UNIVERSIDADE DE BRASÍLIA
PROGRAMA DE PÓS-GRADUAÇÃO EM CIÊNCIAS E TECNOLOGIAS EM SAÚDE
EDITAL 001/2021
SELEÇÃO DE CANDIDATOS ÀS VAGAS DO PROGRAMA DE PÓS-GRADUAÇÃO EM CIÊNCIAS E TECNOLOGIAS EM SAÚDE PARA OS CURSOS DE MESTRADO ACADEMICO E DOUTORADO, INGRESSO SEGUNDO PERÍODO LETIVO DE 2021

COMUNICADO

Aos: Candidatos do Edital 001/2021 – Seleção de candidatos a Alunos Regulares do Programa de Pós-Graduação em Ciências e Tecnologias em Saúde (PPGCTS)

Assunto: Etapa 4 do Processo Seletivo - Avaliação Oral Individual

Prezados(as) candidatos(as),

De acordo com o Edital 001/2021, a Etapa 4 do Processo Seletivo, referente a Avaliação Oral Individual que ocorrerá entre os dias 20 e 26/10/2021.

A avaliação será realizada pela Plataforma Institucional **Microsoft Teams**.

As bancas com as respectivas datas e horários de cada candidato e o link do evento estão apresentados na Tabela 1 (Anexo 1).

Atenção para o passo-a-passo de como acessar a sala:

Passo 1.

1a) Crie uma conta no Microsoft Teams, caso você ainda não a tenha.

1b) Link para acessar o Microsoft Teams e criar sua conta:

https://www.microsoft.com/pt-br/microsoft-365/microsoft-teams/group-chat-software

1c) Baixe o aplicativo do Microsoft Teams em seu computador (Figura 1). Não use o celular, pois você precisará do recurso de apresentação de tela para projetar sua apresentação.

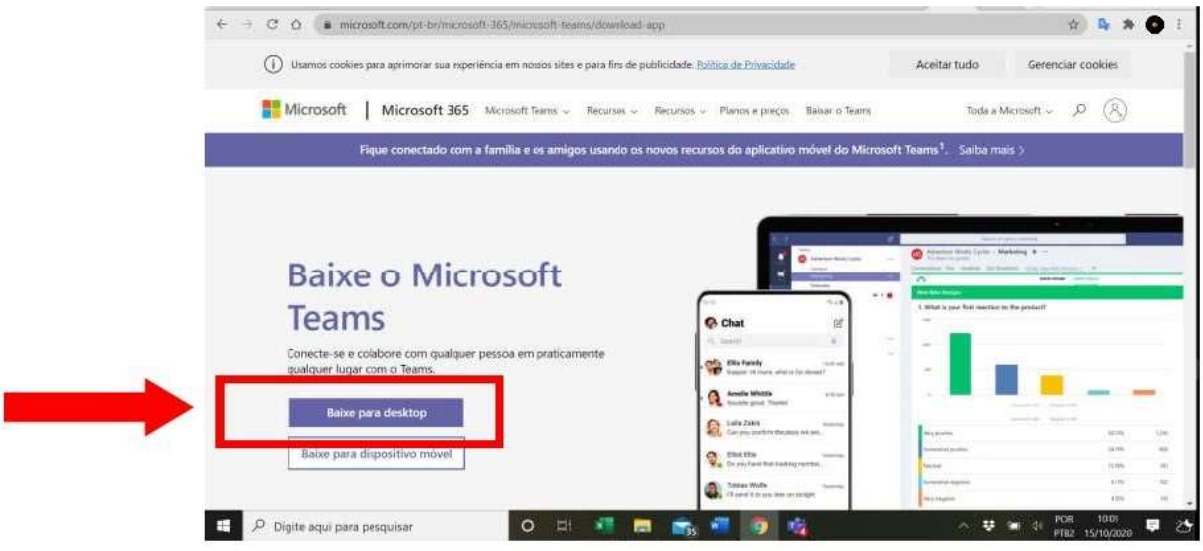

Figura 1

Passo 2.

2a) Após criar a sua conta, acesse o link da reunião no dia e horário que estão apresentados na Tabela 1 (Anexo 1).

Passo 3

3a. - Você deverá solicitar permissão para acessar a sala virtual e aguardar até o momento que o avaliador autorize conforme **Figura 2**. Após a permissão de sua entrada na sala virtual, você será convidado a entrar na reunião que está em andamento.

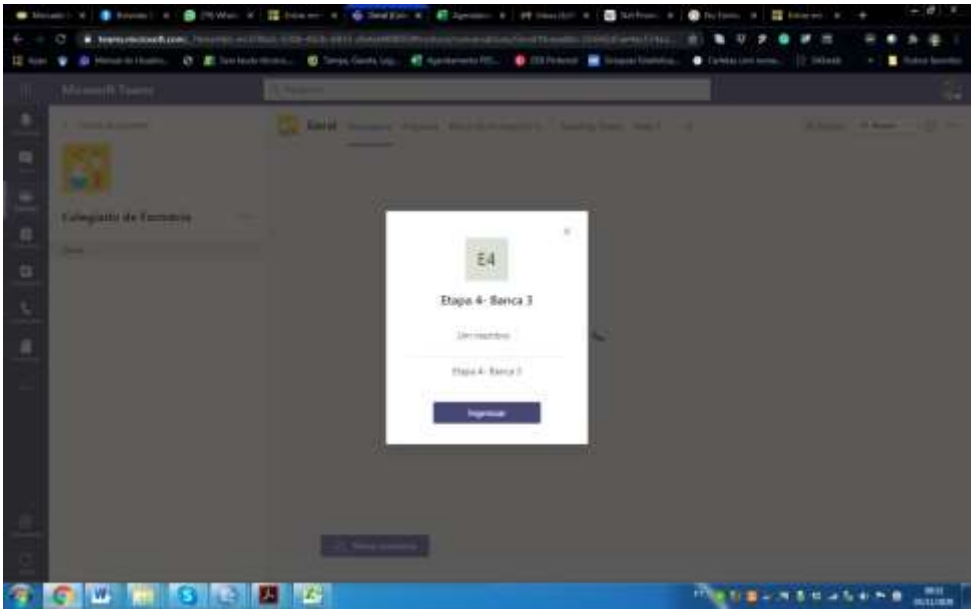

Figura 2

Informações Importantes:

- Acesse a sala por meio de um **computador que possibilite o uso de câmera de forma nítida**. Vocês permanecerão com as câmeras ligadas durante todo o período da Avaliação.

- A entrada do(a) candidato(a) no evento será permitida pelos membros da banca apenas na data e horário descritos na Tabela 1 (Anexo 1), referente ao seu número de inscrição.

- Ao entrar no evento mantenha a câmera ligada o tempo todo. Será solicitado que você confirme seu nome, CPF e faça a conferência por meio de algum documento com foto.

- Será de sua responsabilidade escolha do programa para a confecção da apresentação do memorial e do artigo, bem como o manejo do recurso audiovisual.

- Para fins de registro desta etapa haverá gravação efetuada pela banca examinadora.

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Anexo 1

Equipe	Linha	Nº Inscrição	Data	Horário	Link da Sala
Equipe 1	Estratégias diagnósticas, terapêuticas e assistenciais para o desenvolvimento da saúde e funcionalidade humana.	202100676038021	20/10/2021	14:00	https://teams.microsoft.com/l/meetup-join/19%3aGIbsXu53KQ3F3eGK6_f8C9FaK82-63iQxFPpsoW7Kkg1%40thread.tacv2/1634230056469?context=%7b%22Tid%22%3a%22ec359ba1-630b-4d2b-b833-c8e6d48f8059%22%2c%22Oid%22%3a%22ea630b1e-32e1-48b0-80e2-6ab50ed94040%22%7d
		202100676038031	20/10/2021	14:40	https://teams.microsoft.com/l/meetup-join/19%3aGIbsXu53KQ3F3eGK6_f8C9FaK82-63iQxFPpsoW7Kkg1%40thread.tacv2/1634230157638?context=%7b%22Tid%22%3a%22ec359ba1-630b-4d2b-b833-c8e6d48f8059%22%2c%22Oid%22%3a%22ea630b1e-32e1-48b0-80e2-6ab50ed94040%22%7d
		202100676038026	20/10/2021	15:20	https://teams.microsoft.com/l/meetup-join/19%3aGIbsXu53KQ3F3eGK6_f8C9FaK82-63iQxFPpsoW7Kkg1%40thread.tacv2/1634230466085?context=%7b%22Tid%22%3a%22ec359ba1-630b-4d2b-b833-c8e6d48f8059%22%2c%22Oid%22%3a%22ea630b1e-32e1-48b0-80e2-6ab50ed94040%22%7d
		202100676037665	20/10/2021	16:00	https://teams.microsoft.com/l/meetup-join/19%3aGIbsXu53KQ3F3eGK6_f8C9FaK82-63iQxFPpsoW7Kkg1%40thread.tacv2/1634230648229?context=%7b%22Tid%22%3a%22ec359ba1-630b-4d2b-b833-c8e6d48f8059%22%2c%22Oid%22%3a%22ea630b1e-32e1-48b0-80e2-6ab50ed94040%22%7d
		202100676037624	21/10/2021	09:20	https://teams.microsoft.com/l/meetup-join/19%3aGIbsXu53KQ3F3eGK6_f8C9FaK82-63iQxFPpsoW7Kkg1%40thread.tacv2/1634234209058?context=%7b%22Tid%22%3a%22ec359ba1-630b-4d2b-b833-c8e6d48f8059%22%2c%22Oid%22%3a%22ea630b1e-32e1-48b0-80e2-6ab50ed94040%22%7d
		202100676037977	21/10/2021	10:00	https://teams.microsoft.com/l/meetup-join/19%3aGIbsXu53KQ3F3eGK6_f8C9FaK82-63iQxFPpsoW7Kkg1%40thread.tacv2/1634236626030?context=%7b%22Tid%22%3a%22ec359ba1-630b-4d2b-b833-c8e6d48f8059%22%2c%22Oid%22%3a%22ea630b1e-32e1-48b0-80e2-6ab50ed94040%22%7d
		202100676038045	21/10/2021	10:40	https://teams.microsoft.com/l/meetup-join/19%3aGIbsXu53KQ3F3eGK6_f8C9FaK82-63iQxFPpsoW7Kkg1%40thread.tacv2/1634234476922?context=%7b%22Tid%22%3a%22ec359ba1-630b-4d2b-b833-c8e6d48f8059%22%2c%22Oid%22%3a%22ea630b1e-32e1-48b0-80e2-6ab50ed94040%22%7d
		202100676037887	21/10/2021	11:20	https://teams.microsoft.com/l/meetup-join/19%3aGIbsXu53KQ3F3eGK6_f8C9FaK82-63iQxFPpsoW7Kkg1%40thread.tacv2/1634236034920?context=%7b%22Tid%22%3a%22ec359ba1-630b-4d2b-b833-c8e6d48f8059%22%2c%22Oid%22%3a%22ea630b1e-32e1-48b0-80e2-6ab50ed94040%22%7d

		202100676038013	22/10/2021	14:00	https://teams.microsoft.com/l/meetup-join/19%3aGIbsXu53KQ3F3eGK6_f8C9FaK82-63iQxFPpsoW7Kkg1%40thread.tacv2/1634236184477?context=%7b%22Tid%22%3a%22ec359ba1-630b-4d2b-b833-c8e6d48f8059%22%2c%22Oid%22%3a%22ea630b1e-32e1-48b0-80e2-6ab50ed94040%22%7d
		202100676037862	22/10/2021	14:40	https://teams.microsoft.com/l/meetup-join/19%3aGIbsXu53KQ3F3eGK6_f8C9FaK82-63iQxFPpsoW7Kkg1%40thread.tacv2/1634235772343?context=%7b%22Tid%22%3a%22ec359ba1-630b-4d2b-b833-c8e6d48f8059%22%2c%22Oid%22%3a%22ea630b1e-32e1-48b0-80e2-6ab50ed94040%22%7d

Equipe	Linha	Nº Inscrição	Data	Horário	Link da Sala
Equipe 2	**Nanobiotecnologia Aplicada à Saúde**	202100676037915	20/10/2021	09:20	https://teams.microsoft.com/l/meetup-join/19%3asPvNUzW_4Fwbnm2rXj278m5x54YVEqGZQffpRMjwg5o1%40thread.tacv2/1634236791213?context=%7b%22Tid%22%3a%22ec359ba1-630b-4d2b-b833-c8e6d48f8059%22%2c%22Oid%22%3a%22ea630b1e-32e1-48b0-80e2-6ab50ed94040%22%7d
		202100676037927	20/10/2021	10:00	https://teams.microsoft.com/l/meetup-join/19%3asPvNUzW_4Fwbnm2rXj278m5x54YVEqGZQffpRMjwg5o1%40thread.tacv2/1634236866162?context=%7b%22Tid%22%3a%22ec359ba1-630b-4d2b-b833-c8e6d48f8059%22%2c%22Oid%22%3a%22ea630b1e-32e1-48b0-80e2-6ab50ed94040%22%7d
		202100676038030	20/10/2021	14:40	https://teams.microsoft.com/l/meetup-join/19%3asPvNUzW_4Fwbnm2rXj278m5x54YVEqGZQffpRMjwg5o1%40thread.tacv2/1634236961035?context=%7b%22Tid%22%3a%22ec359ba1-630b-4d2b-b833-c8e6d48f8059%22%2c%22Oid%22%3a%22ea630b1e-32e1-48b0-80e2-6ab50ed94040%22%7d
		202100676038001	20/10/2021	16:00	https://teams.microsoft.com/l/meetup-join/19%3asPvNUzW_4Fwbnm2rXj278m5x54YVEqGZQffpRMjwg5o1%40thread.tacv2/1634237035959?context=%7b%22Tid%22%3a%22ec359ba1-630b-4d2b-b833-c8e6d48f8059%22%2c%22Oid%22%3a%22ea630b1e-32e1-48b0-80e2-6ab50ed94040%22%7d
		202100676037675	21/10/2021	16:00	https://teams.microsoft.com/l/meetup-join/19%3asPvNUzW_4Fwbnm2rXj278m5x54YVEqGZQffpRMjwg5o1%40thread.tacv2/1634237087507?context=%7b%22Tid%22%3a%22ec359ba1-630b-4d2b-b833-c8e6d48f8059%22%2c%22Oid%22%3a%22ea630b1e-32e1-48b0-80e2-6ab50ed94040%22%7d

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Equipe	Linha	N º Inscrição	Data	Horário	Link da Sala
Equipe 3	Determinantes sócio biológicos e cuidado em saúde.	202100676038039	21/10/2021	08:00	https://teams.microsoft.com/l/message/19:KbQfjhoMB4lvinbHphFokzPg8Cl5MlF_vjlHO18tcNQ1@thread.tacv2/1634237793690?tenantId=ec359ba1-630b-4d2b-b833-c8e6d48f8059&groupId=b8878247-2647-4385-a3ae-1e8785e0e4d5&parentMessageId=1634237793690&teamName=Equipe%203%20-%20Determinantes%20s%C3%B3cio%20biol%C3%B3gicos%20e%20cuidados%20em%20sa%C3%BAde&channelName=Geral&createdTime=1634237793690
		202100676037668	21/10/2021	08:40	https://teams.microsoft.com/l/meetup-join/19%3aKbQfjhoMB4lvinbHphFokzPg8Cl5MlF_vjlHO18tcNQ1%40thread.tacv2/1634237869273?context=%7b%22Tid%22%3a%22ec359ba1-630b-4d2b-b833-c8e6d48f8059%22%2c%22Oid%22%3a%22ea630b1e-32e1-48b0-80e2-6ab50ed94040%22%7d
		202100676037934	25/10/2021	08:00	https://teams.microsoft.com/l/message/19:KbQfjhoMB4lvinbHphFokzPg8Cl5MlF_vjlHO18tcNQ1@thread.tacv2/1634238191972?tenantId=ec359ba1-630b-4d2b-b833-c8e6d48f8059&groupId=b8878247-2647-4385-a3ae-1e8785e0e4d5&parentMessageId=1634238191972&teamName=Equipe%203%20-%20Determinantes%20s%C3%B3cio%20biol%C3%B3gicos%20e%20cuidados%20em%20sa%C3%BAde&channelName=Geral&createdTime=1634238191972
		202100676038005	25/10/2021	08:40	https://teams.microsoft.com/l/meetup-join/19%3aKbQfjhoMB4lvinbHphFokzPg8Cl5MlF_vjlHO18tcNQ1%40thread.tacv2/1634238278280?context=%7b%22Tid%22%3a%22ec359ba1-630b-4d2b-b833-c8e6d48f8059%22%2c%22Oid%22%3a%22ea630b1e-32e1-48b0-80e2-6ab50ed94040%22%7d
		202100676038036	25/10/2021	09:20	https://teams.microsoft.com/l/meetup-join/19%3aKbQfjhoMB4lvinbHphFokzPg8Cl5MlF_vjlHO18tcNQ1%40thread.tacv2/1634238374097?context=%7b%22Tid%22%3a%22ec359ba1-630b-4d2b-b833-c8e6d48f8059%22%2c%22Oid%22%3a%22ea630b1e-32e1-48b0-80e2-6ab50ed94040%22%7d
		202100676038004	25/10/2021	10:00	https://teams.microsoft.com/l/meetup-join/19%3aKbQfjhoMB4lvinbHphFokzPg8Cl5MlF_vjlHO18tcNQ1%40thread.tacv2/1634238474595?context=%7b%22Tid%22%3a%22ec359ba1-630b-4d2b-b833-c8e6d48f8059%22%2c%22Oid%22%3a%22ea630b1e-32e1-48b0-80e2-6ab50ed94040%22%7d
		202100676037626	26/10/2021	08:00	https://teams.microsoft.com/l/meetup-join/19%3aKbQfjhoMB4lvinbHphFokzPg8Cl5MlF_vjlHO18tcNQ1%40thread.tacv2/1634238602590?context=%7b%22Tid%22%3a%22ec359ba1-630b-4d2b-b833-c8e6d48f8059%22%2c%22Oid%22%3a%22ea630b1e-32e1-48b0-80e2-6ab50ed94040%22%7d
		202100676037817	26/10/2021	08:40	https://teams.microsoft.com/l/meetup-join/19%3aKbQfjhoMB4lvinbHphFokzPg8Cl5MlF_vjlHO18tcNQ1%40thread.tacv2/1634238674039?context=%7b%22Tid%22%3a%22ec359ba1-630b-4d2b-b833-c8e6d48f8059%22%2c%22Oid%22%3a%22ea630b1e-32e1-48b0-80e2-6ab50ed94040%22%7d

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Equipe	Linha	Nº Inscrição	Data	Horário	Link da Sala
Equipe 4	Políticas, Programas, Serviços, Educação e Sociabilidade em Saúde	202100676037657	21/10/2021	14:00	https://teams.microsoft.com/l/meetup-join/19%3atbLDGfq90AG9g6FtKY0WEfBlW6K_ILlfyUt2h1Vfpyo1%40thread.tacv2/1634239039419?context=%7b%22Tid%22%3a%22ec359ba1-630b-4d2b-b833-c8e6d48f8059%22%2c%22Oid%22%3a%22ea630b1e-32e1-48b0-80e2-6ab50ed94040%22%7d
		202100676037959	21/10/2021	14:40	https://teams.microsoft.com/l/meetup-join/19%3atbLDGfq90AG9g6FtKY0WEfBlW6K_ILlfyUt2h1Vfpyo1%40thread.tacv2/1634239115129?context=%7b%22Tid%22%3a%22ec359ba1-630b-4d2b-b833-c8e6d48f8059%22%2c%22Oid%22%3a%22ea630b1e-32e1-48b0-80e2-6ab50ed94040%22%7d
		202100676037822	22/10/2021	08:40	https://teams.microsoft.com/l/meetup-join/19%3atbLDGfq90AG9g6FtKY0WEfBlW6K_ILlfyUt2h1Vfpyo1%40thread.tacv2/1634239179356?context=%7b%22Tid%22%3a%22ec359ba1-630b-4d2b-b833-c8e6d48f8059%22%2c%22Oid%22%3a%22ea630b1e-32e1-48b0-80e2-6ab50ed94040%22%7d
		202100676038025	22/10/2021	09:20	https://teams.microsoft.com/l/meetup-join/19%3atbLDGfq90AG9g6FtKY0WEfBlW6K_ILlfyUt2h1Vfpyo1%40thread.tacv2/1634239301930?context=%7b%22Tid%22%3a%22ec359ba1-630b-4d2b-b833-c8e6d48f8059%22%2c%22Oid%22%3a%22ea630b1e-32e1-48b0-80e2-6ab50ed94040%22%7d
		202100676038019	22/10/2021	10:00	https://teams.microsoft.com/l/meetup-join/19%3atbLDGfq90AG9g6FtKY0WEfBlW6K_ILlfyUt2h1Vfpyo1%40thread.tacv2/1634239445257?context=%7b%22Tid%22%3a%22ec359ba1-630b-4d2b-b833-c8e6d48f8059%22%2c%22Oid%22%3a%22ea630b1e-32e1-48b0-80e2-6ab50ed94040%22%7d
		202100676037722	22/10/2021	14:40	https://teams.microsoft.com/l/meetup-join/19%3atbLDGfq90AG9g6FtKY0WEfBlW6K_ILlfyUt2h1Vfpyo1%40thread.tacv2/1634239530154?context=%7b%22Tid%22%3a%22ec359ba1-630b-4d2b-b833-c8e6d48f8059%22%2c%22Oid%22%3a%22ea630b1e-32e1-48b0-80e2-6ab50ed94040%22%7d
		202100676037677	22/10/2021	15:20	https://teams.microsoft.com/l/meetup-join/19%3atbLDGfq90AG9g6FtKY0WEfBlW6K_ILlfyUt2h1Vfpyo1%40thread.tacv2/1634239656318?context=%7b%22Tid%22%3a%22ec359ba1-630b-4d2b-b833-c8e6d48f8059%22%2c%22Oid%22%3a%22ea630b1e-32e1-48b0-80e2-6ab50ed94040%22%7d
		202100676038011	22/10/2021	16:00	https://teams.microsoft.com/l/meetup-join/19%3atbLDGfq90AG9g6FtKY0WEfBlW6K_ILlfyUt2h1Vfpyo1%40thread.tacv2/1634239738537?context=%7b%22Tid%22%3a%22ec359ba1-630b-4d2b-b833-c8e6d48f8059%22%2c%22Oid%22%3a%22ea630b1e-32e1-48b0-80e2-6ab50ed94040%22%7d

		202100676038038	25/10/2021	14:00	https://teams.microsoft.com/l/meetup-join/19%3atbLDGfq90AG9g6FtKY0WEfBlW6K_ILlfyUt2h1Vfpyo1%40thread.tacv2/1634239819876?context=%7b%22Tid%22%3a%22ec359ba1-630b-4d2b-b833-c8e6d48f8059%22%2c%22Oid%22%3a%22ea630b1e-32e1-48b0-80e2-6ab50ed94040%22%7d
		202100676038022	25/10/2021	14:40	https://teams.microsoft.com/l/meetup-join/19%3atbLDGfq90AG9g6FtKY0WEfBlW6K_ILlfyUt2h1Vfpyo1%40thread.tacv2/1634239909205?context=%7b%22Tid%22%3a%22ec359ba1-630b-4d2b-b833-c8e6d48f8059%22%2c%22Oid%22%3a%22ea630b1e-32e1-48b0-80e2-6ab50ed94040%22%7d
		202100676038027	26/10/2021	14:00	https://teams.microsoft.com/l/meetup-join/19%3atbLDGfq90AG9g6FtKY0WEfBlW6K_ILlfyUt2h1Vfpyo1%40thread.tacv2/1634239970383?context=%7b%22Tid%22%3a%22ec359ba1-630b-4d2b-b833-c8e6d48f8059%22%2c%22Oid%22%3a%22ea630b1e-32e1-48b0-80e2-6ab50ed94040%22%7d
		202100676037758	26/10/2021	14:40	https://teams.microsoft.com/l/meetup-join/19%3atbLDGfq90AG9g6FtKY0WEfBlW6K_ILlfyUt2h1Vfpyo1%40thread.tacv2/1634239970383?context=%7b%22Tid%22%3a%22ec359ba1-630b-4d2b-b833-c8e6d48f8059%22%2c%22Oid%22%3a%22ea630b1e-32e1-48b0-80e2-6ab50ed94040%22%7d

Equipe	Linha	N º Inscrição	Data	Horário	Link da Sala
Equipe 5	**Mecanismos Moleculares e Funcionais da Saúde Humana**	202100676037975	25/10/2021	14:00	https://teams.microsoft.com/l/meetup-join/19%3aWTet7yfvKwbMdlEsmdmB6_eErKq4rWeiTgEx5D6R8vs1%40thread.tacv2/1634237319488?context=%7b%22Tid%22%3a%22ec359ba1-630b-4d2b-b833-c8e6d48f8059%22%2c%22Oid%22%3a%22ea630b1e-32e1-48b0-80e2-6ab50ed94040%22%7d
		202100676037985	25/10/2021	14:40	https://teams.microsoft.com/l/meetup-join/19%3aWTet7yfvKwbMdlEsmdmB6_eErKq4rWeiTgEx5D6R8vs1%40thread.tacv2/1634237492980?context=%7b%22Tid%22%3a%22ec359ba1-630b-4d2b-b833-c8e6d48f8059%22%2c%22Oid%22%3a%22ea630b1e-32e1-48b0-80e2-6ab50ed94040%22%7d

Referência para a avaliação oral individual:

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Supplementary Appendix

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

Supplement to: The REMAP-CAP, ACTIV-4a, and ATTACC Investigators. Therapeutic anticoagulation with heparin in critically ill patients with Covid-19. N Engl J Med. DOI: 10.1056/NEJMoa2103417.

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Table of Contents

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1.5.2 ATTACC

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1.5.4 Disclaimer

The views expressed in this publication are those of the author(s) and not necessarily those of the National Health Service (UK), the National Institute for Health Research (UK), the Department of Health and Social Care (UK), or of the National Institutes of Health (USA).

Section 2 – Supplemental Methods

Introduction and Trial Design

The multi-platform randomized controlled trial described herein represents a global collaboration whereby three organizationally distinct platforms (REMAP-CAP, ACTIV4a, and ATTACC) harmonized protocols and worked together to answer the important question of whether a strategy of empiric therapeutic-dose anticoagulation with heparin benefits patients with Covid-19 compared to usual-care thromboprophylaxis.

The concept of the multiplatform randomized controlled trial was borne out of discussion and shared interest among clinical trialists and leaders of three major international platforms to evaluate the efficacy of therapeutic-dose anticoagulation for inpatients with Covid-19. To answer the question as quickly as possible and with maximal generalizability, three protocols were harmonized to create a single multiplatform trial with common eligibility criteria, study intervention details, and key primary and secondary outcomes. Data collection, leadership, and oversight were shared across the platforms, and an agreement was established to federate the data collected within each platform into one overarching analysis. Trial data providers were SOCAR (ATTACC, ACTIV IV), SPIRAL (REMAP-CAP), and UPMC (REMAP-CAP). Statisticians from Berry Consultants served as trial statisticians for all three platforms with an independent group comprising the statistical analysis committee for the multiplatform trial. With agreed upon stopping rules for efficacy and futility for the primary endpoint, the trial operated under a unified multiplatform analysis plan with monthly interim analyses (See Protocol Appendix Statistical Analysis Plan). The investigators for all three platforms collaborated on making all major decisions.

Oversight was executed collaboratively across the three platforms, each with its own independent data and safety monitoring board (DSMB). Each trial DSMB maintained its responsibilities within its platform. The interim efficacy and safety analyses were reported to the DSMBs for each of the trials. Since safety data were not aggregated across trials, safety analysis reports for each platform were shared with the DSMBs of other platforms. Upon viewing safety reports, each DSMB reached a consensus on safety topics, and the DSMB chairs or designees from each of the platforms communicated with one another to discuss the efficacy and safety results across trials. Platform leadership and DSMB chairs agreed that individual platforms would not make public disclosures of efficacy without the agreement of all three oversight boards. A pre-defined publication plan was established by platform investigators for the multiplatform trial.

The results presented in the manuscript reflect the collaborative effort of the network of networks working together to rapidly answer a question of high public health importance. In effort to simplify the data review process, this supplement includes protocol synopses of each contributing platform and three tables that outline the harmonization across the three platforms. A separate protocol appendix contains detailed versions of each individual platform protocol with relevant protocol amendments and the unified mpRCT statistical analysis plan.

Analytical Methods

As described in the Statistical Analysis Plan (Protocol Appendix), the primary analysis was conducted on all patients with confirmed Covid-19, including those with severe disease (the "severe-disease group") and those with moderate disease (the "moderate-disease group"). Patients in both the severe- and moderate-disease groups were included in the model. Weakly informative Dirichlet prior distributions were specified to model the baseline probabilities for each level of organ support-free days in the severe and moderate groups. The model estimated treatment effects for each of the patient groups (those with severe disease, and those with moderate disease stratified by D-dimer), utilizing a Bayesian hierarchical approach. The treatment effects of anticoagulation for the moderate- and severe-disease groups were nested in a hierarchical prior distribution centered on an overall intervention effect estimated with a neutral prior, but distinct group-specific effects are estimated. When consistent effects are observed for the groups, the posterior distribution for each intervention group effect is shrunk towards the overall estimate. As the primary model included information about assignment in patient groups where randomization was ongoing and blinded to the investigators, the primary analysis was run by the fully unblinded statistical analysis committee, who conduct all protocol-specified trial update analyses and report results to the DSMB.

In addition to the primary analysis conducted by the statistical analysis committee, multiple sensitivity analyses were conducted by the investigator team who remain blinded to results of on-going randomization in the moderate patient groups. A sensitivity analysis of the primary outcome was repeated in a second model using only data from patients in the severe Covid-19 patient group (i.e. excluding patients with moderate Covid-19, Table S2). For this analysis there was no adjustment for borrowing from the moderate-disease participants.

Further sensitivity analyses assessed whether results were modified by including patients who were randomized as suspected Covid-19 but ultimately did not a positive polymerase chain reaction (PCR) test for SARS-CoV-2, or whether results were modified by excluding site and time effects from the model. As described in the statistical design plan, the analytical model includes site and time covariate terms to account for variability in treatment effect according to site (random effect) and to variation in the endpoint over time (fixed effect).

As the incidence of major bleeding is an important secondary outcome, and one of the platforms (REMAP-CAP) was testing the additive benefit of antiplatelet therapy concomitant with the anticoagulation domain, an additional sensitivity analysis was performed excluding

patients who were receiving an antiplatelet agent at baseline or who were randomized to either treatment or control in the antiplatelet domain of REMAP-CAP.

To determine the extent to which interpretation of the trial results would be affected by one's prior beliefs and given the widely accepted belief that therapeutic-dose anticoagulation would be beneficial in patients with severe Covid-19, we applied a post hoc prior for enthusiasm for therapeutic-dose anticoagulation to the model. This prior specified a 50% prior probability that the odds ratio would be ≥ 1.75 and a 10% probability of an odds ratio < 1 (inferior), consistent with fairly confident belief that the treatment was beneficial. Assuming a baseline mortality rate of 35%, an odds ratio of 1.75 is equivalent to an approximately 10% absolute risk reduction, consistent with reasonably strong enthusiasm for meaningful clinical benefit. In addition, we applied a post hoc prior for skepticism against therapeutic-dose anticoagulation in the model. This prior specified a 50% prior probability that the odds ratio would be < 1 (inferior) and a 66% probability of futility (OR ≤ 1.2) consistent with reasonable skepticism against a benefit of therapeutic-dose anticoagulation.

Because the use of interleukin-6 receptor antagonists may modulate thrombosis risk owing to the prothrombotic effect of inflammation in Covid-19, the possibility of an interaction between interleukin-6 receptor antagonists and therapeutic-dose anticoagulation was evaluated in a post hoc exploratory analysis. The model for the interaction was computed in patients with confirmed Covid-19 randomized in the therapeutic anticoagulation domain of REMAP-CAP before November 19, 2020 (the date on which randomization to control was discontinued in the Immune Modulation domain of REMAP-CAP). The model was adjusted as described for the primary analysis.

Treatment effect was examined in pre-specified subgroup analyses (See Protocol Appendix Statistical Analysis Plan) including age, sex, and requirement for invasive mechanical ventilation at baseline. To assess for potential heterogeneity of treatment effect according to venous thromboprophylaxis dosing in the usual-care arm, subgroups were defined by whether patients were randomized at a site that used "intermediate dose" venous thromboprophylaxis in more than 50% of usual-care patients, or in less than 50% of usual-care patients. For each subgroup analysis a separate treatment effect is modeled by subgroup. The posterior distribution for each subgroup effect and 95% credible intervals are reported.

There was no imputation of missing outcomes in either the primary or secondary analyses. Cases were excluded on an analysis-by-analysis basis, i.e. patients missing outcome data were included in treatment compliance and safety analyses. The secondary outcomes were also analysed in the unblinded intent-to-treat (ITT) model. The primary safety analysis compared the proportion of patients who developed one or more serious adverse thrombotic or major bleeding events across groups.

Model Equation: Cumulative Logistic Regression

The equation for the cumulative logistic regression is given by the following:

$$\log\left(\frac{\pi_{isy}}{1-\pi_{isy}}\right) = \alpha_{y,s} - \left[\nu_{Site,s} + \lambda_{Time,s} + \theta_{a,s:d} + \beta_{Age,s} + \beta_{Sex,s} + \beta_{d}\right]$$

Where site = site (random effect), time = 2 week epochs of time (fixed effect), a,s:d = arm within sub-type given d-dimer level, age (categorical variable), sex = sex at birth, d = d-dimer. See statistical analysis plan (Protocol Appendix page 484) for more details.

Response-Adaptive Randomization

The REMAP-CAP and ATTACC trials utilized response-adaptive randomization. At the interim analyses the response-adaptive randomization proportions for the respective trials were provided to their randomization services for their continued use of response-adaptive randomization. The ACTIV-4 trial did not use response-adaptive randomization.

The model run for REMAP-CAP for the response-adaptive randomization was different than the model run for the joint efficacy analysis. The REMAP-CAP model was conducted on all randomized patients within the REMAP-CAP trial, accounting for other interventions, to evaluate potential platform conclusions and set the randomization proportions. This *larger model* was not used to trigger success or futility, as the analysis detailed in this report was jointly used and agreed upon to label superiority and futility of the anticoagulation domain. The response-adaptive randomization allocation ratio for REMAP-CAP was updated at each REMAP-CAP specific interim analysis.

The adaptive randomization proportions for the ATTACC platform varied by d-dimer group.

Protocol Synopses

REMAP-CAP

REMAP-CAP: COVID-19 Therapeutic Anticoagulation Domain Summary	
Interventions	• Local standard venous thromboprophylaxis • Therapeutic anticoagulation with intravenous unfractionated heparin or subcutaneous low molecular weight heparin
Unit of Analysis, Strata, and State	This domain is analyzed only in the pandemic statistical model. The pandemic statistical model includes only patients who are in the Pandemic Infection Suspected or Proven (PISOP) stratum. Within this stratum, the unit-of-analysis is defined by illness severity state at time of enrollment, defined as either Moderate State or Severe State. Unit-of-analysis may also be defined by SARS-CoV-2 infection or d-dimer strata or both. Borrowing is permitted between states and strata. If the SARS-CoV-2 strata is applied in analysis, Response Adaptive Randomization will be applied to all PISOP patients, in each illness severity state, using probabilities derived from the SARS-CoV-2 confirmed stratum. Response Adaptive Randomization may also be applied according to D-dimer strata status.
Evaluable treatment-by-treatment Interactions	No interaction will be evaluated with any other domain.
Nesting	None
Timing of Reveal	Randomization with Immediate Reveal and Initiation or Randomization with Deferred Reveal if prospective agreement to participate is required.
Inclusions	Patients will be eligible for this domain if: • COVID-19 infection is suspected by the treating clinician or has been confirmed by microbiological testing • Microbiological testing for SARS-CoV-2 infection of upper or lower respiratory tract secretions or both has occurred or is intended to occur
Domain-Specific Exclusions	Patients will be excluded from this domain if they have any of the following: • More than 48 hours has elapsed since ICU admission (noting that this may be operationalized as more than 48 hours has elapsed since commencement of organ failure support) • Clinical or laboratory bleeding risk or both that is sufficient to contraindicate therapeutic anticoagulation, including intention to continue or commence dual anti-platelet therapy • Therapeutic anticoagulation is already present due to prior administration of any anticoagulant agent that is known or likely to still be active or a clinical decision has been made to commence therapeutic anticoagulation • Enrolment in a trial evaluating anticoagulation for proven or suspected COVID-19 infection, where the protocol of that trial requires continuation of the treatment assignment specified in that trial • Known or suspected previous adverse reaction to UFH or LMWH including heparin induced thrombocytopenia (HIT).

	• The treating clinician believes that participation in the domain would not be in the best interests of the patient
Intervention-Specific Exclusions	None

ATTACC

Study Title:	**A**nti**T**hrombotic **T**herapy to **A**meliorate **C**omplications of **C**OVID-19 (**ATTACC**) in collaboration with Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV-4)
Study Design:	A phase III prospective, open-label, adaptive multi- platform randomized controlled trial
Primary Objective/ Endpoint:	The primary endpoint in the trial is days alive and free of organ support at day 21. This endpoint is defined as the number of days that a patient is alive and free of organ support through the first 21 days after trial entry.
Secondary Objectives:	Secondary Safety Endpoints: - Laboratory confirmed heparin induced thrombocytopenia **(HIT)** - **Major bleeding**, defined according to the International Society on Thrombosis and Haemostasis (ISTH)/Scientific and Standardization Committee (SSC) definitions and bleeding assessment tool in non-surgical patients (Schulman *J Thromb Haemost* 2005): fatal bleeding; and/or symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome; and/or bleeding causing a fall in hemoglobin level of ≥20 g/L, or leading to transfusion of 2 or more units of whole blood or red cells. Secondary Efficacy Endpoints: - A composite endpoint of death, deep vein thrombosis, pulmonary embolism, systemic arterial thromboembolism, myocardial infarction, or ischemic stroke collected during hospitalization or at 28 days and 90 days after enrollment (whichever is earlier) - Ordered categorical endpoint with three possible outcomes based on the worst status of each patient through day 30 following randomization: no invasive mechanical ventilation, invasive mechanical ventilation, or death.

	- All cause mortality assessed at 28 and 90 days following randomization - All cause mortality during initial hospitalization (includes death after 28 days) - Intubation assessed at 30 days following randomization - Ventilator-free days (days alive not on a ventilator) assessed at 28 days following randomization - Hospital-free days (days alive outside hospital assessed at 28 days following randomization) - Vasopressor-free days (days alive not on a vasopressor) assessed at 28 days following randomization - Renal replacement free days (days alive not on renal replacement) assessed at 28 days following randomization - Hospital re-admission within 28 days - Symptomatic proximal venous thromboembolism (DVT or PE) assessed at 28 and 90 days following randomization - Myocardial infarction assessed at 28 and 90 days following randomization - Ischaemic stroke assessed at 28 and 90 days following randomization - Acute kidney injury as defined by KDIGO criteria - Systemic arterial thrombosis or embolism assessed at 28 and 90 days following randomization - Use of extracorporeal membrane oxygenation (ECMO) support - Mechanical circuit (dialysis or ECMO) thrombosis - WHO ordinal scale (peak scale over 28 days, scale at 14 days, and proportion with improvement by at least 2 categories compared to enrollment, at 28 days)
Duration:	The duration of accrual on this study will be ongoing in nature during the COVID-19 pandemic, following outcomes for each patient up to a maximum of 90 days.

Planned Total Sample Size:	The trial is a Bayesian adaptive design and as such is not predicated on a fixed *a priori* sample size. This design was chosen given uncertainty regarding anticipated event rates and potential treatment effect sizes. Approximately 350 to a maximum of 3000 evaluable patients are anticipated to be enrolled in this adaptive trial in combination with the ACTIV 4 and REMAP-CAP trials, with anticipated reprioritization of key subgroups (including D-dimer defined) as the trial is undertaken.
Drug Administration:	Participants randomized to the investigational arm will receive therapeutic anticoagulation for 14 days (or until hospital discharge or liberation from the need for supplemental oxygen, whichever comes first) with preference for low-molecular weight heparin (LMWH), or alternative unfractionated heparin (UFH). Participants randomized to the control arm will receive usual care, which is anticipated to include thromboprophylactic dose anticoagulation according to local practice.
Inclusion/Exclusion Criteria:	Inclusions: 1. Patients ≥18 years of age providing (possibly through a substitute decision maker) informed consent who require hospitalization anticipated to last ≥72 hours, for microbiologically confirmed COVID-19, enrolled < 72 hours of hospital admission **or** of COVID-19 confirmation Exclusions: 1. Requirement for chronic mechanical ventilation via tracheostomy prior to hospitalization 2. Patients for whom the intent is to not use pharmacologic thromboprophylaxis 3. Active bleeding 4. Risk factors for bleeding, including: a. intracranial surgery or stroke within 3 months; b. history of intracerebral arteriovenous malformation; c. cerebral aneurysm or mass lesions of the central nervous system;

	d. intracranial malignancy e. history of intracranial bleeding f. history of bleeding diatheses (e.g., hemophilia) g. history of gastrointestinal bleeding within previous 3 months h. thrombolysis within the previous 7 days i. presence of an epidural or spinal catheter j. recent major surgery <14 days k. uncontrolled hypertension (sBP >200 mmHg, dBP >120 mmHg) l. other physician-perceived contraindications to anticoagulation 5. Platelet count <50 x10^9/L, INR >2.0, or baseline aPTT >50 6. Hemoglobin <80 g/L (to minimize the likelihood of requiring red blood cell transfusion if potential bleeding were to occur) 7. Acute or subacute bacterial endocarditis 8. History of heparin induced thrombocytopenia (HIT) or other heparin allergy including hypersensitivity 9. Current use of dual antiplatelet therapy 10. Patients with an independent indication for therapeutic anticoagulation 11. Patients in whom imminent demise is anticipated and there is no commitment to active ongoing intervention 12. Anticipated transfer to another hospital that is not a study site within 72 hours 13. Enrollment in other trials related to anticoagulation or antiplatelet therapy
Study Assessments:	Study assessments are depicted in the study schedule.
Safety Variables & Analysis:	The safety of therapeutic anticoagulation with LWMH or intravenous UFH infusion will be evaluated by AE reports. Treatment-related AEs include bleeding and HIT.
Efficacy Assessments & Analysis	The efficacy of therapeutic-dose parenteral anticoagulation with subcutaneous LMWH or

	intravenous UFH will be evaluated in comparison to usual care.
Reasons for premature discontinuation of therapy:	Treatment will continue until any of the following occurs: • Heparin induced thrombocytopenia or other heparin allergy/hypersensitivity • Thrombocytopenia (platelet count <50 x10^9/L) • Major bleeding, defined based closely on the International Society on Thrombosis and Haemostasis (ISTH)/Scientific and Standardization Committee (SSC) definitions and bleeding assessment tool in non-surgical patients • Coagulopathy associated with an elevated INR (e.g., >2.0) or hypofibrinogemia • Following invasive procedures where heparin is deemed unsafe to re-institute • Patients requiring systemic fibrinolytic therapy • Treating physician discretion
Statistical Analysis:	Data will be analyzed by an intention to treat analysis for the primary analysis; a per-protocol analysis will also be completed as a secondary analysis. Patients who receive at least one dose of drug will be evaluable for safety and efficacy. Response-adaptive randomization based on D-dimer subgroups is embedded.

ACTIV-4a

Title	A Multicenter, Adaptive, Randomized, Open Label Controlled Platform Trial of the Safety and Efficacy of Antithrombotic Strategies in Hospitalized Adults with COVID-19
Short Title	ACTIV-4 ACUTE
Brief Summary	This is a randomized, open label, adaptive platform trial to compare the effectiveness of antithrombotic strategies for prevention of adverse outcomes in COVID-19 positive inpatients
Objectives	1. To determine the most effective antithrombotic strategy for increasing the number of days free of organ support and reducing death. 2. To determine the most effective antithrombotic strategy on the composite endpoint of death, deep vein thrombosis (DVT), pulmonary embolism (PE), myocardial infarction (MI), ischemic stroke, or other systemic arterial thrombosis (AT). 3. To assess the safety of antithrombotic strategies through the endpoint of major bleeding as defined by ISTH. 4. To compare the effect of antithrombotic strategies on the endpoint of all-cause mortality in the study population. Assessment of efficacy and safety will yield information of the net clinical benefit of different antithrombotic strategies in the study population. It will also yield information on outcomes specific to under-represented minority populations, specifically African- and Hispanic- descent persons.
Methodology	Adaptive Randomized Platform Trial

Endpoints	Primary Endpoint: 21 Day Organ Support Free Days, which is defined as the number of days that a patient is alive and free of organ support through the first 21 days after trial entry. Organ Support is defined as receipt of invasive or non-invasive mechanical ventilation, high flow nasal oxygen, vasopressor therapy, or ECMO support, with death at any time (including beyond 21 days) during the index hospitalization assigned -1 days. Key Secondary Endpoint: Composite endpoint of death, pulmonary embolism, systemic arterial thromboembolism, myocardial infarction, or ischemic stroke at hospital discharge or 28 days, whichever occurs first. Other Secondary Endpoints: Composite endpoint of death, deep vein thrombosis, pulmonary embolism, systemic arterial thromboembolism, myocardial infarction, or ischemic stroke at hospital discharge or 28 days, whichever occurs first. Acute kidney injury defined by KDIGO criteria, Individual endpoints comprising the key secondary endpoint, death during hospitalization, 28 Day Ventilator-Free Days, 28 Day Vasopressor Free Days, 28 Day Renal Replacement Free Days, WHO clinical scale, 28 Day Hospital Free Days, 28 day organ support free days, and all-cause mortality at 90 days. Primary Safety Endpoint: Major bleeding (as defined by the ISTH) Secondary Safety Endpoint: Confirmed heparin induced thrombocytopenia (HIT)
Study Duration	Approximately 1 year
Participant Duration	Hospital duration with periodic contact at post-discharge, including at 90 days, with potential contact up to 1 year
Duration of assigned treatment strategy	During hospitalization (unless otherwise specified in description of arm)
Population	Adult patients hospitalized for COVID-19
Study Sites	Approximately 150 sites
Number of participants	The sample size is described in each arm-specific appendix.
Description of Study Agents	Randomized arms- see appendix This platform trial allows for multiple therapies to be investigated in this trial over time. The trial is governed by a Master Protocol that describes the trial design, endpoint collection, primary endpoint, and inclusion/exclusion criteria. Different therapies, referred to as arms, are detailed in arm-specific appendices. These arm-specific appendices work in a modular fashion as arms are removed and added to the platform trial.
Key Procedures	Observation during hospitalization, contact at 90 days post-enrollment, and collection of standard of care laboratory results. Ancillary biobanking will be completed in consenting patients at capable centers.

Statistical Analysis	Inferences in this trial are based on a Bayesian statistical model, which considers the variation in outcomes by site, disease state, time, and arm of the trial. The specific analyses for each arm, including interim analysis schedule, are specified in each arm-specific appendix.

Cross-Platform Protocol Comparison Tables

Eligibility Criteria

	REMAP-CAP	ACTIV-4a	ATTACC
Inclusion Criteria			
Age	• Adult (age not specifically listed)	• ≥ 18 years of age	
Duration of hospitalization for COVID-19	• Expected hospital LOS > 48 hours (i.e. not expected to be discharged today or tomorrow)	• Expected hospital LOS ≥ 72 hours	
SARS-CoV-2 infection	• Suspected or confirmed with intent to test for COVID-19*	• Confirmed	
Enrollment Window	• Less than 48 hours from ICU admission (or initiation of ICU-level care)	• <72 hours from admission OR COVID-19 confirmation	
Exclusion Criteria			
Platelet Count		• < 50x 10^9/L	• <50 x10^9/L, INR >2.0, or baseline aPTT >50 seconds
Hemoglobin		• Hemoglobin <80 g/L (8 g/dL) (to minimize the likelihood of requiring red blood cell transfusion if potential bleeding were to occur)	
Heparin Induced Thrombocytopenia (HIT)	• Known or suspected previous adverse reaction to unfractionated heparin or low molecular weight heparin including HIT	• History of heparin-induced thrombocytopenia (HIT) or other heparin allergy including hypersensitivity	
Dual Antiplatelet Therapy	• Intention to continue or commence dual antiplatelet therapy	• Patient on dual antiplatelet therapy, when one of the agents cannot be stopped safely	• Current use of dual antiplatelet therapy
Mechanical Ventilation		• Chronic mechanical ventilation via tracheostomy prior to hospitalization	
Prognosis	• Death is deemed to be imminent and inevitable during the next 24 hours AND • One or more of the patient, substitute decision maker, or attending physician are not committed to full active treatment	• Imminent death	• Patients in whom imminent demise is anticipated and there is no commitment to active ongoing intervention
Co-Enrollment	• Enrollment in a trial evaluating anticoagulation for proven or suspected COVID-19 infection, where the protocol of that trial requires continuation of the	• Co-enrollment in other trials is permitted as long as the other trial does not test agents with antithrombotic	• Enrollment in other trials related to anticoagulation or antiplatelet therapy

	treatment assignment specified in that trial	properties and there is no other scientific contraindication	
Bleeding Risk	• Clinical and/or laboratory bleeding risk or both that is sufficient to contraindicate therapeutic anticoagulation	Contraindication to anticoagulation, including but not limited to: • known bleeding within the last 30 days requiring emergency room presentation or hospitalization • known history of an inherited or active acquired bleeding disorder • recent ischemic stroke	• Intracranial surgery or stroke within 3 months • history of intracerebral arteriovenous malformation • cerebral aneurysm or mass lesions of the central nervous system • intracranial malignancy • history of intracranial bleeding • history of bleeding diatheses (e.g., hemophilia) • history of gastrointestinal bleeding within previous 3 months • thrombolysis within the previous 7 days • presence of an epidural or spinal catheter • recent major surgery <14 days • uncontrolled hypertension (sBP >200 mmHg, dBP >120 mmHg) • other physician-perceived contraindications to anticoagulation
Miscellaneous	• Treating physician does not feel trial participation is in the best interest of the patient	• Pregnancy	

Interventions

	REMAP-CAP	ACTIV-4a	ATTACC
Intervention arm management			
Anticoagulant drug	• Unfractionated heparin or low molecular weight heparin • Patients may be switched between unfractionated heparin and low molecular weight heparin	• Unfractionated heparin or low molecular weight heparin • Patients may be switched between unfractionated heparin and low molecular weight heparin • Patients with impaired renal function were stipulated to received unfractionated heparin	• Unfractionated heparin or low molecular weight heparin • Either agent permitted and patients may be switched between unfractionated heparin and low molecular weight heparin
Dose	• Dosed according to local hospital policy, practice, and guidelines for treatment of venous thromboembolism • For UFH, suggested target for aPTT of 1.5 to 2.5 times the upper limit of normal or therapeutic anti-Xa levels • Low molecular weight heparin dosed according to patient weight	• Low molecular weight heparin dosed according to patient weight and creatinine clearance • For UFH, suggested target of anti-Xa of 0.3-0.7 IU/ml or aPTT 1.5 to 2.5 times the upper limit of normal	• Low molecular weight heparin dosed according to patient weight and creatinine clearance according to local practice and policy • For UFH, suggested target of aPTT 1.5 to 2.5 times the upper limit of normal or therapeutic anti-Xa levels
Duration of intervention	• Up to 14 days or to hospital discharge, whichever comes first • For ICU patients, therapeutic anticoagulation could be discontinued at ICU discharge	• Up to 14 days or to hospital discharge, whichever comes first	• Up to 14 days or until hospital discharge or recovery (defined as liberation from supplemental oxygen>24 hours, provided oxygen was required), whichever comes first
Usual care arm management			
Thromboprophylaxis agent	• Standard venous thromboprophylaxis according to local guidelines or usual practice	• Any one of enoxaparin, dalteparin, tinzaparin, fondaparinux, or heparin according to local preference	• Standard venous thromboprophylaxis according to local guidelines or usual practice
Thromboprophylaxis dose	• Dose of chosen agent should not be sufficient to	• Dose of agent specified to be	• Dose of chosen agent should not be more

	result in therapeutic anticoagulation	consistent with guidelines for low dose thromboprophylaxis	than half of the approved therapeutic dose for the treatment of venous thromboembolism
Duration of thromboprophylaxis	• Up to 14 days or hospital discharge, whichever comes first • After this period, decisions regarding thromboprophylaxis are at discretion of treating clinician	• Up to 14 days or hospital discharge, whichever comes first • After this period, decisions regarding thromboprophylaxis are at discretion of treating clinician	• Up to 14 days or hospital discharge, whichever comes first • After this period, decisions regarding thromboprophylaxis are at discretion of treating clinician

Endpoints

	REMAP-CAP	ACTIV-4a	ATTACC
Primary endpoint	• Days alive and free of organ support to day 21 • An ordered categorical endpoint ranging between 0 and 21; patients who die at any time in hospital are assigned a value of -1		
Secondary efficacy endpoints	• All-cause mortality at 90 days • Hospital length-of-stay censored at day 90	• All-cause mortality at 28 days • All-cause mortality in hospital • Hospital re-admission within 28 days • Hospital length-of-stay • WHO ordinal scale at 14 days, proportion with improvement by at least 2 levels compared to enrolment at 28 days	• All-cause mortality at 28 days and 90 days • Hospital re-admission within 28 days • WHO ordinal scale at 14 days, proportion with improvement by at least 2 levels compared to enrolment at 28 days • Intubation at day 30 • Ordered categorical endpoint with three possible outcomes based on the worst status of each patient through day 30 (not invasively ventilated, invasively ventilated, or death)
Secondary ICU outcomes	• ICU readmission • ICU mortality censored at day 90 • ICU length-of-stay censored at day 90 • Ventilator-free days at 28 days • Tracheostomy censored at 28 days	• Ventilator-free days at 28 days • Hospital-free days at 28 days • Vasopressor-free days at 28 days • Renal replacement-free days at 28 days • Use of ECMO in hospital	
Secondary thrombosis endpoints	• Confirmed deep venous thrombosis in hospital • Confirmed pulmonary embolism • Confirmed ischemic cerebrovascular event • Confirmed acute myocardial infarction • Other thrombotic event including mesenteric ischemia and limb ischemia • Peak troponin between randomization to day 15	• Major thrombotic events (death, pulmonary embolism, systemic arterial thromboembolism, myocardial infarction, or ischemic stroke) at 28 days • Symptomatic proximal venous thromboembolism (DVT or PE) assessed at 28 days • Myocardial infarction at 28 days • Ischemic stroke at 28 days • Acute kidney injury as defined by KDIGO criteria • Systemic arterial thrombosis or embolism at 28 days • Mechanical circuit (dialysis or ECMO) thrombosis	
Safety endpoints	• Major bleeding, defined according to International Society on Thrombosis and Haemostasis (ISTH) definitions • Fatal bleeding		

	• Symptomatic bleeding in a critical area or organ • Bleeding causing a fall in hemoglobin level of ≥20 g/L • Requiring a transfusion of 2 or more units of whole blood or red cells • Laboratory-confirmed heparin-induced thrombocytopenia

Categorization of frequently used low- and intermediate-dose thromboprophylaxis in the ATTACC, ACTIV-4a, and REMAP-CAP multiplatform randomized controlled trial

Drugs/doses used in the trial for prophylaxis other than those listed below were manually categorized, considering participant body weight/BMI and renal function, informed by American Society of Hematology and NICE guidance.

Subcutaneous Enoxaparin

Low dose

- *Standard dose*: 40 mg once daily
- *Possible*: If BMI ≥ 40 kg/m^2 (or weight ≥ 120 kg) and CrCl ≥ 30 mL/min: 40 mg twice daily
- *Possible*: If CrCl < 30 mL/min: 30 mg once daily

Intermediate dose

Twice daily:

- *Standard dose*: up to and including
    - 0.5 mg/kg twice daily + 20% (rounding factor) or
    - 40 mg twice daily (whichever is higher)
- *Possible*: If BMI ≥ 40 kg/m^2 (or weight ≥ 120 kg) and CrCl ≥ 30 mL/min: up to 60 mg twice daily
- *Possible*: If CrCl < 30 mL/min: intermediate twice daily dose not defined

Daily:

- *Standard dose*: up to 1.0 mg/kg once daily + 20% (rounding factor)
- *Possible*: If BMI ≥ 40 kg/m^2 (or weight ≥ 120 kg) and CrCl ≥ 30 mL/min: up to 0.8 mg/kg once daily + 20% (rounding factor)
- *Possible*: If CrCl < 30 mL/min (and weight ≥ 60 kg): up to 0.5 mg/kg once daily +20% (rounding factor)

Subtherapeutic dose

- Between intermediate and therapeutic doses

Therapeutic dose

Twice daily:

- *Standard dose:* starting at 1 mg/kg twice daily minus 10% (rounding factor)
- *Possible:* If BMI ≥ 40 kg/m^2 (or weight ≥ 120 kg) and CrCl ≥ 30 mL/min: starting at 0.8 mg/kg twice daily minus 10% (rounding factor)
- *Possible:* If CrCl < 30 mL/min: therapeutic twice daily dose not defined

Daily:

- *Standard dose:* starting at 1.5 mg/kg once daily minus 10% (rounding factor)
- *Possible:* CrCl < 30 mL/min: starting at 1 mg/kg once daily minus 10% (rounding factor)
- *Possible:* If BMI ≥ 40kg/m^2 and CrCl ≥ 30 mL/min: therapeutic once daily dose not defined

Subcutaneous Dalteparin

Low dose

- *Standard dose*: 5,000 units once daily
- *Possible*: If BMI ≥ 40 kg/m^2 (or weight ≥ 120 kg) and CrCl ≥ 30 mL/min: 7,500 units once daily

Intermediate dose

- *Standard dose*: 5,000 units twice daily
- *Possible*: If BMI ≥ 40 kg/m^2 (or weight ≥ 120 kg) and CrCl ≥ 30 mL/min: 7,500 units twice daily

Subtherapeutic dose

- Between intermediate and therapeutic doses

Therapeutic dose

Twice daily:

- *Standard dose:* 100 U/kg twice daily minus 10% (rounding factor)

Daily:

- *Standard dose:* starting at 200 U/kg once daily minus 10% (rounding factor)

Subcutaneous Tinzaparin

Low dose

- *Standard dose*: up to and including
    - 75 anti-Xa units/kg + 20% (rounding factor) once daily or
    - 4,500 units once daily (whichever is higher)
- *Possible*: If BMI ≥ 40 kg/m^2 (or weight ≥ 120 kg) and CrCl ≥ 30 mL/min: 8,000 units once daily

Intermediate dose

- *Standard dose*: 4,500 units twice daily
- *Possible*: If BMI ≥ 40 kg/m^2 (or weight ≥ 120 kg) and CrCl ≥ 30 mL/min: 8,000 units twice daily

Subtherapeutic dose

- Between intermediate and therapeutic doses

Therapeutic dose

- *Standard dose:* 175 anti-Xa units/kg once daily minus 10% (rounding factor)

Unfractionated heparin

Low dose (subcutaneous)

- *Standard dose*: 5,000 units twice or three times daily
- *Possible*: If BMI ≥ 40 kg/m^2 (or weight ≥ 120 kg) and CrCl ≥ 30 mL/min: 7,500 units twice daily

Intermediate dose (subcutaneous)

- *Standard dose*: 7,500 units three times daily or 10,000 units twice daily
- *Possible*: If BMI ≥ 40 kg/m^2 (or weight ≥ 120 kg) and CrCl ≥ 30 mL/min: 10,000 units twice daily

Subtherapeutic dose

- Not defined for unfractionated heparin

Therapeutic dose (intravenous)

- *Standard dose:* continuous intravenous administration per local protocol

Endpoint Definitions

REMAP-CAP

The following are the definitions for the outcomes reported by site investigators, as outlined in the Domain Specific Appendix (DSA) and/or the Case Report Form Data Completion Guide.

Major bleeding

Fatal bleeding, symptomatic or clinically manifest bleeding in a critical are or organ (such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular, pericardial, or intramuscular with compartment syndrome), OR

Blood loss above 300mls or bleeding causing a fall in haemoglobin of ≥2g/dL (20g/L, 1.24mmol/L), or leading to the transfusion of 2 or more whole blood or red cell units

Acute Myocardial Infarction (AMI)

The definition of an AMI requires detection of rise and fall or just a fall of cardiac biomarkers, such as any form of troponin assay, with at least one value above the upper reference limit (URL) PLUS evidence of myocardial ischemia with at least one of the following:

- Symptoms of cardiac ischemia
- ECG changes indicative of new ischemia (new ST-T changes or new LBBB)*
- Development of pathological Q waves in the ECG**
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality

*ECG manifestation of acute myocardial ischemia (in the absence of LVH and LBBB):

- ST Elevation - New ST elevation at the J-point in two contiguous leads with the cut-off points of ≥ 0.2 mV in men or ≥ 0.15 mV in women in leads V2-V3 and/or ≥ 0.1 mV in other leads.
- ST depression and T-wave changes – New horizontal or down-sloping ST depression ≥ 0.05 mV in two contiguous leads; and/or T inversion ≥ 0.1 mV in two contiguous leads with prominent R waves or R/S ratio >1.

**Pathological Q waves:

- Any Q-wave in leads V2-V3 ≥ 0.02 seconds or QS complex in leads V2 and V3
- Q-wave ≥ 0.03 seconds and ≥ 0.1 mV deep or QS complex in leads I, II, aVL, aVF, or V4-V6 an any two leads of a contiguous lead grouping (I, aVL, V6; V4-V6; II, III, aVF; V7-V9).
- R-wave ≥ 0.04 s in V1–V2 and R/S ≥ 1 with a concordant positive T-wave in the absence of a conduction defect

Confirmed deep vein thrombosis

Proximal deep vein thrombosis is a thrombus located in axillary vein or more proximal, including the internal jugular vein, and a thrombus located in popliteal vein or more proximal. Confirmation requires imaging with techniques that include ultrasound or CT scan.

Confirmed pulmonary embolus

Segmental or multi-sub-segmental pulmonary emboli that is confirmed using CT pulmonary angiography or has a high probability ventilation: perfusion lung scan

Confirmed ischemic cerebrovascular event

An acute ischemic stroke is defined as central nervous system infarction defined as brain, spinal cord, or retinal cell death attributable to ischemiased on:

- Pathological, imaging, or other objective evidence of cerebral, spinal cord, or retinal focal ischemic injury in a defined vascular distribution; OR
- Clinical evidence of cerebral, spinal cord, or retinal focal ischemic injury based on symptoms persisting ≥24 hours or until death, and other etiologies excluded. (Note: CNS infarction includes types I and II hemorrhagic infarctions) OR
- Infarction or hemorrhage in the brain, spinal cord, or retina because of thrombosis of a cerebral venous structure. Symptoms or signs caused by reversible oedema without infarction or hemorrhage do not qualify as stroke.

Mesenteric ischemia

Mesenteric Ischemia for arterial or venous mesenteric ischemia diagnosed on contrast imaging by CT or angiography or diagnosed at laparotomy or via laparoscopy.

Limb ischemia

Limb ischemia if evidence of acute limb ischemia sufficient to require surgical revascularization including bypass procedure, intraarterial thrombolysis, or embolectomy; amputation of a limb due to acute ischemia; or decision to withdraw or limit treatment because of acute limb ischemia. It is not sufficient for there to be evidence of limb ischemia that does not result in surgical intervention or determine a decision to institute palliative care. Ischemia attributed to vasopressor medication is insufficient unless also meets the above definition.

Heparin induced thrombocytopenia (HIT)

Definite HIT:

- Positive Serotonin Release Assay (SRA) or equivalent functional HIT confirmatory test
- Positive Enzyme-linked immunosorbent assay (ELISA) AND treated as HIT
- Positive quantitative rapid immunoassay (RIA) AND treated as HIT

Possible HIT:

- Positive ELISA or quantitative RIA AND any heparin/LMWH anticoagulation stopped
- 4T score >3 (high or intermediate), no Laboratory testing for HIT done, AND treated as HIT

No HIT:

- Negative HIT ELISA, or Negative Quantitative RIA
- Negative SRA, or Negative equivalent functional confirmatory assay
- No laboratory testing for HIT done AND not treated as HIT (heparin continued or discontinued for other reason and uneventful course - defined as absence of thrombotic event and platelet count recovery during follow-up).

Derived endpoints

The following are the definitions for the endpoints outlined in the Statistical Analysis Plan for the Anticoagulation Domain which are derived from the domain-specific secondary endpoints:

Systemic arterial thrombosis or embolism

Clinical evidence of sudden significant worsening of organ or limb perfusion and either confirmation of arterial obstruction (e.g. by imaging, hemodynamics, intraoperative findings or pathology evaluation) or requirement for intervention (thrombolysis, thrombectomy or urgent bypass).

Major thrombotic event

A composite dichotomous endpoint of pulmonary embolism, ischemic cerebrovascular event, myocardial infarction, or systemic arterial thromboembolism diagnosed at any time during the index hospitalization.

All thrombotic events

A composite dichotomous endpoint of deep vein thrombosis, pulmonary embolism, ischemic cerebrovascular event, myocardial infarction, or systemic arterial thromboembolism diagnosed at any time during the index hospitalization or death in hospital.

ATTACC

The full list of secondary endpoints is available in the trial protocol. Among these, the following secondary efficacy endpoints will be adjudicated by the CEC:

- Venous thromboembolism (DVT or PE) assessed at 28 and 90 days following randomization
- Myocardial infarction assessed at 28 and 90 days following randomization
- Ischemicstroke assessed at 28 and 90 days following randomization
- Systemic arterial thrombosis or embolism assessed at 28 and 90 days following randomization

The following secondary safety events will be adjudicated by the CEC (sites instructed to report events occurring during the intervention window as defined in the protocol):

- Laboratory confirmed HIT
- Major bleeding, defined according to the International Society on Thrombosis and Haemostasis (ISTH)/Scientific and Standardization Committee (SSC) definitions and bleeding assessment tool in non-surgical patients (Schulman *J Thromb Haemost* 2005).

ATTACC endpoint definitions are as described below for ACTIV-4a

ACTIV-4a

The full list of secondary endpoints is available in the trial protocol. The CEC will consider for adjudication all cases of the following:

- Deep venous thromboembolism
- Pulmonary embolism
- Arterial thromboembolism
- Myocardial infarction
- Stroke
- Major bleeding
- Death due to cardiovascular, non-cardiovascular, and undetermined cause

Deep Venous Thromboembolism

The diagnosis of definite symptomatic deep venous thromboembolism (DVT) requires symptoms of venous thromboembolism with at least one of the following:

- Abnormal compression ultrasound consistent with DVT or abnormal flow pattern or direct clot visualization in veins not amenable to compression.

- One or more new filling defects by venography, CT venography, or MR venography.
- Abnormal compression ultrasound where compression had been normal or, if known to be non-compressible, a substantial increase (≥4mm) in the diameter of a previously non-compressible venous segment.
- Point-of-care ultrasound (POCUS) performed by a provider and documenting DVT in a note.
- An extension of an intraluminal filling defect, or a new intraluminal filling defect, or an extension of non-visualization of veins in the presence of a sudden cut-off on venography.
- Proximal DVT is defined as clot at or proximal to the trifurcation of the popliteal vein (in the lower extremity) OR clot at or proximal to the axillary vein segment (in the upper extremity).
- Distal DVT is defined as clot distal to the trifurcation of the popliteal vein (in the lower extremities) OR clot at or distal to the brachial vein segment (in the upper extremities).
- Non-limb venous thrombosis includes thrombosis of the cerebral, portal, mesenteric, hepatic, gonadal, splenic, renal, or retinal veins, or thrombosis of the superior or inferior vena cava.

The diagnosis of presumed deep venous thromboembolism requires the following:

- In the absence of objective testing, high pre-test probability according to investigator assessment
    - OR adjudicator's gestalt
    - OR Wells score
- AND a treatment plan for DVT was initiated (initiation of anticoagulation, or escalation of anticoagulation dose, frequency, or duration).

Pulmonary Embolism

The diagnosis of definite pulmonary embolism requires at least one of the following:

- New intraluminal filling defect at CT pulmonary angiography in a subsegmental or larger vessel.
- New intraluminal filling defect, or an extension of an existing defect, or a new sudden cut-off of vessels > 2.5 mm in diameter at pulmonary angiogram,
- Inconclusive CT pulmonary angiography, pulmonary angiography, or VQ scan evidence of a new or recurrent PE with demonstration of a new or recurrent DVT in the lower extremities by compression ultrasonography or venography. [2, 3]
- New clot or intraluminal filling defect noted in the right heart ("clot in transit") or the pulmonary vasculature at echocardiogram
- High probability (revised PIOPED criteria) on planar ventilation/perfusion (V/Q) scan OR positive PE on SPECT ventilation perfusion (V/Q) scan.
- Pulmonary embolism found at autopsy

The diagnosis of presumed pulmonary embolism requires the following:
Clinical signs and symptoms of pulmonary embolism, including but not limited to: dyspnea, cough, hypoxemia, tachycardia, appropriate electrocardiographic changes, or evidence of right heart strain on echocardiogram; AND chest CT or pulmonary angiography are unable to be

performed AND therapeutic dose anticoagulation or fibrinolytic therapy is prescribed by a physician

Arterial Thromboembolism

The diagnosis of arterial thromboembolism is defined as the following:

- A clinical history and presentation consistent with a sudden significant worsening of end organ or limb perfusion AND

EITHER

- Confirmation of arterial obstruction by imaging, hemodynamics, intraoperative findings, or pathological evaluation

OR

- Requirement for thrombolysis, thrombectomy, or urgent bypass.

Note that arterial thromboembolism includes both acute *in situ* thrombotic events and acute embolic events. Note that while ischemic stroke and myocardial infarction can be arterial thromboembolic events, those events will be adjudicated according to the separate standardized criteria included below.

Myocardial Infarction

COVID-19 patients are well known to have elevations in cardiac troponin concentrations, and these elevations often do not represent arterial thrombosis and downstream myocardial ischemia. Therefore, the CEC will make an effort to distinguish true myocardial infarction from coronary artery obstruction, typically from atherothrombosis (usually considered a "type 1 myocardial infarction") from myocardial infarction due to demand ischemia (usually defined as a "type 2 myocardial infarction") and myocardial injury (an elevation in cardiac troponin typically without symptoms of chest pain or signs of arterial thrombosis). These definitions will be consistent with the 4th Universal Definition of Myocardial Infarction and will

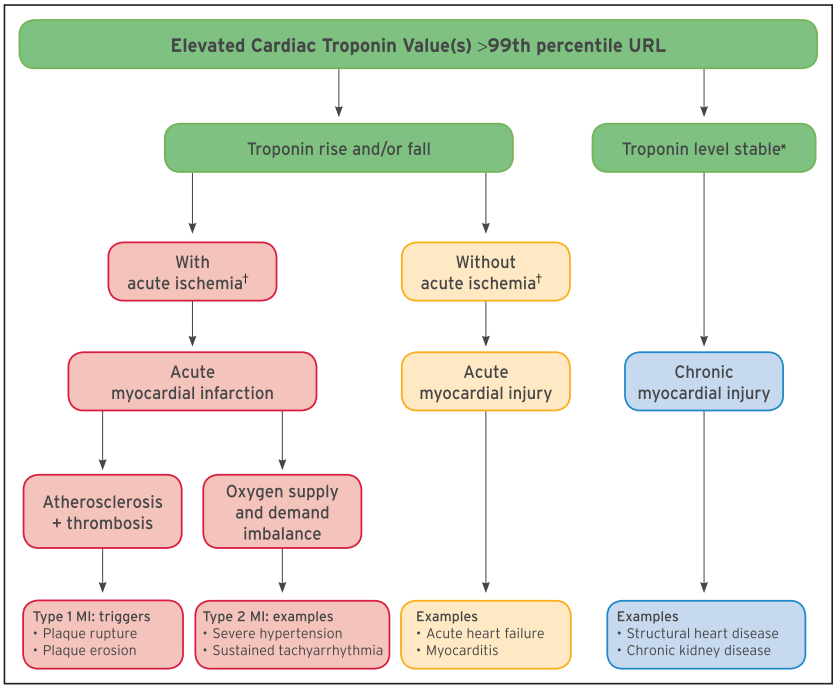


Figure 1. Model for interpreting myocardial injury.[1]

take into considerations suggestions made about classification of certain conditions as type 1 as compared to type 2 myocardial infarction.[1, 4] Regional coronary venous thrombosis with associated regional myocardial infarction has been reported in COVID. If this mechanism is documented, these will be considered a type 1 MI. The trial and CEC are focused on ascertaining and adjudicating cases of acute myocardial injury and acute myocardial infarction, and classifying those cases as described below. COVID also causes microvascular thrombi which are associated with patchy myocardial necrosis. These will be grouped with myocardial injury.

2. UNIVERSAL DEFINITIONS OF MYOCARDIAL INJURY AND MYOCARDIAL INFARCTION: SUMMARY

Universal definitions of myocardial injury and myocardial infarction
Criteria for myocardial injury
The term myocardial injury should be used when there is evidence of elevated cardiac troponin values (cTn) with at least 1 value above the 99th percentile upper reference limit (URL). The myocardial injury is considered acute if there is a rise and/or fall of cTn values.
Criteria for acute myocardial infarction (types 1, 2 and 3 MI)
The term acute myocardial infarction should be used when there is acute myocardial injury with clinical evidence of acute myocardial ischemia and with detection of a rise and/or fall of cTn values with at least 1 value above the 99th percentile URL and at least 1 of the following: • Symptoms of myocardial ischemia; • New ischemic ECG changes; • Development of pathological Q waves; • Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology; • Identification of a coronary thrombus by angiography or autopsy (not for types 2 or 3 MIs). Postmortem demonstration of acute atherothrombosis in the artery supplying the infarcted myocardium meets criteria for *type 1 MI*. Evidence of an imbalance between myocardial oxygen supply and demand unrelated to acute atherothrombosis meets criteria for *type 2 MI*. Cardiac death in patients with symptoms suggestive of myocardial ischemia and presumed new ischemic ECG changes before cTn values become available or abnormal meets criteria for *type 3 MI*.
Criteria for coronary procedure–related myocardial infarction (types 4 and 5 MI)
Percutaneous coronary intervention (PCI)–related MI is termed *type 4a MI*. Coronary artery bypass grafting (CABG)–related MI is termed *type 5 MI*. Coronary procedure–related MI ≤48 hours after the index procedure is arbitrarily defined by an elevation of cTn values >5 times for *type 4a MI* and >10 times for *type 5 MI* of the 99th percentile URL in patients with normal baseline values. Patients with elevated preprocedural cTn values, in whom the preprocedural cTn level are stable (≤20% variation) or falling, must meet the criteria for a >5 or >10 fold increase and manifest a change from the baseline value of >20%. In addition with at least 1 of the following: • New ischemic ECG changes (this criterion is related to *type 4a MI* only); • Development of new pathological Q waves; • Imaging evidence of loss of viable myocardium that is presumed to be new and in a pattern consistent with an ischemic etiology; • Angiographic findings consistent with a procedural flow-limiting complication such as coronary dissection, occlusion of a major epicardial artery or graft, side-branch occlusion-thrombus, disruption of collateral flow or distal embolization. Isolated development of new pathological Q waves meets the *type 4a MI* or *type 5 MI* criteria with either revascularization procedure if cTn values are elevated and rising but less than the prespecified thresholds for PCI and CABG. Other types of 4 MI include *type 4b MI* stent thrombosis and *type 4c MI* restenosis that both meet *type 1 MI* criteria. Postmortem demonstration of a procedure-related thrombus meets the *type 4a MI* criteria or *type 4b MI* criteria if associated with a stent.
Criteria for prior or silent/unrecognized myocardial infarction
Any 1 of the following criteria meets the diagnosis for prior or silent/unrecognized MI: • Abnormal Q waves with or without symptoms in the absence of nonischemic causes. • Imaging evidence of loss of viable myocardium in a pattern consistent with ischemic etiology. • Patho-anatomical findings of a prior MI.

CABG indicates coronary artery bypass grafting; cTn, cardiac troponin; ECG, electrocardiogram; MI, myocardial infarction; PCI, percutaneous coronary intervention; URL, upper reference limit.

Figure 2. Table from the 4th Universal Definition of Myocardial Infarction summarizing the different definitions of myocardial injury and infarction.[1]

Myocardial Injury: The increasing sensitivity of cardiac troponin (cTn) assays means that ongoing myocardial injury is frequently detected. Myocardial injury is a prerequisite for myocardial infarction (MI), but as noted below, criteria in addition to myocardial injury are necessary to make the diagnosis of MI. Adjudicators must distinguish between acute

myocardial injury that is not secondary to ischemia but may be due to other conditions (Table 2).

Criteria for Myocardial Injury: Detection of an elevated cTn value above the 99th percentile upper reference limit (URL) is defined as myocardial injury. The injury is considered acute if there is a rise and/or fall of cTn values.[1]
Criteria for Procedure Related Myocardial Injury: Cardiac procedural myocardial injury is arbitrary defined by increased in cTn values (>99th percentile URL) in patients with normal baseline values (<99th percentile URL) or a rise of cTn values >20% of the baseline value when it is the above the 99th percentile URL but is stable or falling.

Myocardial Infarction Type 1: Detection of rise and/or fall of cardiac biomarkers with at least one value above the 99th percentile of the upper reference limit (URL) together with evidence of myocardial ischemia with at least one of the following:

Table 2. Causes of non-ischemic myocardial injury[1, 5]
Heart failure
Myocarditis
Cardiomyopathy
Takotsubo syndrome
Coronary revascularization procedure
Cardiac procedure other than revascularization
Catheter ablation
Defibrillator shocks
Cardiac contusion
Sepsis, infectious disease
Chronic kidney disease
Stroke, subarachnoid hemorrhage
Pulmonary embolism, pulmonary hypertension
Infiltrative disease, e.g., amyloidosis, sarcoidosis
Chemotherapeutic agents
Critically ill patients
Strenuous exercise
Other

- Symptoms of ischemia
- New ischemic ECG changes indicative of new ischemia (new ST-T changes or new LBBB)*
- Development of pathological Q waves in the ECG**
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology
- Identification of a coronary thrombus by angiography including intracoronary imaging or by autopsy†
- *ECG manifestation of acute myocardial ischemia (in the absence of LVH and LBBB):
    - ST Elevation: New ST elevation at the J-point in two contiguous leads with the cut-point: ≥ 1 mm in all leads other than leads V2-V3, where the following cut-points apply: ≥2mm in men ≥40 years; ≥2.5 mm in men <40 years; or ≥ 1.5 mm in women regardless of age.
    - ST-depression and T-wave changes: New horizontal or down-sloping ST depression ≥ 0.5 mm in 2 contiguous leads and/or T inversion ≥ 1 mm in two contiguous leads with prominent R waves or R/S ratio >1.
- **Pathological Q waves:
    - Any Q-wave in leads V2-V3 >0.02 seconds or QS complex in leads V2-V3
    - Q-wave ≥ 0.03 seconds and ≥1 mm deep or QS complex in leads I, II, aVL, aVF, or V4-V6 in any 2 leads of a contiguous lead grouping (I, aVL;V1-V6; II, III, aVF; V7-V9).

    - R-wave ≥ 0.04s in V1–V2 and R/S ≥ 1 with a concordant positive T-wave in the absence of a conduction defect
- †Postmortem demonstration of an atherothrombus in the artery supplying the infarcted myocardium, or a macroscopically large circumscribed area of necrosis with or without intramyocardial hemorrhage meets the type 1 MI criteria regardless of cTn values.
- Consideration will be given to recent proposals to modify myocardial infarction type 1 to include coronary obstruction by spontaneous coronary artery dissection, coronary embolism, or coronary vasospasm or microvascular dysfunction.[4]

Myocardial Infarction Type 2: Detection of a rise and/or fall of cTn values with at least 1 value above the 99th percentile URL, and evidence of imbalance between myocardial oxygen supply and demand unrelated to coronary atherothrombosis, requiring at least 1 of the following:

- Symptoms of acute myocardial ischemia
- New ischemic ECG changes
- Development of pathological Q waves;
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with ischemic etiology

Myocardial Infarction Type 3: Patients who suffer cardiac death, with symptoms suggestive of myocardial ischemia accompanied by presumed new ischemic ECG changes or ventricular fibrillation but die before blood samples for biomarkers can be obtained, or before increases in cardiac biomarkers can be identified, or MI is detected by autopsy examination.

Myocardial infarction Type 4a and 4b (myocardial infarction associated with percutaneous coronary intervention): Criteria for percutaneous coronary intervention (PCI)-related MI ≤48 hours after the index procedure are as follows: Coronary intervention-related MI is arbitrarily defined by an elevation of cTn values >5 times the 99the percentile URL in patients with normal baseline values. In patients with elevated preprocedural cTn in whom the cTn levels are stable (≤20% variation) or falling, the post procedure cTn must rise by >20%. However, the absolute procedural value must still be at least 5 times the 99th percentile URL. In addition, 1 of the following elements is required:

- New ischemic ECG changes
- Development of new pathological Q waves; note that the development of new pathological Q waves meets the criteria for procedure-related MI if the cTn values are elevated and rising but <5 times the 99th percentile URL.
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology
- Angiographic findings consistent with a procedural flow-limiting complication such as coronary dissection, occlusion of a major epicardial artery or side branch occlusion/thrombus, disruption of collateral flow, or distal embolization.
- Type 4a MI is an MI associated with PCI
- Type 4b MI is an MI associated with stent/scaffold thrombosis

Myocardial Infarction Type 4c: A type 4c MI is an MI associated with restenosis associated with prior PCI. Possible Type 4c MI is evaluated using the same criteria as Type 1 MI.

Myocardial Infarction Type 5: Criteria of coronary artery bypass grafting (CABG)-related MI ≤ 48 hours after the index procedure. CABG-related MI is arbitrarily defined as elevation of cTn values >10 times the 99th percentile URL in patients with normal baseline cTn values. In patients with elevated preprocedural cTn in whom cTn are stale (≤20% variation) or falling, the post procedure cTn must rise by >20%. However, the absolute postprocedural values must still be >10 times the 99th percentile URL. In addition, 1 of the following elements is required:

- Development of new pathological Q waves; note that the development of new pathological Q waves meets the criteria for procedure-related MI if the cTn values are elevated and rising but <10 times the 99th percentile URL.
- Angiographically documented new graft occlusion or new native coronary artery occlusion;
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology

Special or unusual circumstances: Further guidance on distinguishing myocardial injury from myocardial infarction in the context of non-cardiac surgery, heart failure, myocarditis, Takotsubo syndrome, kidney disease, and in critically ill patients, and myocardial infarction nonobstructive coronary arteries is included in the 4th Universal Definition of MI.[1]

Stroke

The definition of stroke used here is drawn from the definitions proposed by Hicks et al. and Sacco et al.[6, 7] Stroke is defined as the acute onset of focal neurological dysfunction caused by brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction. Note that while all strokes will be adjudicated, only ischemic stroke is part of the primary efficacy endpoint. Hemorrhagic stroke is considered a major bleed (see section 6.7).

A stroke is the acute onset of a new persistent neurological deficit attributed to an obstruction in cerebral blood flow with no apparent nonvascular cause (e.g. tumor, trauma, infection). Available neuroimaging studies will be considered to support the clinical impression and to determine if there is a demonstrable lesion compatible with an acute stroke. To the extent possible, all strokes will be classified as ischemic, hemorrhagic or unknown. While all types of strokes will be adjudicated by the CEC, only ischemic strokes will be included in the primary endpoint.

For the diagnosis of stroke, the following criteria should be fulfilled:

1. Rapid onset of a focal neurological deficit not related to any other known non-cerebrovascular process with at least one of the following:

- Change in level of consciousness
- Hemiplegia

- Hemiparesis
- Numbness or sensory loss affecting one side of the body
- Dysphasia/aphasia
- Hemianopia
- Other new neurological sign/symptom(s) consistent with stroke
- If the timing of onset is uncertain, a diagnosis of stroke may be made provided that there are no plausible non-stroke causes for the clinical presentation.

AND

2. Duration of a focal/global neurological deficit that is:

- EITHER ≥ 24 hours,
- OR < 24 hours if:
    - Resolution of symptoms is due to least one of the following interventions:
        1. Pharmacologic: intravenous or intraarterial thrombolysis
        2. Non-pharmacologic: (i.e. neuro-interventional procedure such as intracranial angioplasty)
    - OR available MRI clearly documents a new hemorrhage or infarct
    - OR available head CT clearly documents a new hemorrhage or infarct or excludes a mimic of stroke
    - OR the neurological deficit results in death.

Ideally, at least one of should be present to confirm the diagnosis of stroke:

- Confirmation by neurology or neurosurgery specialist
- Brain imaging procedure (at least one of the following): CT scan, MRI scan, or cerebral vessel angiography
- Lumbar puncture (i.e. spinal fluid analysis diagnostic of intracranial hemorrhage)

If the acute focal signs represent a worsening of a previous deficit, these signs must persist for more than 24 hours and be accompanied by an appropriate new MRI or CT scan finding.

Strokes are sub-classified as follows:

Ischemic (non-hemorrhagic): An acute episode of focal cerebral, spinal, or retinal dysfunction caused by infarction of central nervous system tissue. Hemorrhage may be a consequence of ischemic stroke. In this situation, the stroke is an ischemic stroke with hemorrhagic transformation and not a hemorrhagic stroke but would also be listed as a major bleeding safety event.

Hemorrhagic: An acute episode of focal or global cerebral or spinal dysfunction caused by intraparenchymal, intraventricular, or subarachnoid hemorrhage. Hemorrhage in the brain is documented by neuroimaging or autopsy or lumbar puncture. Note that subdural hematomas are intracranial hemorrhagic events and not strokes.

Undetermined: An acute episode of focal or global neurological dysfunction caused by presumed brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction but with insufficient information to allow categorization as either ischemic or hemorrhagic.

Major Bleeding

Major bleeding is defined as acute clinically overt bleeding associated with one or more of the following (as per ISTH guidelines):[8, 9]

- Decrease in hemoglobin of 2 g/dL or more;
- Transfusion of 2 units or more of packed red blood cells;
- Bleeding that occurs in at least one of the following critical sites:
    - Intracranial
    - Intraspinal
    - Intraocular (within the corpus of the eye. A conjunctival bleed is not an intraocular bleed)
    - Pericardial
    - Intraarticular
    - Retroperitoneal
    - Intramuscular with compartment syndrome
- Bleeding that leads to death (primary cause of death or contributes directly to death)

Definitions of Cardiovascular, Non-cardiovascular, and Undetermined Cases of Death

Definitions of Cardiovascular, Non-Cardiovascular, and Undetermined Cases of Death

The classifications for death are drawn from Hicks et al.[6] Death is classified into one of three categories: cardiovascular, non-cardiovascular, and undetermined cause of death. The intent is to identify one of these categories as the underlying cause of death. The key priority is differentiating between cardiovascular and non-cardiovascular causes of death. Death attribution can be difficult, particularly for sudden death, even when witnessed. While all deaths will be adjudicated by the CEC, only those deemed to be of cardiovascular cause will be included as part of the trial primary composite endpoint. Deaths of non-cardiovascular cause will not be included in the primary efficacy endpoint. Deaths of undetermined cause will not be part of the primary efficacy endpoint of PROMINENT.

Cardiovascular death can be due to acute myocardial infarction (MI), sudden cardiac death, heart failure, stroke, pulmonary embolism, a cardiovascular procedure, cardiovascular hemorrhage, or other cardiovascular cause.

Cardiovascular death due to acute MI: Death by any cardiovascular mechanism (arrhythmia, sudden death, heart failure, stroke, pulmonary embolus, PAD) within 30 days after an acute MI, related to the immediate consequences of the MI, such as progressive heart failure or recalcitrant arrhythmia. While there may be assessable (attributable) mechanisms of cardiovascular death during this time period, for simplicity, if the cardiovascular death occurs within 30 days of an acute MI, it will be considered a death due to MI.

Note: Acute MI should be verified to the extent possible by the diagnostic criteria outlined for acute MI or by autopsy findings showing recent MI or recent coronary thrombosis. Death resulting from a procedure to treat an MI (PCI or CABG), or to treat a complication resulting from MI, should also be considered death due to acute MI. Death resulting from an elective coronary procedure to treat myocardial ischemia (i.e., chronic stable angina) or death due to an MI that occurs as a direct consequence of a cardiovascular investigation/ procedure/operation should be considered as a death due to a cardiovascular procedure.

Cardiovascular death due to sudden cardiac death: Death that occurs unexpectedly and not within 30 days of an acute MI. Sudden cardiac death includes the following scenarios:

- Death witnessed and occurring without new or worsening symptoms
- Death witnessed within 60 min of the onset of new or worsening cardiac symptoms unless the symptoms suggest acute MI
- Death witnessed and attributed to an identified arrhythmia (e.g., captured on an electrocardiographic recording, witnessed on a monitor, or unwitnessed but found on ICD review)
- Death after unsuccessful resuscitation from cardiac arrest (e.g., ICD unresponsive sudden cardiac death, pulseless electrical activity arrest)
- Death after successful resuscitation from cardiac arrest and without identification of a specific cardiac or non-cardiac etiology
- Unwitnessed death in a subject seen alive and clinically stable ≤24 h before being found dead without any evidence supporting a specific non- cardiovascular cause of death (information about the patient's clinical status preceding death should be provided if available)

Unless additional information suggests an alternate specific cause of death (e.g., Death due to Other Cardiovascular Causes), if a patient is seen alive ≤24 h before being found dead, sudden cardiac death should be recorded. For patients who were not observed alive within 24 h of death, undetermined cause of death should be recorded (e.g., a subject found dead in bed but who had not been seen by family members for >24 h).

Cardiovascular death due to heart failure (HF): Death associated with clinically worsening symptoms and/or signs of HF, regardless of HF etiology. Note: Deaths due to HF can have various etiologies, including single or recurrent MIs, ischemic or nonischemic cardiomyopathy, hypertension, or valvular disease.

Death due to stroke: Death after a stroke that is either a direct consequence of the stroke or a complication of the stroke. Note: acute stroke should be verified to the extent possible by the diagnostic criteria outlined for stroke.

Cardiovascular death due to cardiovascular procedure: Death caused by the immediate complication(s) of a cardiovascular procedure.

Cardiovascular death due to cardiovascular hemorrhage: Death related to hemorrhage such as a non-stroke intracranial hemorrhage (e.g., subdural hematoma) nonprocedural or non-traumatic vascular rupture (e.g., aortic aneurysm), or hemorrhage causing cardiac tamponade.

Cardiovascular death due to other cardiovascular causes: Cardiovascular death not included in the above categories with specific, known cause (e.g., PE, PAD).

Definition of Non-cardiovascular Death: When death is due to a non-cardiovascular cause, a cardiovascular cause of death is excluded.

- Pulmonary (excludes malignancy)
- Renal
- Gastrointestinal (disease of the esophagus, stomach, or intestines (excludes malignancy)
- Hepatobiliary (disease of the liver, gall bladder, or biliary ducts (excludes malignancy)
- Pancreatic (disease of the pancreas (excludes malignancy)
- Infection (including sepsis)
- Inflammatory/immune (death attributable to an inflammatory or immune-mediated disease or process, including systemic inflammatory response syndrome (SIRS), immunological, and autoimmune disease and disorders. Includes anaphylaxis from environmental allergies)
- Hemorrhage (bleeding that is not considered cardiovascular hemorrhage or stroke
- Non-CV procedure or surgery (death caused by the immediate complications of a non-cardiovascular procedure or surgery)
- Trauma (death attributable to trauma. Includes homicide)
- Suicide
- Nonprescription drug reaction or overdose
- Prescription drug reaction or overdose (includes anaphylaxis)
- Neurological (excludes malignancy, as well as death from ischemic stroke, hemorrhagic stroke, or undetermined cause of stroke, or cardiovascular hemorrhage of central nervous system)
- Malignancy (leukemia, lymphoma, or other malignancy)
- Other (death attributable to a cause other than those listed in this classification; specify organ system)

Undetermined cause of death: Causality may be difficult to determine if information available from the time of death is minimal or nonexistent. Deaths of undetermined cause will not be considered presumed cardiovascular, and thus will not be part of the primary efficacy endpoint of PROMINENT.

Section 3 – Supplemental Tables

Table S1 – Anticoagulation Regimens

	Therapeutic-dose anticoagulation N=536	Usual care pharmacological thromboprophylaxis N=567
Anticoagulant drug – n (%)[a]	N=519	N=551
Enoxaparin	252 (48.6)	287 (52.1)
Dalteparin	175 (33.7)	181 (32.8)
Tinzaparin	35 (6.7)	28 (5.1)
Subcutaneous unfractionated heparin	7 (1.3)	25 (4.5)
Intravenous unfractionated heparin	50 (9.6)	6 (1.1)
Fondaparinux	0 (0)	0 (0)
Direct oral anticoagulant	0 (0)	1 (0.2)
None	6 (1.2)	24 (4.4)
Other	1 (0.2)	4 (0.7)
Post-randomization dosage equivalents[a]	N=469	N=493
Low dose thromboprophylaxis	16 (3.4)	199 (40.4)
Intermediate dose thromboprophylaxis	50 (8.3)	255 (51.7)
Subtherapeutic dose anticoagulation	39 (8.3)	9 (1.8)
Therapeutic dose anticoagulation	364 (77.6)	30 (6.1)

[a] Data reported reflects those in whom specific dosing information was available at the time the dataset was locked for analysis; drug and dose reported are those prescribed on post-randomization day 1

Table S2 – Sensitivity Analyses

	Therapeutic-dose anticoagulation	Usual care pharmacological thromboprophylaxis
Excluding the moderate-disease group from the model[a]	N=534	N=564
Organ support-free days		
Median, (IQR)	1 (–1, 16)	4 (–1, 16)
Adjusted odds ratio (95% CrI)	0.82 (0.66, 1.03)	1 (Reference)
Probability of futility[b], %	>99.9	-
Probability of superiority[c], %	4.5	-
Probability of inferiority[d], %	95.5	-
Hospital survival		
No. of patients/total no. (%)	335/534 (62.7)	364/564 (64.5)
Adjusted odds ratio (95% CrI)	0.83 (0.63, 1.10)	1 (Reference)
Probability of superiority[c], %	10.4	-
Probability of inferiority[d], %	89.6	-
Assuming enthusiastic prior in favor of therapeutic-dose anticoagulation[a]	N=534	N=564
Organ support-free days		
Adjusted odds ratio (95% CrI)	0.86 (0.70, 1.07)	1 (Reference)
Probability of futility[b], %	99.8	-
Probability of superiority[c], %	9.4	-
Probability of inferiority[d], %	90.6	-
Assuming skeptical prior in favor of therapeutic-dose anticoagulation[a]	N=534	N=564
Organ support-free days		
Adjusted odds ratio (95% CrI)	0.83 (0.67, 1.03)	1 (Reference)
Probability of futility[b], %	99.9	-
Probability of superiority[c], %	5.2	-
Probability of inferiority[d], %	94.8	-
Patients with either confirmed or suspected Covid-19[a]	N=579	N=596
Organ support-free days		
Median, (IQR)	3 (–1, 16)	5 (–1, 16)
Adjusted odds ratio (95% CrI)	0.85 (0.69, 1.05)	1 (Reference)
Probability of futility[b], %	99.9	-
Probability of superiority[c], %	7.0	-
Probability of inferiority[d], %	93.0	-

	Therapeutic-dose anticoagulation	Usual care pharmacological thromboprophylaxis
Hospital survival		
Adjusted odds ratio (95% CrI)	0.85 (0.65, 1.11)	1 (Reference)
Probability of superiority[c], %	12.2	-
Probability of inferiority[d], %	87.8	-
Patients with confirmed Covid-19 - site and time effects excluded from model[a]		
	N=534	N=564
Organ support-free days		
Adjusted odds ratio (95% CrI)	0.86 (0.70, 1.06)	1 (Reference)
Probability of futility[b], %	99.9	-
Probability of superiority[c], %	7.5	-
Probability of inferiority[d], %	92.5	-
Hospital survival		
Adjusted odds ratio (95% CrI)	0.85 (0.66, 1.10)	1 (Reference)
Probability of superiority[c], %	10.9	-
Probability of inferiority[d], %	89.1	-
Excluding concomitant antiplatelet agents or randomization to antiplatelet domain of REMAP-CAP[a]		
	N=448	N=456
Organ support-free days		
Adjusted odds ratio (95% CrI)	0.83 (0.65, 1.05)	1 (Reference)
Probability of futility[b], %	99.9	-
Probability of superiority[c], %	6.5	-
Probability of inferiority[d], %	93.5	-
Hospital survival		
Adjusted odds ratio (95% CrI)	0.87 (0.64, 1.19)	1 (Reference)
Probability of superiority[c], %	19.6	-
Probability of inferiority[d], %	80.4	-
Major bleeding		
Adjusted odds ratio (95% CrI)	2.20 (1.03, 5.04)	1 (Reference)
Probability of superiority[c], %	2.1	-
Probability of inferiority[d], %	97.9	-

Probabilities represent posterior probabilities of therapeutic-dose anticoagulation compared to thromboprophylaxis

Odds ratios represent the posterior median; IQR – Interquartile Range; CrI – Credible Interval

[a] The primary analysis included information borrowed from the moderate-disease group. For the first sensitivity analysis presented here, as well as for all other sensitivity analyses marked with this reference, the information from the moderate-disease group was not included.

[b] Futility is defined as odds ratio <1.2

[c] For organ support-free days and hospital survival, superiority is defined as odds ratio >1; for major bleeding, superiority is defined as odds ratio <1

[d] For organ support-free days and hospital survival, inferiority is defined as odds ratio <1; for major bleeding, inferiority is defined as odds ratio >1

Table S3 – Exploratory Analysis of Interaction Between Therapeutic-Dose Anticoagulation with Heparin and Interleukin-6 Receptor Antagonists in REMAP-CAP

	Therapeutic-dose anticoagulation (n=297)[a]	**Usual care pharmacological thromboprophylaxis (n=262)[a]**
Organ support-free days		
No assignment in immune modulation domain (N)	147[b]	139
Median, IQR	0, (–1, 14)	5 (–1, 16)
Control - immune modulation domain (N)	71	64
Median, IQR	0 (–1, 15)	5 (–1, 14)
Interleukin-6 receptor antagonist - immune modulation domain (N)	79	59
Median, IQR	6 (–1, 16)	11 (–1, 17)
Adjusted model results		
Therapeutic-dose anticoagulation with heparin		
Adjusted proportional odds ratio (95% CrI)	0.64 (0.45-0.89)	1 (Reference)
Probability of futility, %	>99.9%	-
Probability of superiority, %	0.6%	-
Probability of inferiority, %	99.4%	-
Interleukin-6 receptor antagonist		
Adjusted proportional odds ratio (95% CrI)	1.49 (0.87-2.56)	1 (Reference)
Probability of futility, %	22.2%	-
Probability of superiority, %	92.1%	-
Probability of inferiority, %	7.9%	-
Interaction of therapeutic-dose anticoagulation and interleukin-6 receptor antagonism		
Adjusted proportional odds ratio (95% CrI)	1.11 (0.58-2.15)	1 (Reference)
Probability of interaction odds ratio > 1	62.9%	
Probability of interaction odds ratio < 1	37.1%	
Combination of therapeutic-dose anticoagulation and Interleukin-6 receptor antagonist		
Adjusted proportional odds ratio (95% CrI)	1.06 (0.61-1.81)	1 (Reference)
Probability of superiority, %	57.7%	-
Probability of inferiority, %	42.3%	-

a. Population of patients randomized in REMAP-CAP therapeutic anticoagulation domain on or before November 20, 2020 (date on which randomization to control was discontinued in REMAP-CAP immune modulation domain)
b. Organ support-free days to day 21 known for 146 of these patients

Table S4 – Thrombotic Events

	Therapeutic-dose anticoagulation	Usual-care pharmacological thromboprophylaxis
Number of patients in whom thrombotic event outcomes were available as of April 8th, 2021	530	559
Number of patients with a major thrombotic event	34	58
Number of patients with any thrombotic event	38	62
Thrombotic event breakdown – n[a]		
Total Events	36	64
Pulmonary Embolism	13	42
Myocardial Infarction	7	10
Ischemic Cerebrovascular Event	8	9
Systemic Arterial Thromboembolism	8	3
Deep Venous Thrombosis[b]	6	6

[a] Some patients had more than one event; total events are reported

[b]Deep venous thrombosis was not included in the composite endpoint of major thrombotic events

Section 4 – Supplemental Figures

Figure S1 - Empirical distribution of organ support-free days to day 21 by randomization to therapeutic anticoagulation versus control and randomization in the Immune Modulation domain.

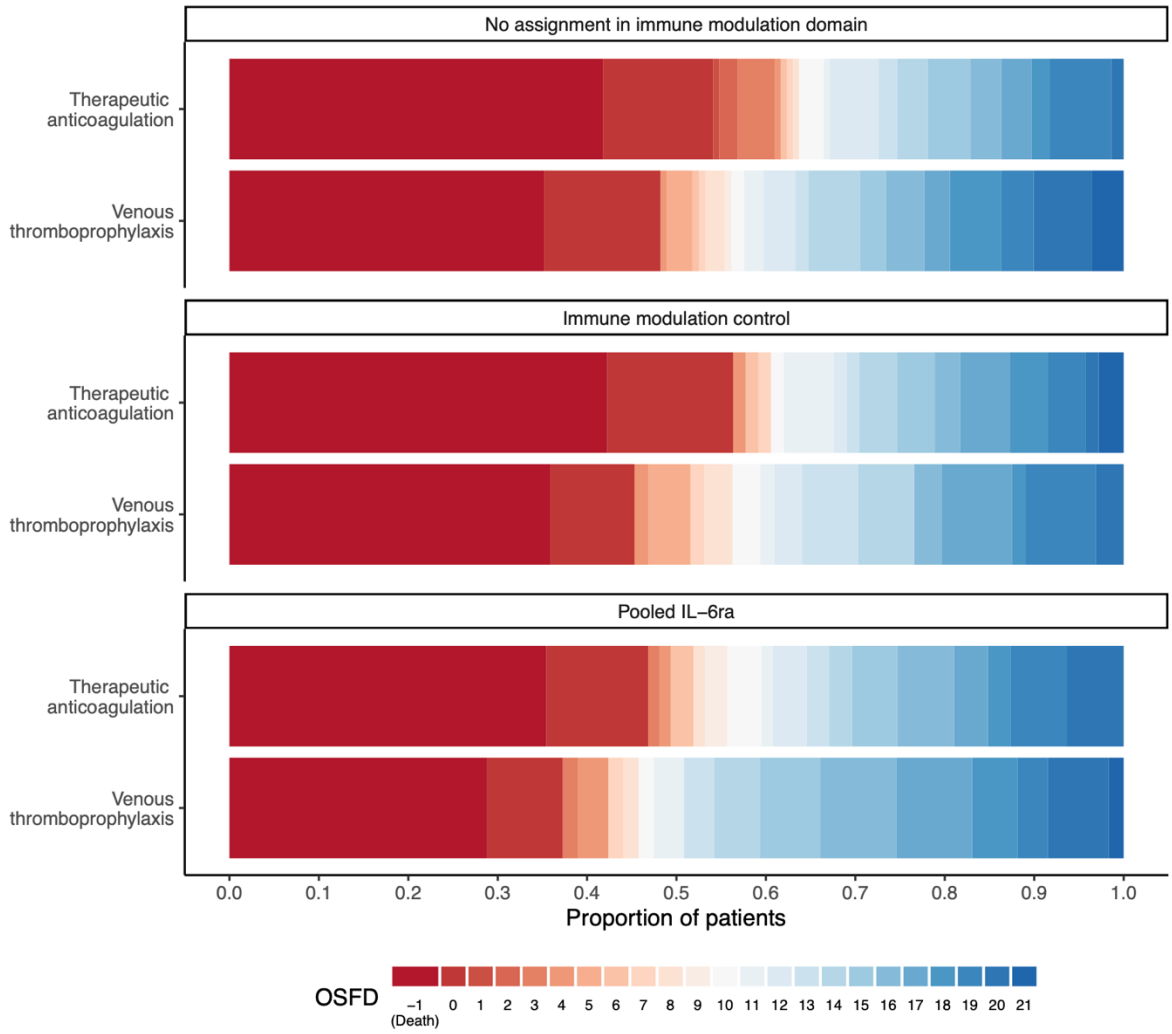
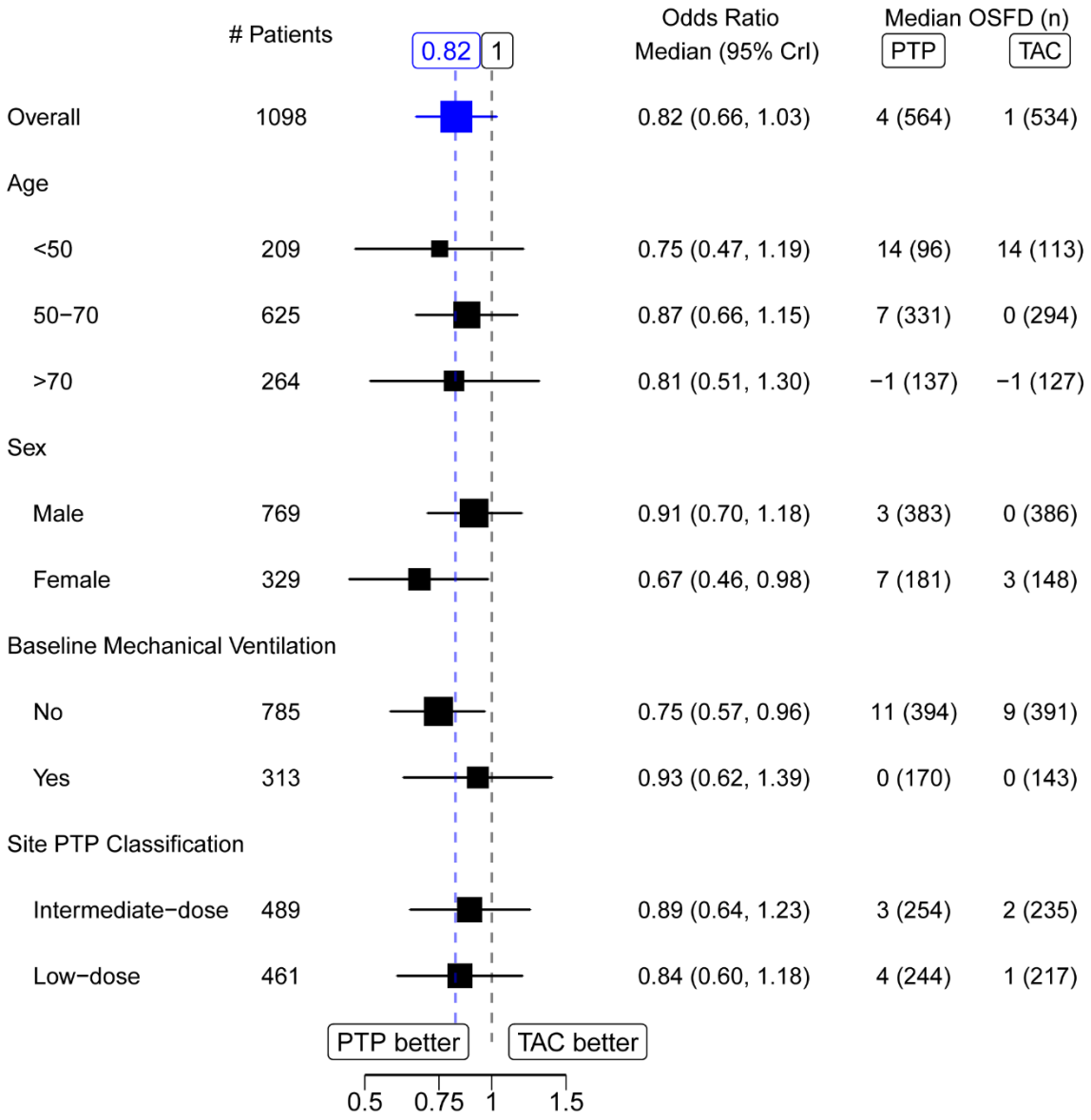


Figure S2 - Subgroup analyses of organ support-free days to day 21 in patients with severe Covid-19 (without borrowing from moderate Covid-19 patient groups).
PTP - usual care pharmacological thromboprophylaxis, TAC – therapeutic-dose anticoagulation



Section 6 – References

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Therapeutic Anticoagulation with Heparin in Critically Ill Patients with Covid-19

The REMAP-CAP, ACTIV-4a, and ATTACC Investigators*

ABSTRACT

BACKGROUND

Thrombosis and inflammation may contribute to morbidity and mortality among patients with coronavirus disease 2019 (Covid-19). We hypothesized that therapeutic-dose anticoagulation would improve outcomes in critically ill patients with Covid-19.

METHODS

In an open-label, adaptive, multiplatform, randomized clinical trial, critically ill patients with severe Covid-19 were randomly assigned to a pragmatically defined regimen of either therapeutic-dose anticoagulation with heparin or pharmacologic thromboprophylaxis in accordance with local usual care. The primary outcome was organ support–free days, evaluated on an ordinal scale that combined in-hospital death (assigned a value of –1) and the number of days free of cardiovascular or respiratory organ support up to day 21 among patients who survived to hospital discharge.

RESULTS

The trial was stopped when the prespecified criterion for futility was met for therapeutic-dose anticoagulation. Data on the primary outcome were available for 1098 patients (534 assigned to therapeutic-dose anticoagulation and 564 assigned to usual-care thromboprophylaxis). The median value for organ support–free days was 1 (interquartile range, –1 to 16) among the patients assigned to therapeutic-dose anticoagulation and was 4 (interquartile range, –1 to 16) among the patients assigned to usual-care thromboprophylaxis (adjusted proportional odds ratio, 0.83; 95% credible interval, 0.67 to 1.03; posterior probability of futility [defined as an odds ratio <1.2], 99.9%). The percentage of patients who survived to hospital discharge was similar in the two groups (62.7% and 64.5%, respectively; adjusted odds ratio, 0.84; 95% credible interval, 0.64 to 1.11). Major bleeding occurred in 3.8% of the patients assigned to therapeutic-dose anticoagulation and in 2.3% of those assigned to usual-care pharmacologic thromboprophylaxis.

CONCLUSIONS

In critically ill patients with Covid-19, an initial strategy of therapeutic-dose anticoagulation with heparin did not result in a greater probability of survival to hospital discharge or a greater number of days free of cardiovascular or respiratory organ support than did usual-care pharmacologic thromboprophylaxis. (REMAP-CAP, ACTIV-4a, and ATTACC ClinicalTrials.gov numbers, NCT02735707, NCT04505774, NCT04359277, and NCT04372589.)

The members of the executive writing committee and the block writing committee assume responsibility for the overall content and integrity of this article. The full names, academic degrees, and affiliations of the members of the executive writing committee and the block writing committee are listed in the Appendix. Address reprint requests to Dr. Zarychanski at the Sections of Hematology/Oncology and Critical Care, University of Manitoba, Winnipeg, MB, Canada R3E 0V9, or at rzarychanski@cancercare.mb.ca.

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Coronavirus disease 2019 (COVID-19) is associated with inflammation and thrombosis.[1-4] Critically ill patients with Covid-19 are at high risk for thrombosis despite receiving standard-dose pharmacologic thromboprophylaxis.[5-8] Circulating biomarkers reflecting systemic inflammation and coagulation activation (e.g., D-dimer and C-reactive protein) are independently associated with a greater risk of respiratory failure, thrombosis, and death in patients with Covid-19.[2,9,10] Inflammation and thrombosis may therefore be important contributors to poor outcomes.

Unfractionated and low-molecular-weight heparins are parenteral anticoagulants with antiinflammatory properties and possible antiviral properties.[11,12] Given the reports of excess thrombotic risk, enhanced-dose anticoagulation strategies have been incorporated into some Covid-19 guidance statements, especially for critically ill patients.[13,14] However, the effectiveness and safety of therapeutic-dose anticoagulation given to improve outcomes in Covid-19 are uncertain.

We conducted an international, adaptive, multiplatform, randomized, controlled trial to determine whether an initial strategy of therapeutic-dose anticoagulation with unfractionated or low-molecular-weight heparin improves in-hospital survival and reduces the duration of intensive care unit (ICU)–level cardiovascular or respiratory organ support in critically ill patients with Covid-19.

METHODS

TRIAL DESIGN AND OVERSIGHT

Early in the Covid-19 pandemic, the lead investigators of three international adaptive platform trials harmonized their protocols and statistical analysis plans (available with the full text of this article at NEJM.org) to study the effect of therapeutic-dose anticoagulation in patients who were hospitalized for Covid-19 in one integrated, multiplatform, randomized clinical trial to accelerate the generation of evidence and maximize the external validity of the results (see the Supplementary Appendix, available at NEJM.org). The platforms included the Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP),[15] A Multicenter, Adaptive, Randomized Controlled Platform Trial of the Safety and Efficacy of Antithrombotic Strategies in Hospitalized Adults with COVID-19 (ACTIV-4a), and the Antithrombotic Therapy to Ameliorate Complications of Covid-19 (ATTACC) trial.[16] The platforms aligned the trial design, eligibility criteria, interventions, outcome measures, and statistical analysis plan (comparisons of the three platforms are provided in the Supplementary Appendix). Each platform was overseen by independent data and safety monitoring boards following a collaborative cross-platform interaction plan. The members of the writing committees vouch for the accuracy and completeness of the data and for the fidelity of the trials to the protocols.

The multiplatform trial was conducted in accordance with the principles of the Good Clinical Practice guidelines of the International Council for Harmonisation. Ethics and regulatory approval were obtained at each participating center. Written or oral informed consent, in accordance with regional regulations, was obtained from all patients or their surrogates. The trial was supported by multiple international funding organizations that had no role in the design, analysis, or reporting of the trial results, with the exception of the ACTIV-4a protocol, which received input on design from professional staff members at the National Institutes of Health and from peer reviewers.

PATIENTS

All three platforms enrolled patients who were hospitalized for Covid-19. Although REMAP-CAP enrolled patients with suspected or confirmed Covid-19, only patients with infection confirmed by laboratory testing were included in the primary analysis of the multiplatform trial. The trial was designed to evaluate the effect of therapeutic-dose anticoagulation in patients with severe Covid-19 and in those with moderate Covid-19 stratified according to D-dimer level (high, low, or unknown). This report describes the results of the analyses involving patients with severe Covid-19; the results of analyses involving patients with moderate Covid-19 are reported separately.[17]

Severe Covid-19 was defined as Covid-19 that led to receipt of ICU-level respiratory or cardiovascular organ support (oxygen through a high-flow nasal cannula, noninvasive or invasive mechanical ventilation, extracorporeal life support, vasopressors, or inotropes) in an ICU. In ACTIV-4a, in which definitions of an ICU were thought to

be challenging to operationalize during the pandemic, receipt of ICU-level organ support, irrespective of hospital setting, was used to define ICU-level care. Patients were ineligible if they had been admitted to the ICU with Covid-19 for 48 hours or longer (in REMAP-CAP) or to a hospital for 72 hours or longer (in ACTIV-4a and ATTACC) before randomization. They were also ineligible if they were at imminent risk for death and there was no ongoing commitment to full organ support, or if they were at high risk for bleeding, were receiving dual antiplatelet therapy, had a separate clinical indication for therapeutic-dose anticoagulation, or had a history of heparin sensitivity, including heparin-induced thrombocytopenia. Detailed exclusion criteria for the platforms are provided in the Supplementary Appendix.

RANDOMIZATION

Randomization was performed with the use of separate central Web-based systems for each platform. Patients were randomly assigned to receive therapeutic-dose anticoagulation with unfractionated or low-molecular-weight heparin or to receive usual-care pharmacologic thromboprophylaxis in an open-label fashion. Patients in ACTIV-4a underwent randomization in a 1:1 ratio. The other two platforms specified response-adaptive randomization; randomization probabilities could be updated for those platforms during the period from each monthly adaptive interim analysis in the multiplatform trial to the end of enrollment (as described in the Supplementary Appendix).

Therapeutic-dose anticoagulation was administered according to local site protocols for the treatment of acute venous thromboembolism for up to 14 days or until recovery (defined as either hospital discharge or discontinuation of supplemental oxygen for at least 24 hours). Usual-care thromboprophylaxis was administered at a dose and duration determined by the treating clinician according to local practice, which included either standard low-dose thromboprophylaxis or enhanced intermediate-dose thromboprophylaxis. The anticoagulation and thromboprophylaxis regimens that were specified by each platform are detailed in the Supplementary Appendix. Some of the patients who were enrolled in REMAP-CAP also underwent randomization in the antiplatelet-agent domain and in other domains of that trial. There were no additional active domains in ACTIV-4a and ATTACC.

OUTCOME MEASURES

The primary outcome, organ support–free days, was evaluated on an ordinal scale indicating the number of days free of cardiovascular or respiratory organ support up to day 21 among patients who survived to hospital discharge; patients who died in the hospital by day 90 were assigned a value of –1. Among the patients who survived to hospital discharge, the number of days free of respiratory organ support (high-flow nasal cannula, noninvasive or invasive ventilation, or extracorporeal life support) and cardiovascular organ support (vasopressors or inotropes) through day 21 was recorded. A higher number of organ support–free days indicates a better outcome. Patients who were discharged from the hospital before day 21 were assumed to be alive and free of organ support through day 21.

Prespecified secondary outcomes included survival to hospital discharge, major thrombotic events or death (a composite of myocardial infarction, pulmonary embolism, ischemic stroke, systemic arterial embolism, or in-hospital death), and any thrombotic events (major thrombotic events or deep-vein thrombosis) or death. The outcomes of major thrombotic events or death and any thrombotic events or death were assessed through 28 days (in ACTIV-4a and ATTACC) or through hospital discharge (REMAP-CAP). Safety outcomes included major bleeding during the treatment period, as defined by the International Society of Thrombosis and Hemostasis for nonsurgical patients,[18] and laboratory-confirmed heparin-induced thrombocytopenia. Thrombotic and bleeding events were adjudicated by independent platform-specific adjudication committees, the members of which were unaware of the treatment assignments. Definitions of all the outcomes are provided in the Supplementary Appendix.

STATISTICAL ANALYSIS

The multiplatform trial analyzed combined individual patient data from all platforms with the use of a single overarching Bayesian model (as described in the Supplementary Appendix and in the protocol). Monthly interim analyses of combined data from all platforms were planned within each of the prespecified patient cohorts. Randomization continued within each cohort until a sta-

tistical conclusion of superiority (defined as >99% posterior probability of a proportional odds ratio of >1) or futility (>95% posterior probability of a proportional odds ratio of <1.2) was made for a cohort. The stopping criteria for a statistical conclusion applied independently to each cohort, with the exception of the cohort with unknown D-dimer levels.

The primary analysis involved a Bayesian cumulative logistic-regression model (shown in the Supplementary Appendix) that was used to calculate the posterior distribution for the proportional odds ratio for organ support–free days. The primary model was adjusted for age, sex, trial site, and enrollment time interval (in 2-week intervals). Patients in the severe-disease and moderate-disease cohorts were included in the model. Weakly informative Dirichlet prior probability distributions were specified to model the baseline probabilities for each value for organ support–free days in the severe-disease and moderate-disease cohorts. The model was used to estimate treatment effects in each of the cohorts (the severe-disease cohort and the moderate-disease cohort stratified according to D-dimer level), with the use of a Bayesian hierarchical approach.[19] The treatment effects of anticoagulation in the severe-disease and moderate-disease cohorts were nested in a hierarchical prior distribution centered on an overall intervention effect that had been estimated with a neutral prior distribution, but distinct cohort-specific effects were estimated. When consistent effects were observed between the cohorts, the posterior distribution for the intervention effect in each cohort was shrunk toward the overall estimate. For the purposes of this report, the primary analysis involved all the patients enrolled in the multiplatform trial (including the severe-disease and moderate-disease cohorts) for whom data on the primary outcome were available as of April 8, 2021. The analysis of this data set was prespecified in the statistical analysis plan.

The primary model was fit with the use of a Markov chain Monte Carlo algorithm with 100,000 samples from the joint posterior distribution, which allowed calculation of the posterior distributions for the odds ratios, including medians and 95% credible intervals, and the posterior probabilities of superiority (indicated by an odds ratio of >1), futility (indicated by an odds ratio of <1.2), or inferiority (indicated by an odds ratio of <1). A similar model was run for survival to hospital discharge. Prespecified sensitivity analyses of the primary model are described in the Supplementary Appendix. To assess the influence of potential prior enthusiasm for therapeutic-dose anticoagulation (i.e., a prior distribution expressing a higher probability of success with therapeutic-dose anticoagulation than with usual-care thromboprophylaxis), a sensitivity analysis was conducted with the use of an enthusiastic prior distribution (prior mean odds ratio, 1.75; 95% credible interval, 0.74 to 4.15; prior probability of superiority, 90%).

For the key secondary end points, similar models were restricted to the severe-disease cohort without borrowing information from the moderate-disease cohort. Subgroup analyses assessed whether the treatment effect varied according to age, sex, receipt of mechanical ventilation at baseline, and intensity of thromboprophylaxis dosing in the group that received usual-care thromboprophylaxis (defined on the basis of the pattern of practice at each site, as described in the Supplementary Appendix). In a post hoc exploratory analysis, a possible interaction between assignment to therapeutic-dose anticoagulation or usual-care thromboprophylaxis and assignment to receive an interleukin-6 receptor antagonist or standard care (control) in REMAP-CAP was evaluated.

RESULTS

CHARACTERISTICS OF THE PATIENTS

The first patient underwent randomization on April 21, 2020. During the trial, randomization proportions were modified in the REMAP-CAP platform to 0.388 for therapeutic-dose anticoagulation and 0.612 for usual-care pharmacologic thromboprophylaxis on the basis of an adaptive interim analysis on November 20, 2020 (see the Supplementary Appendix). Enrollment was discontinued in the severe-disease cohort on December 19, 2020, after an adaptive interim analysis showed that the statistical criterion for futility had been met. At that time, a total of 1207 patients with severe suspected or confirmed Covid-19 had undergone randomization at 393 sites in 10 countries (with 591 assigned to receive therapeutic-dose anticoagulation and 616 assigned to receive usual-care thromboprophylaxis) (Fig. 1). Of these patients, 23 withdrew consent and 81 did

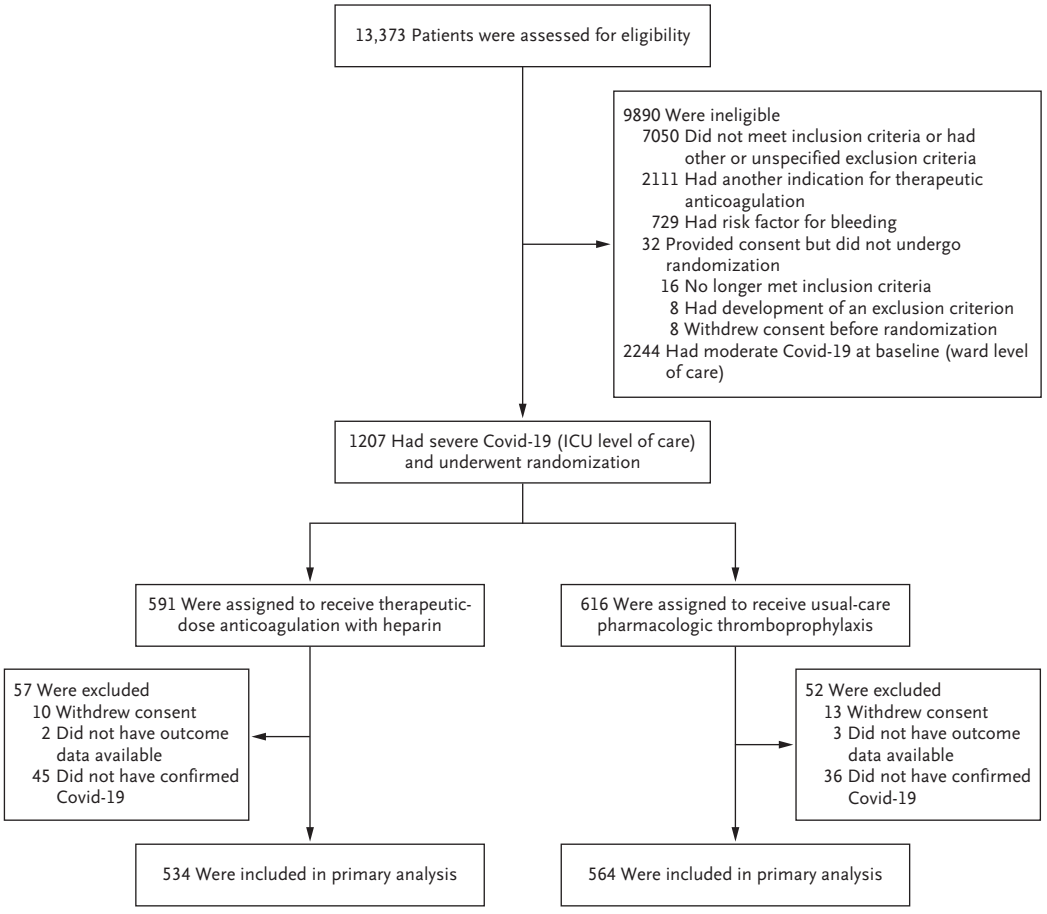

Figure 1. Screening, Enrollment, Randomization, and Inclusion in Analysis.

Sites used varying screening and documentation practices during the pandemic to identify eligible patients (shown in the protocol); as reported, 3799 were assessed for eligibility in ACTIV-4a, 7202 in ATTACC, and 2372 in REMAP-CAP. "Other" exclusion criteria included an absence of a diagnosis of coronavirus disease 2019 (Covid-19) and a duration of hospital stay anticipated to be less than 72 hours. Patients who had moderate Covid-19 at baseline may have been included in calculations for covariate adjustment and dynamic borrowing.

not have laboratory-confirmed Covid-19; data on the primary outcome were not available for an additional 5 patients as of April 8, 2021. The current report presents the results of the primary analysis involving 1103 patients with severe confirmed Covid-19; data on the primary outcome were available for 1098 of these patients.

The baseline characteristics of the patients were similar in the two intervention groups (Table 1). The majority of patients were enrolled through REMAP-CAP (929 of 1103 enrolled patients, 84%). The pattern of anticoagulant administration in the intervention groups is described in Table S1 in the Supplementary Appendix. Among the patients who were assigned to receive usual-care thromboprophylaxis and for whom data were available, the initial postrandomization dose equivalent corresponded to standard low-dose thromboprophylaxis in 41% and to enhanced intermediate-dose thromboprophylaxis in 51%.

PRIMARY OUTCOME

Among the patients assigned to receive therapeutic-dose anticoagulation, the median value for organ support–free days was 1 (interquartile range, –1 to 16); among the patients assigned to usual-care pharmacologic thromboprophylaxis, the median value was 4 (interquartile range, –1 to 16). The median adjusted proportional odds ratio for the effect of therapeutic-dose anticoagulation

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Therapeutic-Dose Anticoagulation (N = 536)	Usual-Care Thromboprophylaxis (N = 567)
Age — yr	60.4±13.1	61.7±12.5
Male sex — no. (%)	387 (72.2)	385 (67.9)
Race — no./total no. (%)†		
White	316/427 (74.0)	332/449 (73.9)
Asian	69/427 (16.2)	71/449 (15.8)
Black	25/427 (5.9)	20/449 (4.5)
Other	17/427 (4.0)	26/449 (5.8)
Country of enrollment — no. (%)		
United Kingdom	389 (72.6)	395 (69.7)
United States	79 (14.7)	97 (17.1)
Canada	40 (7.5)	54 (9.5)
Brazil	12 (2.2)	6 (1.1)
Other‡	16 (3.0)	15 (2.6)
Platform of enrollment — no. (%)		
REMAP-CAP§	454 (84.7)	475 (83.8)
ATTACC	19 (3.5)	21 (3.7)
ACTIV-4a	63 (11.8)	71 (12.5)
Median body-mass index (IQR)¶	30.4 (26.9–36.1)	30.2 (26.4–34.9)
No. of patients with data	470	488
Median APACHE II score (IQR)‖	14 (8–21)	13 (8–19)
No. of patients with data	429	443
Preexisting conditions — no./total no. (%)		
Diabetes mellitus (type 1 or 2)	171/536 (31.9)	191/567 (33.7)
Severe cardiovascular disease**	44/524 (8.4)	45/558 (8.1)
Chronic kidney disease	58/509 (11.4)	43/521 (8.3)
Chronic respiratory disease††	129/517 (25.0)	129/537 (24)
Chronic liver disease	6/516 (1.2)	3/548 (0.5)
Treatments at baseline — no./total no. (%)‡‡		
Antiplatelet agent§§	37/485 (7.6)	38/494 (7.7)
Remdesivir	174/532 (32.7)	172/564 (30.5)
Glucocorticoids	426/522 (81.6)	458/555 (82.5)
Tocilizumab¶¶	11/532 (2.1)	9/564 (1.6)
Baseline organ support — no. (%)		
Low-flow nasal cannula or face mask or no supplemental oxygen	8 (1.5)	7 (1.2)
High-flow nasal cannula	170 (31.7)	188 (33.2)
Noninvasive ventilation	215 (40.1)	200 (35.3)
Invasive mechanical ventilation	143 (26.7)	172 (30.3)
Vasopressors or inotropes	94 (17.5)	109 (19.2)
Median Pao_2:FIo_2 ratio (IQR)‖	118 (88.5–159.5)	118.5 (90.2–160.8)
No. of patients with data	391	406

Table 1. (Continued.)

Characteristic	Therapeutic-Dose Anticoagulation (N = 536)	Usual-Care Thromboprophylaxis (N = 567)
D-dimer level ≥2 times ULN at site — no./total no. (%)	100/210 (47.6)	107/223 (48)
Median laboratory values (IQR)		
D-dimer level — ng/ml	823 (433–1740)	890 (386.2–1844.2)
No. of patients with data	189	196
International normalized ratio	1.1 (1–1.2)	1.1 (1–1.2)
No. of patients with data	327	324
Neutrophil count — per mm^3	7900 (5500–10,600)	7800 (5600–10,700)
No. of patients with data	446	478
Lymphocyte count — per mm^3	700 (500–1000)	700 (500–900)
No. of patients with data	447	482
Platelet count — per mm^3	247,000 (190,200–316,500)	244,000 (182,000–312,000)
No. of patients with data	530	561

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. IQR denotes interquartile range, and ULN upper limit of the normal range.
† Race was reported by the patients.
‡ The other countries were Ireland, the Netherlands, Australia, Nepal, Saudi Arabia, and Mexico.
§ REMAP-CAP also enrolled patients with suspected but not confirmed coronavirus disease 2019 (Covid-19) (45 of those assigned to receive therapeutic-dose anticoagulation and 36 of those assigned to receive usual-care pharmacologic thromboprophylaxis).
¶ The body-mass index is the weight in kilograms divided by the square of the height in meters.
‖ Scores on the Acute Physiology and Chronic Health Evaluation (APACHE) II and the ratio of the partial pressure of oxygen (PaO_2) to the fraction of inspired oxygen (FIO_2) were available only in REMAP-CAP. APACHE II scores range from 0 to 71, with higher scores indicating a greater severity of illness.
** Severe cardiovascular disease was defined in REMAP-CAP as a baseline history of New York Heart Association class IV symptoms and was defined in ACTIV-4a and ATTACC as a baseline history of heart failure, myocardial Infarction, coronary artery disease, peripheral artery disease, or cerebrovascular disease (stroke or transient ischemic attack).
†† Chronic respiratory disease was defined as a baseline history of asthma, chronic obstructive pulmonary disease, bronchiectasis, interstitial lung disease, primary lung cancer, pulmonary hypertension, active tuberculosis, or the receipt of home oxygen therapy.
‡‡ Treatments used recently or in the long term are included.
§§ Patients who underwent concurrent randomization in the REMAP-CAP antiplatelet domain are not included here (47 of those assigned to therapeutic-dose anticoagulation and 66 of those assigned to usual-care pharmacologic thromboprophylaxis).
¶¶ Patients who underwent concurrent randomization in the REMAP-CAP immunomodulation domain are not included here (150 of those assigned to therapeutic-dose anticoagulation and 123 of those assigned to usual-care pharmacologic thromboprophylaxis).

on organ support–free days was 0.83 (95% credible interval, 0.67 to 1.03), yielding a posterior probability of futility of 99.9% and a posterior probability of inferiority of 95.0% (Table 2 and Fig. 2). A total of 335 of 534 patients (62.7%) assigned to receive therapeutic-dose anticoagulation and 364 of 564 patients (64.5%) assigned to receive usual-care thromboprophylaxis survived to hospital discharge. The median adjusted proportional odds ratio for survival to hospital discharge was 0.84 (95% credible interval, 0.64 to 1.11; posterior probability of inferiority, 89.2%). The median adjusted absolute difference in the percentage of patients who survived to hospital discharge (therapeutic-dose anticoagulation minus usual-care thromboprophylaxis) was –4.1 percentage points (95% credible interval, –10.7 to 2.4).

SENSITIVITY AND SUBGROUP ANALYSES

In sensitivity analyses of the primary outcome (Table S2), incorporation of prior enthusiasm for therapeutic-dose anticoagulation did not modify the conclusion (median adjusted proportional odds ratio, 0.86; 95% credible interval, 0.70 to 1.07). The inclusion of patients with suspected Covid-19 or exclusion of patients who were concomitantly

Table 2. Primary and Secondary Outcomes.

Outcome	Therapeutic-Dose Anticoagulation (N=536)	Usual-Care Thromboprophylaxis (N=567)	Adjusted Difference in Risk (95% Credible Interval)	Adjusted Odds Ratio (95% Credible Interval)*	Probability of Superiority	Probability of Futility	Probability of Inferiority
	median no. (IQR)		*percentage points*		%	%	%
Organ support–free days up to day 21†‡	1 (–1 to 16)	4 (–1 to 16)	—	0.83 (0.67 to 1.03)	5.0	99.9	95.0
	no. of patients/total no. (%)						
Survival to hospital discharge‡	335/534 (62.7)	364/564 (64.5)	–4.1 (–10.7 to 2.4)	0.84 (0.64 to 1.11)	10.8	99.6	89.2
Major thrombotic events or death§	213/531 (40.1)	230/560 (41.1)	1.0 (–5.6 to 7.4)	1.04 (0.79 to 1.35)	40.3	—	59.7
Major thrombotic events¶	34/530 (6.4)	58/559 (10.4)	—	—	—	—	—
Death in hospital	199/534 (37.3)	200/564 (35.5)	—	—	—	—	—
Any thrombotic events or death§	217/531 (40.9)	232/560 (41.4)	1.5 (–4.9 to 8.0)	1.06 (0.81 to 1.38)	33.4	—	66.6
Any thrombotic events‖	38/530 (7.2)	62/559 (11.1)	—	—	—	—	—
Death in hospital	199/534 (37.3)	200/564 (35.5)	—	—	—	—	—
Major bleeding§	20/529 (3.8)	13/562 (2.3)	1.1 (–0.6 to 4.4)	1.48 (0.75 to 3.04)	12.8	—	87.2

* Odds ratios were adjusted for age, sex, trial site, and enrollment time interval.
† Days free of cardiovascular or respiratory organ support was evaluated on an ordinal scale that combined in-hospital death (assigned a value of –1) and the number of days free of organ support up to day 21 among patients who survived to hospital discharge. Outcomes were known for 534 patients assigned to therapeutic-dose anticoagulation and for 564 patients assigned to usual-care pharmacologic thromboprophylaxis. The odds ratio is an adjusted proportional odds ratio.
‡ The probabilities of superiority (odds ratio, >1), inferiority (odds ratio, <1), and futility (odds ratio, <1.2) of therapeutic-dose anticoagulation were computed from the posterior distribution.
§ The probabilities of superiority (odds ratio, <1) and inferiority (odds ratio, >1) of therapeutic-dose anticoagulation were computed from the posterior distribution.
¶ Major thrombotic events include pulmonary embolism, myocardial infarction, ischemic cerebrovascular event, and systemic arterial thromboembolism.
‖ Any thrombotic events include major thrombotic events or deep-vein thrombosis.

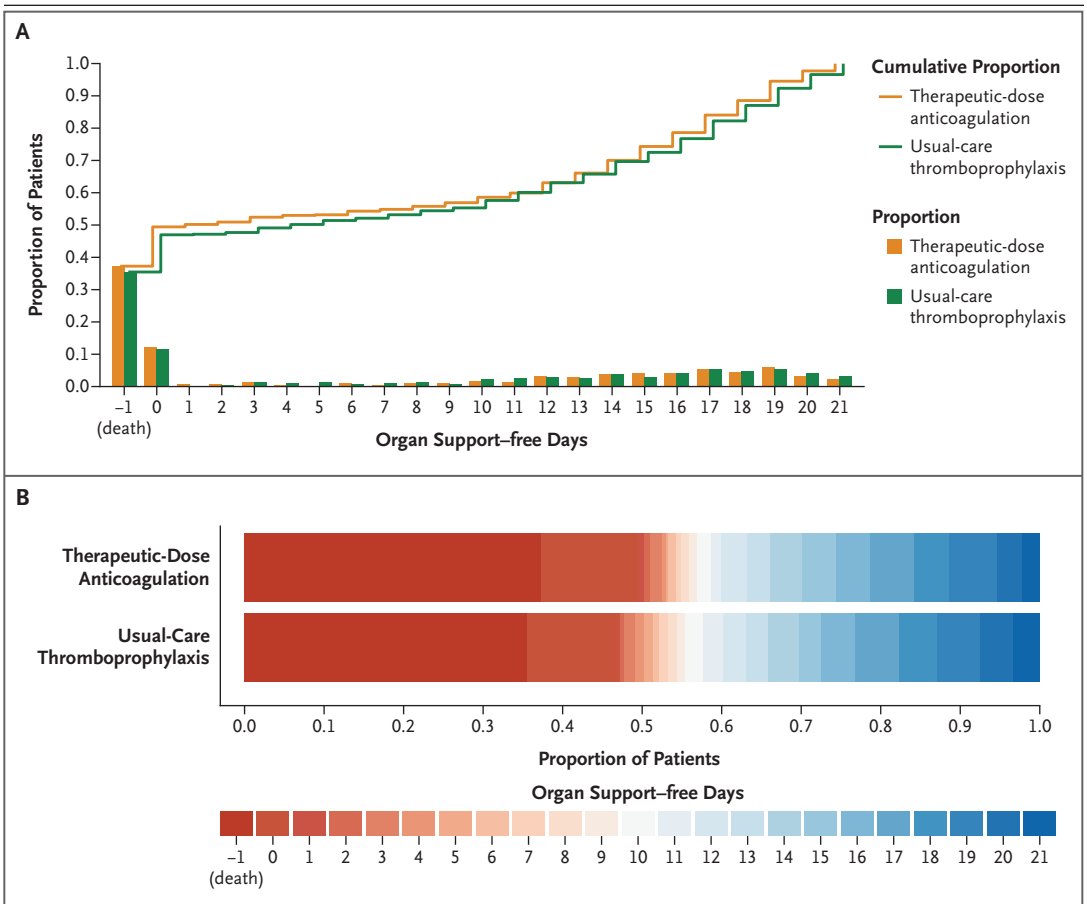

Figure 2. Organ Support–free Days Up to Day 21.

Panel A shows the proportions of patients in each intervention group with each value for organ support–free days, with death listed first on the x axis (–1). Curves that rise more slowly indicate a more favorable distribution in the number of days alive and free of organ support. The height of each curve at –1 indicates the in-hospital mortality associated with each intervention. The height of each curve at any point from 0 to 21 days indicates the proportion of patients with that number of organ support–free days or fewer (e.g., at 10 days, the curve indicates the proportion of patients with ≤10 organ support–free days). The difference in height between the two curves at any point represents the difference in the cumulative probability of having a number of organ support–free days less than or equal to that number on the x axis. Panel B shows the values for organ support–free days as horizontally stacked proportions for each intervention group. Red represents worse outcomes and blue better outcomes. The median adjusted odds ratio in the primary analysis was 0.83 (95% credible interval, 0.67 to 1.03; posterior probability of futility, 99.9%). Among the patients in REMAP-CAP, 12 patients assigned to receive therapeutic-dose anticoagulation and 19 patients assigned to receive usual-care pharmacologic thromboprophylaxis had 21 organ support–free days; the cardiovascular or respiratory organ support these patients had been receiving at the time of randomization was discontinued within 12 hours after randomization.

receiving an antiplatelet agent at baseline or those who underwent concomitant randomization in the REMAP-CAP antiplatelet-agent domain also yielded similar results. Among the 273 patients with severe confirmed Covid-19 who had also been randomly assigned to receive either an interleukin-6 receptor antagonist or no immunomodulation in REMAP-CAP, there was no evidence of a meaningful interaction between the anticoagulation and immunomodulation domains (Table S3 and Fig. S1). In prespecified subgroup analyses, the estimated effect did not vary meaningfully according to age, sex, baseline receipt of invasive mechanical ventilation, or the site-specific dosing pattern for usual-care pharmacologic thromboprophylaxis (intermediate vs. low dose) (Fig. S2).

SECONDARY OUTCOMES

Although fewer patients had major thrombotic events in the group assigned to receive therapeutic-dose anticoagulation than in the group assigned to receive usual-care pharmacologic thromboprophylaxis (6.4% vs. 10.4%), the incidence of the secondary efficacy outcome of major thrombotic events or death was similar in the two groups (40.1% and 41.1%, respectively; median adjusted odds ratio, 1.04; 95% credible interval, 0.79 to 1.35) (Table 2). An analysis incorporating deep-vein thrombosis showed similar results. A breakdown of the thrombotic events is provided in Table S4. A major bleeding event occurred during the treatment period in 3.8% of the patients assigned to receive therapeutic-dose anticoagulation and in 2.3% of those assigned to receive usual-care thromboprophylaxis (Table 2).

DISCUSSION

In this multiplatform, randomized trial involving more than 1000 critically ill patients with confirmed Covid-19, therapeutic-dose anticoagulation did not increase the probability of survival to hospital discharge or the number of days free of cardiovascular or respiratory organ support and had a 95% probability of being inferior to usual-care pharmacologic thromboprophylaxis. There was an 89% probability that therapeutic-dose anticoagulation led to a lower probability of survival to hospital discharge than usual-care thromboprophylaxis. Bleeding complications were infrequent in both intervention groups.

Our results refute the hypothesis that routine therapeutic-dose anticoagulation benefits critically ill patients with Covid-19. This hypothesis was based in part on observational studies that reported an association between therapeutic-dose anticoagulation and improved outcomes.[14,20,21] Multiple small and moderate-size randomized trials continue to evaluate different anticoagulation strategies in Covid-19.[22]

The net effect of anticoagulation on clinical outcomes in patients with Covid-19 may depend on the timing of initiation in relation to disease course and may vary with the severity of illness (and the degree of coagulation or inflammation) at the time that therapy is commenced.[23-25] Despite demonstrable activation of coagulation in multiple organ systems in patients with severe Covid-19, it is possible that initiation of therapeutic-dose anticoagulation after severe Covid-19 has developed may be too late to alter the consequences of established disease processes.

In this trial, the probability of inferiority of therapeutic-dose anticoagulation with respect to the primary outcome was 95%. Mechanisms accounting for likely harm are uncertain. Although the incidence of major bleeding was numerically higher with therapeutic-dose anticoagulation than with usual-care thromboprophylaxis, it was still low (3.8%). Autopsy findings in patients with Covid-19 and severe acute respiratory distress syndrome have included microthrombosis but also alveolar hemorrhage.[26] It is possible that in the presence of marked pulmonary inflammation, therapeutic-dose anticoagulation might exacerbate alveolar hemorrhage, leading to worse outcomes.

In this multiplatform trial, a harmonized pragmatic trial protocol was implemented by three platform networks spanning five continents. The interventions that were evaluated are familiar and widely available, rendering the findings broadly applicable to critically ill patients with severe Covid-19. The collaboration allowed us to reach a conclusion of futility with probable harm much more quickly than would have been possible as independent platforms.

One limitation of our trial is the open-label design, which may have introduced bias in the ascertainment of thrombotic events. A second possible limitation is that a substantial majority of the patients who were enrolled in the severe-disease cohort were in the United Kingdom, where national practice guidelines changed during the trial to recommend that patients with Covid-19 who were admitted to an ICU receive intermediate-dose anticoagulation for thromboprophylaxis.[13] Many patients in the usual-care thromboprophylaxis group therefore received intermediate-dose thromboprophylaxis. It is possible that the effect of therapeutic-dose anticoagulation in patients with severe Covid-19 varies according to the type of treatment given to the comparator group, although we did not find evidence of meaningful differences in treatment effect according to site proclivity for low-dose or intermediate-dose thromboprophylaxis. Recent data also suggest that intermediate-dose thromboprophylaxis is not superior to standard or low-dose thromboprophylaxis for the treatment of critically ill patients.[27]

In critically ill patients with Covid-19, an ini-

tial strategy of therapeutic-dose anticoagulation with unfractionated or low-molecular-weight heparin was not associated with a greater probability of survival to hospital discharge or a greater number of days free of cardiovascular or respiratory organ support than was usual-care pharmacologic thromboprophylaxis. The probability that therapeutic-dose anticoagulation was inferior to usual-care thromboprophylaxis with respect to these outcomes was high.

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APPENDIX

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