Guidelines

Japanese rapid/living recommendations on drug management for COVID-19: updated guidelines (July 2022)

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Background: Coronavirus disease (COVID-19), an infectious disease caused by the novel coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), 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-SSCG.

Methods: The Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) approach was used to determine the certainty of the evidence and strength of recommendations. The first edition of this guideline was released on September 9, 2020, and this is the revised edition (version 5.0; released on July 15, 2022). Clinical questions (CQs) were set for the following 10 drugs: favipiravir (CQ1), remdesivir (CQ2), corticosteroids (CQ4), tocilizumab (CQ5), anticoagulants (CQ7), baricitinib (CQ8), casirivimab/imdevimab (CQ9-1), sotrovimab (CQ9-2), molnupiravir (CQ10), and nirmatrelvir/ritonavir (CQ11).

Recommendations: Favipiravir is not suggested for all patients with COVID-19 (GRADE 2C). Remdesivir is suggested for patients with mild COVID-19 who do not require oxygen, and patients with moderate COVID-19 requiring supplemental oxygen/hospitalization

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(both GRADE 2B). Corticosteroids are recommended for moderate and severe COVID-19 (GRADE 1B, 1A). However, their administration is not recommended for mild COVID-19 (GRADE 1B). Tocilizumab is suggested for moderate and severe COVID-19 (GRADE 2B, 2C). Anticoagulant administration is recommended for moderate and severe COVID-19 (Good Practice Statement). Baricitinib is suggested for moderate and severe COVID-19 (both GRADE 2C). Casirivimab/imdevimab and sotrovimab are recommended for mild COVID-19 (both GRADE 2C). Molnupiravir and nirmatrelvir/ritonavir are recommended for mild COVID-19 (both GRADE 2C). SARS-CoV-2 mutant strains emerge occasionally, and each time, the treatment policy at clinics is forced to change drastically. We ask healthcare professionals in the field to refer to the recommendations in these guidelines and use these to keep up to date with COVID-19 epidemiological information.

BACKGROUND

CORONAVIRUS DISEASE 2019 (COVID-19), an infectious disease caused by the novel coronavirus 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. Initially, COVID-19 severely affected some elderly individuals and those with underlying diseases, and its lethal course became a socially critical problem. The main cause of COVID-19 pneumonia is severe respiratory failure caused by pneumonia. At the same time, clarification of its pathophysiology has progressed, including the intertwining of various complex pathologies, such as coagulation disorders and multiorgan dysfunction. In addition, various specific therapeutic agents, such as antiviral drugs, anti-inflammatory drugs, and antibody therapeutics, have been developed and used in clinical settings. Stringent policies have been implemented to control the infectious disease, such as lockdowns worldwide. Medical practice to save the lives of patients with COVID-19 has been carried out day and night in the medical field.

In Japan, the replacement of omicron strains began in early 2022, and the status of antibody treatment and antiviral drugs has drastically changed. Against the background of the magnitude and urgency of social impact, clinical evidence of various qualities has been published daily regarding various drug therapies. 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 COVID-19 drug management 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 September 9, 2020, and the English edition was previously published.[1,2] This document is the revised 5.0 edition (released on July 15, 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 in the preprint server articles. However, clinicians have limited time to obtain 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 patients with COVID-19. It included 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 on this clinical practice guideline. All Task Force members were physicians familiar with the treatment of sepsis and COVID-19. One core working member was commissioned as an expert on the GRADE approach adopted in this clinical practice guideline.

Table 1. Clinical questions (CQs) and recommendations on drug management for COVID-19

CQ1	**Should favipiravir be administered to patients with COVID-19?**
Recommendation	• We suggest against favipiravir administration to all patients with COVID-19 (weak recommendation/low certainty of evidence: GRADE 2C)
CQ2	**Should remdesivir be administered to patients with COVID-19?**
Recommendation	• We suggest remdesivir administration to patients with mild COVID-19 who do not require oxygen and patients with moderate COVID-19 requiring oxygen/hospitalization (weak recommendation/moderate certainty of evidence: GRADE 2B)
	• We suggest against remdesivir administration to patients with severe COVID-19 requiring mechanical ventilation/intensive care (weak recommendation/low certainty of evidence: GRADE 2C)
CQ4-1	**Should corticosteroid be administered to COVID-19 patients?**
Recommendation	• We recommend against corticosteroid administration to patients with mild COVID-19 who do not require oxygen (strong recommendation/moderate certainty of evidence: GRADE 1B)
	• We recommend corticosteroid administration to patients with moderate COVID-19 requiring oxygen/hospitalization (strong recommendation/moderate certainty of evidence: GRADE 1B)
	• We recommend corticosteroid administration to patients with severe COVID-19 requiring mechanical ventilation/intensive care (strong recommendation/high certainty of evidence: GRADE 1A)
CQ4-2	**Should corticosteroid pulse therapy be administered to patients with moderate/severe COVID-19?**
Recommendation	• We have not made clear recommendations on corticosteroid pulse therapy to patients with moderate COVID-19 requiring oxygen administration/hospitalization or patients with severe COVID-19 requiring mechanical ventilation/intensive care (no recommendation)
CQ5	**Should tocilizumab be administered for COVID-19 patients?**
Recommendation	• We have not made a clear recommendation on tocilizumab administration to patients with mild COVID-19 who do not require oxygen (no recommendation)
	• We suggest tocilizumab administration to patients with moderate COVID-19 requiring oxygen/hospitalization (weak recommendation/moderate certainty of evidence: GRADE 2B)
	• We suggest tocilizumab administration to patients with severe COVID-19 requiring mechanical ventilation/intensive care (weak recommendation/low certainty of evidence: GRADE 2C)
CQ7-1	**Should anticoagulants be administered to patients with COVID-19?**
Recommendation	• We suggest against anticoagulant administration to patients with mild COVID-19 who do not require oxygen (weak recommendation/low evidence: GRADE 2C)
	• We recommend anticoagulant administration to patients with moderate COVID-19 requiring oxygen administration/hospitalization and patients with severe COVID-19 requiring mechanical ventilation/intensive care (good practice statement)
CQ7-2	**What doses of anticoagulants should be administered to patients with COVID-19?**
Recommendation	• We suggest therapeutic doses of anticoagulant administration to patients with moderate COVID-19 requiring oxygen administration/hospitalization (weak recommendation/low certainty of evidence: GRADE 2C)
	• We suggest prophylactic doses of anticoagulant administration to patients with severe COVID-19 requiring ventilator management/intensive care (weak recommendation/moderate certainty of evidence: GRADE 2B)
CQ8	**Should baricitinib be administered to patients with COVID-19?**
Recommendation	• We have not made a clear recommendation on baricitinib administration to patients with mild COVID-19 who do not require oxygen (no recommendation)
	• We suggest baricitinib administration to patients with moderate COVID-19 requiring oxygen/hospitalization (weak recommendation/low certainty of evidence: GRADE 2C)
	• We suggest baricitinib administration to patients with severe COVID-19 requiring mechanical ventilation/intensive care (weak recommendation/low certainty of evidence: GRADE 2C)
CQ9-1	**Should casirivimab/imdevimab be administered to patients with COVID-19?**
Recommendation	• We suggest casirivimab/imdevimab administration to patients with mild COVID-19 who do not require oxygen (weak recommendation/low certainty of evidence: GRADE 2C)
	• We have not made a clear recommendation on casirivimab/imdevimab administration to patients with moderate COVID-19 requiring oxygen/hospitalization or patients with severe COVID-19 requiring mechanical ventilation/intensive care (no recommendation)

Table 1. (Continued)

CQ9-2 Recommendation	**Should sotrovimab be administered to patients with COVID-19?** • We suggest sotrovimab administration to patients with mild COVID-19 who do not require oxygen (weak recommendation/low certainty of evidence: GRADE 2C) • We have not made a clear recommendation on sotrovimab administration to patients with moderate COVID-19 requiring oxygen/hospitalization or patients with severe COVID-19 requiring mechanical ventilation/intensive care (no recommendation)
CQ10 Recommendation	**Should molnupiravir be administered to patients with COVID-19?** • We suggest molnupiravir administration to patients with mild COVID-19 who do not require oxygen (weak recommendation/low certainty of evidence: GRADE 2C) • We have not made a clear recommendation on molnupiravir administration to patients with moderate COVID-19 requiring oxygen/hospitalization or patients with severe COVID-19 requiring mechanical ventilation/intensive care (no recommendation)
CQ11 Recommendation	**Should nirmatrelvir/ritonavir be administered to patients with COVID-19?** • We suggest nirmatrelvir/ritonavir administration to patients with mild COVID-19 who do not require oxygen (weak recommendation/low certainty of evidence: GRADE 2C). • We have not made a clear recommendation on nirmatrelvir/ritonavir administration to patients with moderate COVID-19 requiring oxygen/hospitalization or those with severe COVID-19 requiring mechanical ventilation/intensive care (no recommendation).

Two CQs (hydroxychloroquine [CQ3] and ciclesonide [CQ6]) were retrieved in the updated version.

Devising ways to reflect the values and preferences of the target group

No qualitative research on the values and preferences of patients was conducted.

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.

Dissemination of this clinical practice guideline

These clinical practice guidelines 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) Authoring and Publication Platform (MAGICapp) and provided in a form easy to use in clinical settings.

Funding

This clinical practice guideline was prepared with funding from the Japanese Society of Intensive Care Medicine and Japanese Association for Acute Medicine. None of the members received any reward for their 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 revisions will last until the COVID-19 epidemic period ends. 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

THE JAPANESE RAPID/LIVING recommendations on drug management for COVID-19 were prepared in accordance with the GIN-McMaster guideline development

Visual summary of recommendations

		Mild	Moderate	Severe
	Oxygen saturation	$SpO_2 > 93\%$	$SpO_2 \leq 93\%$	
	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
Antiviral	Remdesivir	Recommendation (weak)	Recommendation (weak)	Recommendation against (weak)
Antiviral	Molnupiravir Nirmatrelvir/Ritonavir	Recommendation (weak)	No recommendation	
Neutralizing antibody	Casirivimab / Imdevimab Sotrovimab	Recommendation (weak)	No recommendation	
Immunosuppressive	Corticosteroid	Recommendation against (strong)	Recommendation (strong)	Recommendation (strong)
Immunosuppressive	Corticosteroid pulse	No recommendation		
Immunosuppressive	Tocilizumab	No recommendation	Recommendation (weak)	Recommendation (weak)
Immunosuppressive	Baricitinib	No recommendation	Recommendation (weak)	Recommendation (weak)
Other	Anticoagulants	Recommendation against (weak)	Recommendation (GPS)	
Other	Type (Dose) of anticoagulants		Therapeutic dose (weak)	Prophylactic dose (weak)

Fig. 1. Visual summary of recommendations on drug management for COVID-19. The recommendations for each medication are visually summarized. For each medication, recommendations are provided depending on the severity of COVID-19: mild, moderate, or severe. GPS, good practice statement.

checklist (extension of the Guideline Development Checklist for rapid guidelines),[3] 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, a drug with high clinical importance was selected as a clinical question (CQ) among the drug therapies available in clinical practice. The selection was decided by consensus of the Task Force members. The agreement criteria were acceptance by two-thirds or more of all participating members, and the degree of disagreement was evaluated using the Rand/UCLA method.[4]

PICOT settings for recommendations

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

Target patient population

The target population was adult patients with COVID-19. It included 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."[5] As a general rule, recommendations were made according to

severity and, if necessary, 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 discussions with 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.

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., a 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; however, 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 the development of practical and trustworthy guidelines

The "GRADE-ADOLOPMENT" approach to guideline production combines adoption, adaptation, and, as needed,

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Table 2. COVID-19 severity classification in this guideline

Severity	Oxygen saturation	Clinical condition	Place of medical treatment
Mild	SpO$_2$ > 93%	No respiratory symptoms Cough only, no shortness of breath	Need medical treatment outside the medical institution (home and hotels)
Moderate	SpO$_2$ ≤ 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$_2$, saturated oxygen in arterial blood.

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de novo development of recommendations. The information sources of existing evidence synthesis that we used are the COVID-living NMA (https://covid-nma.com/living_data/index.php) and PubMed Central. We also included non-peer-reviewed preprint server articles. Conference abstracts and press releases were excluded. This version 5.0 is created based on the evidence obtained as of May 31, 2022.

Evaluation of the certainty of the body of evidence using GRADE

Definition and evaluation method for the certainty of the 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: five factors might lead to a 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[6] was used.

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 the methodology to report and assess the balance of benefits and harms in the context of fully contextualizing the certainty of evidence across outcomes.[7] 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 considering 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 the direction and strength of recommendations using the GRADE/DECIDE Evidence-to-Decision frameworks,[8] which include four key criteria (certainty of evidence, balance of benefits and harms, patient values and preferences, and cost/resource use), as well as acceptability and feasibility. According to GRADE/

Evidence-to-Decision, the Panel graded the strength of the recommendations as strong or conditional (for or against the intervention of interest). If the overall certainty of the evidence across the critical outcome was very low, it was not recommended. The panel committee voted and reached a consensus using the Rand/UCLA appropriateness method.[4]

For the CQ that handled extremely common themes and for which randomized controlled trials (RCTs) were theoretically impossible, we made recommendations using the decision algorithm of good practice statement.[9]

Prompt disclosure of recommendations

For the rapid publication of recommendations, MAGICapp, designed by MAGIC, was utilized, which supports efficient guideline writing, dissemination, dynamic updating, and consultation decision-making in the medical field.[10]

RECOMMENDATIONS AND THEIR RATIONALES

CQ1 Should favipiravir be administered to patients with COVID-19?

Recommendation

- We suggest against favipiravir administration to all patients with COVID-19 (weak recommendation/low certainty of evidence: GRADE 2C).

Background Favipiravir is an antiviral drug developed for the treatment of new or re-emerging influenza virus infections. Its effect on RNA virus is expected due to the selective inhibition of RNA polymerase by the triphosphorylated product converted in vivo. Although the drug is expected to be effective against COVID-19, its efficacy has not yet been determined, and it is likely to have great clinical significance in planning CQs.

Recommendation rationale
■ Balance between benefits and harm
   There were 11 RCTs[11–23] with adopted evidence. Point estimates were not expected to have a clinically meaningful effect on clinical improvement at 28 days (an increase of 14 per 1,000). Serious adverse events were unlikely to occur; however, the previously mentioned teratogenicity should be noted. The assessment of mortality outcomes was inadequate because the patients targeted for RCTs predominantly had mild symptoms.

   Based on the above statements on the balance between benefit and harm, it was determined that favipiravir administration was not beneficial for all patients with COVID-19.

■ Certainty of evidence

The certainty of the evidence was judged to be "low" in terms of clinical improvement, all-cause mortality, and serious adverse events. Taking this direction into consideration, the overall certainty of the evidence was judged to be "low" for all patients with COVID-19.

CQ2 Should remdesivir be administered to patients with COVID-19?

Recommendation

• We suggest remdesivir administration to patients with mild COVID-19 who do not require oxygen and patients with moderate COVID-19 requiring oxygen/hospitalization (weak recommendation/moderate certainty of evidence: GRADE 2B).

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

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 self-replication of RNA viruses. In Japan, it was approved as a therapeutic drug for the novel coronavirus infection on May 7, 2020. Therefore, it is considered to be of great clinical significance in the formulation of this CQ.

Recommendation rationale
■ Balance between benefits and harm

There were seven RCTs[24–30] with the adopted evidence. Mild cases were expected to have a small effect on all-cause mortality (no difference per 1,000) and improvement in clinical symptoms (increase of 47 per 1,000). In moderate cases, moderate effects were expected for all-cause mortality (decrease of 17 per 1,000) and improvement in clinical symptoms (increase of 68 per 1,000) (Fig. 2). In severe cases, there was no expected effect on all-cause mortality (increase of 47 per 1,000) or improvement in clinical symptoms (decrease of 20 per 1,000). There was no increase in the incidence of serious adverse events (decrease of 26 per 1,000) of any severity.

Based on the above, it was determined that the benefits of remdesivir administration outweigh those of mild and moderate diseases. However, it was determined that the harm caused by the administration of remdesivir outweighed the benefits for critically ill patients.

■ Certainty of evidence

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

■ Others (tolerability and feasibility)

Although the recommended directions differ between moderate and severe, it is difficult to make a strict distinction between the two severities. On April 22, 2022, the World Health Organization updated the recommendation and suggested treatment with remdesivir for nonsevere patients; however, the recommendation for severe patients is under review. There was no information regarding the mutant strain of COVID-19 in the adopted RCT. Patients with vaccination were excluded in "Robert 2022," and there was no information about the vaccination in other adopted RCT. Recommendations may change owing to the accumulation of evidence.

CQ4-1 Should corticosteroids be administered to patients with COVID-19?

Recommendation

• We recommend against corticosteroid administration to patients with mild COVID-19 who do not require oxygen (strong recommendation/moderate certainty of evidence: GRADE 1B).

• We recommend corticosteroid administration to patients with moderate COVID-19 requiring oxygen/hospitalization (strong recommendation/moderate certainty of evidence: GRADE 1B).

• We recommend corticosteroid administration to patients with severe COVID-19 requiring mechanical ventilation/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 in the host, such as viral pneumonia (H5N1 influenza, SARS, and H1N1 influenza) that was prevalent in the past. Corticosteroids are expected to attenuate immune responses. Therefore, CQ planning is considered to have a significant clinical significance.

Recommendation rationale
■ Balance between benefits and harm

There were nine RCTs[31–39] with the adopted evidence (Fig. 3). 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
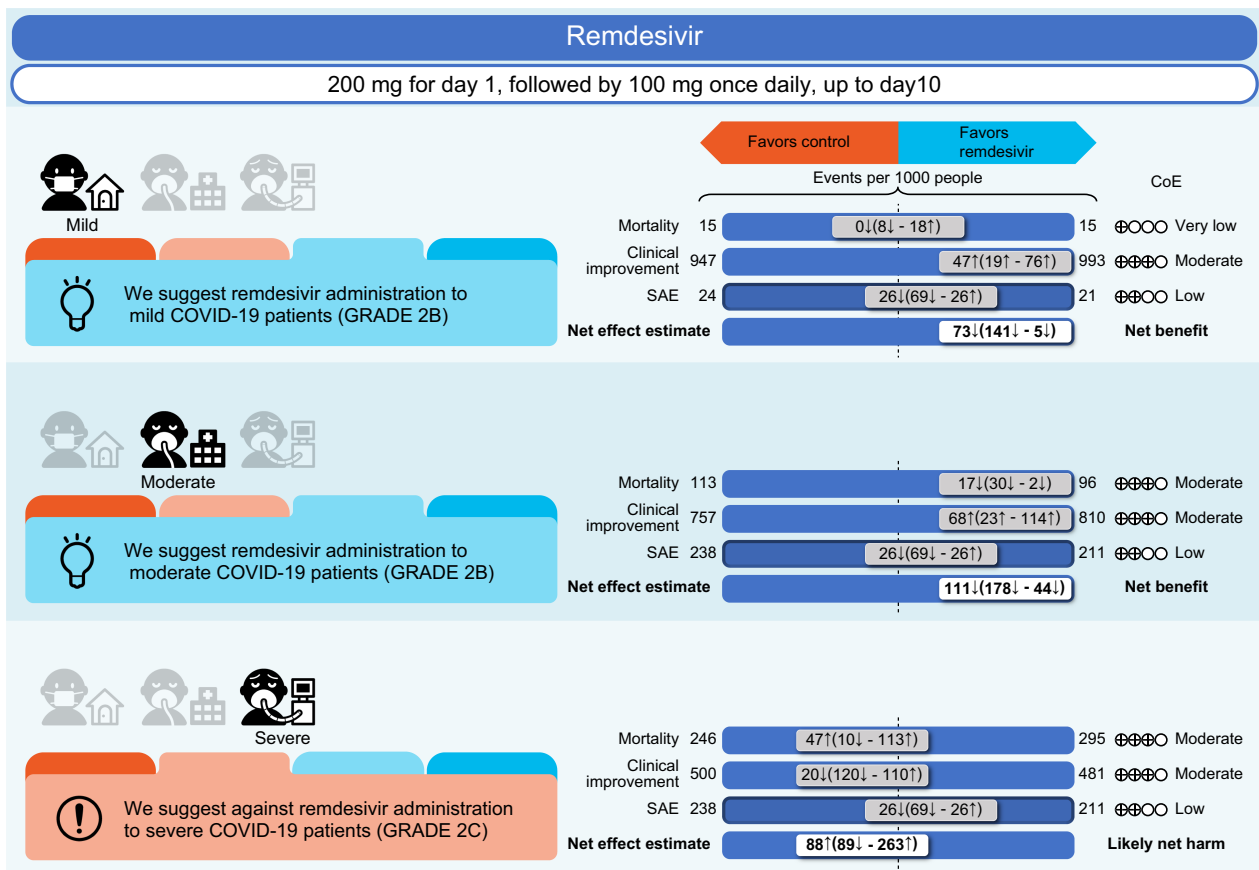
Fig. 2. Recommendations of remdesivir for management for COVID-19 (CQ2). We suggest remdesivir administration to patients with mild and moderate COVID-19 and against administration to patients with severe COVID-19. Net effect estimates of remdesivir in all patients with COVID-19 were calculated with the effects of each outcome, in which the importance of mortality was considered to be the same in mild and moderate COVID-19 and two times higher in severe COVID-19 compared with those of other outcomes. Overall imprecisions across outcomes were assessed as "net benefit" in mild and moderate COVID-19 and "likely net harm" in severe COVID-19 based on the magnitude of the 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.

or any serious adverse events. In the moderate COVID-19 group, four RCTs with 4,293 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, seven RCTs with 2047 cases were adopted, and it was expected to have a great effect on all-cause mortality and clinical improvement (decrease of 279 per 1,000). There were a few serious adverse events.

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

■ 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 COVID-19 and "high" high for severe COVID-19.

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

Recommendation

• We have not made clear recommendations on corticosteroid pulse therapy to patients with moderate COVID-19
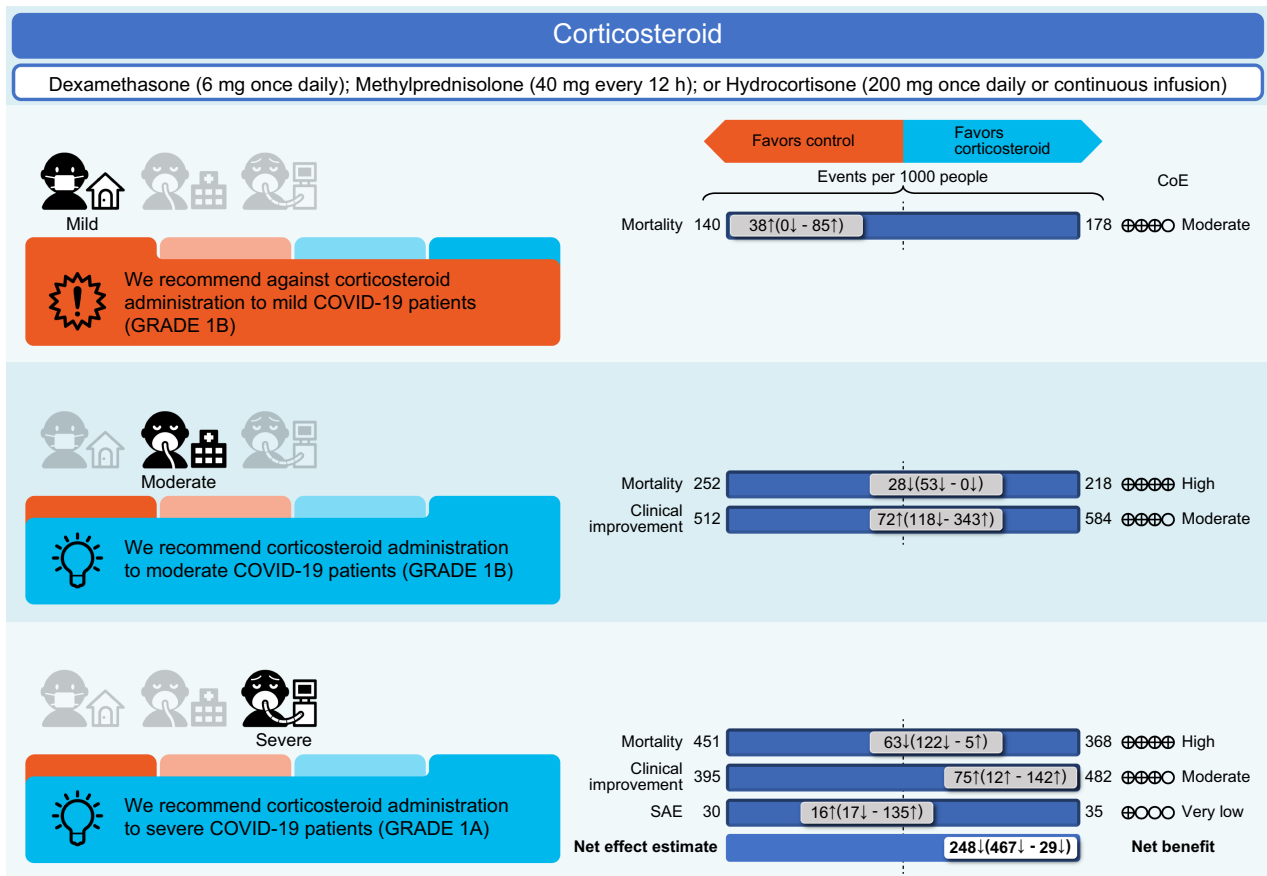
Fig. 3. Recommendations of corticosteroid for management for COVID-19 (CQ4-1). We recommend against corticosteroid administration to patients with mild COVID-19 and recommend its administration to patients with moderate and severe COVID-19. Net effect estimates of corticosteroids in patients with severe COVID-19 were calculated using the effects of each outcome, in which the importance of mortality was considered to be three times higher than that 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. Abbreviations: CoE, certainty of evidence; GRADE, Grades of Recommendation, Assessment, Development, and Evaluation; SAE, severe adverse events.

requiring oxygen administration/hospitalization and to patients with severe COVID-19 requiring mechanical ventilation/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.

Recommendation rationale
■ Balance between benefits and harm

We adopted two RCTs for hospitalized patients.[40,41] These RCTs determined that the target patients were admitted to the intensive care unit but were not ventilated. As such, it was classified as "moderate" in this guideline.

Three hundred sixty-three cases were adopted, and a moderate effect was expected in all-cause mortality at the time of discharge (decrease of 104 per 1,000). No data were available for clinical improvement, and serious adverse events were expected to have a slight effect (25 per 1,000 reductions). However, the quality of the RCTs was low, and the overall certainty of the evidence was very low. Therefore, the balance between these effects was unclear.

■ Certainty of evidence
The overall certainty of evidence was set to "very low."

CQ5 Should tocilizumab be administered to patients with COVID-19?

Recommendation

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

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

Recommendation rationale
- ■ Balance between benefits and harm

In 15 RCTs[42–56] with 8,318 cases of severe/moderate COVID-19, tocilizumab for moderate COVID-19 was expected to decrease all-cause mortality by 32 per 1,000 and increase clinical improvement by 35 per 1,000 on day 28. For severe COVID-19, a decrease of 16 per 1,000 was expected for all-cause mortality at 28 days, and an increase of 12 per 1,000 was expected for improvement of clinical symptoms (Fig. 4). The incidence of serious adverse events did not increase in the severe/moderate COVID-19 cases (18 per 1,000 decrease).

Based on the above statements, it was determined that the benefit of tocilizumab administration would outweigh the harm in patients with severe/moderate COVID-19. The balance between the benefits and harms of tocilizumab was undeterminable in patients with mild COVID-19.
- ■ Certainty of evidence

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

CQ7-1 Should anticoagulants be administered to patients with COVID-19?

Recommendation

- We suggest against anticoagulant administration to patients with mild COVID-19 who do not require oxygen (weak recommendation/low certainty of evidence: GRADE 2C).
- We recommend anticoagulant administration to patients with moderate COVID-19 requiring oxygen administration/hospitalization and to patients with severe COVID-19 requiring mechanical ventilation/intensive care (good practice statement).

Background   Coagulopathy due to angiopathy associated with a viral infection is considered a pathological condition of COVID-19. Pulmonary embolism is one of the causes of death from COVID-19, and prevention of thrombus formation is expected to lead to improvement in patient prognosis. Given the clinical significance of examining the effectiveness of anticoagulant therapy, including the dose, this CQ was formulated.
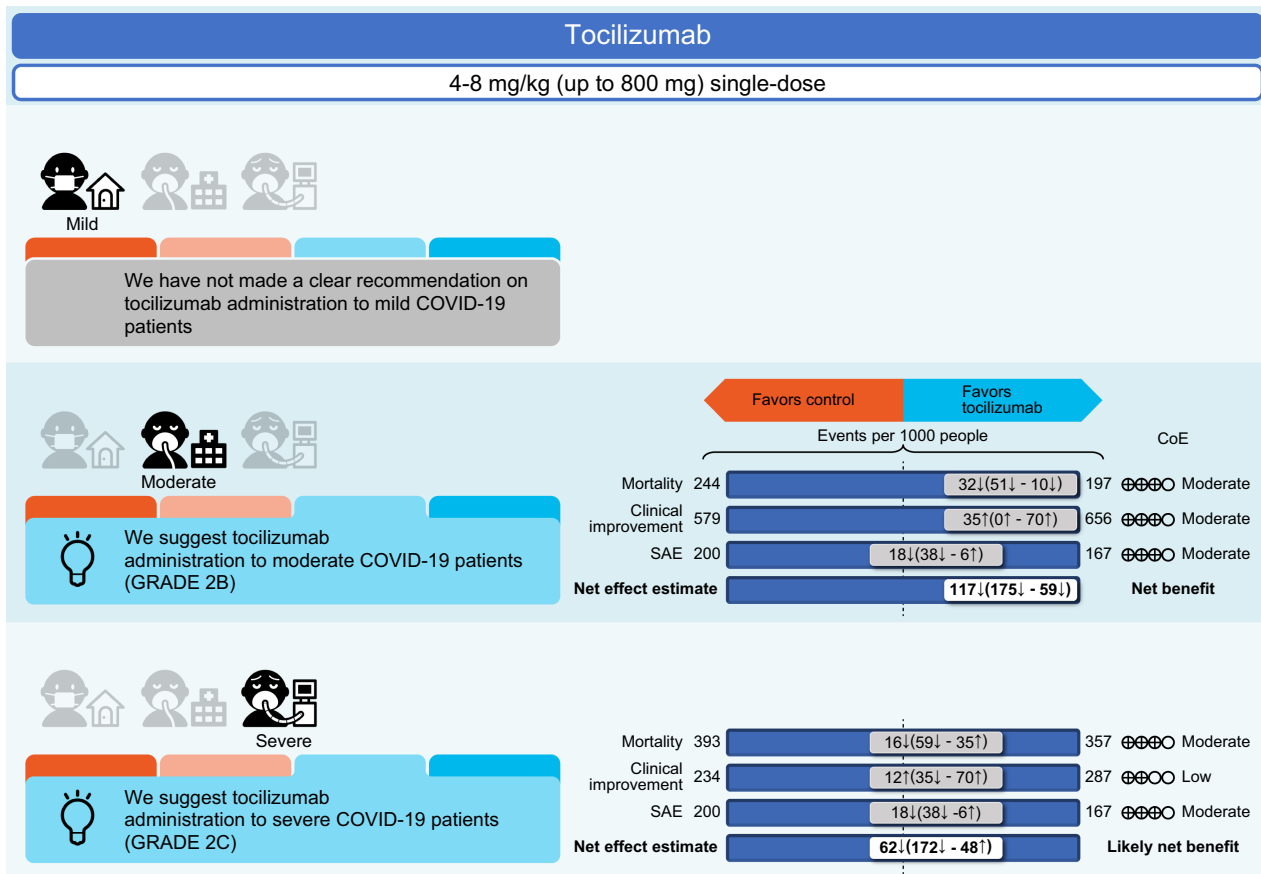
Recommendation rationale
- ■ Balance between benefit and harm

There was one RCT[57] with adopted evidence for patients with mild COVID-19. Anticoagulant therapy in patients with mild COVID-19 had an absolute effect of an increase of 3 per 1,000 for all-cause deaths and cardiovascular events, 24 per 1,000 for medical visits within 45 days, and 53 per 1,000 for all bleeding events (Fig. 5). Thus, it was determined that the benefit of not receiving anticoagulant therapy exceeded that of receiving it.

Multiple RCTs related to anticoagulant therapy in patients with moderate-to-severe COVID-19 have been reported, but no RCT comparing the presence or absence of anticoagulant therapy has been reported. As far as the comparative control groups in the RCTs reported so far have been evaluated, the discussion is premised on providing anticoagulant therapy. As such, we believe that the implementation of anticoagulant therapy is a good practice statement.
- ■ Certainty of evidence

Evidence for all-cause mortality and cardiovascular events, visits to medical institutions within 45 days, and the combined outcome of all bleeding events was determined to be "low" in patients with mild COVID-19.

Fig. 4. Recommendations of tocilizumab for management for COVID-19 (CQ5). We have not made a clear recommendation on tocilizumab administration to patients with mild COVID-19 and suggest its administration to patients with moderate and severe COVID-19. Net effect estimates of tocilizumab in patients with moderate and severe COVID-19 were calculated using the effects of each outcome, in which the importance of mortality was considered to be twice as high as 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 the 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.

CQ7-2 What doses of anticoagulants should be administered to patients with COVID-19?

Recommendation

- We suggest therapeutic doses of anticoagulant administration to patients with moderate COVID-19 requiring oxygen administration/hospitalization (weak recommendation/low certainty of evidence: GRADE 2C).
- We suggest prophylactic doses of anticoagulant administration to patients with severe COVID-19 requiring ventilator management/intensive care (weak recommendation/moderate certainty of evidence: GRADE 2B).

Background Anticoagulant therapies have been tested using two administration methods: a prophylactic dose and a therapeutic dose for thrombosis. To date, multiple RCTs have compared prophylactic and therapeutic doses in patients with moderate and severe COVID-19. Therefore, this CQ was formulated as follows.

Recommendation rationale
- Balance between benefit and harm

There are five RCTs[58–62] including 3,365 patients with the adopted evidence for patients with moderate COVID-19 (Fig. 5). In studies comparing therapeutic and prophylactic doses, the absolute effect of anticoagulant therapy on all-cause mortality in patients with moderate COVID-19 was increased by 2 per 1,000, organ support-free at day 28 was increased by 38 per 1,000, and severe bleeding was increased by 12 per 1,000. Based on the above, it was
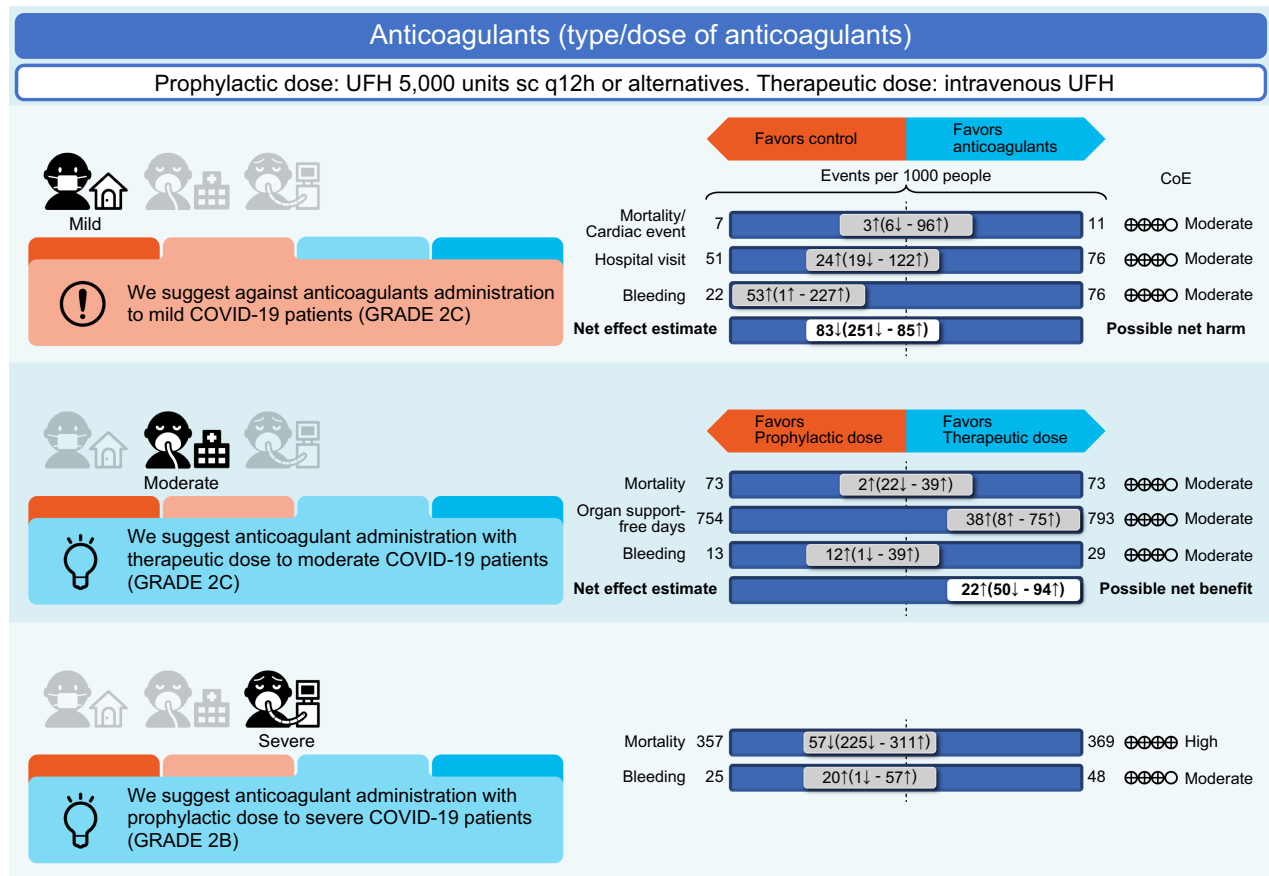
Fig. 5. Recommendations of anticoagulants for management for COVID-19 (CQ7-1 and CQ7-2). We suggest against anticoagulant administration to patients with mild COVID-19, suggest anticoagulant administration with therapeutic dose to patients with moderate COVID-19, and suggest administration with prophylactic dose to patients with mild COVID-19. The net effect estimates of anticoagulants in patients with mild and moderate COVID-19 were calculated with the effects of each outcome, in which the importance of mortality was considered to be twice as high as those of other outcomes. Overall imprecisions across outcomes were assessed as "possible net harm" in mild COVID-19 and "possible net benefit" in moderate COVID-19 based on the magnitude of the point estimate and 95% confidence intervals of the calculated net effect estimates. Abbreviation: CoE, certainty of evidence; GRADE, Grades of Recommendation, Assessment, Development, and Evaluation; UFH, unfractionated heparin.

determined that the benefit of the therapeutic dose of anticoagulant therapy would outweigh the harm in patients with moderate COVID-19.

There are three RCTs[62–64] including 1,123 patients with the adopted evidence for patients with severe COVID-19. In studies comparing the therapeutic and prophylactic doses of anticoagulant therapy for patients with severe COVID-19, the absolute effect of all-cause mortality was 57 fewer per 1,000 patients, and severe bleeding was 20 more per 1,000 patients. The adjusted odds ratio of the therapeutic dose to the prophylactic dose for organ support-free days up to day 21 was 0.83 (0.67–1.03). Based on the above, it was determined that the benefit of prophylactic doses of anticoagulant therapy would outweigh the harm in severe patients.

■ Certainty of evidence

Evidence for all-cause mortality, organ support-free status, and severe bleeding outcomes was assessed as "low" in patients with moderate COVID-19 and "moderate" in patients with severe COVID-19.

CQ8 Should baricitinib be administered to patients with COVID-19?

Recommendation

• We have not made a clear recommendation on baricitinib administration to patients with mild COVID-19 who do not require oxygen (no recommendation).

- We suggest baricitinib administration to patients with moderate COVID-19 requiring oxygen/hospitalization (weak recommendation/low certainty of evidence: GRADE 2C).
- We suggest baricitinib administration to patients with severe COVID-19 requiring mechanical ventilation/intensive care (weak recommendation/low certainty of evidence: GRADE 2C).

Background The aggravation of COVID-19 has been attributed to excessive immune response. Baricitinib is an orally administered selective inhibitor of Janus kinases 1 and 2. It suppresses excessive immune responses by suppressing the intracellular cytokine signaling pathway. In Japan, it was approved for use in combination with

remdesivir in cases requiring supplemental oxygen on April 23, 2021. The efficacy of baricitinib has not yet been determined and it is considered to have great clinical significance in planning CQs.

Recommendation rationale

■ Balance between benefit and harm

In three RCTs[65–67] with 2,659 cases of severe/moderate COVID-19, baricitinib for moderate COVID-19 was expected to decrease all-cause mortality by 42 per 1,000 and increase clinical improvement by 33 per 1,000 (Fig. 6). The incidence of serious adverse events did not increase (decrease of 40 per 1,000). The net effect estimates were 199 fewer per 1,000 when the weighted importance of mortality
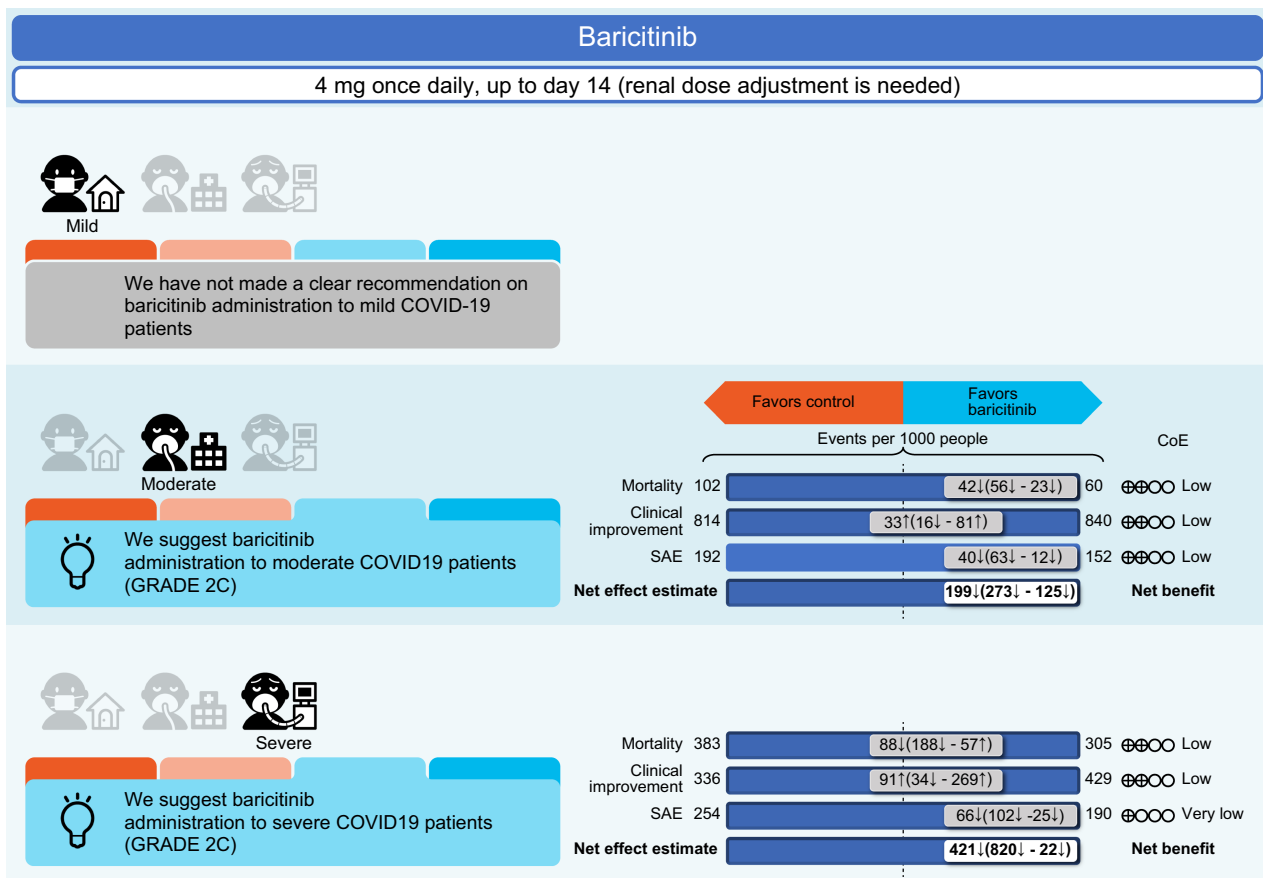
Fig. 6. Recommendations of baricitinib for management for COVID-19 (CQ8). We have not made a clear recommendation on baricitinib administration to patients with mild COVID-19 and suggest baricitinib administration to patients with moderate and severe COVID-19. Net effect estimates of baricitinib in patients with moderate and severe COVID-19 were calculated using the effects of each outcome, in which the importance of mortality was considered to be 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. Abbreviations: CoE, certainty of evidence; GRADE, Grades of Recommendation, Assessment, Development, and Evaluation; SAE, severe adverse events.

outcomes was tripled over other outcomes, and the directionality was the same as when it was not weighted. Therefore, we believe that the benefits outweighed the harm.

Baricitinib for severe COVID-19 was expected to decrease all-cause mortality by 88 per 1,000 and increase clinical improvement by 91 per 1,000. The incidence of serious adverse events did not increase (decrease of 66 per 1,000). The net effect estimates were 421 fewer per 1,000 when the weighted importance of mortality outcomes was tripled over other outcomes, and the directionality was the same as when it was not weighted. Therefore, we believe that the benefits outweighed the harm.

■ Certainty of evidence

The certainty of evidence at each outcome was "low" or "very low" in moderate/severe COVID-19. Considering the net effect estimate, the overall certainty of the evidence was determined as "low" in patients with moderate/severe COVID-19.

■ Others (tolerability and feasibility)

Baricitinib has been approved in Japan for the treatment of COVID-19 in combination with remdesivir. The efficacy of the combined use of the three drugs (baricitinib, remdesivir, and steroid) has not been fully evaluated.

Q9-1 Should casirivimab/imdevimab be administered to patients with COVID-19?

Recommendation

• We suggest casirivimab/imdevimab administration to patients with mild COVID-19 who do not require oxygen (weak recommendation/low certainty of evidence: GRADE 2C).

• We have not made a clear recommendation on casirivimab/imdevimab administration to patients with moderate COVID-19 requiring oxygen/hospitalization or patients with severe COVID-19 requiring mechanical ventilation/intensive care (no recommendation).

Background Casirivimab/imdevimab is an antibody cocktail therapy that simultaneously administers two monoclonal antibodies against SARS-CoV-2 and is expected to be effective against COVID-19. However, its effectiveness has not been established; hence, we formulated this CQ.

Recommendation rationale
■ Balance between benefit and harm

In 5,665 cases of mild COVID-19 in four RCTs,[68–71] all-cause mortality was expected to decrease by 9 per 1,000, clinical improvement was expected to increase by 29 per 1,000, and the incidence of serious adverse events did not

increase (decrease of 30 per 1,000; Fig. 7). In all outcomes, the intervention group showed benefits. We determined that the benefits likely outweighed the harm.

In contrast, in 9,811 moderate/severe cases in two RCTs, all-cause mortality was expected to decrease by 25 per 1,000, clinical improvement was expected to increase by 14 per 1,000, and the incidence of serious adverse events did not increase (decrease of 42 per 1,000). However, the overall certainty of evidence was very low, and the balance between benefit and harm was determined to be uncertain in patients with moderate/severe COVID-19.

■ Certainty of evidence

The certainty of evidence in all-cause mortality, clinical improvement, and serious adverse events was "very low," "low," and "very low," respectively, in patients with mild COVID-19, and "very low," "low," "very low," respectively, in patients with moderate/severe COVID-19. The inaccuracies in the net effect estimate across all outcomes were "Net benefit" in mild COVID-19 and "Likely net benefit" in moderate/severe COVID-19. From the above, it was ultimately determined that the overall evidence certainty was "low" in mild COVID-19 and "very low" in moderate/severe COVID-19.

■ Others (tolerability and feasibility)

Drug efficacy is likely to vary depending on the genotype of the mutant strain. Thus, indications should be judged based on the latest epidemiological information.

CQ9-2 Should sotrovimab be administered to patients with COVID-19?

Recommendation

• We suggest sotrovimab administration to patients with mild COVID-19 who do not require oxygen (weak recommendation/low certainty of evidence: GRADE 2C).

• We have not made a clear recommendation on sotrovimab administration to patients with moderate COVID-19 requiring oxygen/hospitalization or patients with severe COVID-19 requiring mechanical ventilation/intensive care (no recommendation).

Background Sotrovimab is a monoclonal antibody that binds to a specific site different from the ACE2 receptor on the SARS-CoV-2 spike protein, exhibiting a neutralizing effect on SARS-CoV-2. The drug targets a highly conservative epitope shared by SARS-CoV-2 and SARS-CoV-1, which is inconsistent with the site of a genetic mutation previously reported in the mutant strain. Therefore, it is expected to exert similar effects on future mutant strains. Hence, this CQ has been raised as an essential issue to be addressed.
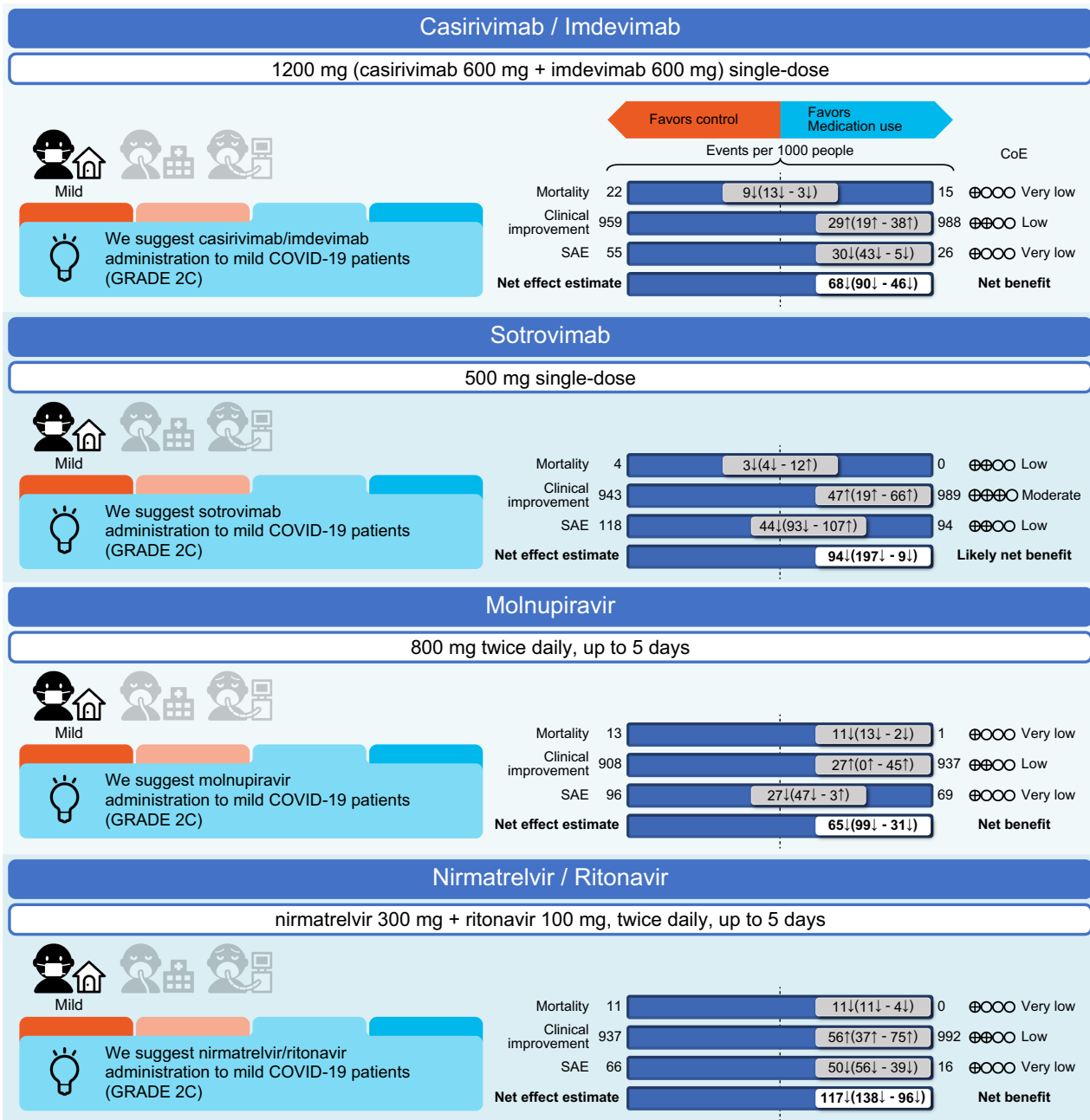
Fig. 7. Recommendations of casirivimab/imdevimab, sotrovimab, molnupiravir, and nirmatrelvir/ritonavir for management for COVID-19 (CQ9-1, CQ9-2, CQ10, and CQ11). We suggest casirivimab/imdevimab, sotrovimab, molnupiravir, and nirmatrelvir/ritonavir administration to patients with mild COVID-19. Net effect estimates of casirivimab/imdevimab, sotrovimab, molnupiravir, and nirmatrelvir/ritonavir in patients with mild COVID-19 were calculated with the effects of each outcome, in which the importance of mortality was considered to be the same as those of other outcomes. Overall imprecisions across outcomes were assessed as "net benefit" in casirivimab/imdevimab, molnupiravir, and nirmatrelvir/ritonavir and "likely net benefit" in sotrovimab based on the magnitude of the point estimate and 95% confidence intervals of the calculated net effect estimates. Abbreviations: CoE, certainty of evidence; GRADE, Grades of Recommendation, Assessment, Development, and Evaluation; SAE, severe adverse events.

Recommendation rationale

■ Balance between benefit and harm

In two RCTs[72,74] with 1,409 patients with mild COVID-19, the administration of sotrovimab decreased all-cause mortality by 3 per 1,000, clinical symptom improvement by 47 per 1,000, and serious adverse events by 44 per 1,000 (Fig. 7). Sotrovimab administration to patients with mild COVID-19 positively affected each outcome. Meanwhile, in patients with moderate COVID-19, we did not obtain sufficient results to make a recommendation. In addition, no RCTs that examined the drug effects on patients with severe COVID-19 were detected. These results showed that the benefit of drug administration outweighed the harm in patients with mild COVID-19, while it was impossible to judge the balance of benefit and harm in patients with moderate to severe COVID-19.

■ Certainty of evidence

For patients with mild COVID-19, the certainty of evidence regarding all-cause mortality, clinical improvement, and serious adverse events was judged to be "low," "moderate," and "low," respectively. Considering the inaccuracy of the net effect estimate across all outcomes, the overall evidence certainty was determined to be "low."

■ Others (tolerability and feasibility)

Drug efficacy is likely to vary depending on the genotype of the mutant strain. Thus, indications should be judged based on the latest epidemiological information.

CQ10 Should molnupiravir be administered to patients with COVID-19?

Recommendation

• We suggest molnupiravir administration to patients with mild COVID-19 who do not require oxygen (weak recommendation/low certainty of evidence: GRADE 2C).

• We have not made a clear recommendation on molnupiravir administration to patients with moderate COVID-19 requiring oxygen/hospitalization and patients with severe COVID-19 requiring mechanical ventilation/intensive care (no recommendation).

Background Molnupiravir is a low-molecular-weight nucleotide prodrug of N-hydroxycytidine with activity against RNA viruses such as SARS-CoV-2. It is an agent that introduces mutations into viral RNA sequences by acting on RNA-dependent RNA polymerase, which is essential for self-replication of RNA viruses, and inhibits the growth of viruses. The drug was approved in Japan for the treatment of COVID-19 on December 24, 2021. It is important to reduce the pathological deterioration of patients at risk of

severe disease, and this is considered to be of great clinical significance in the formulation of this CQ.

Recommendation rationale

■ Balance between benefit and harm

There was one RCT[75] with the adopted evidence (Fig. 7). In mild COVID-19 cases, a small effect is expected on all-cause mortality (decrease of 11 per 1,000) and improvement in clinical symptoms (increase of 27 per 1,000). There was no increase in the incidence of serious adverse events (decrease of 27 per 1,000). Therefore, for patients with mild COVID-19, it was determined that the benefit of molnupiravir administration outweighed the harm. There was no evidence for moderate or severe COVID-19, and it was deemed indeterminate.

■ Certainty of evidence

The certainty of evidence for each outcome is "low." The net effect estimate was considered and determined to be "low".

■ Others (tolerability and feasibility)

As the adopted evidence does not include omicron strains, caution should be exercised against their effects. In addition, the adopted RCTs were conducted on unvaccinated people, different from the current situation in Japan, where the vaccination rate is over 80%.

CQ11 Should nirmatrelvir/ritonavir be administered to patients with COVID-19?

Recommendation

• We suggest nirmatrelvir/ritonavir administration to patients with mild COVID-19 who do not require oxygen (weak recommendation/low certainty of evidence: GRADE 2C).

• We have not made a clear recommendation on nirmatrelvir/ritonavir administration to patients with moderate COVID-19 requiring oxygen/hospitalization or those with severe COVID-19 requiring mechanical ventilation/intensive care (no recommendation).

Background Nirmatrelvir/ritonavir is a combination of nirmatrelvir, which inhibits the main protease (Mpro) essential for viral replication of SARS-CoV-2, and ritonavir, which inhibits CYP3A4 that metabolizes it, and maintains effective blood concentration. It is important to reduce the deterioration of patients at risk of severe disease, and this is likely of great clinical significance in the formulation of CQs.

Recommendation rationale

■ Balance between benefit and harm

One RCT with 2,246 cases was adopted (Fig. 7).[76] In mild cases, nirmatrelvir/ritonavir was expected to decrease all-cause mortality by 11 per 1,000 and increase clinical improvement by 56 per 1,000. The incidence of serious

adverse events did not increase (decrease of 50 per 1,000). Based on these data, the benefits outweighed harm in patients with mild COVID-19, whereas they were indeterminate in patients with moderate/severe COVID-19.

■ Certainty of evidence

The certainty of evidence for each outcome was "low" or "very low" in patients with mild COVID-19. Taking this into consideration, the overall certainty of evidence was determined to be "low" for patients with mild COVID-19.

■ Others (tolerability and feasibility)

As the adopted evidence does not include omicron strains, caution should be exercised against their effects. In addition, the adopted RCTs were conducted on unvaccinated people, different from the current situation in Japan, where the vaccination rate is over 80%.

RECOMMENDATIONS THAT STOPPED THE UPDATES

TWO YEARS HAVE passed since the emergence of COVID-19. Some drugs that were initially expected to be effective against COVID-19 have been rejected, and several other novel drugs have been developed. Considering these clinical situations about COVID-19, the panel decided to stop the updates of two CQs (hydroxychloroquine [CQ3] and ciclesonide [CQ6]) in the updated version. Dated recommendations were as follows.[1]

CQ3 Should hydroxychloroquine be administered to patients with COVID-19? (last updated July 11, 2021)

Recommendation

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

CQ6 Should ciclesonide be administered by inhalation to patients with COVID-19? (last updated January 27, 2021)

Recommendation

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

ACKNOWLEDGMENTS

DISCLOSURE

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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:

Table S1 Task Force for the Japanese Rapid/Living recommendations on drug management for COVID-19.