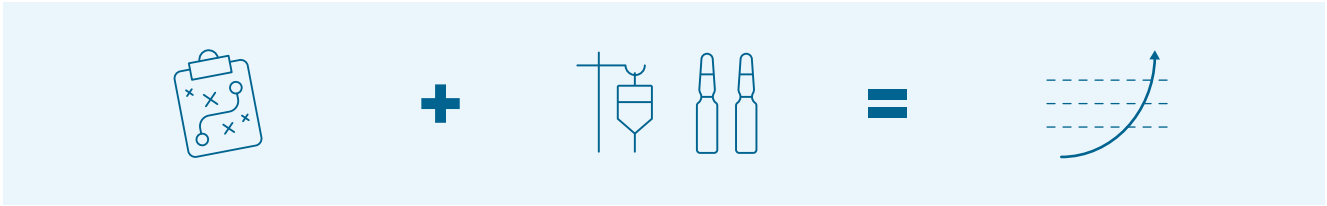
Important new insights into the treatment of severely ill COVID-19 patients

Context

A large, intensive study conducted in the past **3 months** involving **172 patients** revealed that:

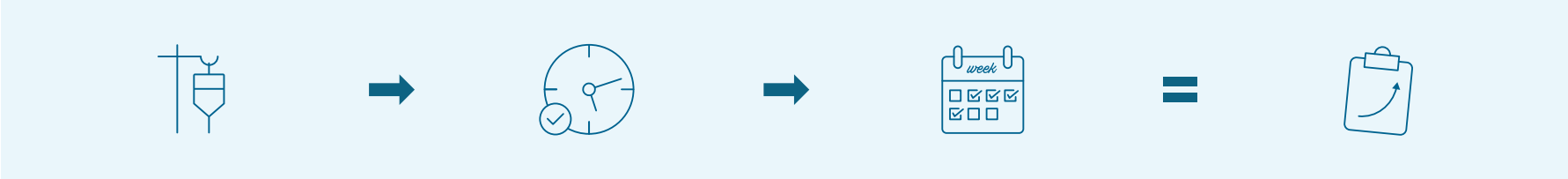


The **correct** treatment using **immunosuppressant** drugs can **significantly improve** the **prognosis** of COVID-19 patients with a cytokine storm.

zuyderland

Important new insights into the treatment of severely ill COVID-19 patients

The treatment team in **Zuyderland Medical Centre** played a **pivotal role**, with their **research** demonstrating that:



The administration of targeted immunosuppression – **high dose Methylprednisolone, followed by Tocilizumab if necessary** –

at the **right time**,

for **several days**,

yields **very promising results.**

Context

zuyderland

Important new insights into the treatment of severely ill COVID-19 patients

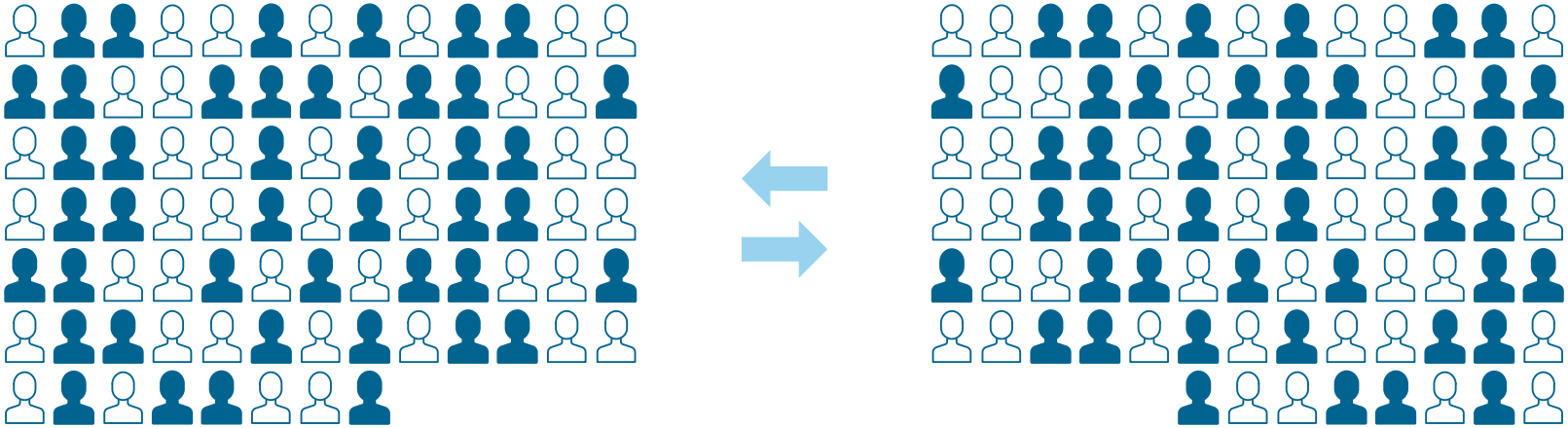
The chances of recovery were 79% higher and occurred on average 7 days sooner;

The risk of death was reduced by 65%;

The chances of ending up on a ventilator in ICU were 71% lower.

Important new insights into the treatment of severely ill COVID-19 patients

Worldwide this is the first published medical treatment substantiated by a control group that has an effect on mortality for COVID-19.



The group of patients (86 people) for whom this treatment strategy was used according to the current protocol was compared with a group of patients that was as closely matched as possible (86 people) who received standard care.

Methylprednisolone is **available worldwide** and **is cheap.**

Important new insights into the treatment of severely ill COVID-19 patients

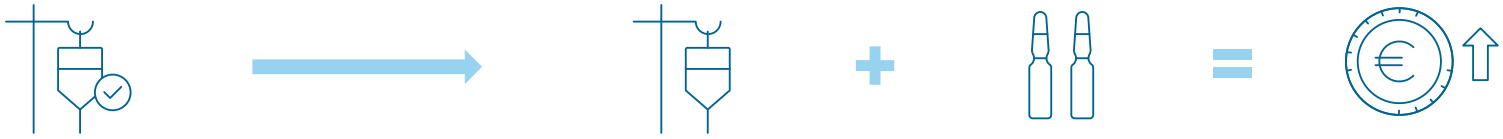
This treatment is possible almost anywhere, including in **low-income countries**

The Middle East

Asia

Africa

South America



For the majority of the patients, treatment with **Methylprednisolone** will suffice

In the case of **inadequate effect,** the treatment can be **expanded**

to include a newer and **more expensive medication: tocilizumab**

Important new insights into the treatment of severely ill COVID-19 patients

The Zuyderland team

Composition of the **Team for multi-disciplinary meetings** (MDM) COVID-19

Dr. R. Mostard

Pulmonologist, Zuyderland MC

Prof. dr. R. Landewé

Rheumatologist Zuyderland MC and Department of Clinical Immunology & Rheumatology, Amsterdam University Medical Center, Amsterdam

Dr. J. Buijs

Internist, Zuyderland

Ms. C. van Dongen

Rheumatologist, Zuyderland MC

Ms. M. Gronenschild

Pulmonologist, Zuyderland MC

Dr. E. van Haren

Pulmonologist, Zuyderland MC

zuyderland

Important new insights into the treatment of severely ill COVID-19 patients

Composition of the **Team for multi-disciplinary meetings** (MDM) COVID-19

Dr. D. van Kraaij

Cardiologist, Zuyderland MC

Dr. C. Magro Checa

Rheumatologist, Zuyderland MC

Dr. R. Peeters

Rheumatologist, Zuyderland MC

Dr. S. Ramiro

Rheumatologist, Zuyderland MC and Leiden University Medical Center

Important new insights into the treatment of severely ill COVID-19 patients

CHIC Study Team (Covid High-intensity Immunosuppression in Cytokine release syndrome):

Dr. S. Ramiro

First author, Rheumatologist, Zuyderland MC and Leiden University Medical Center

Dr. R. Mostard

Principal investigator, Pulmonologist, Zuyderland MC

Dr. C. Magro Checa

Rheumatologist, Zuyderland MC

Ms. C. van Dongen

Rheumatologist, Zuyderland MC

Dr. T. Dormans

Internist/Intensive Care specialist, Zuyderland MC

Dr. J. Buijs

Internist, Zuyderland

Dr. E. van Haren

Pulmonologist, Zuyderland MC

Ms. M. Gronenschild

Pulmonologist, Zuyderland MC

Dr. M. de Kruif

Pulmonologist, Zuyderland MC

Important new insights into the treatment of severely ill COVID-19 patients

Onderzoeksteam CHIC (Covid High-intensity Immunosuppression in Cytokine release syndrome):

Ms. T. van Kraaij

Dept. of Pulmonary Diseases, Zuyderland MC

Dr. M. Leers

Clinical chemist, Zuyderland MC

Dr. R. Peeters

Rheumatologist, Zuyderland MC

Dr. D. Wong

Clinical pharmacologist, Zuyderland MC

Prof. dr. R. Landewé

Corresponding author; Rheumatologist Zuyderland MC and Department of Clinical Immunology & Rheumatology, Amsterdam University Medical Center, Amsterdam

Important new insights into the treatment of severely ill COVID-19 patients

Outline of the situation

Zuyderland Medical Centre was one of the **most severely affected** hospitals in the Netherlands,

both in terms of **patient numbers**

and in terms of **the burden of care** of COVID-19.

zuyderland

Important new insights into the treatment of severely ill COVID-19 patients

In total, the Zuyderland MC admitted and treated over **750 COVID-19 patients**

between **3 March 2020** and **10 June 2020**

of whom **more than 120** were treated in **ICU**.

One of the major problems with **COVID-19** is that the **immune system** sometimes goes **completely haywire**.

Important new insights into the treatment of severely ill COVID-19 patients

A **cytokine storm**

is indicative of an
immune system that is out of control.

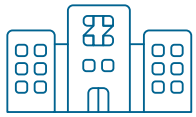
This does **more harm than good**.

A **cytokine storm**

occurs in approximately **one quarter (25%)**
of all hospitalised patients

with **COVID-19**.

Important new insights into the treatment of severely ill COVID-19 patients



Approximately **20%**
of all the COVID-19 patients

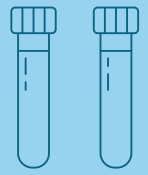
admitted to
Zuyderland MC **died**.

The risk of **death**

due to **COVID-19**
with a cytokine storm

is almost **50%**.

Important new insights into the treatment of severely ill COVID-19 patients



In the hospital, we can **confirm** a suspected cytokine storm using **simple tests**

This may sound counter-intuitive for a viral infection, but **sometimes** a **cytokine storm** needs to be **inhibited** with **immunosuppressant drugs**.

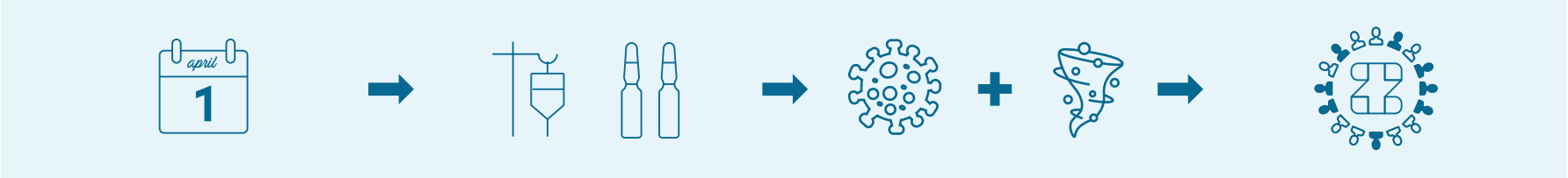
This effectively means that you are counteracting the **body's immune system**.

There are many **immunosuppressant drugs** available. The best known is **prednisone**, but many **anti-arthritis drugs** (such as the biologicals) also have an immunosuppressant effect.

Important new insights into the treatment of severely ill COVID-19 patients

Approach

Diving in at the **height of the outbreak** around **1 April 2020**:
most **medical specialists concurred:** we have to do **something NOW!**



From **1 April**

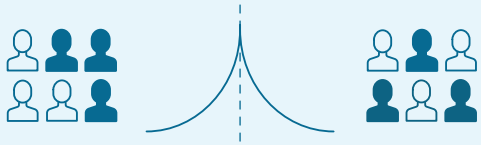
we started treatment using **immunosuppressant drugs**

for **COVID-19** patients **with a cytokine storm**.

Since then, **more than 100 patients** who met these criteria were treated with immunosuppressants in the **Zuyderland MC**.

zuyderland

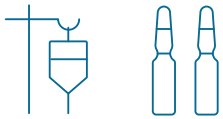
Important new insights into the treatment of severely ill COVID-19 patients



Patients from this group were **compared with 'similar' (identical) patients** from the group of **COVID-19 patients with cytokine storm** who are/were **admitted from 3 weeks prior to 1 April 2020**.

2 x 86
patients

= 172
patients in total



All patients
being treated with these medicines

were discussed by the **Multi-disciplinary team for COVID-19**

on a **daily basis**
(seven days per week, week after week).

Important new insights into the treatment of severely ill COVID-19 patients

Treatment with a **short**, but **high dose, course** of **Methylprednisolone**, followed by **Tocilizumab** if necessary**,** in patients with a **cytokine storm** resulted in (the data speak for themselves):

A faster and better recovery in 79% of the patients from 14 to 7 days

Risk of death caused by COVID-19 with cytokine storm **was 65% lower (from almost 50% to slightly more than 20%),** approximately 1 extra life saved for every 3 treated patients

Important new insights into the treatment of severely ill COVID-19 patients

The chances of ending up on a ventilator in **ICU were 71% lower.**

Less than half of the patients with cytokine storm required **a biological (Tocilizumab)** after Methylprednisolone;

COVID-19 patients with cytokine storm require intense, multi-disciplinary monitoring.

There are many impending **acute complications**,

such as **thrombosis**

and we know very little about the **long-term effects**.

Important new insights into the treatment of severely ill COVID-19 patients

A brief, intense treatment with Methylprednisolone and Tocilizumab was found to be safe within the duration of the study.

Refraining from the use of a randomised research design, and thus the selection of our current reseach design, was a deliberate and well-considered choice, in which patients enter the study during the same period and are randomly assigned to a group that would receive immunosuppressants and a comparative group receiving only supportive care. *'We felt that such a study was unethical, as half of these critically ill patients would not receive medication and 50% of them would die.'*

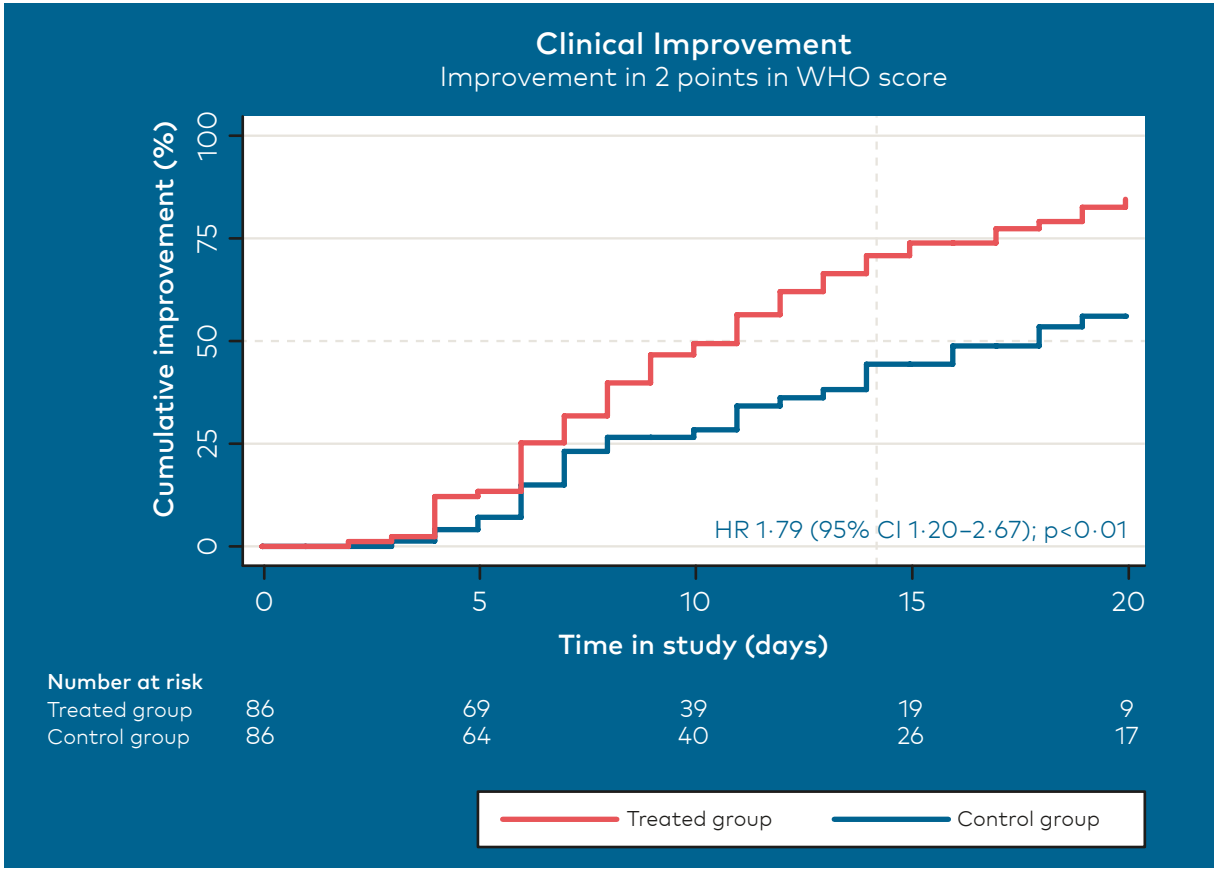
This is **the first thoroughly performed, published study in the world**, which demonstrates obvious positive results for medicinal treatment of COVID-19 in terms of both clinical improvement and mortality.

As it will take (too) long for reliable information from randomised studies to become available and positive study results from a British team were also announced in the press recently, it is now vital to treat COVID-19 patients with cytokine storm based on sound and substantiated second-best information and to save many lives, particularly in countries where the coronavirus epidemic has not peaked yet, such as the United States, South American countries (such as Brazil and Mexico), India, and parts of Africa.

Important new insights into the treatment of severely ill COVID-19 patients

Figure 1B

Clinical Improvement



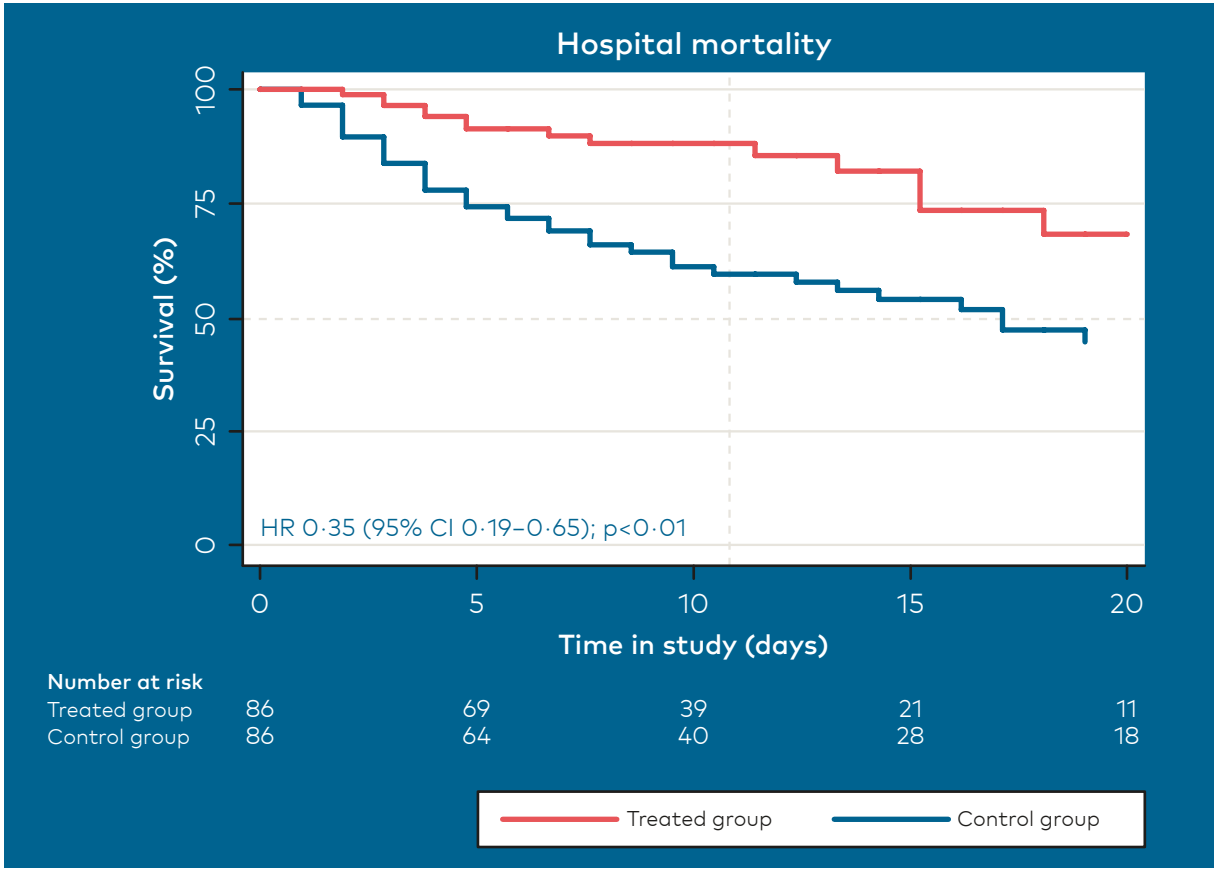
Here we see the **number of patients** who achieved **clinical improvement** in each group. Clinical improvement is measured as an **improvement by 2 points on a scale of 2-7**, where 2 was discharged, 3 hospitalised without supplemental oxygen, 4 hospitalised with supplemental oxygen, 5 nasal high-flow oxygen therapy (type of extra oxygen machine), 6 invasive ventilation, 7 death. In **comparison with the control group**: patients in the **treated group had** a **79% higher chance of clinical improvement**. If a patient achieved clinical improvement, this happened on average after **14 days in the control group** and **7 days in the treated group**, so 7 days earlier in the treated group.

zuyderland

Important new insights into the treatment of severely ill COVID-19 patients

Figure 1B

Mortality



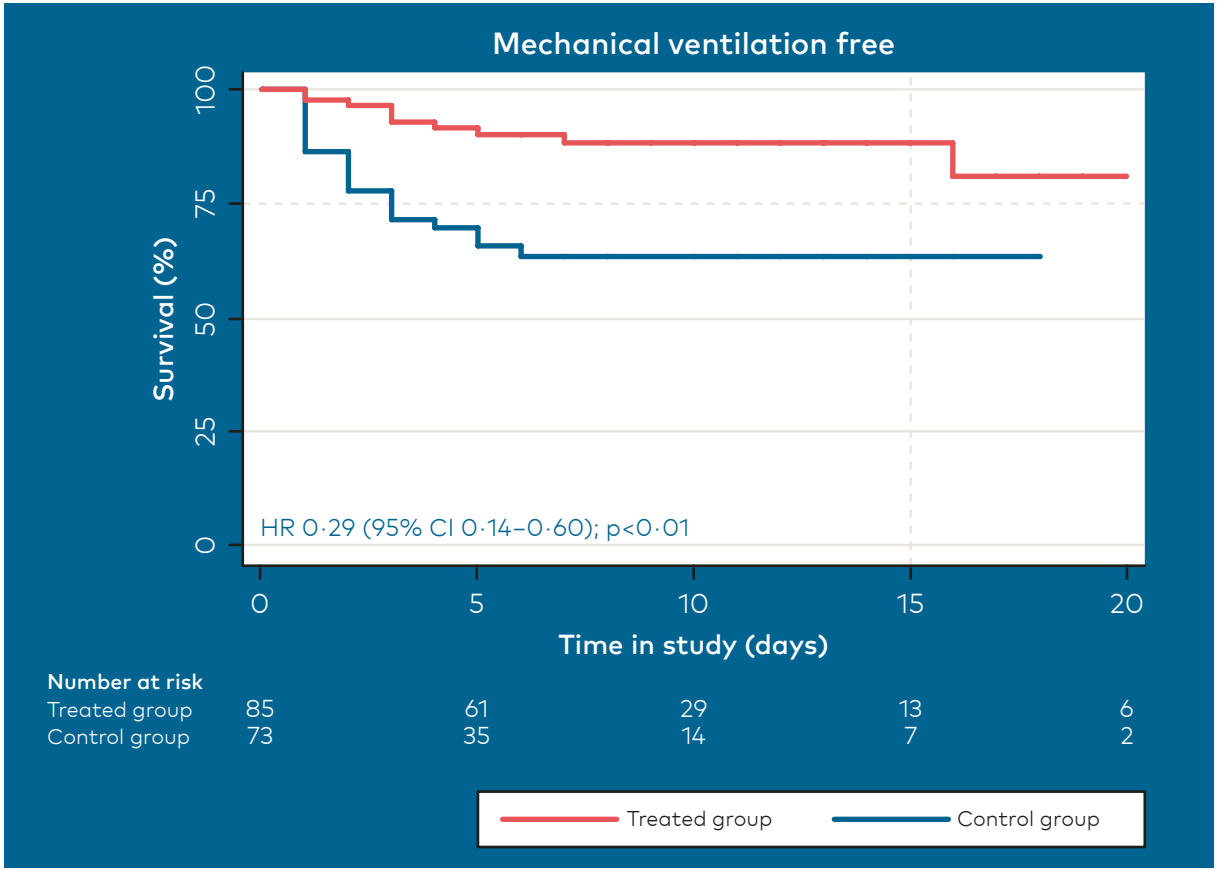
Here we see the **number of patients** who **died while in hospital** in each group. Mortality was **65% lower in the treated group** in comparison with the **control groep** (HR 0.35 means a 65% lower chance; 100%-65%=35%, 0.35

zuyderland

Important new insights into the treatment of severely ill COVID-19 patients

Figure 1C

Invasive ventilation



Here we see the **number of patients** who **required invasive ventilation after inclusion in the study** in each group. The risk of invasive ventilation was **71% lower** in the **treated group** in comparison with the **control group**.

zuyderland