**Supplementary Appendix**

This appendix has been provided by the authors to give readers additional information about their work.

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All the authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. The statistical team at the coordinating center analyzed the data and vouches for its accuracy. The first draft of the manuscript was drafted by the first author and approved by all members of the trial steering and writing committees. No one who is not an author contributed to the writing of the manuscript.

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# **Supplementary Figures**

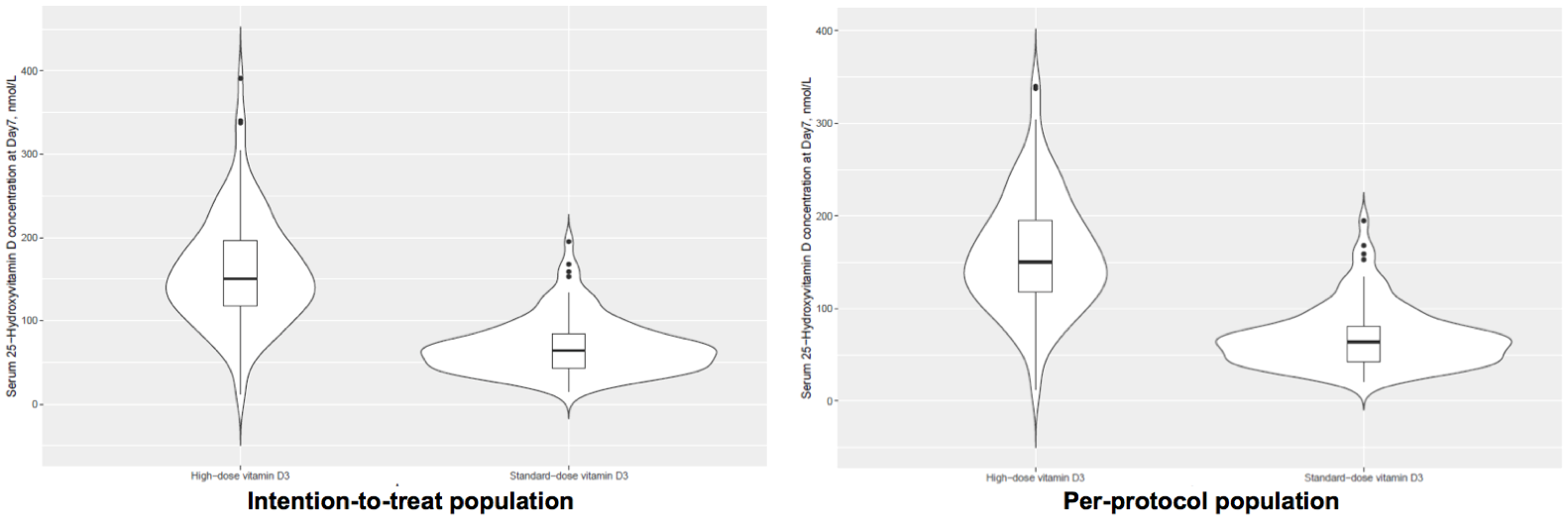
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**Figure A. Age distribution of participants included in the COVIT-TRIAL study (n = 254)**

**(a)**



**(b)**

****

**Figure B. Violin plots showing (a) the distribution of the serum 25-hydroxyvitamin D concentration (nmol/L) at baseline and day 7, and (b) the distribution of the serum 25-hydroxyvitamin D concentration (nmol/L) at day 7 in the high-dose and standard-dose vitamin D3 groups.\***

Serum 25-hydroxyvitamin D concentration was measured during the baseline and day 7 visits only. Data regarding the measures of 25-hydroxyvitamin D concentration were missing in 16 participants at baseline, and in 40 participants at day 7. To convert the values of 25-hydroxyvitamin D to nanograms per milliliter, divide by 2.496.

In the intent-to-treat population, the median (interquartile range) serum 25-hydroxyvitamin D was 53 (26-84) nmol/L at baseline in the high-dose vitamin D3 group, and 43 (26-67) nmol/L in the standard-dose group; it achieved 151 (117-197) nmol/L at day 7 in the high-dose group, and 65 (43-85) nmol/L in the standard-dose group. In the per-protocol population, the median 25-hydroxyvitamin D was 52 (26-81) nmol/L at baseline in the high-dose vitamin D3 group, and 42 (26-66) nmol/L in the standard-dose group; it achieved 151 (117-196) nmol/L at day 7 in the high-dose group, and 64 (43-81) nmol/L in the standard-dose group. The two graphs in Fig. Bb were superimposable.

\* This plot aims to compare the distribution of both variables as a function of visit. The boxes indicate the 75th percentile (upper horizontal line), median (black bold horizontal line), and 25th percentile (lower horizontal line) of the distribution. Surrounding the boxes on each side is a rotated kernel density plot.

**(a)**



**(b)**



## Figure C. Time to death according to trial groups in the (a) intention-to-treat population (n = 252) and (b) per-protocol population (n = 242).\*

## Death at 28 days (the secondary outcome) occurred in 19 of 126 participants (15%) in the high-dose vitamin D group and in 21 of 126 participants (17%) in the standard-dose vitamin D group.

\* Shown are Kaplan–Meier estimates of the time from the intervention (administration of high-dose or standard-dose vitamin D supplementation) to the death. Data on vital status at day 28 were missing for one participant in the high-dose vitamin D group and one participant in the standard-dose vitamin D group.

**(a)**



**(b)**

## 

**Figure D. Mortality due to COVID-19 at 14 days in the (a) intention-to-treat population and (b) per-protocol population.**

## Death due to COVID-19 at 14 days occurred in 7 of 126 participants (6%) in the high-dose vitamin D group and in 14 of 127 participants (11%) in the standard-dose vitamin D group. The insert shows the same data on an expanded y axis.

# **Supplementary Tables**

## Table A. Major violations to the protocol leading to exclusion of the per-protocol population.

|  |  |  |
| --- | --- | --- |
| **Major violations** | **High-dose**  **vitamin D3 group**  (n=127) | **Standard-dose vitamin D3 group**  (n=127) |
| Inclusion and non-inclusion criteria |  |  |
| Presence of at least one non-inclusion criteria | 3 | 0 |
| Deviation in treatment administration protocol |  |  |
| Allocated treatment not started | 1 | 0 |
| No adherence to the allocated treatment (50% of the planned dose administered) | 1 | 0 |
| Administration of outside-of-trial vitamin D supplements to participants in the standard-dose vitamin D group | NA | 5 |

NA=not applicable.

**Table B. Adjudicated causes of death according to trial groups**

|  |  |  |
| --- | --- | --- |
| **Adjudicated cause of death** | **no./total no. (%)** | |
| **High-dose**  **vitamin D3 group**  (n=19) | **Standard-dose**  **vitamin D3 group**  (n=21) |
| COVID-19 | 16 (84) | 21 (100) |
| Acute pulmonary edema | 1 | 0 |
| Digestive bleeding | 1 | 0 |
| Urinary sepsis | 1 | 0 |

## Table C. Effect of allocation to high-dose or standard-dose vitamin D3 supplementation on mortality due to COVID-19, in intention-to-treat and per-protocol populations.\*

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Outcome** | **High-dose**  **vitamin D3 supplementation** | **Standard-dose vitamin D3 supplementation** | **Relative risk (95% CI)**  ***P-value*** | **Risk Difference** | **Unadjusted hazard ratio**  **(95% CI)**  ***P-value*** | **Adjusted hazard ratio**  **(95% CI)**  ***P-value*** |
| **no./total no. (%)** | |  | **(%)** |  |  |
|  | **Intent-to-treat population** | | | | | |
| 14-day mortality due to COVID-19† | 7/126 (6) | 14/127 (11) | 0.50 (0.21-1.21)  *0.12* | 5.4 | 0.49 (0.20-1.23)  *0.13* | 0.33 (0.12-0.86)  *0.02* |
| 28-day mortality due to COVID-19‡ | 16/123 (13) | 21/126 (17) | 0.78 (0.43-1.42)  *0.42* | 3.7 | 0.76 (0.40-1.45)  *0.40* | 0.55 (0.27-1.12)  *0.10* |
|  | **Per-protocol population** | | | | | |
| 14-day mortality due to COVID-19† | 6/121 (5) | 14/122 (11) | 0.43 (0.17-1.09)  *0.07* | 6.5 | 0.42 (0.16-1.09)  *0.08* | 0.28 (0.10-0.77)  *0.013* |
| 28-day mortality due to COVID-19‡ | 14/118 (12) | 21/121 (17) | 0.68 (0.37-1.28)  *0.23* | 5.5 | 0.66 (0.33-1.29)  *0.22* | 0.48 (0.23-0.99)  *0.047* |

\*Data regarding vital status at day 28 were missing for 1 participant in the high-dose vitamin D group and 1 participant in the standard-dose vitamin D group. Adjusted analyses were controlled for randomisation strata (ie, age, oxygen requirement, hospitalization, and use of antibiotics, anti-infective drugs and/or corticosteroids) and baseline imbalances in important prognostic factors (ie, sex, ongoing cancers, profuse diarrhea and delirium at baseline). CI=confidence interval.

†Excluding one death due to another reason than COVID-19

‡Excluding three deaths due to other reasons than COVID-19

**Protocol S1.**

See the following reference (noted as Reference 15 in the manuscript): Annweiler C, Beaudenon M, Gautier J, et al. COVID-19 and high-dose VITamin D supplementation TRIAL in high-risk older patients (COVIT-TRIAL): study protocol for a randomized controlled trial. Trials. 2020;21:1031.