality	6	vitamin D3, calcifediol, calcitriol	no significant differences	1x⊕○○○, 5x⊕⊕○○
ICU admission	5	vitamin D3, calcifediol, calcitriol	no significant differences in 4 studies significantly less with calcifediol than without in 1 study (RR 0,040; 95%-CI 0,006–0,289)	2x⊕○○○, 1x⊕⊕○○, 1x⊕⊕⊕○
Hospital length of stay	4	vitamin D3, calcifediol, calcitriol	no significant differences	1x⊕○○○, 2x⊕⊕○○, 1x⊕⊕⊕○
Need for mechanical ventilation	4	vitamin D3, calcifediol, calcitriol	no significant differences	3x⊕○○○, 1x⊕⊕○○
Viral burden (SARS-CoV-2 negativity)	2	vitamin D3	no significant differences in 1 study significantly more frequently negative PCR-test before day 21 with vitamin D3 than with placebo in 1 study (RR 3,000; 95%-CI 1,260–7,142)	⊕⊕○○, ⊕○○○
AEs	6	vitamin D3, calcifediol, calcitriol	no severe adverse events reported <u>one case</u> of vomiting directly after vitamin D administration in 6 studies reporting AEs	-

Certainty of Evidence: very low ⊕○○○, low ⊕⊕○○, moderate ⊕⊕⊕○, high ⊕⊕⊕⊕

Discussion and Conclusions:

- 9 published RCTs as of November 2022, two investigate calcifediol, one calcitriol and six vitamin D3.
- High variation** within the studies **regarding dosing regimens, disease severity and proportion of vitamin D deficiency.**
- Currently **no standardized/recommended** level of what constitutes a (beneficial) **"high dose"**.
- None of the studies investigated quality of life.
- Many of the **studies** are very **small** and **certainty of evidence** is **predominantly low or very low.**
- 25 RCTs are ongoing, 5 of them with over 1,000 patients. → According to a Google update search for registry numbers done in June 2022 two of the **ongoing studies** have been published.