

## Original Article

## Japanese rapid/living recommendations on drug management for COVID-19

Kazuma Yamakawa,<sup>1</sup> Ryo Yamamoto,<sup>2</sup> Go Ishimaru,<sup>3</sup> Hideki Hashimoto,<sup>4</sup> Takero Terayama,<sup>5</sup> Yoshitaka Hara,<sup>6</sup> Daisuke Hasegawa,<sup>6</sup> Tadashi Ishihara,<sup>7</sup> Haruki Imura,<sup>8</sup> Hiromu Okano,<sup>9</sup> Chihiro Narita,<sup>10</sup> Takuya Mayumi,<sup>11</sup> Hideto Yasuda,<sup>12</sup> Kohei Yamada,<sup>13</sup> Hiroyuki Yamada,<sup>14</sup> Tatsuya Kawasaki,<sup>15</sup> Nobuaki Shime,<sup>16</sup> Kent Doi,<sup>17</sup> Moritoki Egi,<sup>18</sup> Hiroshi Ogura,<sup>19</sup> Morio Aihara,<sup>20</sup> Hiroshi Tanaka,<sup>7</sup> Osamu Nishida,<sup>6</sup> and the Special Committee of the Japanese Clinical Practice Guidelines for the Management of Sepsis and Septic Shock 2020 (J-SSCG 2020), the COVID-19 Task Force

<sup>1</sup>Department of Emergency Medicine, Osaka Medical and Pharmaceutical University, Takatsuki, Japan,

<sup>2</sup>Department of Emergency and Critical Care Medicine, Keio University School of Medicine, Tokyo, Japan,

<sup>3</sup>Department of General Internal Medicine, Soka Municipal Hospital, Soka, Japan, <sup>4</sup>Department of Infectious

Diseases, The University of Tokyo Hospital, Tokyo, Japan, <sup>5</sup>Department of Psychiatry, School of Medicine,

National Defense Medical College, Tokorozawa, Japan, <sup>6</sup>Department of Anesthesiology and Critical Care

Medicine, Fujita Health University School of Medicine, Toyoake, Japan, <sup>7</sup>Department of Emergency and Critical

Care Medicine, Juntendo University Urayasu Hospital, Urayasu, Japan, <sup>8</sup>Department of Infectious Diseases,

Rakuwakai Otowa Hospital/Department of Health Informatics, School of Public Health, Kyoto University, Kyoto,

Japan, <sup>9</sup>Department of Critical Care and Emergency Medicine, National Hospital Organization Yokohama Medical

Center, Kanagawa, Japan, <sup>10</sup>Department of Emergency Medicine and Intensive Care Medicine, Shizuoka General

Hospital, Shizuoka, Japan, <sup>11</sup>Department of Cardiovascular Medicine, Graduate School of Medical Science,

Kanazawa University, Kanazawa, Japan, <sup>12</sup>Department of Emergency and Critical Care Medicine, Jichi Medical

University Saitama Medical Center, Saitama, Japan, <sup>13</sup>Department of Traumatology and Critical Care Medicine,

National Defense Medical College, Tokorozawa, Japan, <sup>14</sup>Department of Primary Care and Emergency Medicine,

Kyoto University Hospital, Kyoto, Japan, <sup>15</sup>Department of Pediatric Critical Care, Shizuoka Children's Hospital,

Shizuoka, Japan, <sup>16</sup>Department of Emergency and Critical Care Medicine, Graduate School of Biomedical and

Health Sciences, Hiroshima University, Hiroshima, Japan, <sup>17</sup>Department of Acute Medicine, The University of

Tokyo, Tokyo, Japan, <sup>18</sup>Division of Anesthesiology, Department of Surgery Related, Kobe University Graduate

School of Medicine, Kobe, Japan, <sup>19</sup>Department of Traumatology and Acute Critical Medicine, Osaka University

Medical School, Suita, Japan, and <sup>20</sup>Department of Gastroenterology and Hematology, Graduate School of

Medicine of Hirosaki University, Hirosaki, Japan

The coronavirus disease (COVID-19) has spread worldwide since early 2020, and there are still no signs of resolution. The Japanese Clinical Practice Guidelines for the Management of Sepsis and Septic Shock (J-SSCG) 2020 Special Committee created the Japanese rapid/living recommendations on drug management for COVID-19 using the experience of creating the J-SSCGs. The Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) approach was used to determine the certainty of the evidence and strength of the recommendations. The first edition of this guideline was released on 9 September, 2020, and this document is the revised edition (version 3.1) (released 30 March, 2021). Clinical questions (CQs) were set for the following seven drugs: favipiravir (CQ1), remdesivir (CQ2), hydroxychloroquine (CQ3), corticosteroids (CQ4), tocilizumab (CQ5), ciclesonide (CQ6), and anticoagulants (CQ7). Favipiravir is recommended for patients with mild COVID-19 not requiring supplemental oxygen (GRADE 2C); remdesivir for moderate COVID-19 patients requiring supplemental oxygen/hospitalization (GRADE 2B). Hydroxychloroquine is not recommended for all COVID-19 patients (GRADE 1B). Corticosteroids are recommended for moderate COVID-19 patients requiring supplemental oxygen/

hospitalization (GRADE 1B) and severe COVID-19 patients requiring ventilator management/intensive care (GRADE 1A); however, their use is not recommended for mild COVID-19 patients not requiring supplemental oxygen (GRADE 1B). Tocilizumab is recommended for moderate COVID-19 patients requiring supplemental oxygen/hospitalization (GRADE 2B). Anticoagulant therapy is recommended for moderate COVID-19 patients requiring supplemental oxygen/hospitalization and severe

**Corresponding:** Kazuma Yamakawa, MD, PhD, Department of Emergency Medicine, Osaka Medical and Pharmaceutical University, 2-7 Daigakumachi, Takatsuki, Osaka 569-8686, Japan. E-mail: kyamakawa-osk@umin.ac.jp.

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COVID-19 patients requiring ventilator management/intensive care (GRADE 2C). We hope that these clinical practice guidelines will aid medical professionals involved in the care of COVID-19 patients.

**Key words:** Coronavirus, evidence-based medicine, GRADE approach, practice guideline, SIRS-CoV-2

## BACKGROUND

THE CORONAVIRUS DISEASE (COVID-19), an infectious disease caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that developed at the end of 2019, has spread worldwide since the beginning of 2020, and there are still no signs of resolution. Most COVID-19 patients have an asymptomatic or mild course, but some of them develop a severe and fatal course, especially the elderly and those with underlying diseases. The main pathological condition is severe respiratory failure triggered by pneumonia, but it also presents with coagulopathy and multiple organ failure, and the mechanism has not been fully elucidated.

Stringent policies have been implemented to control infectious diseases worldwide, such as lockdowns. Medical care to save the lives of COVID-19 patients is being offered day and night in the medical field. Based on the intensity and urgency of the social impact, clinical evidence of various qualities is being published daily in preprint and top journals regarding various drug therapies. In the presence of evidence of varying quality, clinicians have limited time to sift through the reliable evidence needed for decision making.

Therefore, the Japanese Clinical Practice Guidelines for the Management of Sepsis and Septic Shock (J-SSCG) 2020 Special Committee, jointly organized by the Japanese Society of Intensive Care Medicine and the Japanese Association for Acute Medicine, made use of their experience to create the J-SSCG based on the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) system. We aimed to create a special edition specializing in the COVID-19 drug management in order to provide the latest information on the websites of both societies and support evidence-based medical care. The first edition of this clinical practice guideline was released on 9 September, 2020. This document is the revised 3.1 edition (released 30 March, 2021) (Table 1, Fig. 1).

## OVERVIEW AND BASIC PRINCIPLES OF THIS CLINICAL PRACTICE GUIDELINE

### Purpose of the guideline

COVID-19 is a serious disease that affects all age groups. It is of great social significance to create

reliable clinical practice guidelines to support clinical practice. A variety of clinical evidence exists around preprint servers. However, clinicians have limited time to identify high-quality information. This clinical practice guideline aims to support appropriate decision-making in COVID-19 clinical practice.

### Target patient population for the recommendations

The target population was adult COVID-19 patients. It covered all patients, including mildly ill patients who were undergoing medical treatment outside the medical institution (home and hotels), moderately ill patients who required supplemental oxygen or hospitalization, and severely ill patients who required intensive care management.

### Participation of representatives of relevant expert groups and external evaluation by experts

A task force within the J-SSCG 2020 Special Committee was selected to work this clinical practice guideline. All Task Force members were physicians who were familiar with the treatment of sepsis and COVID-19. One core working member (MA) was commissioned as an expert on the GRADE approach adopted in this clinical practice guideline.

### Devising ways to reflect the values and preferences of the target group (patients and the general public)

The number of people with COVID-19 was limited, and no qualitative research on the values and preferences of patients was carried out.

### Users of this clinical practice guideline

This includes all medical professionals such as physicians, nurses, pharmacists, physiotherapists, clinical engineers, pharmacists, and registered dietitians who are engaged in or involved in COVID-19 medical care.

**Table 1.** Clinical questions (CQ) and recommendations

CQ1	Should favipiravir be administered to COVID-19 patients?
Recommendation	<ul style="list-style-type: none"> <li>✔ We suggest favipiravir administration to mild COVID-19 patients who do not require oxygen (weak recommendation/low certainty of evidence: GRADE 2C)</li> <li>✔ We have not made a clear recommendation on favipiravir administration to moderate COVID-19 patients requiring oxygen/inpatient care and severe COVID-19 patients requiring ventilator management/intensive care (no recommendation)</li> </ul>
CQ2	Should remdesivir be administered to COVID-19 patients?
Recommendation	<ul style="list-style-type: none"> <li>✔ We have not made a clear recommendation on remdesivir administration to mild COVID-19 patients who do not require oxygen (no recommendation).</li> <li>✔ We suggest remdesivir administration to moderate COVID-19 patients requiring oxygen/hospitalization (weak recommendation/moderate certainty of evidence: GRADE 2B).</li> <li>✔ We suggest against remdesivir administration to severe COVID-19 patients requiring mechanical ventilation/intensive care (weak recommendation/moderate certainty of evidence: GRADE 2B).</li> </ul>
CQ3	Should hydroxychloroquine be administered to COVID-19 patients?
Recommendation	✔ We recommend against hydroxychloroquine administration to all COVID-19 patients (strong recommendation/moderate certainty of evidence: GRADE 1B).
CQ4-1	Should corticosteroid be administered to COVID-19 patients?
Recommendation	<ul style="list-style-type: none"> <li>✔ We recommend against corticosteroid administration to mild COVID-19 patients who do not require oxygen (strong recommendation/moderate certainty of evidence: GRADE 1B).</li> <li>✔ We recommend corticosteroid administration to moderate COVID-19 patients requiring oxygen/hospitalization (strong recommendation/moderate certainty of evidence: GRADE 1B).</li> <li>✔ We recommend corticosteroid administration to severe COVID-19 patients requiring ventilator management/intensive care (strong recommendation/high certainty of evidence: GRADE 1A).</li> </ul>
CQ4-2	Should corticosteroid pulse therapy be administered to moderate/severe COVID-19 patients?
Recommendation	✔ We have not made clear recommendations on corticosteroid pulse therapy to moderate COVID-19 patients requiring oxygen administration/hospitalization, or severe COVID-19 patients requiring ventilator management/intensive care (no recommendation).
CQ5	Should tocilizumab be administered to COVID-19 patients?
Recommendation	<ul style="list-style-type: none"> <li>✔ We have not made a clear recommendation on tocilizumab administration to mild COVID-19 patients who do not require oxygen (no recommendation).</li> <li>✔ We suggest tocilizumab administration to moderate COVID-19 patients requiring oxygen/hospitalization (weak recommendation/moderate certainty of evidence: GRADE 2B).</li> <li>✔ We have not made a clear recommendation on tocilizumab administration to severe COVID-19 patients requiring mechanical ventilation/intensive care (no recommendation).</li> </ul>
CQ6	Should ciclesonide be administered by inhalation to COVID-19 patients?
Recommendation	✔ We have not made a clear recommendation on ciclesonide inhalation to all COVID-19 patients (no recommendation).
CQ7	Should anticoagulants be administered to COVID-19 patients?
Recommendation	<ul style="list-style-type: none"> <li>✔ We have not made a clear recommendation on anticoagulant administration to mild COVID-19 patients who do not require oxygen (no recommendation).</li> <li>✔ We suggest anticoagulant administration to moderate COVID-19 patients requiring oxygen administration/hospitalization and severe COVID-19 patients requiring ventilator management/intensive care (weak recommendation/low certainty of evidence: GRADE 2C).</li> </ul>




### Dissemination of this clinical practice guideline

This clinical practice guideline will be published free of charge on the websites of the Japanese Society of Intensive Care Medicine and the Japanese Association for Acute Medicine. In addition, the latest version will be released on the Making GRADE the Irresistible Choice (MAGIC) app and

will be provided in a form that is easy to use in clinical settings.

### Funding

This clinical practice guideline was prepared with funding from the Japanese Society of Intensive Care Medicine and the Japanese Association for Acute Medicine.

Visual summary of recommendations			
	 Mild	 Moderate	 Severe
Oxygen saturation	SpO <sub>2</sub> > 93%	SpO <sub>2</sub> ≤ 93%	
Symptoms and conditions	-No respiratory symptoms -Cough without shortness of breath	-Shortness of breath -Symptoms of pneumonia -Need for oxygen administration	-Need for mechanical ventilation
Place of treatment	Home/hotels	Medical institution	Intensive care unit
Favipiravir	Recommendation (weak)	No recommendation	
Remdesivir	No recommendation	Recommendation (weak)	Recommendation against (weak)
Hydroxychloroquine	Recommendation against (strong)		
Corticosteroid	Recommendation against (strong)	Recommendation (strong)	Recommendation (strong)
Corticosteroid pulse	No recommendation		
Tocilizumab	No recommendation	Recommendation (weak)	No recommendation
Ciclesonide	No recommendation		
Anticoagulants	No recommendation	Recommendation (weak)	

**Fig. 1.** Visual summary of recommendations on drug management for COVID-19. For each medication, recommendations are provided depending on the severity of COVID-19: mild, moderate, and severe.

None of the members received any remuneration for the work.

### Transparency in creating clinical practice guidelines

Audit committee members were appointed to conduct an internal peer review of various work processes in real time. The economic conflict of interest was applied and disclosed for 3 years from 2017, in accordance with the guidance on the criteria for participation in the formulation of clinical practice guidelines of the Japanese Association of Medical Sciences.

### Revision schedules

Updates will be made accordingly as evidence is modified or added. The period for continuing revision will last until the COVID-19 epidemic period is over. The decision to end the revision will be made by the board of directors of both the academic societies.

### METHOD OF PREPARING THIS CLINICAL PRACTICE GUIDELINE

**T**O PREPARE THE Japanese Rapid/Living recommendations on drug management for COVID-19, the task was carried out in accordance with the GIN-McMaster guideline development checklist (extension of the Guideline Development Checklist for rapid guidelines),<sup>1</sup> and the GRADE approach was adopted to determine the strength and certainty of the evidence and recommendations.

### Scope and clinical question planning

According to the current situation of COVID-19 medical care in Japan, of the drug therapies available in clinical practice, those drugs with high clinical importance were selected as the focus of clinical questions (CQ). The selection was decided by the consensus of the Task Force members. The agreement criteria were two-thirds or more of all participating members, and the degree of disagreement was evaluated using the Rand/UCLA method.<sup>2</sup>

### PICOT settings for recommendations

For a fully formulated comparative effectiveness systematic review topic as the base of recommendations, key questions in their final form concretely specify the patient populations, interventions, comparators, outcome measures of interest, timing (PICOT) to be addressed in the review.

### Target patient population

The target population was adult COVID-19 patients. It covered all patients, including mildly ill patients who were undergoing medical treatment outside the medical institution (home and hotels), moderately ill patients who required supplemental oxygen or hospitalization, and severely ill patients who required intensive care management. The COVID-19 severity classification is defined as shown in Table 2 with reference to the Ministry of Health, Labor, and Welfare “Clinical Management of Patients with COVID-19”.<sup>3</sup> As a general rule, recommendations were made according to severity and, if necessary, recommendations were presented for each target subgroup depending on the CQ.

### Intervention treatment

The target drugs were selected as appropriate, taking into consideration the state of evidence collection and social conditions at that time, through the discussion and voting of the governing committee and task force.

### Comparison

Only direct (head-to-head) comparison was included in this practice guideline: intervention treatment versus standard treatment (or conventional care, placebo treatment) of interest.

**Table 2.** COVID-19 severity classification in this guideline

Severity	Oxygen saturation	Clinical condition	Place of medical treatment
Mild	SpO <sub>2</sub> > 93%	No respiratory symptoms Cough only, no shortness of breath	Need medical treatment outside the medical institution (home and hotels)
Moderate	SpO <sub>2</sub> ≤ 93%	Shortness of breath, symptoms of pneumonia Oxygen	administration required
Need			hospitalization at a medical institution
Severe		Need a mechanical ventilator	Need treatment in the intensive care unit

SpO<sub>2</sub>, saturated oxygen in arterial blood.

## Outcome

The importance of outcomes was graded using a 1–9 point scale (9 being most patient-important). Ultimately, we set three significant patient outcomes (i.e., rated scale of 7–9) for making recommendations: all-cause mortality, clinical improvement, and serious adverse events.

## Time frame

As a general rule, the outcome was measured 28 days after the intervention, but depending on the evidence obtained, if there were no (or few) outcomes after 28 days, we also adopted those after 7 or 14 days.

## GRADE-ADOLOPMENT for development of practical and trustworthy guideline

The GRADE-ADOLOPMENT approach to guideline production combines adoption, adaptation, and, as needed, de novo development of recommendations. The information sources of existing evidence synthesis that we used is the COVID-living NMA (<https://covid-nma.com/>) and PubMed Central. We also included non-peer-reviewed preprint server articles. Conference abstracts and press releases were not adopted. This version 3.1 is created based on the evidence obtained as of 28 February, 2021.

## Evaluation of the certainty of body of evidence using GRADE

### Definition and evaluation method for the certainty of evidence

We assessed the certainty of evidence using the GRADE approach, and rated the certainty for each outcome as high (A), moderate (B), low (C), or very low (D) based on the following: eight factors of GRADE, that is, five factors might lead to the rating down of the certainty of evidence (risk of bias [RoB], inconsistency, indirectness, imprecision, and publication bias), and three factors might lead to the rating up (large effect, plausible confounding, and dose–response gradient). For individual studies and the overall evidence of RoB, Cochrane RoB 2.0<sup>4</sup> was used for randomized controlled trials (RCTs) and the risk of bias in non-randomized studies of interventions (ROBINS-I) tool<sup>5</sup> for non-randomized studies.

### Calculation of net effect estimates for overall outcomes (net effect estimate)

The GRADE Working Group introduced the concept of certainty of net benefit to clarify and simplify methodology to

report and assess the balance of benefits and harms in the context of fully contextualizing certainty of evidence across outcomes.<sup>6</sup> Specifically, it can be predicted that the three critical outcomes set in this guideline are not equally patient-important. Therefore, to evaluate the balance between benefit and harm, the effects of these outcomes were integrated by taking into account the difference in importance (utility value), and the importance-adjusted net effect estimate was then calculated. The overall imprecision across outcomes was assessed based on the magnitude and confidence intervals of the calculated net effect estimates.

## Formulation of recommendations and consensus building

The Panel Committee determined direction and strength of recommendation using the GRADE/DECIDE Evidence-to-Decision frameworks,<sup>7</sup> which includes four key criteria (certainty of evidence, balance of benefits and harms, patient values and preferences, cost/resource use), as well as acceptability and feasibility. According to GRADE/Evidence-to-Decision, the Panel graded the strength of recommendations as strong or conditional (for or against intervention of interest). If the overall certainty of evidence across the critical outcome was very low; however, it was decided to be no recommendation. The Panel Committee voted to reach consensus using the Rand/UCLA appropriateness method.<sup>2</sup>

## Prompt disclosure of recommendations

For the rapid publication of recommendations, the MAGIC Authoring and Publication Platform (MAGICapp) was utilized, designed by MAGIC that supports efficient guideline writing, dissemination, dynamic updating, and consultation decision-making in the medical field.<sup>8</sup>

## RECOMMENDATIONS AND THEIR RATIONALES

### CQ1: Should favipiravir be administered to COVID-19 patients?

#### Recommendation

- ✔ We suggest favipiravir administration to mild COVID-19 patients who do not require oxygen (weak recommendation/low certainty of evidence: GRADE 2C).
- ✔ We have not made a clear recommendation on favipiravir administration to moderate COVID-19 patients requiring oxygen/inpatient care and severe COVID-19 patients requiring ventilator management/intensive care (no recommendation).

## Background

Favipiravir is an antiviral drug approved in March 2014 for new or re-emerging influenza virus infections. The effect on RNA virus is expected due to the selective inhibition of RNA polymerase by the triphosphorylated product converted *in vivo*. Since the early days of the pandemic, drugs have been provided for compassionate use, and multiple RCTs have been carried out. Although the drug is expected to be effective against COVID-19, its efficacy has not been determined, and it is likely to have great clinical significance in planning CQs (Fig. 2).

## Balance of benefits and harm

In five RCTs<sup>9-13</sup> with 579 cases, point estimates were expected to have a moderate effect on clinical improvement in 7–11 days (an increase of 129 per 1,000). Serious adverse events were unlikely to occur, but the previously mentioned teratogenicity should be noted. The assessment of mortality outcomes was inadequate because the patients targeted for RCTs had predominantly mild symptoms.

Based on the above statements, on the balance between benefit and harm, it was determined that favipiravir administration was more beneficial for patients with mild COVID-

19. However, for patients with moderate and severe COVID-19, the balance between the benefits and harms of favipiravir could not be determined.

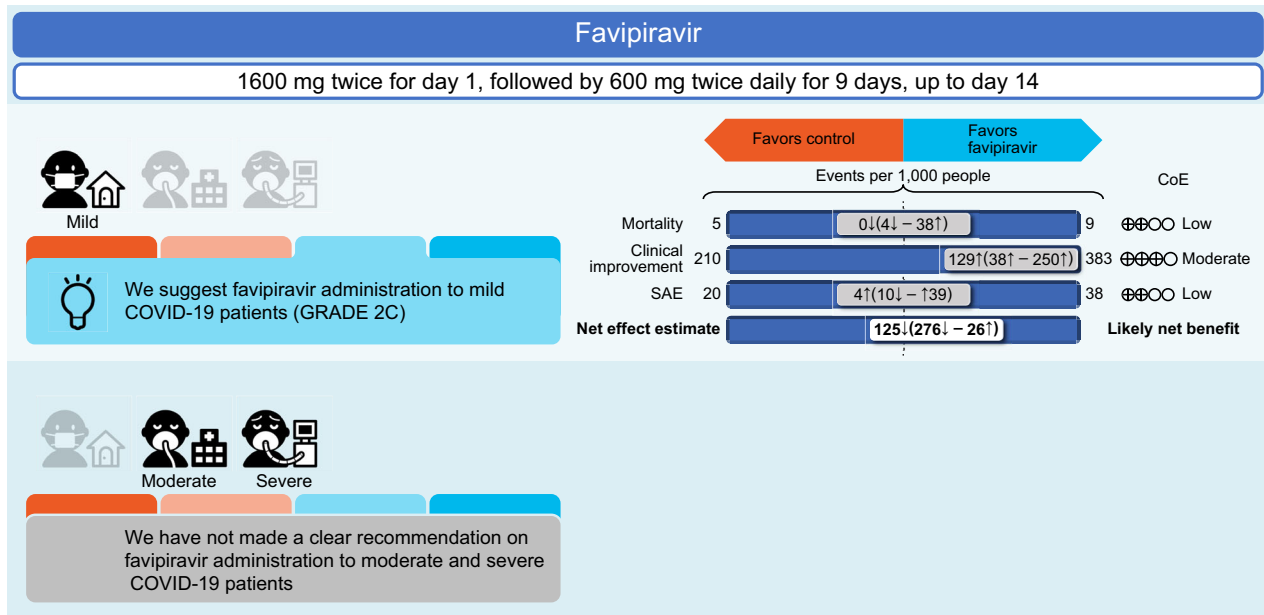
## Certainty of evidence

The certainty of evidence was judged to be “moderate” or “low” in terms of clinical improvement, all-cause mortality, and serious adverse events. Taking this direction into consideration, the overall certainty of evidence was judged to be “low” for mild COVID-19 patients and “no adopted studies” for patients with moderate or severe COVID-19.

## CQ2: Should remdesivir be administered to COVID-19 patients?

### Recommendation

- ✓ We have not made a clear recommendation on remdesivir administration to mild COVID-19 patients who do not require oxygen (no recommendation).
- ✓ We suggest remdesivir administration to moderate COVID-19 patients requiring oxygen/hospitalization (weak recommendation/moderate certainty of evidence: GRADE 2B).



**Fig. 2.** Recommendations of favipiravir for COVID-19. We suggest favipiravir administration to mild COVID-19 patients and have not made a clear recommendation on favipiravir administration to moderate and severe COVID-19 patients. Net effect estimates of favipiravir in patients with mild COVID-19 were calculated with the effects of each outcome, in which importance of mortality was considered as five times higher than those of other outcomes. Overall imprecision across outcomes was assessed as “likely net benefit”, based on the magnitude of point estimate and 95% confidence intervals of the calculated net effect estimates. CoE, certainty of evidence; GRADE, Grades of Recommendation, Assessment, Development, and Evaluation; SAE, severe adverse events.

✍ We suggest against remdesivir administration to severe COVID-19 patients requiring mechanical ventilation/intensive care (weak recommendation/moderate certainty of evidence: GRADE 2B).

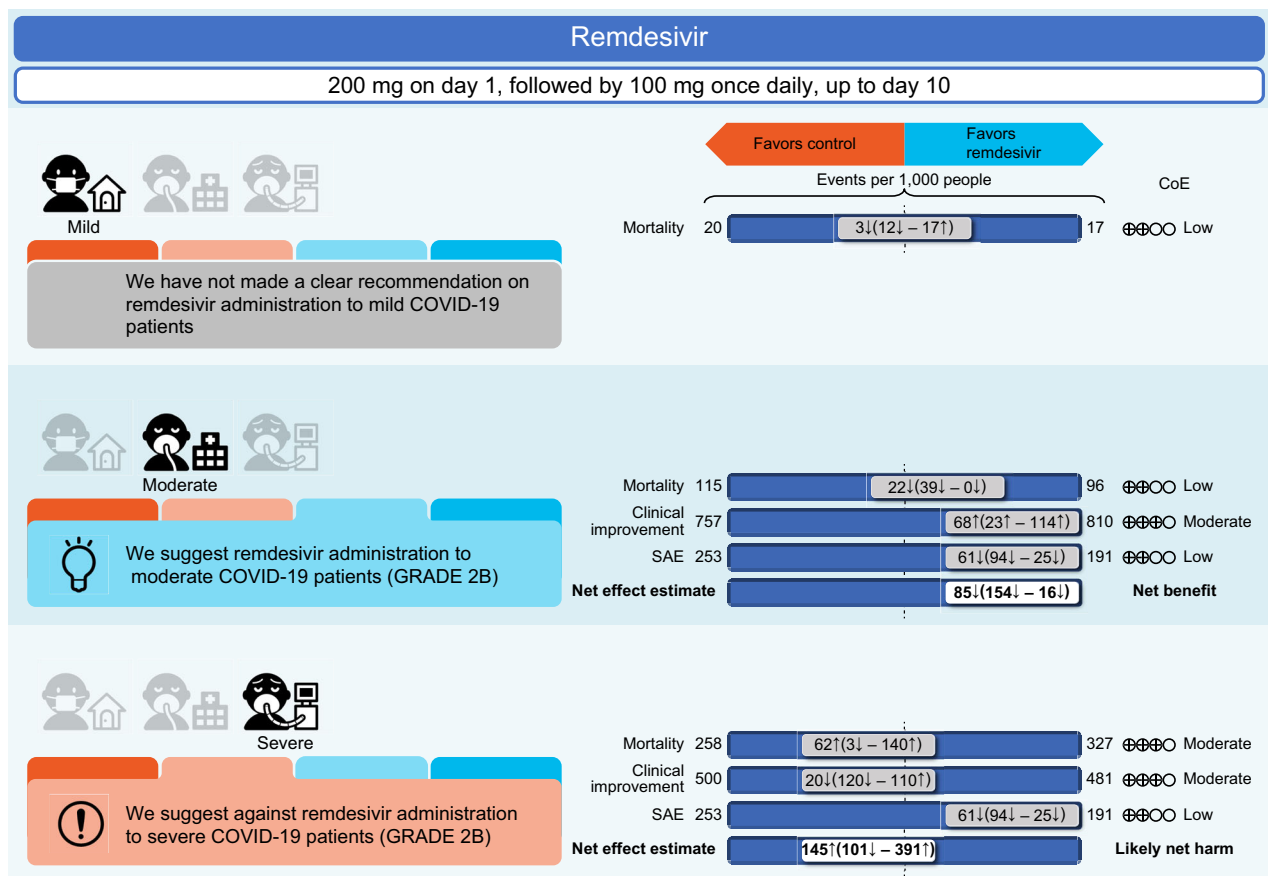
### Background

Remdesivir, developed as a therapeutic drug for Ebola hemorrhagic fever and Marburg virus infection, has been shown to have antiviral activity against single-stranded RNA viruses such as Middle East respiratory syndrome (MERS) virus, severe acute respiratory syndrome (SARS) virus, and SARS-CoV-2. It is a drug whose therapeutic target is RNA-

dependent RNA polymerase, which is essential for the self-renewal of RNA viruses. In Japan, it was approved as a therapeutic drug for the novel coronavirus infection on 7 May, 2020, under the “special approval system.” It was officially approved in the United States on 22 October, 2020. Therefore, it is considered to be of great clinical significance in planning CQs (Fig. 3).

### Balance of benefits and harm

There were four RCTs<sup>14-17</sup> with the adopted evidence. The effect on all-cause mortality in patients with mild COVID-19 is unclear (a decrease of 3 per 1,000). Small effects were



**Fig. 3.** Recommendations of remdesivir for COVID-19. We have not made a clear recommendation on remdesivir administration to mild COVID-19 patients, suggest remdesivir administration to moderate COVID-19 patients, and suggest against remdesivir administration to severe COVID-19 patients. Net effect estimates of remdesivir in patients with moderate and severe COVID-19 were calculated with the effects of each outcome, in which importance of mortality was considered as twice higher in moderate COVID-19 and three times higher in severe COVID-19, compared with those of other outcomes. Overall imprecisions across outcomes were assessed as “net benefit” in moderate COVID-19 and “likely net benefit” in severe COVID-19, based on the magnitude of point estimate and 95% confidence intervals of the calculated net effect estimates. CoE, certainty of evidence; GRADE, Grades of Recommendation, Assessment, Development, and Evaluation; SAE, severe adverse events.



expected for all-cause mortality (decrease of 22 per 1,000) and clinical improvement (increase of 68 per 1,000) in patients with moderate COVID-19. No effect was expected for all-cause mortality (increase of 62 per 1,000) or clinical improvement (decrease of 20 per 1,000) in patients with severe COVID-19. There was no increase in the incidence of serious adverse events in patients with moderate and severe COVID-19 (a decrease of 61 per 1,000).

For mild COVID-19, the range of estimated effects was wide and undeterminable, and for moderate COVID-19, the benefit of remdesivir administration was determined to be greater. However, it was determined that the harm caused by the administration of remdesivir would be greater in severe COVID-19 patients.

### Certainty of evidence

The certainty of evidence for each outcome ranged from “low” to “moderate.” Analysis was undertaken according to the severity, and it was judged to be “low” for mild COVID-19, “moderate” for moderate COVID-19, and “moderate” for severe COVID-19.

### Others (tolerability and feasibility)

On 20 November, 2020, the World Health Organization made a conditional recommendation, but no severity classification was made. Although the recommended directions differ between moderate and severe, it is difficult to make a strict distinction between these two severities. However, recommendations may change due to the accumulation of evidence.

## CQ3: Should hydroxychloroquine be administered to COVID-19 patients?

### Recommendation

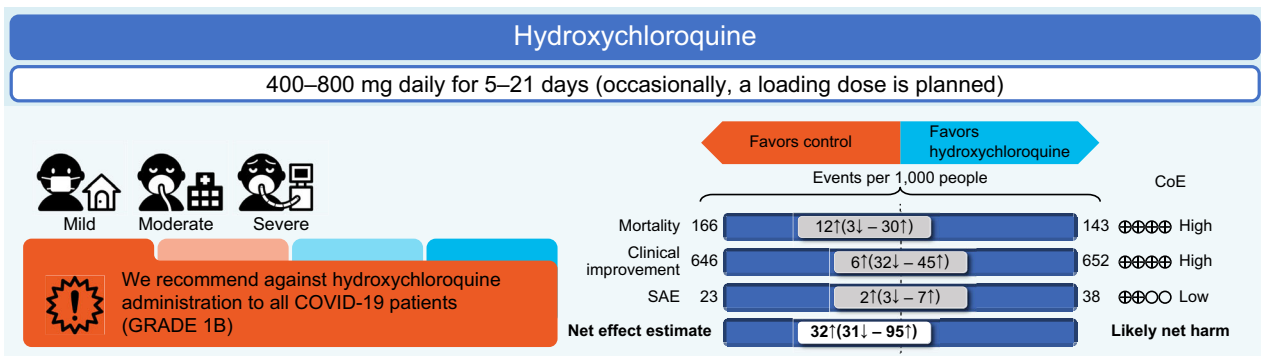
✓ We recommend against hydroxychloroquine administration to all COVID-19 patients (strong recommendation/moderate certainty of evidence: GRADE 1B).

### Background

Hydroxychloroquine is a therapeutic agent for malaria and has been used for the treatment of autoimmune diseases because of its immunomodulatory effects. In Japan, its manufacturing and marketing were approved in July 2015 for systemic lupus erythematosus. In recent years, it has become known for its antiviral effect against coronaviruses that cause SARS and MERS. Once it was found to have *in vitro* activity against SARS-CoV-2, it has been used mainly in the United States as a drug expected to be effective against COVID-19. However, its effectiveness has not been determined, and it was judged that the clinical significance was significant in CQ planning (Fig. 4).

### Balance of benefits and harm

There were 17 RCTs<sup>18-34</sup> with the adopted evidence. In 16 RCTs with 9,767 cases, the absolute effect on all-cause mortality at 28 days was expected to increase by 12 per 1,000 according to point estimation. In addition, in seven RCTs with 6,428 cases, the clinical improvement on day 28 was expected to increase by 6 per 1,000. On the contrary, in 14



**Fig. 4.** Recommendations of hydroxychloroquine for COVID-19. We recommend against hydroxychloroquine administration to mild, moderate, and severe COVID-19 patients. Net effect estimates of hydroxychloroquine in patients with mild, moderate, and severe COVID-19 were calculated with the effects of each outcome, in which importance of mortality was considered as three times higher than those of other outcomes. Overall imprecision across outcomes was assessed as “likely net harm”, based on the magnitude of point estimate and 95% confidence intervals of the calculated net effect estimates. CoE, certainty of evidence; GRADE, Grades of Recommendation, Assessment, Development, and Evaluation; SAE, severe adverse events.

RCTs with 7,314 cases, serious adverse events were expected to increase by 2 per 1,000. When the relative importance of mortality outcomes fluctuated between 1–5 times the other outcomes, the net effect estimate for adverse effects increased from 8 to 56 per 1,000. In either case, the point estimates indicate the harm of hydroxychloroquine. Therefore, it was determined that the harm caused by hydroxychloroquine administration was greater than the benefit.

### Certainty of evidence

The certainty of evidence for all-cause mortality, clinical improvement, and serious adverse events was judged to be “high,” “high,” and “low,” respectively. Considering the imprecision of the net effect estimate across all outcomes, the overall certainty of evidence was set to be “moderate.”

### CQ4-1: Should corticosteroid be administered to COVID-19 patients?

#### Recommendation

- ✔ We recommend against corticosteroid administration to mild COVID-19 patients who do not require oxygen (strong recommendation/moderate certainty of evidence: GRADE 1B).
- ✔ We recommend corticosteroid administration to moderate COVID-19 patients requiring oxygen/hospitalization (strong recommendation/moderate certainty of evidence: GRADE 1B).
- ✔ We recommend corticosteroid administration to severe COVID-19 patients requiring ventilator management/intensive care (strong recommendation/high certainty of evidence: GRADE 1A).

### Background

Various types of corticosteroids have been used for the treatment of various diseases for a long time. It is speculated that the mechanism by which COVID-19 becomes severe is that organ damage occurs due to an excessive immune response to the host, such as viral pneumonia (H5N1 influenza, SARS, and H1N1 influenza) that were prevalent in the past. Corticosteroids are expected to attenuate immune responses. Therefore, CQ planning is considered to have a significant clinical significance (Fig. 5).

### Balance of benefits and harm

There were seven RCTs<sup>26,35–40</sup> with the adopted evidence. In the mild COVID-19 group, one RCT with 1,535 cases

was adopted, and no effect was expected on all-cause mortality. No data were available for clinical improvement or any serious adverse events. In the moderate COVID-19 group, four RCTs with 4,314 cases were adopted, and a moderate effect was expected in all-cause mortality and clinical improvement (decrease of 156 per 1,000). No data were available for serious adverse events. In the severe COVID-19 group, five RCTs with 1,967 were adopted, and it was expected to have a great effect on all-cause mortality and clinical improvement (decrease of 284 per 1,000). There were a few serious adverse events.

Therefore, regarding the balance of benefit and harm, it was judged that the benefit was superior in moderate/severe COVID-19 patients, and the harm was greater in mild COVID-19 patients.

### Certainty of evidence

Only one outcome was adopted for mild COVID-19, and the overall certainty of evidence was “moderate.” It was rated as “moderate” in the moderate and “high” in the severe groups.

### CQ4-2: Should corticosteroid pulse therapy be administered to moderate/severe COVID-19 patients?

#### Recommendation

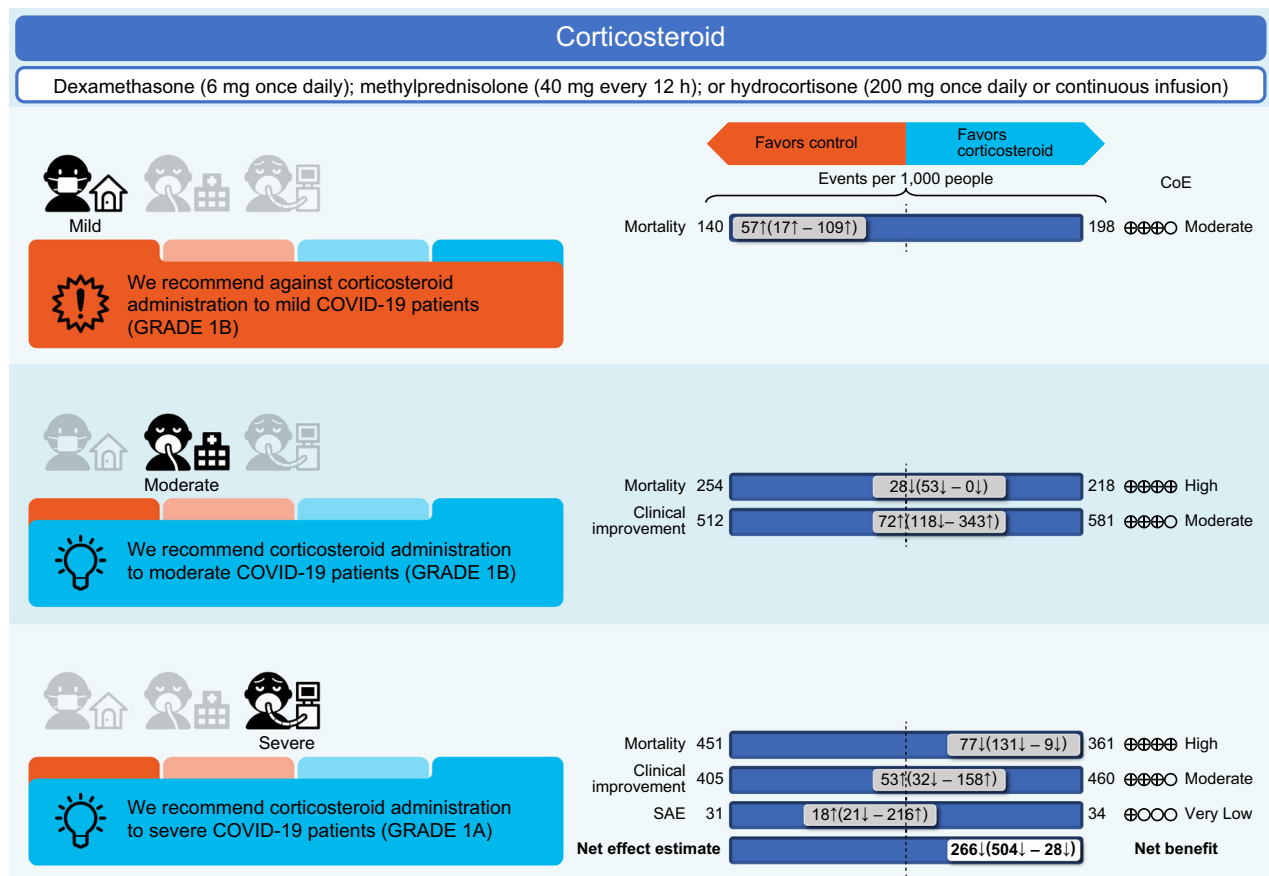
- ✔ We have not made clear recommendations on corticosteroid pulse therapy for moderate COVID-19 patients requiring oxygen administration/hospitalization and severe COVID-19 patients requiring ventilator management/intensive care (no recommendation).

### Background

Corticosteroid pulse therapy is a treatment method that has been investigated for its effectiveness in patients with viral pneumonia, such as SARS, and in patients with extremely severe respiratory failure, such as acute respiratory distress syndrome, to whom high-dose corticosteroids are administered. It is a treatment method that sets it apart from other corticosteroid therapies, and a new CQ was developed for patients with severe illness.

### Balance of benefits and harm

We adopted one RCT for hospitalized patients.<sup>41</sup> This RCT determined that the target patients were admitted to the intensive care unit but were not ventilated. As such, it was classified as “moderate” in the classification of this guideline. However, approximately 75% received high-flow or



**Fig. 5.** Recommendations of corticosteroid for COVID-19. We recommend against corticosteroid administration to mild COVID-19 patients and recommend corticosteroid administration to moderate and severe COVID-19 patients. Net effect estimates of corticosteroid in patients with severe COVID-19 were calculated with the effects of each outcome, in which importance of mortality was considered as three times higher than those of other outcomes. Overall imprecisions across outcomes were assessed as “net benefit”, based on the magnitude of point estimate and 95% confidence intervals of the calculated net effect estimates. CoE, certainty of evidence; GRADE, Grades of Recommendation, Assessment, Development, and Evaluation; SAE, severe adverse events.

high-concentration oxygen therapy and targeted the more severe group among patients with moderate COVID-19.

Sixty-two cases were adopted, and a large effect was expected in all-cause mortality at the time of discharge (decrease of 369 per 1,000). No data were available for clinical improvement, and serious adverse events were expected to have a slight effect (13 per 1,000 reductions). However, the quality of the RCT was low, the dose of corticosteroids was different from the general dose in Japan, and the overall certainty of evidence was very low. As such, the balance of the effects was unclear.

**Certainty of evidence**

The overall certainty of evidence was set to “very low.”

**CQ5: Should tocilizumab be administered to COVID-19 patients?**

**Recommendation**

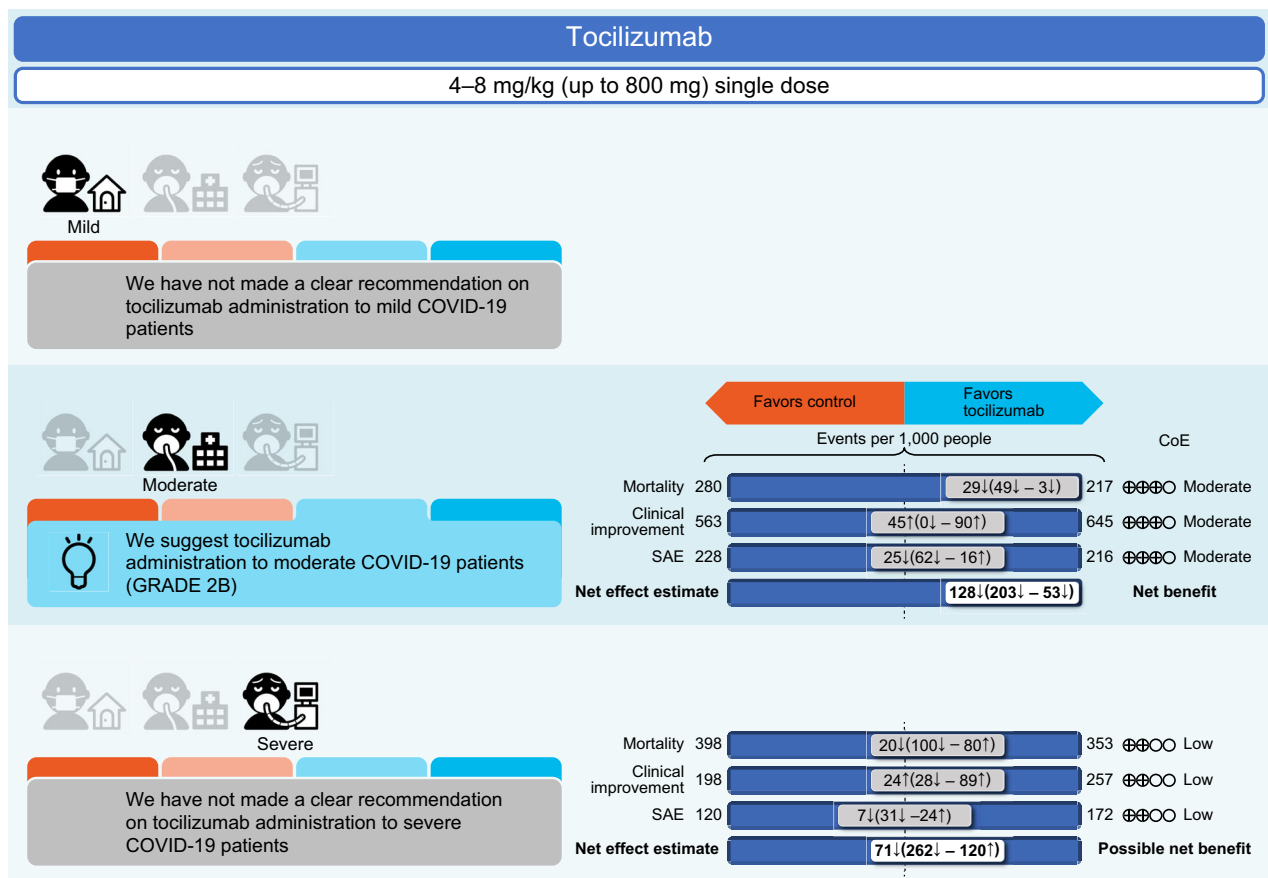
- ✍ We have not made a clear recommendation on tocilizumab administration to mild COVID-19 patients who do not require oxygen (no recommendation).
- ✍ We suggest tocilizumab administration to moderate COVID-19 patients requiring oxygen/hospitalization (weak recommendation/moderate certainty of evidence: GRADE 2B).
- ✍ We have not made a clear recommendation on tocilizumab administration to severe COVID-19 patients requiring mechanical ventilation/intensive care (no recommendation).

### Background

Increased production of inflammatory cytokines, including interleukin 6 (IL-6), has been reported to be associated with disease progression in COVID-19 patients. Tocilizumab, an IL-6 receptor antagonist, is expected to suppress the action of inflammatory cytokines in COVID-19 patients and improve prognosis. As such, many clinical studies have been carried out; however, its effectiveness has not been clarified. This CQ was formulated because it is likely to have great clinical significance as a candidate for COVID-19 therapeutic drugs (Fig. 6).

### Balance of benefits and harm

In nine RCTs<sup>42-50</sup> with 6,376 cases of severe/moderate COVID-19 inpatients, tocilizumab for moderate COVID-19 was expected to decrease all-cause mortality by 29 per 1,000 and increase clinical improvement by 45 per 1,000 on day 28. The incidence of serious adverse events did not increase (a decrease of 25 per 1,000). For severe COVID-19, a decrease of 20 per 1,000 was expected for all-cause mortality at 28 days, and an increase of 24 per 1,000 for improvement of clinical symptoms. The incidence of serious adverse events did not increase (7 per 1,000 decrease).



**Fig. 6.** Recommendations of tocilizumab for COVID-19. We have not made a clear recommendation on tocilizumab administration to mild and severe COVID-19 patients and suggest tocilizumab administration to moderate COVID-19 patients. Net effect estimates of tocilizumab in patients with moderate and severe COVID-19 were calculated with the effects of each outcome, in which importance of mortality was considered as twice higher than those of other outcomes. Overall imprecisions across outcomes were assessed as “net benefit” in moderate COVID-19 and “possible net benefit” in severe COVID-19, based on the magnitude of point estimate and 95% confidence intervals of the calculated net effect estimates. CoE, certainty of evidence; GRADE, Grades of Recommendation, Assessment, Development, and Evaluation; SAE, severe adverse events.

Based on the above statements, it was determined that the benefit of tocilizumab administration would outweigh harm in moderate COVID-19 patients. In critically ill patients, the certainty of evidence for the overall outcome was very low; therefore, we decided not to specify the recommendation. The balance between the benefits and harm of tocilizumab was undeterminable in patients with mild COVID-19.

### Certainty of evidence

The certainty of evidence for each outcome was “moderate” in moderate COVID-19 patients and “low” in severe COVID-19 patients. Considering the net effect estimate, the overall certainty of evidence was judged to be “moderate” for moderate COVID-19 patients and “very low” for severe COVID-19 patients.

### CQ6: Should ciclesonide be administered by inhalation to COVID-19 patients?

#### Recommendation

✓ We have not made a clear recommendation on ciclesonide inhalation to all COVID-19 patients (no recommendation).

#### Background

Ciclesonide is an inhaled corticosteroid used worldwide for the treatment of bronchial asthma. It is one of the drugs widely used for the treatment of COVID-19 in Japan because the effectiveness of the drug was reported at the beginning of the COVID-19 pandemic. However, the drug is not frequently used as a therapeutic drug in other countries, and its effectiveness is controversial. Therefore, it likely has a great clinical significance as to whether or not the drug should be used as a therapeutic drug for COVID-19, and this CQ was formulated.

#### Recommendation rationale

Regarding ciclesonide inhalation, no RCTs with officially published results as of 28 February, 2021, were found in the living systematic review. Similarly, non-randomized studies were also unavailable there. Therefore, in this CQ, we undertook our own additional search on PubMed, CENTRAL, and others. As a result, one observational study<sup>51</sup> that suggested the benefits of ciclesonide was extracted. However, the risk of bias was high, such as unadjusted confounding factors, and the sample size was very small ( $n = 23$ ). From the viewpoint of quality, this study was not included in the analysis.

Based on the above statements, it was determined that it is not possible to present a clear recommendation at this time.

On the contrary, some of the results of the RACCO Study (jRCTs031190269), an RCT for asymptomatic and mild COVID-19 patients in Japan, were released. It should be noted that the result refuted the benefit of ciclesonide (in the ciclesonide group, exacerbation of pneumonia on chest computed tomography was significantly higher).

### CQ7: Should anticoagulants be administered to COVID-19 patients?

#### Recommendation

✓ We have not made a clear recommendation on anticoagulant administration to mild COVID-19 patients who do not require oxygen (no recommendation).  
 ✓ We suggest anticoagulant administration to moderate COVID-19 patients requiring oxygen administration/hospitalization and severe COVID-19 patients requiring ventilator management/intensive care (weak recommendation/low certainty of evidence: GRADE 2C).

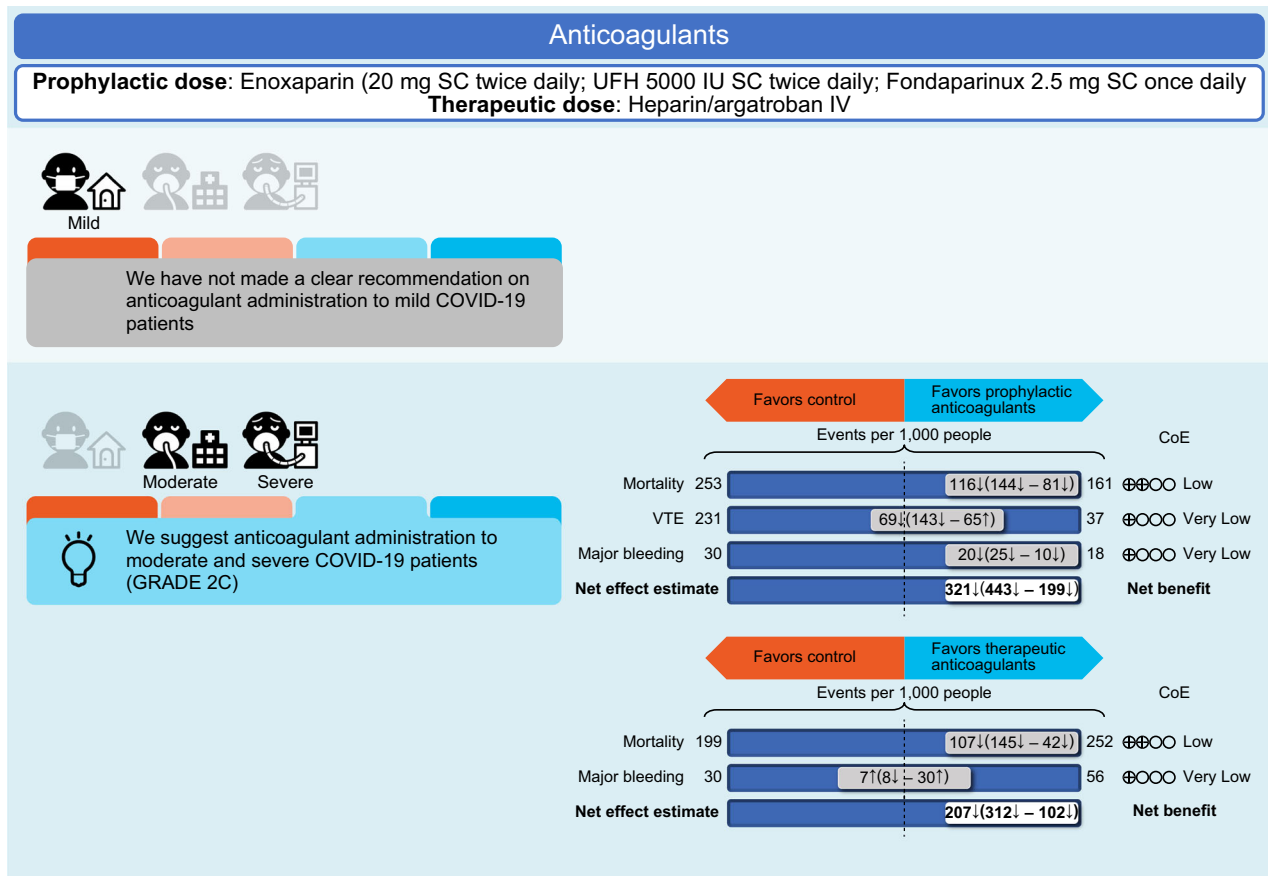
#### Background

Coagulopathy due to angiopathy associated with viral infection is considered a pathological condition of COVID-19. Pulmonary embolism is one of the causes of death from COVID-19, and it is expected that prevention of thrombus formation will lead to improvement in patient prognosis. There are two administration methods for anticoagulant therapy: prophylactic and therapeutic. Given that the clinical significance of examining the effectiveness of anticoagulant therapy itself, including the dose, is likely great, this CQ was formulated (Fig. 7).

#### Balance of benefits and harm

There were 17 observational studies<sup>52-68</sup> with the adopted evidence. Anticoagulant therapy for moderate and severe COVID-19 patients is expected to have a moderate effect on prophylactic/therapeutic doses for all-cause mortality at discharge (prophylactic dose; decrease of 116 per 1,000, therapeutic dose: decrease of 107 per 1,000). Prophylactic doses are not expected to be effective for venous thromboembolism (VTE) (a decrease of 69 per 1,000). The effects of therapeutic doses on VTEs are unknown. The occurrence of severe bleeding does not increase with the prophylactic dose (decrease of 20 per 1,000) and therapeutic dose (increase of 7 per 1,000).

Based on the above statements, it was determined that the benefits of anticoagulant therapy would outweigh the harm



**Fig. 7.** Recommendations of anticoagulants for COVID-19. We have not made a clear recommendation on anticoagulant administration to mild COVID-19 patients and suggest anticoagulant administration to moderate and severe COVID-19 patients. Net effect estimates of prophylactic and therapeutic anticoagulants in patients with moderate and severe COVID-19 were calculated with the effects of each outcome, in which importance of mortality was considered as twice higher than those of other outcomes. Overall imprecisions across outcomes were assessed as “net benefit” for both prophylactic and therapeutic anticoagulants, based on the magnitude of point estimate and 95% confidence intervals of the calculated net effect estimates. CoE, certainty of evidence; GRADE, Grades of Recommendation, Assessment, Development, and Evaluation; VTE, venous thromboembolism.

in patients with moderate and severe COVID-19. There was no evidence for anticoagulant therapy in patients with mild COVID-19 and, therefore, it was indeterminate.

**Certainty of evidence**

For all-cause mortality, VTE, and severe bleeding outcomes, the certainty of evidence was “low” for both prophylactic and therapeutic doses. Therefore, the overall certainty of evidence was judged to be “low”.

**DISCLOSURE**

Approval of the research protocol: N/A.

Informed consent: N/A.

Registry and the registration no. of the study/trial: N/A.

Animal studies: N/A.

Conflict of interest: The Japanese Society of Intensive Care Medicine and the Japanese Association for Acute Medicine submitted this conflict of interest (COI) disclosure jointly, based on the same policy issued by the Japanese Association of Medical Sciences. In accordance with these guidelines, organizations are only required to disclose COI that relate to associated companies or for-profit organizations as financial COI. We asked all members to submit their financial and academic COI for the past three years (2017–2019), in accordance with the current policy, shown in Document S1.

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## SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

**Doc. S1.** The financial and academic conflict of interest forms of all members for the past three years (2017–2019).