ASCOT Anticoagulation Statistical Analysis Report

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2022-06-30

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1 Introduction

1.1 Purpose

The trial steering committee (TSC) closed randomisation to the anticoagulation domain on 8 April 2022. The blinded statistical analysis working group prepared a statistical analysis plan (SAP) for reporting the results of the anticoagulation domain. The unblinded team of statisticians undertook these analysis using the relevant records as extracted from the database on 2022-06-06.

This report summarises the data and results for the anticoagulation domain. The report restricts these summaries and analyses to the interventions available in the anticoagulation domain and does not report on the interventions in the antiviral domain.

1.2 Interventions

There were four mutually exclusive interventions in the anticoagulation domain. They were:

- standard dose (control)
- intermediate dose
- standard dose plus aspirin
- therapeutic dose

For full details of the interventions, refer to the domain specific appendix to the protocol.

1.3 Outcomes

1.4 Modelling

1.4.1 General Considerations

All binary outcomes were analysed assuming a logistic regression model, ordinal outcomes by assuming a cumulative logistic model with proportional odds, and the time to recovery outcome by a discrete-time competing-risk (death) time-to-event model (multinomial logistic regression). Weakly informative priors were specified for all models.

The (pre-specified) primary model for all outcomes included fixed terms for:

- anticoagulation intervention
- antiviral intervention
- intervention ineligibility
- age group (< 60, ≥ 60)
- region of enrolment (India, Australia/New Zealand, Nepal)

Hierarchical terms were also included for:

- site of enrolment (nested within region)
- epoch of enrolment (4-week groupings)

Outcomes are coded such that an odds ratio less than 1 implies a decrease in the outcome, for example, lower odds of 28 day mortality, fewer days alive and free of hospital, etc. Therefore, depending on the outcome, an odds ratio less than 1 may imply benefit or harm, but this will be made clear for each outcome.

In general, the reference group (to which the model intercept(s) or baseline hazard applies) was taken to be a patient who was:

- randomised to the anticoagulation domain (equal weighting across all interventions)
- *not* randomised to the antiviral domain
- eligible for all anticoagulation interventions
- less than 60 years of age
- enrolled in India during the most recent epoch

Bayesian models were computed using Stan via `cmdstanr` (0.5.2 and cmdstan version 2.29.2) in R (4.2.1). For each model, 8 chains were used with a warm-up of 1000 iterations and sampling for 2500 iterations per chain resulting in 20,000 posterior draws per model. Standard diagnostics were assessed for each model (divergent transitions, trace plots, R-hat). If an issue was identified (e.g. divergent transitions) then the default sampling parameters may have been adjusted (e.g. increasing target acceptance rate or increasing maximum tree depth). If any convergence issues resulted for the pre-specified models, then they are reported along with the model results. If the model was amended in any way to satisfy convergence criteria (e.g. aggregation of groups, removal of model terms) then this is reported in the relevant section. Sampling was run using a different (randomly selected) random seed for each model, and these were recorded for replication.

Due to the small number of enrolments at New Zealand sites, in models where country of enrolment were included as a term, Australia and New Zealand were combined into one region. The hierarchical site effects for centres in Australia and New Zealand were nested within this joint region rather than each country individually. For models where site was included as a random effect, sites with less than 5 participants were aggregated within region into an "other sites" grouping. Similarly, for models where epoch was included, epochs with less than 10 participants were aggregated with the adjacent epoch.

Missing outcome data were not imputed for any of the models (with the exception of the deterministic imputation used in the best-case/worst-case sensitivity analyses).

1.4.2 Further Details

1.5 Trial Decision Criteria

As per the statistical appendix to the core protocol, the following decision quantities were of interest in the anticoagulation domain for the primary outcome model:

- **Superiority**: superiority is assessed using the posterior probability that the intervention has the lowest odds of the outcome amongst all interventions in the domain. If a single intervention had probability exceeding 0.99 superiority would be triggered for that intervention.
- **Effectiveness**: effectiveness is assessed relative to the standard dose arm as the posterior probability that the intervention reduces the odds of the outcome. If any intervention

had probability exceeding 0.99 than effectiveness would be triggered for that intervention.

- **Futility**: futility is assessed relative to the standard dose arm as the posterior probability that the intervention reduces the odds of the outcome by no more than a factor of 1/1.1. If any intervention had probability exceeding 0.95 than futility would be triggered for that intervention.
- **Equivalence**: equivalence is assessed relative to the standard dose arm as the posterior probability that the intervention alters the odds of the outcome by a factor bounded by (1/1.1, 1.1).

2 Results

2.1 Study Population

2.1.1 Summary

At the time of database lock for the anticoagulation domain, 1,599 participants had been enrolled onto the study platform and 1,574 participants had been randomised to the anticoagulation domain. The first participant was randomised on 2021-02-08 and the last participant enrolled into the anticoagulation domain was randomised on 2022-03-29.

2.1.2 Analysis Sets

The SAP for the anticoagulation domain defines a number of analysis populations.

The primary analysis population includes all participants who were randomised to the anticoagulation domain. For the intention-to-treat (ITT) analyses, all participants randomised to the anticoagulation domain were analysed according to their aside regimen irrespective of deviations or non-adherence. This set is referred to as the anticoagulation ITT set (ACS-ITT).

Secondary analyses expand the analysis set to include all participants randomised to the platform including those who were not randomised to the anticoagulation domain for the purpose of additional covariate information. This is referred to as the full analysis set ITT (FAS-ITT)

Per-protocol (PP) analyses restrict both of the analysis sets to only those participants who sufficiently adhered to the protocol as determined by blinded review. Participants who were not PP had their outcomes set to missing, (ACS-PP and FAS-PP).

Additional analysis sets are defined for the purpose of comparing the interventions restricted to the timing of concurrent randomisation. For this purpose, the following additional analysis sets are specified:

- ACS-ITT-intermediate: ACS-ITT set restricted to only patients randomised into either standard dose or intermediate dose intervention.
- ACS-ITT-aspirin: ACS-ITT set restricted to patients randomised between 2021-02-08 (domain start) and 2021-09-10 (closure of aspirin arm) who were eligible for the standard dose plus aspirin intervention
- ACS-ITT-therapeutic: ACS-ITT set restricted to patients randomised under protocol version 5.0 (which introduced the therapeutic dose arm), noting that each site may have activated version 5.0 of the protocol at different times (or may never have activated it).

The patients included in any analysis is also conditional on the outcome: participants who were missing the outcome of interest were excluded from each set for undertaking any analyses.

Table 2.1: Overview of the analysis sets used in this report.

Name	Definition
FAS-ITT	All participants who were randomised to at least one study domain. Participants will be analysed as randomised, irrespective of withdrawal from treatment, treatment compliance, or other protocol deviations.
ACS-ITT	Subset of FAS-ITT who were randomised to the anticoagulation domain.
ACS-ITT-intermediate	Subset of ACS-ITT who were randomised to intermediate or standard dose only.
ACS-ITT-aspirin	Subset of ACS-ITT who were randomised prior to closure of the standard plus aspirin arm and were eligible for the aspirin arm.
ACS-ITT-therapeutic	Subset of ACS-ITT who were randomised after introduction of the therapeutic dose arm at a site where it became available.
ACS-PP	All participants who were randomised to the anticoagulation domain and satisfied platform, domain, and intervention protocol requirements.

2.1.2.1 ACS-ITT

The ACS-ITT population included 1,574 participants randomised to the anticoagulation domain. There were 18 participants who withdrew consent for follow-up leaving 1,556 continu-

ing participants. Of these, 30 were missing the primary outcome and 1,526 primary outcomes were observed. In the anticoagulation domain:

- 610 were assigned to **standard dose** and 596 primary outcomes were observed
- 613 were assigned to **intermediate dose** and 601 primary outcomes were observed
- 283 were assigned to **standard dose plus aspirin group** and 279 primary outcomes were observed
- 50 were assigned to **therapeutic dose** group with 50 primary outcomes observed

2.1.2.2 FAS-ITT

In this set (excluding those who withdrew consent for follow-up):

- 25 were not randomised to the anticoagulation domain
- 610 were assigned to **standard dose** and 596 primary outcomes were observed
- 613 were assigned to **intermediate dose** and 601 primary outcomes were observed
- 283 were assigned to **standard dose plus aspirin group** and 279 primary outcomes were observed
- 50 were assigned to **therapeutic dose** group with 50 primary outcomes observed

2.1.2.3 ACS-ITT-intermediate

In this set (excluding those who withdrew consent for follow-up):

- 610 were assigned to **standard dose** and 596 primary outcomes were observed
- 613 were assigned to **intermediate dose** and 601 primary outcomes were observed

2.1.2.4 ACS-ITT-aspirin

In this set (excluding those who withdrew consent for follow-up):

- 299 were assigned to **standard dose** and 292 primary outcomes were observed
- 298 were assigned to **intermediate dose** and 293 primary outcomes were observed
- 283 were assigned to **standard dose plus aspirin** and 279 primary outcomes were observed

2.1.2.5 ACS-ITT-therapeutic

In this set (excluding those who withdrew consent for follow-up):

- 79 were assigned to **standard dose** and 75 primary outcomes were observed
- 65 were assigned to **intermediate dose** and 62 primary outcomes were observed
- 50 were assigned to **therapeutic dose** and 50 primary outcomes were observed

2.1.2.6 ACS-PP

In this set (excluding those who withdrew consent for follow-up):

- 599 were assigned to **standard dose** and 586 primary outcomes were observed
- 603 were assigned to **intermediate dose** and 592 primary outcomes were observed
- 274 were assigned to **standard dose plus aspirin group** and 271 primary outcomes were observed
- 46 were assigned to **therapeutic dose** group with 46 primary outcomes observed

2.1.3 Disposition

Of the 1,574 participants randomised to the anticoagulation domain, 18 withdrew consent for follow-up leaving 1,556 participants continuing to study day 28. The analyses and summaries included in this report exclude data on participants who withdrew consent for follow-up.

Platform and domain specific flow diagrams are included in Figure 2.1 and Figure 2.2 respectively.

Figure 2.3 presents overall platform enrolments by calendar time with timing of intervention availabilities and interim analyses. Enrolments by country are presented in Figure 2.4. Due to the changes to the trial which occurred independently of the within trial results, the initial allocation ratios were not changed during recruitment to the anticoagulation domain. Therefore, the only trial adaptations which occurred were the cessation of the standard dose plus aspirin intervention in the anticoagulation domain, the opening of the antiviral domain, and the introduction of the therapeutic dose intervention into the anticoagulation domain. Despite this, the timing of interim analyses are indicated on the Figures.

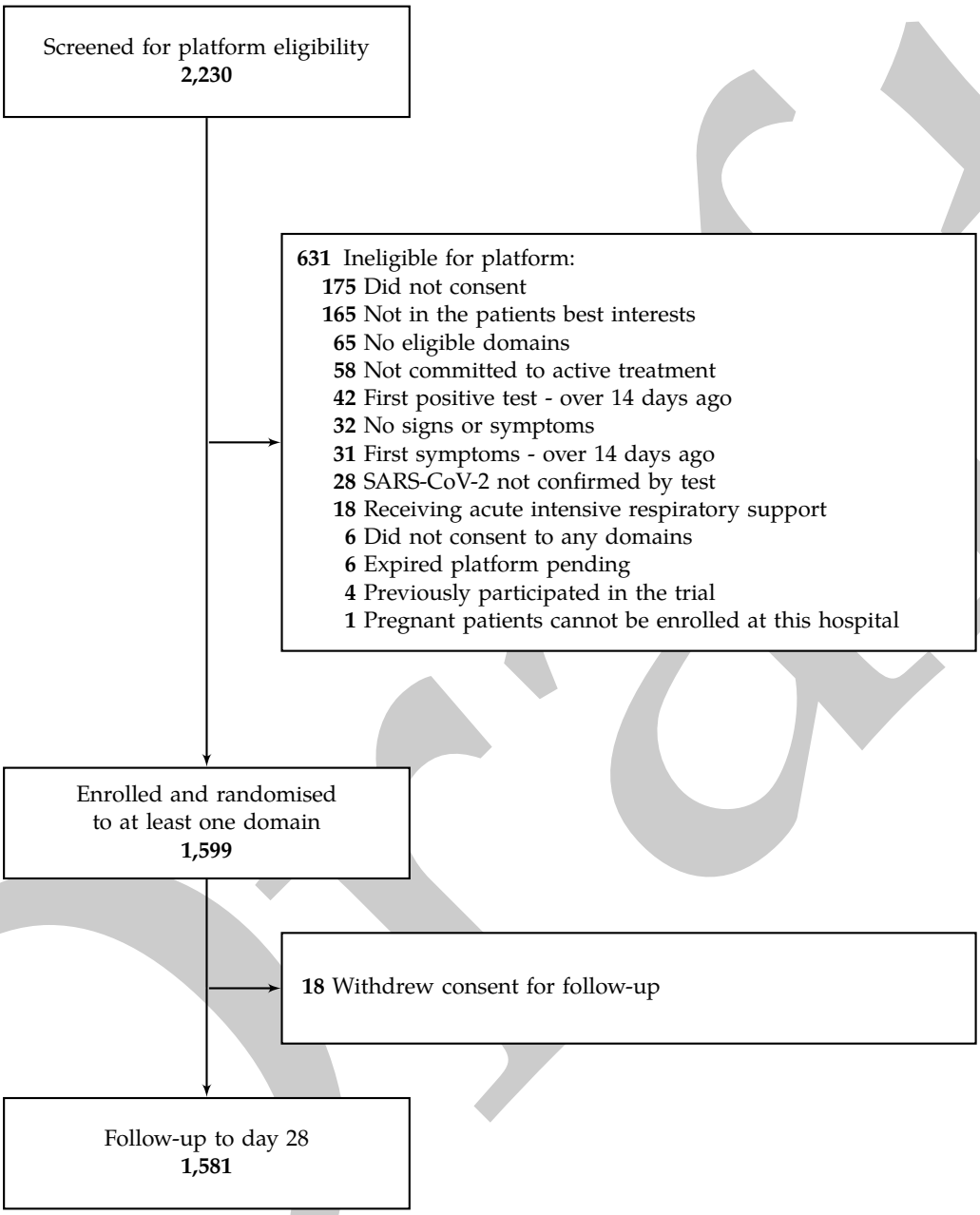

Figure 2.1: Platform flowchart.

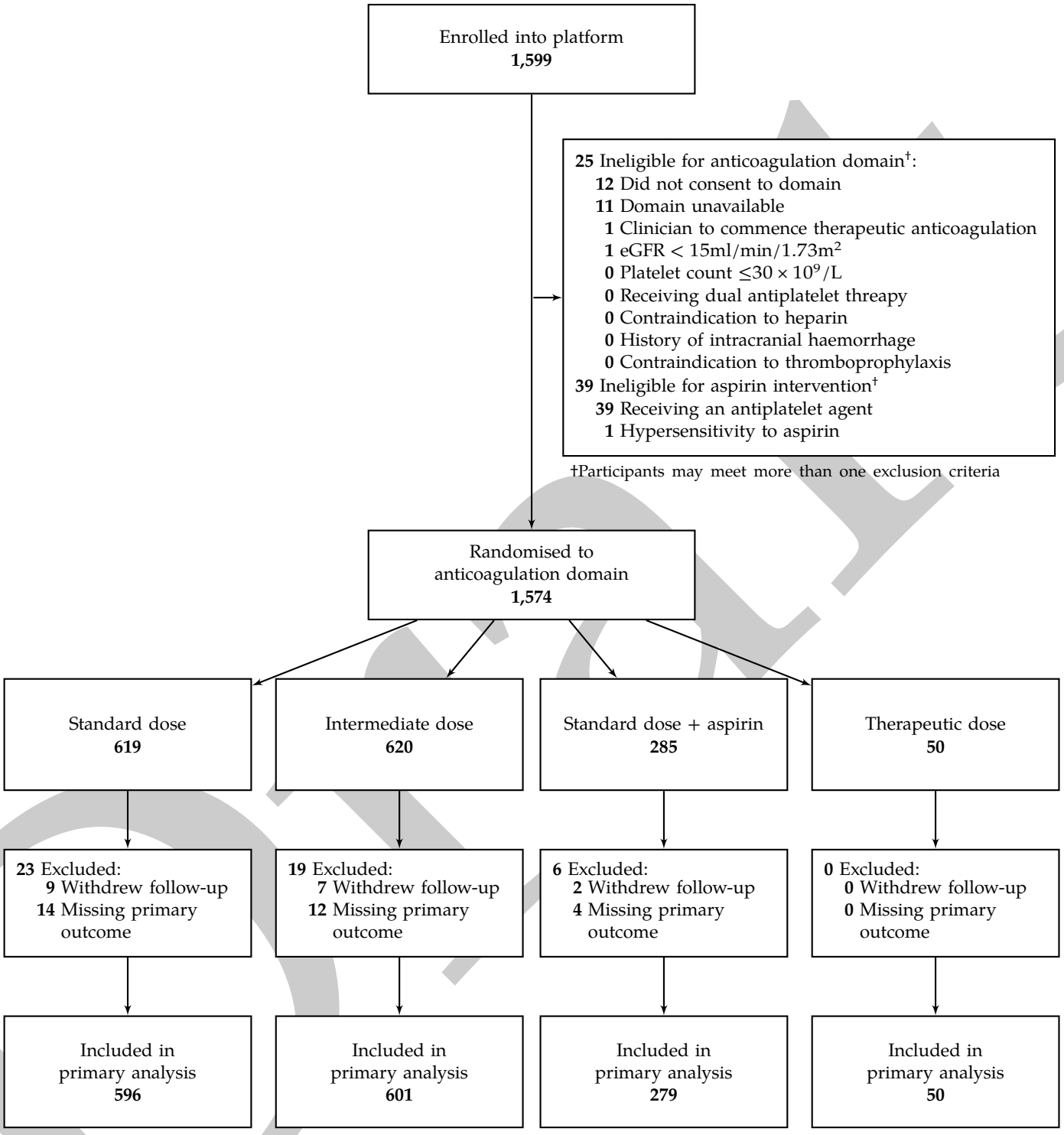

Figure 2.2: Anticoagulation domain flowchart.

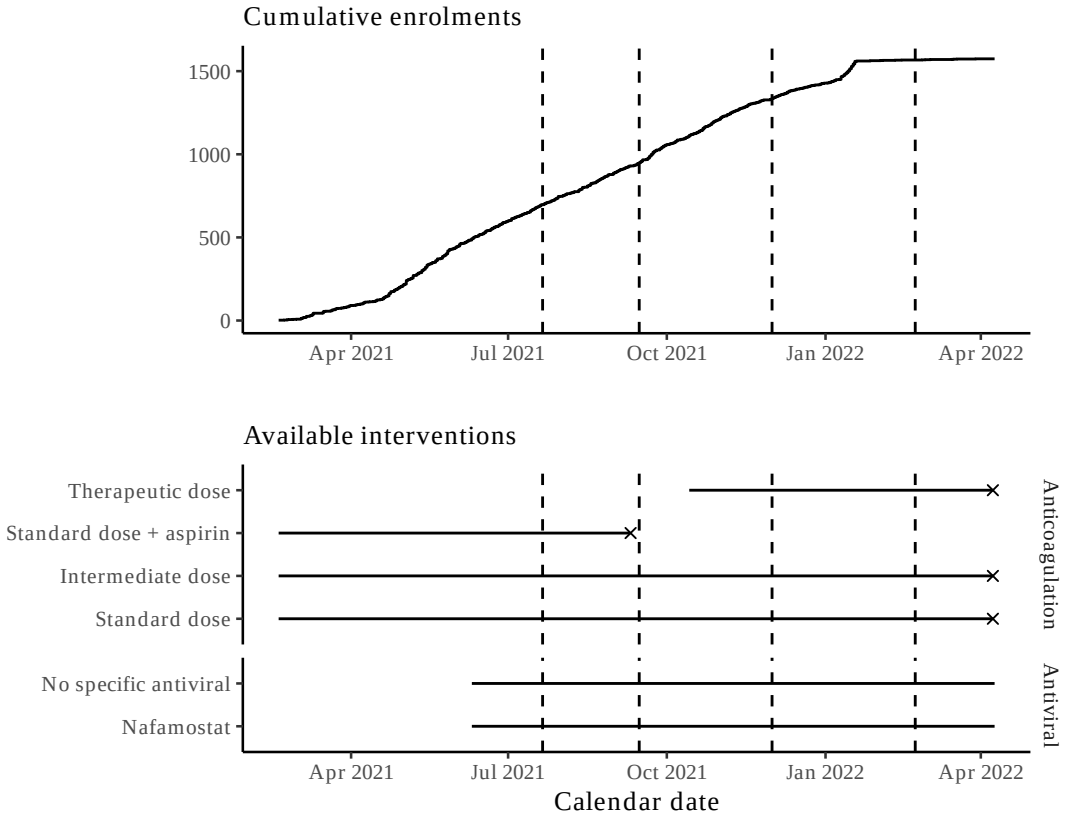

Figure 2.3: Overall enrolment to the anti-coagulation domain and intervention availability. Vertical dashed lines indicate timing of interim analyses.

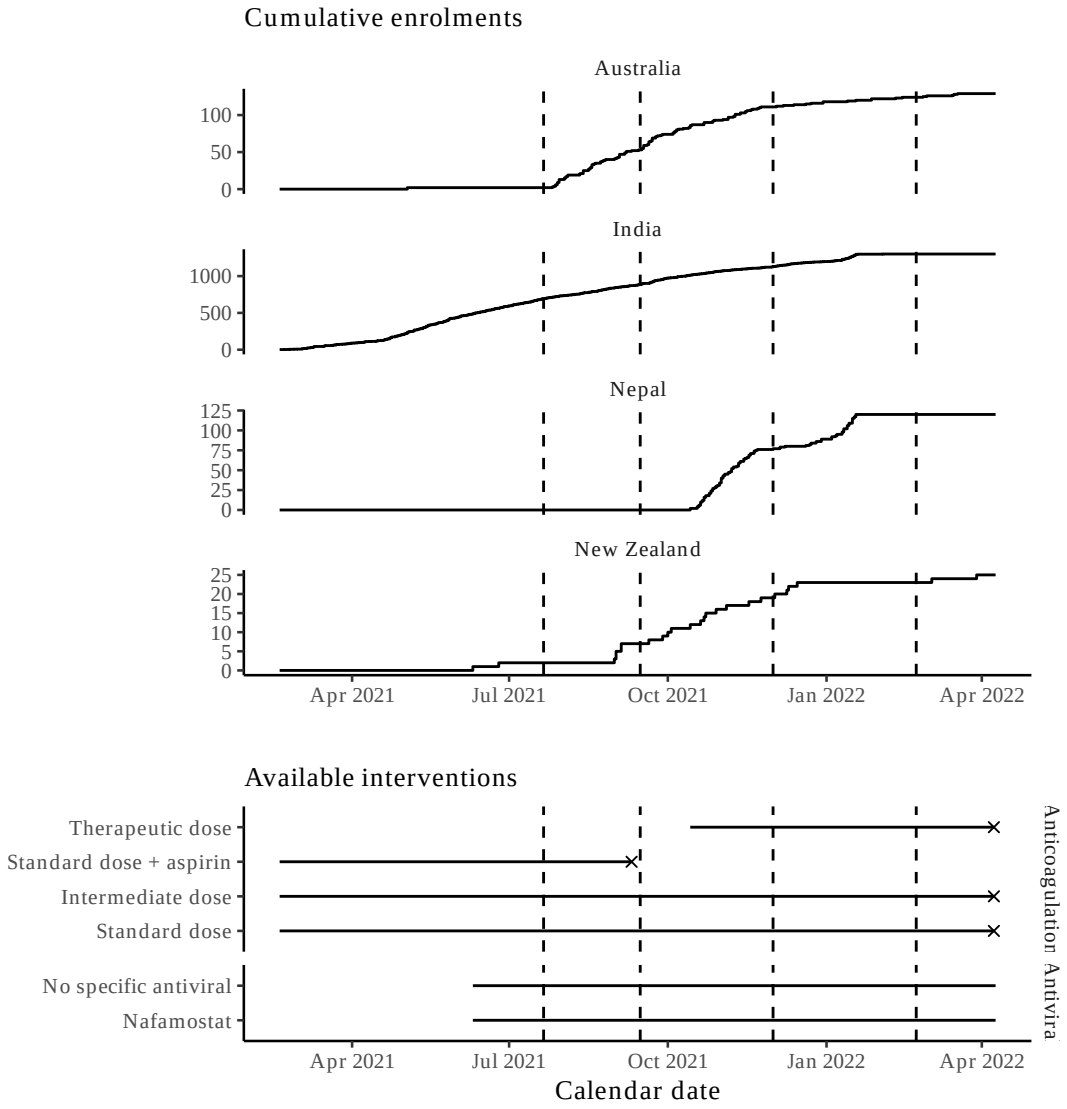

Figure 2.4: Enrolment to platform and intervention availability by country. Vertical dashed lines indicate timing of interim analyses.

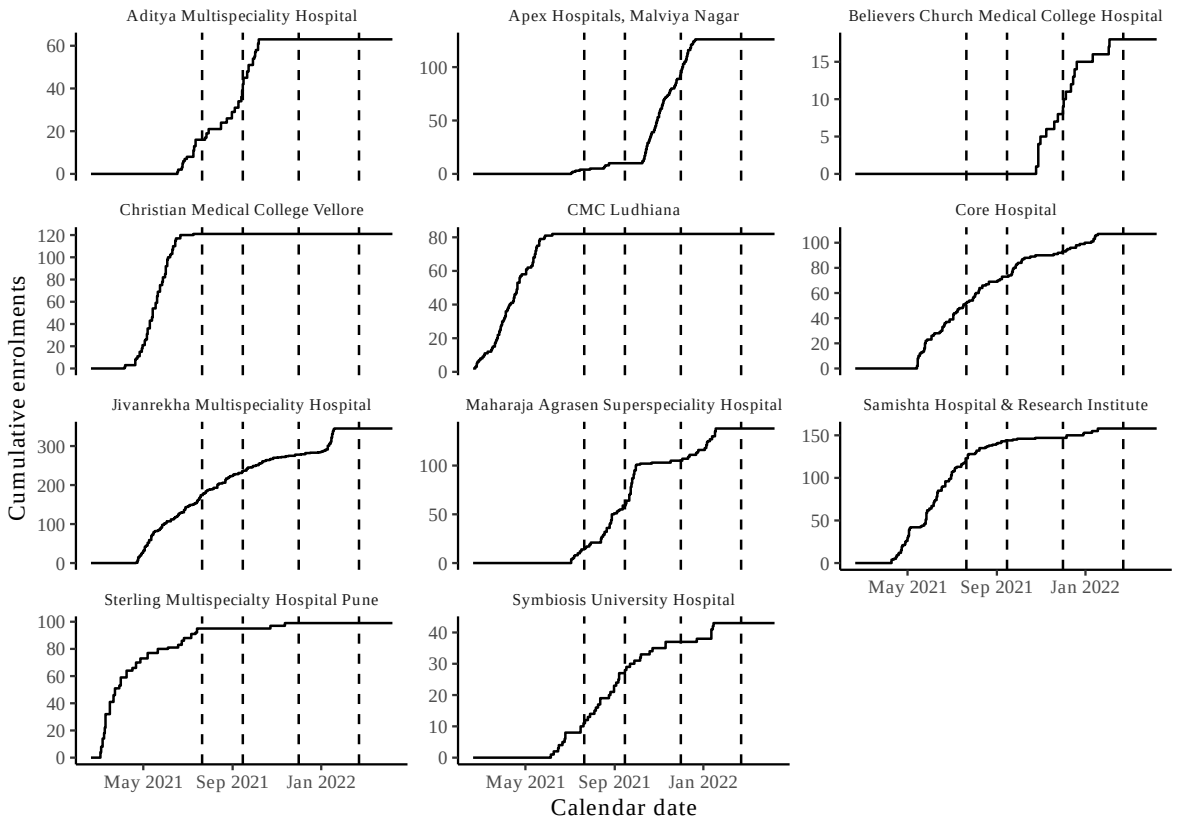

Figure 2.5: Enrolment to sites in India. Vertical dashed lines indicate timing of interim analyses.

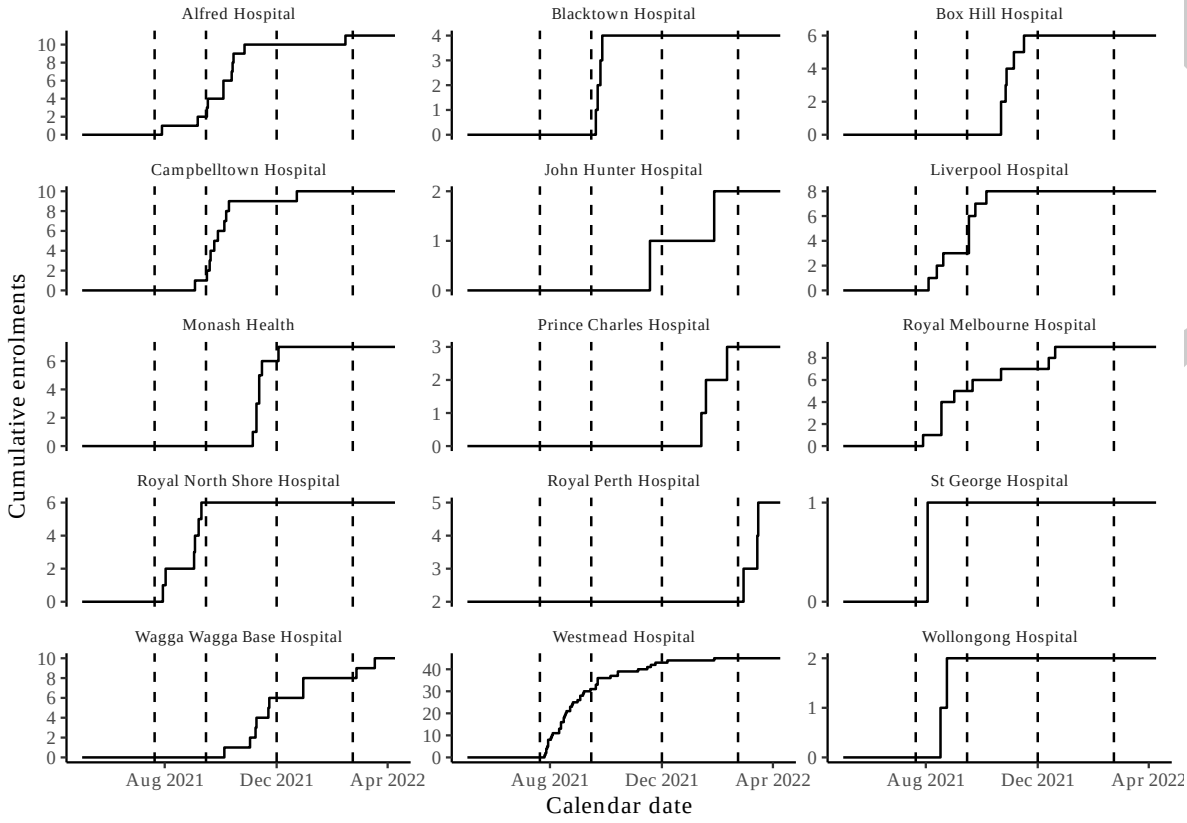

Figure 2.6: Enrolment to sites in Australia. Vertical dashed lines indicate timing of interim analyses.

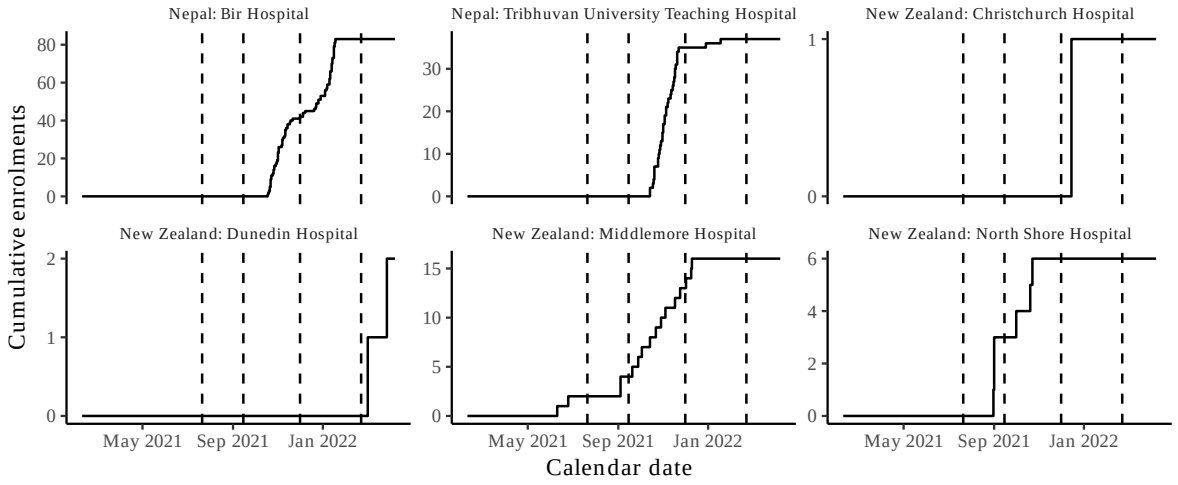

Figure 2.7: Enrolment to sites in Nepal and New Zealand Vertical dashed lines indicate timing of interim analyses.

2.1.4 Intervention Allocations

Due to the trial progression, response adaptive randomisation (RAR) was never activated in the anticoagulation domain. Therefore, target allocations to the interventions were uniform across all available interventions from trial start to trial closure. However, the available interventions did change over time and vary by region and site. The following figures summarise treatment allocations over time and by country.

2.1.5 Deviations

Of the 1,599 patients randomised to the platform, there were 55 patients who were not considered to be per-protocol. These were 28 patients who deviated from the intervention protocol, 26 patients who withdrew from the anticoagulation domain intervention, and 1 patient who deviated and withdrew from treatment. The reason for withdrawal from the anticoagulation domain was principally a decision of the primary treating clinician (18 of 26) with the remaining due to withdrawal of patient consent.

2.1.6 Baseline Characteristics

The following baseline summaries exclude participants who withdrew consent for follow-up.

2.1.6.1 Demographics

The age distribution of participants are presented in Figure 2.8.

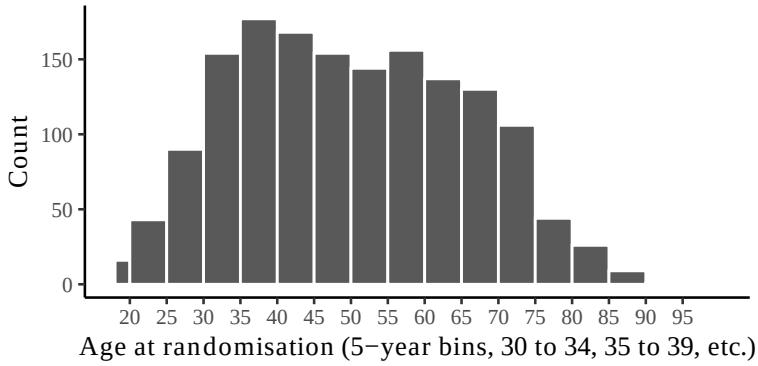

Figure 2.8: Distribution of age amongst participants randomised to the anticoagulation domain.

Baseline demographics stratified by anticoagulation interventions are reported in Table 2.2.

Table 2.2: Baseline demographics for participants randomised to the anticoagulation domain.

Variable	Anticoagulation				Overall
	Standard dose	Intermediate dose	Standard dose plus aspirin	Therapeutic dose	
	(n = 610)	(n = 613)	(n = 283)	(n = 50)	(n = 1556)
Age (years), Median (IQR)	48 (37, 60)	48 (37, 61)	50 (38, 62)	58 (46, 69)	49 (37, 61)
Country					
India, n (%)	493 (81)	516 (84)	275 (97)	4 (8)	1288 (83)
Australia, n (%)	49 (8)	59 (10)	7 (2)	11 (22)	126 (8)
Nepal, n (%)	56 (9)	31 (5)	0 (0)	31 (62)	118 (8)
New Zealand, n (%)	12 (2)	7 (1)	1 (0)	4 (8)	24 (2)
Sex					
Male, n (%)	354 (58)	387 (63)	157 (55)	25 (50)	923 (59)
Female, n (%)	256 (42)	226 (37)	126 (45)	25 (50)	633 (41)
Weight (kg)					
Median, (IQR)	68 (62, 76)	70 (62, 77)	68 (62, 76)	66 (57, 80)	69 (62, 76)
Missing, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Vaccinated[1]					
Yes, n (%)	191 (31)	220 (36)	42 (15)	27 (54)	480 (31)
Missing, n (%)	32 (5)	22 (4)	29 (10)	0 (0)	83 (5)
Ethnicity					
Indian, n (%)	494 (81)	518 (85)	275 (97)	4 (8)	1291 (83)
European, n (%)	21 (3)	18 (3)	4 (1)	4 (8)	47 (3)
Asian, n (%)	20 (3)	12 (2)	1 (0)	10 (20)	43 (3)
Pacific Islander, n (%)	13 (2)	12 (2)	2 (1)	3 (6)	30 (2)
Middle Eastern, n (%)	11 (2)	11 (2)	0 (0)	0 (0)	22 (1)
Maori, n (%)	3 (0)	4 (1)	0 (0)	3 (6)	10 (1)
African, n (%)	1 (0)	0 (0)	1 (0)	0 (0)	2 (0)
Aboriginal, n (%)	0 (0)	1 (0)	0 (0)	1 (2)	2 (0)
Latin American, n (%)	0 (0)	1 (0)	0 (0)	0 (0)	1 (0)
Other, n (%)	45 (7)	28 (5)	0 (0)	23 (46)	96 (6)
Unknown, n (%)	8 (1)	9 (1)	0 (0)	3 (6)	20 (1)
Smoking					
Current, n (%)	17 (3)	21 (3)	3 (1)	5 (10)	46 (3)
Former, n (%)	74 (12)	53 (9)	15 (5)	14 (28)	156 (10)
Never, n (%)	519 (85)	539 (88)	265 (94)	31 (62)	1354 (87)
Missing, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

[1] Site LUD did not have ethics approval for collection of vaccination status.

2.1.6.2 Co-morbidities

Baseline co-morbidities stratified by anticoagulation interventions are reported in Table 2.3.

Table 2.3: Baseline comorbidities for participants randomised to the anticoagulation domain.

Comorbidity	Anticoagulation				Overall (n = 1556)
	Standard dose (n = 610)	Intermediate dose (n = 613)	Standard dose plus aspirin (n = 283)	Therapeutic dose (n = 50)	
None, n (%)	364 (60)	378 (62)	166 (59)	19 (38)	927 (60)
Hypertension, n (%)	147 (24)	140 (23)	68 (24)	14 (28)	369 (24)
Diabetes, n (%)	140 (23)	139 (23)	78 (28)	11 (22)	368 (24)
Obesity, n (%)	23 (4)	22 (4)	3 (1)	5 (10)	53 (3)
Asthma, n (%)	19 (3)	16 (3)	6 (2)	4 (8)	45 (3)
Chronic lung disease, n (%)	16 (3)	13 (2)	1 (0)	7 (14)	37 (2)
Chronic cardiac disease, n (%)	11 (2)	15 (2)	1 (0)	2 (4)	29 (2)
Obstructive sleep apnoea, n (%)	3 (0)	2 (0)	2 (1)	0 (0)	7 (0)
Iatrogenic immunosuppression, n (%)	1 (0)	6 (1)	0 (0)	0 (0)	7 (0)
Chronic kidney disease, n (%)	0 (0)	5 (1)	1 (0)	0 (0)	6 (0)
Malignant neoplasm, n (%)	1 (0)	2 (0)	0 (0)	1 (2)	4 (0)
Moderate or severe liver disease, n (%)	2 (0)	1 (0)	0 (0)	0 (0)	3 (0)
Dialysis, n (%)	0 (0)	1 (0)	0 (0)	0 (0)	1 (0)
HIV infection, n (%)	1 (0)	0 (0)	0 (0)	0 (0)	1 (0)
Dementia, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Missing, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0.0)

2.1.6.3 Prognostics

Baseline prognostics stratified by anticoagulation interventions are reported below.

Variable	Anticoagulation				Overall (n = 1556)
	Standard dose (n = 610)	Intermediate dose (n = 613)	Standard dose plus aspirin (n = 283)	Therapeutic dose (n = 50)	
Was the patient on room air for any of the preceding 24 hours?					
Yes, n (%)	460 (75)	460 (75)	224 (79)	39 (78)	1183 (76)
Missing, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Was the patient's GCS < 15?					
Yes, n (%)	63 (10)	65 (11)	6 (2)	2 (4)	136 (9)
Missing, n (%)	125 (20)	135 (22)	60 (21)	0 (0)	320 (21)
Peripheral oxygen saturation (SpO2) on room air (Lowest)					
Median (IQR)	95 (94, 97)	96 (94, 97)	96 (94, 97)	94 (92, 96)	96 (94, 97)
Missing, n (%)	148 (24)	150 (24)	54 (19)	10 (20)	362 (23)
Highest respiratory rate (breaths/minute)					
Median (IQR)	22 (21, 25)	22 (21, 26)	22 (20, 26)	22 (20, 24)	22 (21, 26)
Missing, n (%)	0 (0)	1 (0)	0 (0)	0 (0)	1 (0)
Highest recorded Urea in the last 24 hours (mmol/L)					
Median (IQR)	4 (3, 5)	5 (4, 6)	4 (3, 6)	4 (3, 6)	4 (3, 6)
Missing, n (%)	30 (5)	33 (5)	16 (6)	1 (2)	80 (5)
Highest recorded CRP in the last 24 hours (mg/L)					
Median (IQR)	70 (37, 190)	75 (38, 220)	77 (44, 223)	68 (33, 129)	73 (39, 200)
Missing, n (%)	74 (12)	59 (10)	18 (6)	29 (58)	180 (12)
APTT[1]					
Median (IQR)	33 (29, 36)	33 (30, 36)	32 (28, 37)	33 (28, 38)	33 (29, 36)
Missing, n (%)	430 (70)	439 (72)	195 (69)	35 (70)	1099 (71)
INR[1]					
Mean (SD)	1.19 (0.39)	1.23 (0.58)	1.32 (1.34)	1.12 (0.18)	1.23 (0.72)
Missing, n (%)	103 (17)	105 (17)	47 (17)	7 (14)	262 (17)
Fibrinogen[1] (g/L)					
Mean (SD)	5.19 (2.01)	5.20 (1.60)	4.75 (1.40)	6.49 (1.52)	5.14 (1.71)
Missing, n (%)	564 (92)	555 (91)	243 (86)	42 (84)	1404 (90)
Prothrombin time[1] (sec)					
Median (IQR)	14 (13, 17)	14 (13, 17)	15 (13, 16)	13 (12, 14)	14 (13, 16)
Missing, n (%)	193 (32)	204 (33)	116 (41)	10 (20)	523 (34)
Taking aspirin					
Yes, n (%)	20 (3)	25 (4)	2 (1)	3 (6)	50 (3)

Missing, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Time from onset of symptoms to hospitalisation					
Median (IQR)	5 (3, 7)	5 (3, 6)	4 (2, 6)	4 (3, 6)	4 (3, 6)
Time from hospitalisation to randomisation					
Median (IQR)	1 (0, 2)	1 (0, 2)	1 (1, 2)	1 (1, 1)	1 (0, 2)

[1] For APTT, INR, Fibrinogen, and Prothrombin only at least one required.

The relative timing (in days) of hospitalisation, symptom onset, randomisation, and first positive test are presented in Figure 2.9.

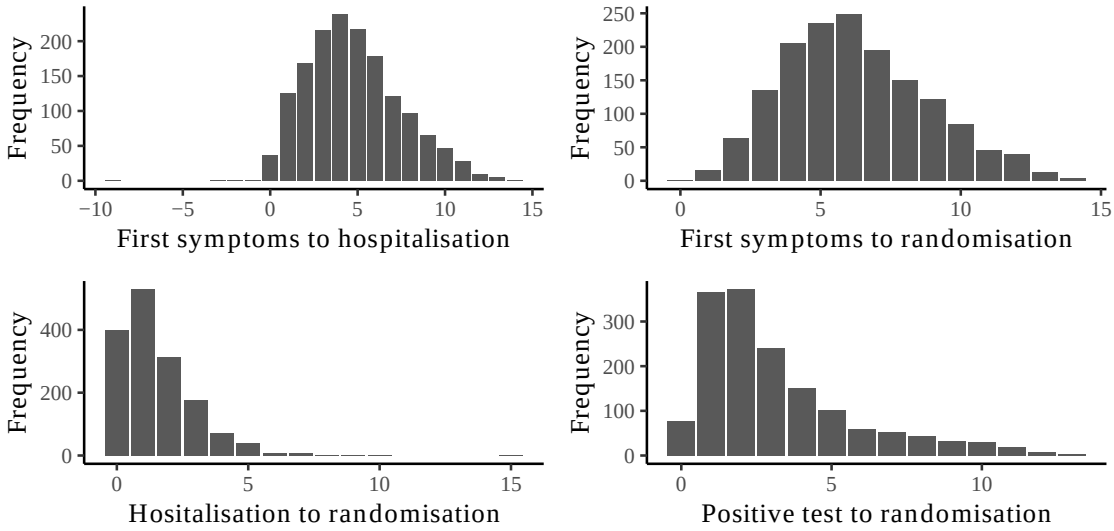

Figure 2.9: Days between events for hospitalisation, randomisation, symptom onset, and first positive test.

2.1.7 Discharge Summaries

2.1.7.1 Drugs Received During Hospital Stay

There were 18 participants without a discharge record (due to withdrawal of consent for follow-up). For the continuing participants, the other medications received during their hospital stay are reported in Table 2.5.

Table 2.5: Drugs received during hospital stay for participants randomised to the anticoagulation domain.

Drug received	Anticoagulation				Overall (n = 1556)
	Standard dose (n = 610)	Intermediate dose (n = 613)	Standard dose plus aspirin (n = 283)	Therapeutic dose (n = 50)	
Antibacterial drugs, n (%)	449 (74)	443 (72)	231 (82)	38 (76)	1161 (75)
Antivirals					
No antiviral, n (%)	125 (20)	120 (20)	44 (16)	39 (78)	328 (21)
Camostat, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Favipiravir, n (%)	97 (16)	100 (16)	34 (12)	0 (0)	231 (15)
Doxycycline, n (%)	76 (12)	81 (13)	22 (8)	2 (4)	181 (12)
Ivermectin, n (%)	201 (33)	200 (33)	91 (32)	0 (0)	492 (32)
Remdesivir, n (%)	286 (47)	289 (47)	169 (60)	10 (20)	754 (48)
Other antiviral, n (%)	3 (0)	1 (0)	1 (0)	0 (0)	5 (0)
Immunomodulatory					
No immunomodulatory, n (%)	60 (10)	68 (11)	38 (13)	6 (12)	172 (11)
Anakinra, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Corticosteroids, n (%)	396 (65)	388 (63)	183 (65)	37 (74)	1004 (65)
Sarilumab, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Azithromycin, n (%)	105 (17)	108 (18)	38 (13)	5 (10)	256 (16)
Tocilizumab, n (%)	12 (2)	11 (2)	5 (2)	2 (4)	30 (2)
Baricitinib, n (%)	36 (6)	50 (8)	11 (4)	6 (12)	103 (7)
Ruxolitinib, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Tofacitinib, n (%)	11 (2)	13 (2)	5 (2)	0 (0)	29 (2)
Zinc, n (%)	388 (64)	394 (64)	173 (61)	13 (26)	968 (62)
Other immunomodulatory, n (%)	20 (3)	20 (3)	11 (4)	1 (2)	52 (3)

2.1.8 Adherence

2.2 Primary Outcome

2.2.1 Descriptive

The primary outcome is a composite comprised of:

- day 28 mortality
- vasopressor/inotropic support within first 28 days
- new intensive respiratory support within first 28 days.

The definition also allowed for patients who had unknown day 28 status, but were discharged against medical advice (DAMA) and designated as likely to die within 28 days. However, no participants met this criteria (all cases of DAMA and likely to die within 28 days had known day 28 status).

The proportion of participants who met the primary outcome, and rates of missingness, are reported in Table 2.6. A breakdown of the composite, including missingness by component is reported in Table 2.7. Missingness was predominantly due to unknown patient status at study day 28. Amongst participants where the primary outcome was observed (1,526), 103 (7%) met the primary outcome criteria, most commonly due to requirement of new intensive ventilation and/or death (Table 2.8).

A summary of the primary outcome by each of the baseline covariates pre-specified to be included in the primary model (or as pre-specified subgroup analyses) are presented in the appendix (Section 3.1).

Table 2.6: Summary of primary composite outcome by treatment group.

n (%)	Standard dose	Intermediate dose	Standard dose plus aspirin	Therapeutic dose	Overall
Randomised	610	613	283	50	1556
Outcome missing	14 (2.3)	12 (2.0)	4 (1.4)	0 (0.0)	30 (1.9)
Outcome observed	596 (97.7)	601 (98.0)	279 (98.6)	50 (100.0)	1526 (98.1)
Met primary outcome	45 (7.6)	30 (5.0)	21 (7.5)	7 (14.0)	103 (6.7)

Table 2.7: Breakdown of primary composite outcome by treatment group.

Outcome	Breakdown	Standard dose (n = 610)	Intermediate dose (n = 613)	Standard dose plus aspirin (n = 283)	Therapeutic dose (n = 50)	Overall (n = 1556)
Primary outcome						
No		551 (90)	571 (93)	258 (91)	43 (86)	1423 (91)
Yes		45 (7)	30 (5)	21 (7)	7 (14)	103 (7)
Unknown	Total	14 (2)	12 (2)	4 (1)	0 (0)	30 (2)
	Day 28 status	13 (2)	10 (2)	2 (1)	0 (0)	25 (2)
	Vasopressor/inotropes	1 (0)	2 (0)	2 (1)	0 (0)	5 (0)
Mortality						
Alive at day 28		577 (95)	588 (96)	271 (96)	44 (88)	1480 (95)
Death within 28 days	Total	19 (3)	15 (2)	10 (4)	6 (12)	50 (3)
	Prior to discharge	15 (2)	11 (2)	10 (4)	4 (8)	40 (3)
	Post-discharge	4 (1)	4 (1)	0 (0)	2 (4)	10 (1)
Unknown		14 (2)	10 (2)	2 (1)	0 (0)	26 (2)
Vasopressor/inotropes						
Not required		580 (95)	589 (96)	272 (96)	48 (96)	1489 (96)
Use within 28 days	Total	17 (3)	12 (2)	7 (2)	2 (4)	38 (2)
	Prior to discharge	5 (1)	6 (1)	6 (2)	2 (4)	19 (1)
	Post-discharge	13 (2)	6 (1)	1 (0)	1 (2)	21 (1)
Unknown		13 (2)	12 (2)	4 (1)	0 (0)	29 (2)
Ventilation						
Not required		567 (93)	581 (95)	268 (95)	44 (88)	1460 (94)
Use within 28 days	Total	29 (5)	19 (3)	13 (5)	5 (10)	66 (4)
	Prior to discharge	29 (5)	19 (3)	13 (5)	5 (10)	66 (4)
	Post-discharge	0 (0)	2 (0)	2 (1)	0 (0)	4 (0)
Unknown		14 (2)	13 (2)	2 (1)	1 (2)	30 (2)

Table 2.8: Breakdown of primary composite combinations by treatment group.

Composite outcomes, n (%)	Standard dose (n = 610)	Intermediate dose (n = 613)	Standard dose plus aspirin (n = 283)	Therapeutic dose (n = 50)	Overall (n = 1556)
None	551 (90)	571 (93)	258 (91)	43 (86)	1423 (91)
Death + Vas./Ino. + Ventilation	5 (1)	3 (0)	3 (1)	1 (2)	12 (1)
Death + Vas./Ino.	1 (0)	0 (0)	0 (0)	1 (2)	2 (0)
Death + Ventilation	9 (1)	7 (1)	2 (1)	3 (6)	21 (1)
Vas./Ino. + Ventilation	0 (0)	3 (0)	1 (0)	0 (0)	4 (0)
Death	4 (1)	5 (1)	5 (2)	1 (2)	15 (1)
Vas./Ino.	11 (2)	6 (1)	3 (1)	0 (0)	20 (1)
Ventilation	15 (2)	6 (1)	7 (2)	1 (2)	29 (2)
Unknown	14 (2)	12 (2)	4 (1)	0 (0)	30 (2)

Table 2.9: Breakdown of primary composite outcomes by treatment group and interim of enrolment.

Outcome	Standard	Intermediate	Standard plus aspirin	Therapuetic
Overall (n = 1556)				
Randomised	610	613	283	50
Known	596 (98)	601 (98)	279 (99)	50 (100)
Met primary outcome	45 (8)	30 (5)	21 (8)	7 (14)
Death	19 (3)	15 (2)	10 (4)	6 (12)
Vasopressor/inotropic support	17 (3)	12 (2)	7 (3)	2 (4)
Intensive respiratory support	29 (5)	19 (3)	13 (5)	5 (10)
Interim 1 (n = 685)				
Randomised	234	226	225	-
Known	227 (97)	222 (98)	222 (99)	-
Met primary outcome	27 (12)	17 (8)	20 (9)	-
Death	13 (6)	11 (5)	9 (4)	-
Vasopressor/inotropic support	8 (4)	5 (2)	7 (3)	-
Intensive respiratory support	17 (8)	11 (5)	13 (6)	-
Interim 2 (n = 246)				
Randomised	90	98	58	-
Known	90 (100)	97 (99)	57 (98)	-
Met primary outcome	2 (2)	3 (3)	1 (2)	-
Death	1 (1)	3 (3)	1 (2)	-
Vasopressor/inotropic support	1 (1)	0 (0)	0 (0)	-
Intensive respiratory support	2 (2)	2 (2)	0 (0)	-
Interim 3 (n = 384)				
Randomised	177	172	-	35
Known	173 (98)	167 (97)	-	35 (100)
Met primary outcome	10 (6)	5 (3)	-	6 (17)
Death	4 (2)	0 (0)	-	5 (14)
Vasopressor/inotropic support	5 (3)	3 (2)	-	2 (6)
Intensive respiratory support	7 (4)	4 (2)	-	5 (14)
Interim 4 (n = 241)				
Randomised	109	117	-	15
Known	106 (97)	115 (98)	-	15 (100)
Met primary outcome	6 (6)	5 (4)	-	1 (7)
Death	1 (1)	1 (1)	-	1 (7)
Vasopressor/inotropic support	3 (3)	4 (3)	-	0 (0)
Intensive respiratory support	3 (3)	2 (2)	-	0 (0)

2.2.2 Primary Analysis (ACS-ITT set)

The primary model was a logistic regression model adjusting for anticoagulation treatment, antiviral treatment, age (≥ 60), and region (India (ref), Australia/New Zealand, and Nepal), with random effects for site (nested within country) and epoch (calendar time 4 week intervals, most recent epoch as reference). The three most recent epochs were combined due to small numbers, and the two earliest epochs were combined for the same reason. Sites with fewer than 5 enrolments were combined within region into an "other sites" category. The primary analysis was based on the ACS-ITT set using the full model as specified in the statistical appendix to the core protocol. An odds ratio less than 1 implies a benefit (reduction in the odds of primary outcome).

In summary:

- **Model**: logistic regression
- **Terms**: anticoagulation intervention, antiviral intervention, aspirin eligibility, age group, region, site nested within region, and epoch
- **Set**: ACS-ITT

The trial decision quantities are reported in Table 2.10 and the model parameter posteriors are summarised in Table 2.11 and Figure 2.11.

Table 2.10: Summary of domain decision qauntities (relative to standard dose) for primary outcome model fit to the ACS-ITT set.

Intervention	Posterior	Superior	Effective	Futile	Equivalent
Standard	1.00 (1.00, 1.00)	0.01	-	-	-
Intermediate	0.63 (0.37, 1.03)	0.66	0.97	0.07	0.06
Standard plus aspirin	0.73 (0.40, 1.31)	0.31	0.86	0.23	0.14
Therapeutic	1.94 (0.67, 5.29)	0.02	0.10	0.92	0.06

Table 2.11: Summary of model parameters (fixed-effects odds-ratios) for primary outcome model fit to the ACS-ITT set.

Parameter	Median	95% CrI	Mean (SD)	Pr(OR < 1)
Intermediate	0.63	(0.37, 1.03)	0.65 (0.17)	0.97
Standard plus aspirin	0.73	(0.40, 1.31)	0.76 (0.23)	0.86
Therapeutic	1.94	(0.67, 5.29)	2.20 (1.22)	0.10
Inelgible aspirin	3.99	(1.26, 11.93)	4.65 (2.85)	0.01
Age 60+	1.96	(1.24, 3.08)	2.01 (0.48)	0.00
Australia/New Zealand	0.94	(0.21, 3.91)	1.22 (1.00)	0.53
Nepal	1.50	(0.39, 5.35)	1.85 (1.38)	0.27

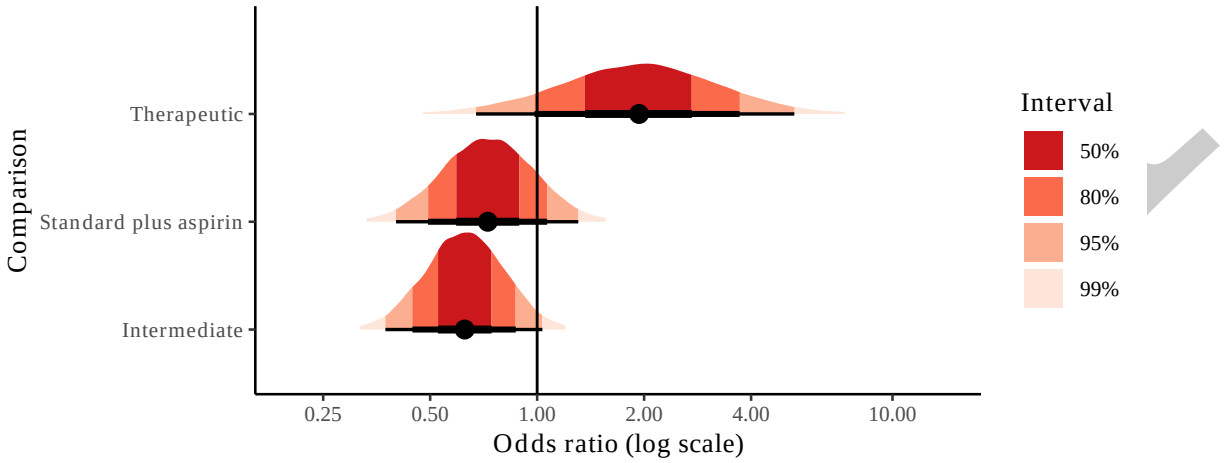

Figure 2.10: Posterior densities for the treatment effect odds ratios.

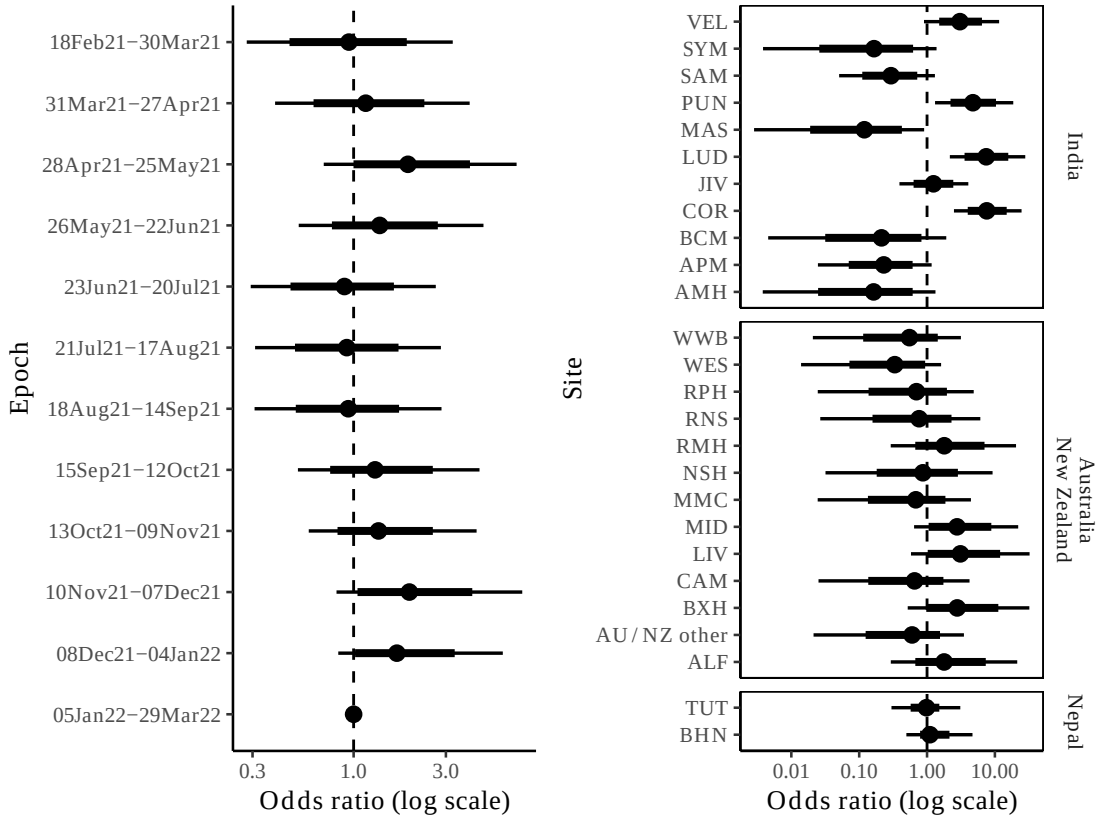

Figure 2.11: Posterior Summaries (point - median, block - 75% CrI, line 0.95% CrI) of odds ratio for epoch and site effects for the primary outcome model fit to the ACS-ITT set.

2.2.3 Subgroups

The pre-specified subgroups where treatment effect heterogeneity was to be investigated were:

- region (India, Australia/New Zealand, Nepal)
- days since symptom onset (< 8 or ≥ 8 days)
- age at enrolment (< 60 or ≥ 60 years of age)
- supplemental oxygen or oxygen saturation less than 94% at randomisation (yes or no)
- receipt of corticosteroid during hospital stay (yes or no)
- receipt of remdesivir during hospital stay (yes or no)
- receipt of other agent intended to be antiviral against SARS-CoV-2 during hospital stay (yes or no)

Domain-specific subgroups were additionally specified as:

- weight (< 120 or ≥ 120 kg)
- patient on aspirin at baseline (yes or no)
- D-dimer above upper limit of normal at baseline (yes or no)

For each sub-group analysis, the primary model was extended to include an interaction term between the covariate of interest and the anticoagulation interventions. In some cases, there may be no information on the subgroup-specific effect (for example, there were no participants in Nepal who were randomised to receive standard dose plus aspirin), but the results are reported in such cases noting that the posterior is driven by the prior.

In these subgroup analyses, the reference group was generally taken to be the largest subgroup and the intervention effect in this reference group has a normal prior with mean 0 and standard deviation 2.5. For each additional subgroup, the interaction between each intervention and subgroup level has a normal prior with mean 0 and standard deviation 1.

2.2.3.1 Region

A subgroup analysis of region is undertaken using the ACS-ITT set. A summary of the primary outcome by country and intervention is reported in Table 2.12. Note that no participants enrolled in Nepal or New Zealand received standard dose plus aspirin due to the timing of its removal from the domain. Despite this, an interaction term for region and standard dose plus aspirin was retained in the model, however, the associated effect (in Nepal) corresponds to the assumed prior given there is little to no data available.

Table 2.12: Summary of participant outcomes by region of enrolment in the ACS-ITT set.

Anticoagulation intervention	Patients	Known	Primary outcome
India			
Standard dose	493	486	37 (8%)
Intermediate dose	516	511	25 (5%)
Standard dose plus aspirin	275	272	21 (8%)
Therapeutic dose	4	4	0 (0%)
Australia/New Zealand			
Standard dose	61	57	4 (7%)
Intermediate dose	66	59	4 (7%)
Standard dose plus aspirin	8	7	0 (0%)
Therapeutic dose	15	15	1 (7%)
Nepal			
Standard dose	56	53	4 (8%)
Intermediate dose	31	31	1 (3%)
Standard dose plus aspirin	0	0	- (-%)
Therapeutic dose	31	31	6 (19%)

Table 2.13: Summary of odds ratios for treatment effects by region of enrolment in the ACS-ITT set.

Region	Median	95% CrI	Mean (SD)	Pr(OR < 1)	Pr(OR > 1/1.1)
Intermediate					
India	0.61	(0.36, 1.00)	0.63 (0.17)	0.97	0.06
Australia/New Zealand	0.87	(0.24, 2.95)	1.06 (0.74)	0.58	0.47
Nepal	0.46	(0.10, 1.78)	0.59 (0.46)	0.86	0.17
Standard plus aspirin					
India	0.71	(0.40, 1.26)	0.74 (0.22)	0.88	0.20
Australia/New Zealand	0.61	(0.09, 3.93)	0.95 (1.10)	0.70	0.33
Nepal	0.71	(0.09, 5.42)	1.22 (1.65)	0.63	0.41
Therapeutic					
India	1.33	(0.35, 4.97)	1.68 (1.27)	0.34	0.71
Australia/New Zealand	1.14	(0.18, 6.16)	1.65 (1.71)	0.44	0.60
Nepal	2.58	(0.77, 8.68)	3.13 (2.14)	0.06	0.95

Table 2.14: Summary of odds ratio comparisons of treatment effects by region of enrolment in the ACS-ITT set, (reference is India).

Region	Median	95% CrI	Mean (SD)	Pr(OR < 1)
Intermediate				
India (ref)	1.00	(1.00, 1.00)	1.00 (0.00)	0.00
Australia/New Zealand	1.44	(0.40, 4.97)	1.76 (1.24)	0.29
Nepal	0.76	(0.17, 2.95)	0.97 (0.75)	0.65
Standard plus aspirin				
India (ref)	1.00	(1.00, 1.00)	1.00 (0.00)	0.00
Australia/New Zealand	0.85	(0.13, 5.24)	1.29 (1.44)	0.57
Nepal	0.99	(0.14, 6.87)	1.63 (2.07)	0.50
Therapeutic				
India (ref)	1.00	(1.00, 1.00)	1.00 (0.00)	0.00
Australia/New Zealand	0.84	(0.16, 4.25)	1.18 (1.17)	0.58
Nepal	1.93	(0.46, 8.18)	2.55 (2.17)	0.18

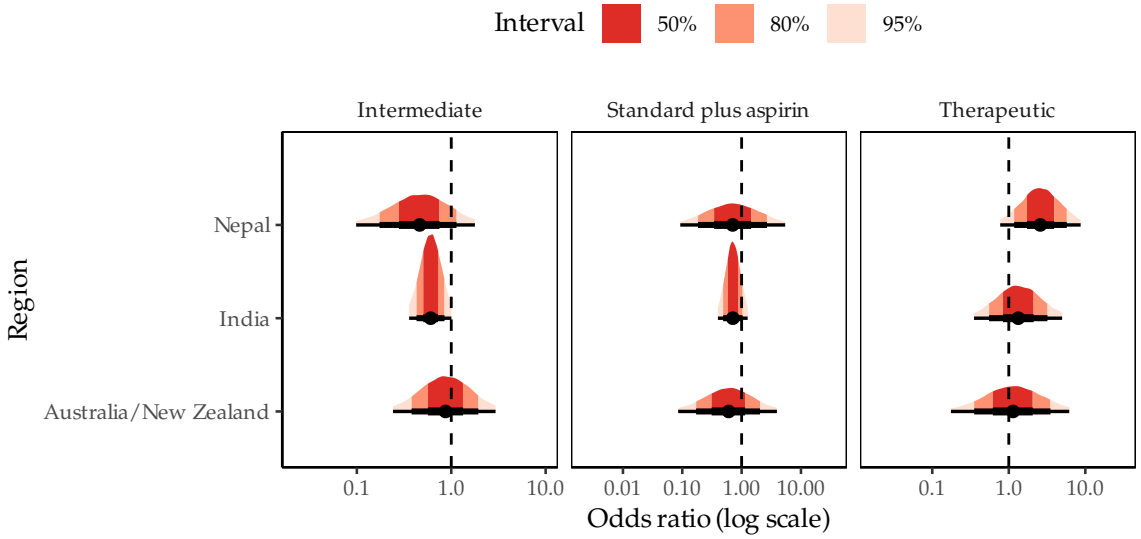

Figure 2.12: Posterior densities of odds ratio for anticoagulation interventions relative to standard dose by region subgroup using ACS-ITT set.

2.2.3.2 Age group

A subgroup analysis of age group (< 60 or ≥ 60 years of age) was undertaken using the ACS-ITT set. A summary of the primary outcome by age group and intervention is reported in Table 2.15.

Table 2.15: Summary of participant outcomes by age group at enrolment in the ACS-ITT set.

Anticoagulation intervention	Patients	Known	Primary outcome
Age < 60 years			
Standard dose	445	436	24 (6%)
Intermediate dose	436	427	17 (4%)
Standard dose plus aspirin	195	192	12 (6%)
Therapeutic dose	26	26	3 (12%)
Age 60+ years			
Standard dose	165	160	21 (13%)
Intermediate dose	177	174	13 (7%)
Standard dose plus aspirin	88	87	9 (10%)
Therapeutic dose	24	24	4 (17%)

Table 2.16: Summary of odds ratios for treatment effects by age of enrolment in the ACS-ITT set.

Age	Median	95% CrI	Mean (SD)	Pr(OR < 1)	Pr(OR > 1/1.1)
Intermediate					
Age < 60	0.67	(0.36, 1.20)	0.70 (0.22)	0.91	0.15
Age 60+	0.54	(0.25, 1.13)	0.58 (0.22)	0.95	0.08
Standard plus aspirin					
Age < 60	0.81	(0.40, 1.60)	0.85 (0.31)	0.73	0.37
Age 60+	0.59	(0.24, 1.36)	0.64 (0.29)	0.89	0.15
Therapeutic					
Age < 60	1.72	(0.55, 5.09)	2.00 (1.22)	0.17	0.87
Age 60+	2.02	(0.54, 6.87)	2.45 (1.73)	0.14	0.89

Table 2.17: Summary of odds ratio comparisons of treatment effects by age of enrolment in the ACS-ITT set.

Age	Median	95% CrI	Mean (SD)	Pr(OR < 1)
Intermediate				
Age < 60 (ref)	1.00	(1.00, 1.00)	1.00 (0.00)	0.00
Age 60+	0.81	(0.33, 1.97)	0.90 (0.43)	0.68
Standard plus aspirin				
Age < 60 (ref)	1.00	(1.00, 1.00)	1.00 (0.00)	0.00
Age 60+	0.73	(0.27, 1.94)	0.82 (0.44)	0.74
Therapeutic				
Age < 60 (ref)	1.00	(1.00, 1.00)	1.00 (0.00)	0.00
Age 60+	1.17	(0.31, 4.48)	1.47 (1.14)	0.41

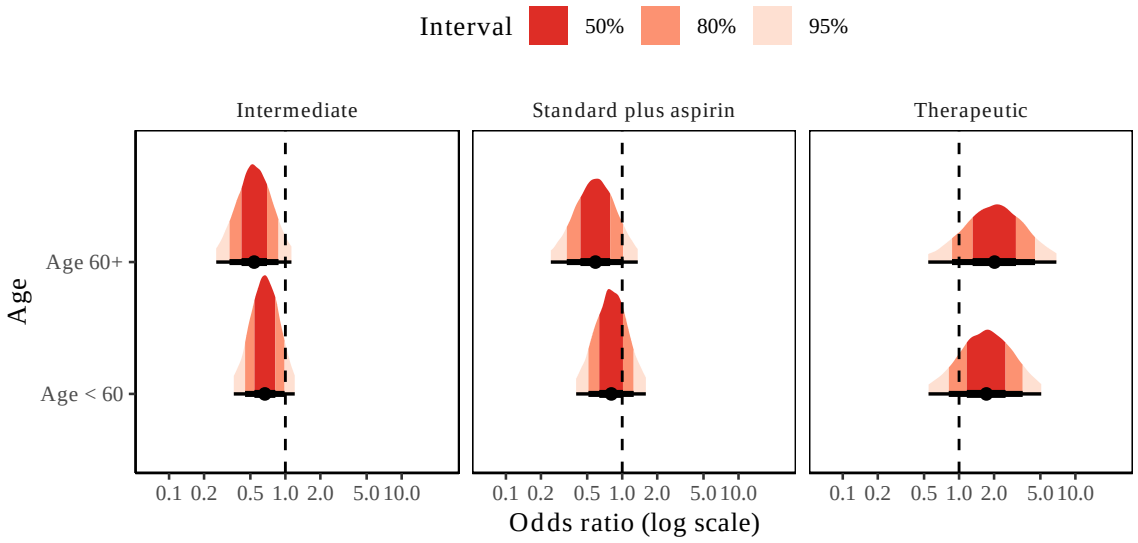

Figure 2.13: Posterior densities of odds ratio for anticoagulation interventions relative to standard dose by age subgroup using ACS-ITT set.

2.2.3.3 Days since symptom onset

A subgroup analysis of days since first symptoms (DSFS) group (≤ 7 or > 7 days) was undertaken using the ACS-ITT set. A summary of the primary outcome by DSFS group and intervention is reported in Table 2.18.

Table 2.18: Summary of participant outcomes by days since symptom onset in the ACS-ITT set.

Anticoagulation intervention	Patients	Known	Primary outcome
Days since first symptoms <= 7			
Standard dose	421	412	32 (8%)
Intermediate dose	432	426	25 (6%)
Standard dose plus aspirin	206	203	15 (7%)
Therapeutic dose	39	39	5 (13%)
Days since first symptoms > 7			
Standard dose	189	184	13 (7%)
Intermediate dose	181	175	5 (3%)
Standard dose plus aspirin	77	76	6 (8%)
Therapeutic dose	11	11	2 (18%)

Table 2.19: Summary of odds ratios for treatment effects by DSFS of enrolment in the ACS-ITT set.

Days since first symptoms	Median	95% CrI	Mean (SD)	Pr(OR < 1)	Pr(OR > 1/1.1)
Intermediate					
DSFS < 8	0.73	(0.42, 1.25)	0.76 (0.22)	0.87	0.22
DSFS ≥ 8	0.35	(0.13, 0.90)	0.39 (0.20)	0.99	0.02
Standard plus aspirin					
DSFS < 8	0.72	(0.38, 1.34)	0.75 (0.25)	0.85	0.23
DSFS ≥ 8	0.69	(0.25, 1.83)	0.78 (0.41)	0.77	0.29
Therapeutic					
DSFS < 8	1.71	(0.61, 4.59)	1.93 (1.05)	0.16	0.88
DSFS ≥ 8	2.75	(0.52, 12.28)	3.65 (3.22)	0.11	0.91

Table 2.20: Summary of odds ratio comparisons of treatment effects by DSFS of enrolment in the ACS-ITT set.

Days since first symptoms	Median	95% CrI	Mean (SD)	Pr(OR < 1)
Intermediate				
DSFS < 8	1.00	(1.00, 1.00)	1.00 (0.00)	0.00
DSFS ≥ 8	0.48	(0.17, 1.32)	0.55 (0.30)	0.92
Standard plus aspirin				
DSFS < 8	1.00	(1.00, 1.00)	1.00 (0.00)	0.00
DSFS ≥ 8	0.97	(0.33, 2.72)	1.11 (0.62)	0.52
Therapeutic				
DSFS < 8	1.00	(1.00, 1.00)	1.00 (0.00)	0.00
DSFS ≥ 8	1.61	(0.36, 6.76)	2.08 (1.73)	0.27

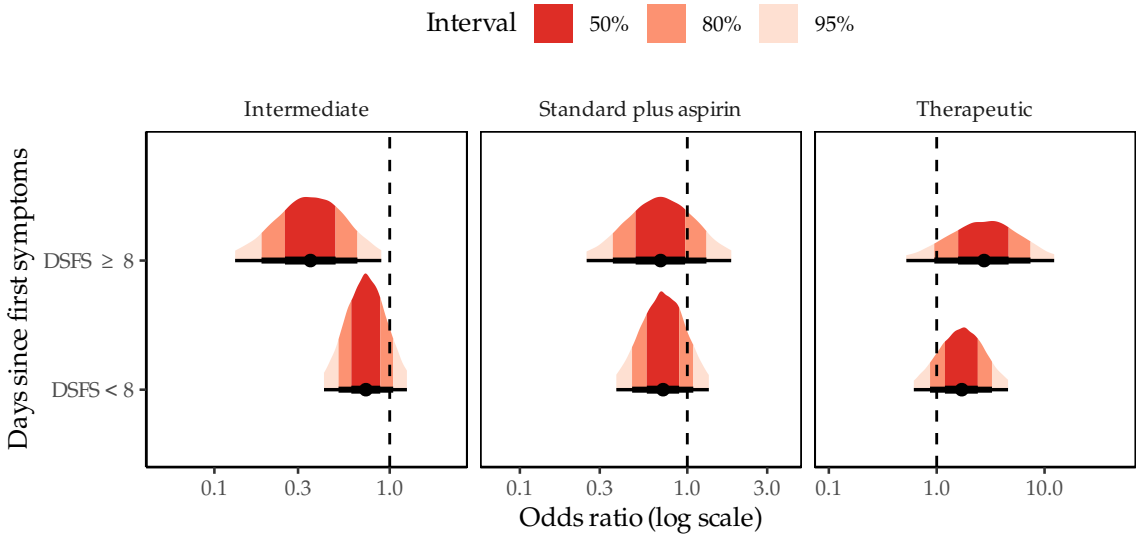

Figure 2.14: Posterior densities of odds ratio for anticoagulation interventions relative to standard dose by days since first symptoms subgroup using ACS-ITT set.

2.2.3.4 Receipt of Corticosteroids

A subgroup analysis by whether patient received corticosteroids (did not receive or did receive) was undertaken using the ACS-ITT set. A summary of the primary outcome by receipt of corticosteroids and intervention is reported in Table 2.21.

It's noted that this subgroup analysis was pre-specified, however receipt of corticosteroids is reported on the discharge summary and is a post-randomisation event (any receipt during their index hospital admission). Therefore, interpretation of this subgroup is challenging (more severe patients may have been more likely to receive corticosteroids, availability may be site specific, etc.).

Table 2.21: Summary of participant outcomes by receipt of corticosteroids during index hospital stay in the ACS-ITT set.

Anticoagulation intervention	Patients	Known	Primary outcome
Did not receive corticosteroids			
Standard dose	214	210	14 (7%)
Intermediate dose	225	223	7 (3%)
Standard dose plus aspirin	100	98	4 (4%)
Therapeutic dose	13	13	1 (8%)
Received corticosteroids			
Standard dose	396	386	31 (8%)
Intermediate dose	388	378	23 (6%)
Standard dose plus aspirin	183	181	17 (9%)
Therapeutic dose	37	37	6 (16%)

Table 2.22: Summary of odds ratios for treatment effects by receipt of corticosteroids in the ACS-ITT set.

Received corticosteroids	Median	95% CrI	Mean (SD)	Pr(OR < 1)	Pr(OR > 1/1.1)
Intermediate					
No	0.54	(0.24, 1.18)	0.58 (0.25)	0.94	0.10
Yes	0.66	(0.36, 1.17)	0.69 (0.21)	0.92	0.14
Standard plus aspirin					
No	0.60	(0.23, 1.41)	0.66 (0.31)	0.87	0.18
Yes	0.75	(0.37, 1.46)	0.79 (0.28)	0.80	0.28
Therapeutic					
No	1.46	(0.38, 5.05)	1.77 (1.26)	0.28	0.76
Yes	2.18	(0.71, 6.34)	2.52 (1.50)	0.09	0.94

Table 2.23: Summary of odds ratio comparisons of treatment effects by receipt of corticosteroids in the ACS-ITT set.

Received corticosteroids	Median	95% CrI	Mean (SD)	Pr(OR < 1)
Intermediate				
No (ref)	1.00	(1.00, 1.00)	1.00 (0.00)	0.00
Yes	1.22	(0.49, 3.12)	1.36 (0.69)	0.34
Standard plus aspirin				
No (ref)	1.00	(1.00, 1.00)	1.00 (0.00)	0.00
Yes	1.24	(0.46, 3.50)	1.43 (0.81)	0.33
Therapeutic				
No (ref)	1.00	(1.00, 1.00)	1.00 (0.00)	0.00
Yes	1.49	(0.40, 5.89)	1.91 (1.50)	0.28

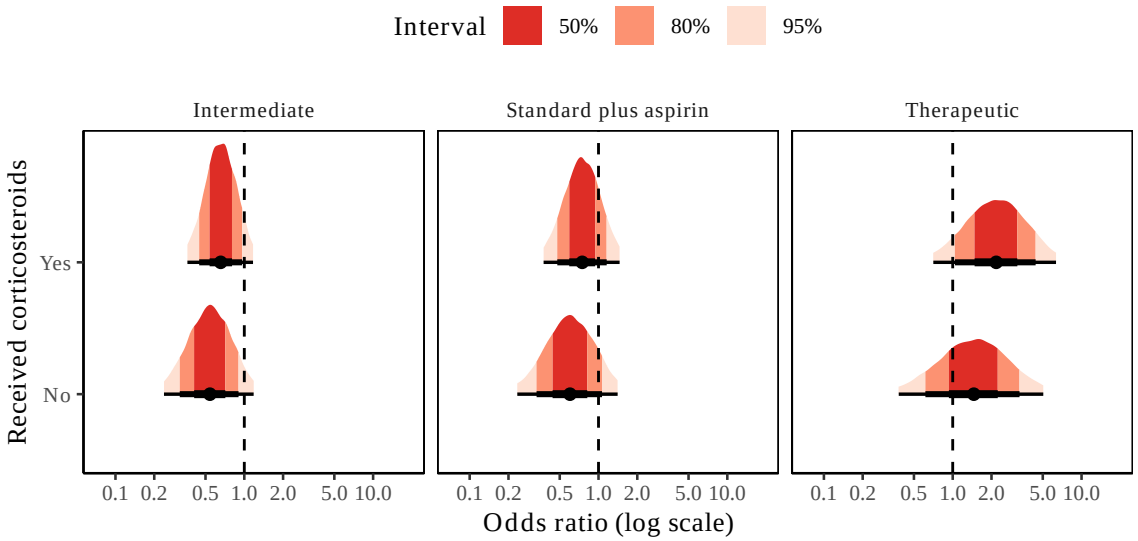

Figure 2.15: Posterior densities of odds ratio for anticoagulation interventions relative to standard dose by receipt of steroids subgroup using ACS-ITT set.

2.2.3.5 Receipt of Remdesivir

A subgroup analysis by whether patient received remdesivir (did not receive or did receive) was undertaken using the ACS-ITT set. A summary of the primary outcome by receipt of remdesivir and intervention is reported in Table 2.24.

Similar for corticosteroids, this subgroup analysis was pre-specified, however receipt of remdesivir is reported on the discharge summary and is a post-randomisation event.

Table 2.24: Summary of participant outcomes by receipt of remdesivir during index hospital stay in the ACS-ITT set.

Anticoagulation intervention	Patients	Known	Primary outcome
Did not receive remdesivir			
Standard dose	324	315	8 (3%)
Intermediate dose	324	316	6 (2%)
Standard dose plus aspirin	114	112	2 (2%)
Therapeutic dose	40	40	5 (12%)
Received remdesivir			
Standard dose	286	281	37 (13%)
Intermediate dose	289	285	24 (8%)
Standard dose plus aspirin	169	167	19 (11%)
Therapeutic dose	10	10	2 (20%)

Table 2.25: Summary of odds ratios for treatment effects by receipt of remdesivir in the ACS-ITT set.

Received remdesivir	Median	95% CrI	Mean (SD)	Pr(OR < 1)	Pr(OR > 1/1.1)
Intermediate					
No	0.66	(0.28, 1.49)	0.71 (0.31)	0.84	0.22
Yes	0.60	(0.33, 1.07)	0.63 (0.19)	0.96	0.08
Standard plus aspirin					
No	0.66	(0.23, 1.81)	0.75 (0.42)	0.79	0.27
Yes	0.66	(0.35, 1.26)	0.70 (0.23)	0.90	0.16
Therapeutic					
No	2.17	(0.73, 6.14)	2.49 (1.44)	0.08	0.94
Yes	1.90	(0.39, 8.67)	2.58 (2.35)	0.21	0.82

Table 2.26: Summary of odds ratio comparisons of treatment effects by receipt of remdesivir in the ACS-ITT set.

Received remdesivir	Median	95% CrI	Mean (SD)	Pr(OR < 1)
Intermediate				
No (ref)	1.00	(1.00, 1.00)	1.00 (0.00)	0.00
Yes	0.91	(0.36, 2.41)	1.03 (0.54)	0.58
Standard plus aspirin				
No (ref)	1.00	(1.00, 1.00)	1.00 (0.00)	0.00
Yes	0.99	(0.34, 3.12)	1.18 (0.75)	0.50
Therapeutic				
No (ref)	1.00	(1.00, 1.00)	1.00 (0.00)	0.00
Yes	0.89	(0.19, 3.88)	1.17 (1.03)	0.57

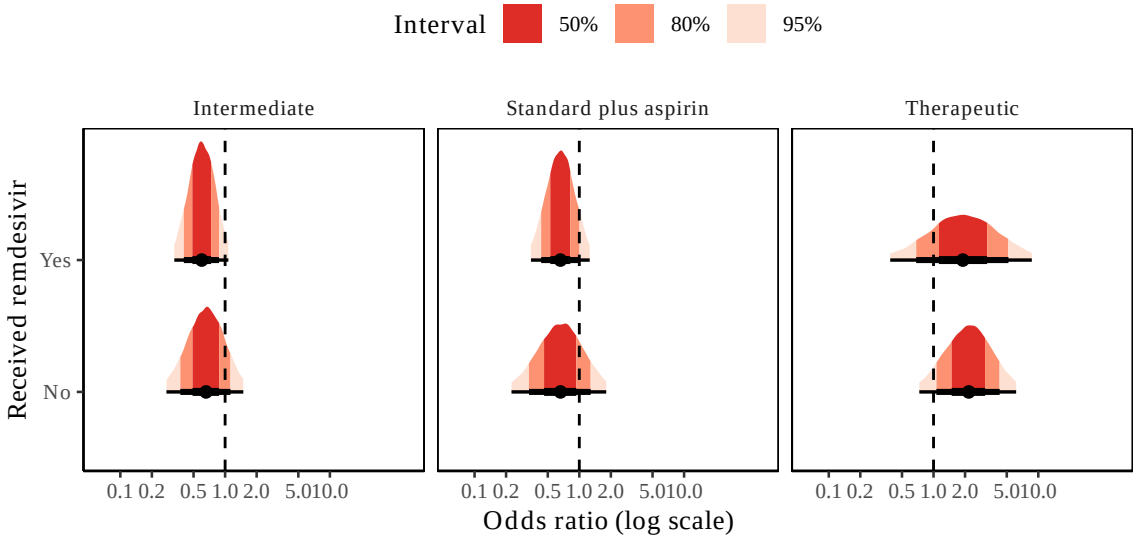

Figure 2.16: Posterior densities of odds ratio for anticoagulation interventions relative to standard dose by receipt of remdesivir subgroup using ACS-ITT set.

2.2.3.6 Receipt of other antiviral agent

A subgroup analysis by whether patient received any other antiviral (other than remdesivir) (did not receive or did receive) was undertaken using the ACS-ITT set. A summary of the primary outcome by receipt of other antiviral and intervention is reported in Table 2.27.

This subgroup analysis was pre-specified, however receipt of an antiviral is reported on the discharge summary and is a post-randomisation event.

Table 2.27: Summary of participant outcomes by receipt of other antiviral during index hospital stay in the ACS-ITT set.

Anticoagulation intervention	Patients	Known	Primary outcome
Did not receive other antiviral			
Standard dose	337	324	36 (11%)
Intermediate dose	340	331	28 (8%)
Standard dose plus aspirin	169	165	14 (8%)
Therapeutic dose	48	48	7 (15%)
Received other antiviral			
Standard dose	273	272	9 (3%)
Intermediate dose	273	270	2 (1%)
Standard dose plus aspirin	114	114	7 (6%)
Therapeutic dose	2	2	0 (0%)

Table 2.28: Summary of odds ratios for treatment effects by receipt of other antiviral in the ACS-ITT set.

Received other antiviral	Median	95% CrI	Mean (SD)	Pr(OR < 1)	Pr(OR > 1/1.1)
Intermediate					
No	0.68	(0.40, 1.15)	0.71 (0.19)	0.92	0.14
Yes	0.31	(0.09, 0.92)	0.36 (0.22)	0.98	0.03
Standard plus aspirin					
No	0.61	(0.32, 1.15)	0.64 (0.21)	0.94	0.11
Yes	1.27	(0.45, 3.44)	1.44 (0.78)	0.32	0.74
Therapeutic					
No	1.88	(0.69, 5.02)	2.12 (1.12)	0.11	0.92
Yes	1.58	(0.20, 11.80)	2.66 (3.41)	0.33	0.70

Table 2.29: Summary of odds ratio comparisons of treatment effects by receipt of other antiviral in the ACS-ITT set.

Received other antiviral	Median	95% CrI	Mean (SD)	Pr(OR < 1)
Intermediate				
No (ref)	1.00	(1.00, 1.00)	1.00 (0.00)	0.00
Yes	0.45	(0.13, 1.38)	0.53 (0.33)	0.91
Standard plus aspirin				
No (ref)	1.00	(1.00, 1.00)	1.00 (0.00)	0.00
Yes	2.07	(0.69, 6.09)	2.40 (1.42)	0.10
Therapeutic				
No (ref)	1.00	(1.00, 1.00)	1.00 (0.00)	0.00
Yes	0.84	(0.13, 5.13)	1.29 (1.43)	0.57

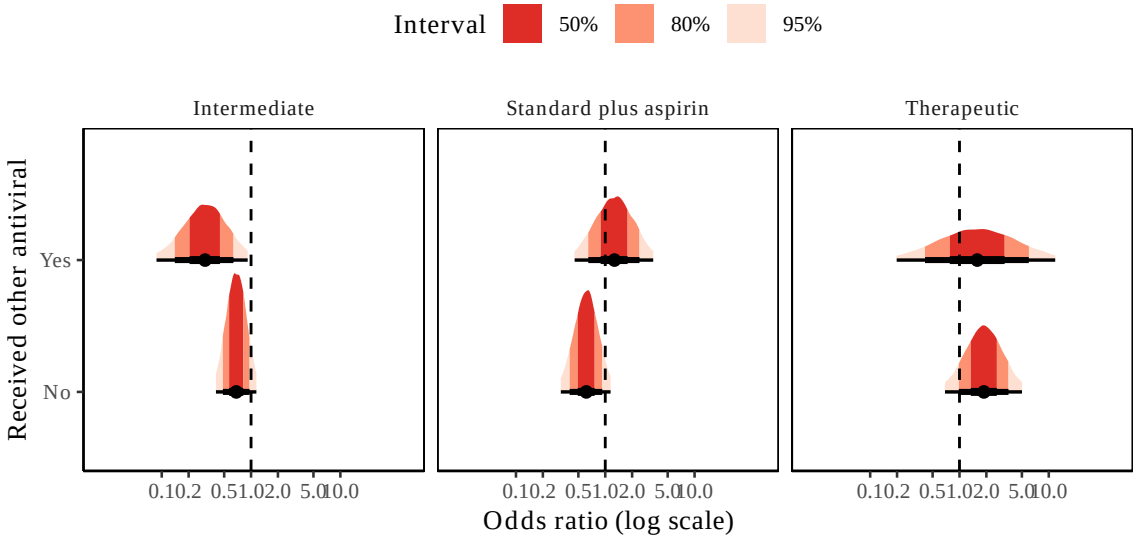

Figure 2.17: Posterior densities of odds ratio for anticoagulation interventions relative to standard dose by receipt of other antiviral subgroup using ACS-ITT set.

2.2.3.7 D-dimer

A subgroup analysis by whether D-dimer was out of range (D-dimer not out of range, D-dimer out of range, D-dimer unknown) was undertaken using the ACS-ITT set. A summary of the primary outcome by subgroup and intervention is reported in Table 2.30. Patients with unknown D-dimer at baseline were included as their own subgroup due to the large number with missing values.

Table 2.30: Summary of participant outcomes by whether D-dimer was out range at enrolment in the ACS-ITT set.

Anticoagulation intervention	Patients	Known	Primary outcome
D-Dimer in range			
Standard dose	311	307	22 (7%)
Intermediate dose	336	332	19 (6%)
Standard dose plus aspirin	184	181	14 (8%)
Therapeutic dose	7	7	0 (0%)
D-Dimer out of range			
Standard dose	182	179	10 (6%)
Intermediate dose	177	174	3 (2%)
Standard dose plus aspirin	63	62	7 (11%)
Therapeutic dose	10	10	1 (10%)
D-Dimer unknown			
Standard dose	117	110	13 (12%)
Intermediate dose	100	95	8 (8%)
Standard dose plus aspirin	36	36	0 (0%)
Therapeutic dose	33	33	6 (18%)

Table 2.31: Summary of odds ratios for treatment effects by whether D-dimer was out range at enrolment in the ACS-ITT set.

D-dimer out of range	Median	95% CrI	Mean (SD)	Pr(OR < 1)	Pr(OR > 1/1.1)
Intermediate					
No	0.67	(0.37, 1.20)	0.70 (0.22)	0.91	0.15
Yes	0.35	(0.11, 1.02)	0.40 (0.24)	0.97	0.04
Unknown	0.69	(0.27, 1.69)	0.77 (0.37)	0.79	0.28
Standard plus aspirin					
No	0.82	(0.42, 1.56)	0.86 (0.30)	0.73	0.37
Yes	1.38	(0.48, 3.82)	1.58 (0.89)	0.27	0.78
Unknown	0.15	(0.04, 0.56)	0.19 (0.14)	1.00	0.00
Therapeutic					
No	1.20	(0.32, 4.22)	1.47 (1.07)	0.39	0.67
Yes	1.53	(0.21, 9.06)	2.32 (2.67)	0.33	0.71
Unknown	2.46	(0.76, 7.96)	2.94 (1.96)	0.07	0.95

Table 2.32: Summary of odds ratio comparisons of treatment effects by whether D-dimer was out range at enrolment in the ACS-ITT set.

D-dimer out of range	Median	95% CrI	Mean (SD)	Pr(OR < 1)
Intermediate				
No (ref)	1.00	(1.00, 1.00)	1.00 (0.00)	0.00
Yes	0.52	(0.15, 1.62)	0.61 (0.39)	0.87
Unknown	1.04	(0.38, 2.83)	1.18 (0.64)	0.47
Standard plus aspirin				
No (ref)	1.00	(1.00, 1.00)	1.00 (0.00)	0.00
Yes	1.69	(0.56, 4.98)	1.97 (1.17)	0.17
Unknown	0.19	(0.04, 0.69)	0.23 (0.17)	0.99
Therapeutic				
No (ref)	1.00	(1.00, 1.00)	1.00 (0.00)	0.00
Yes	1.26	(0.23, 6.60)	1.81 (1.86)	0.39
Unknown	2.07	(0.51, 8.51)	2.67 (2.15)	0.16

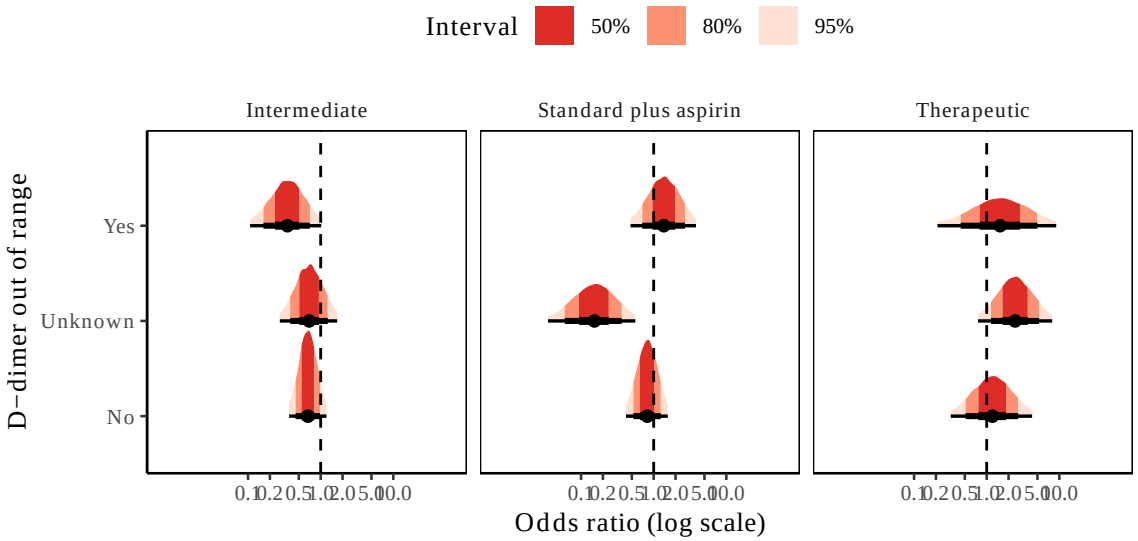

Figure 2.18: Posterior densities of odds ratio for anticoagulation interventions relative to standard dose by D-dimer subgroup using ACS-ITT set.

2.2.3.8 Weight

Due to smaller numbers (18 participants with weight > 120 kg and zero events), this pre-specified subgroup analysis was not undertaken.

Table 2.33: Summary of participant outcomes by weight at baseline in the ACS-ITT set.

Anticoagulation intervention	Patients	Known	Primary outcome
Weight $\leq$ 120 kg			
Standard dose	599	587	45 (8%)
Intermediate dose	605	594	30 (5%)
Standard dose plus aspirin	282	278	21 (8%)
Therapeutic dose	49	49	7 (14%)
Weight > 120 kg			
Standard dose	11	9	0 (0%)
Intermediate dose	8	7	0 (0%)
Standard dose plus aspirin	1	1	0 (0%)
Therapeutic dose	1	1	0 (0%)

2.2.3.9 Aspirin

A subgroup analysis by whether a patient was taking aspirin at baseline (not taking aspirin, or taking aspirin) was undertaken using the ACS-ITT set. A summary of the primary outcome by subgroup and intervention is reported in Table 2.34.

Table 2.34: Summary of participant outcomes by whether patient was taking aspirin at baseline in the ACS-ITT set.

Anticoagulation intervention	Patients	Known	Primary outcome
Patient not taking aspirin			
Standard dose	590	576	39 (7%)
Intermediate dose	588	576	28 (5%)
Standard dose plus aspirin	281	277	20 (7%)
Therapeutic dose	47	47	7 (15%)
Patient taking aspirin			
Standard dose	20	20	6 (30%)
Intermediate dose	25	25	2 (8%)
Standard dose plus aspirin	2	2	1 (50%)
Therapeutic dose	3	3	0 (0%)

Table 2.35: Summary of odds ratios for treatment effects by by whether patient was taking aspirin at baseline in the ACS-ITT set.

Patient taking aspirin	Median	95% CrI	Mean (SD)	Pr(OR < 1)	Pr(OR > 1/1.1)
Intermediate					
No	0.65	(0.39, 1.05)	0.67 (0.17)	0.96	0.09
Yes	0.41	(0.10, 1.64)	0.52 (0.43)	0.90	0.13
Standard plus aspirin					
No	0.73	(0.40, 1.29)	0.76 (0.23)	0.86	0.22
Yes	1.13	(0.18, 6.81)	1.72 (1.90)	0.45	0.59
Therapeutic					
No	1.91	(0.70, 5.05)	2.15 (1.13)	0.10	0.93
Yes	1.31	(0.17, 9.35)	2.16 (2.86)	0.39	0.64

Table 2.36: Summary of odds ratio comparisons of treatment effects by whether patient was taking aspirin at baseline in the ACS-ITT set.

Patient taking aspirin	Median	95% CrI	Mean (SD)	Pr(OR < 1)
Intermediate				
No (ref)	1.00	(1.00, 1.00)	1.00 (0.00)	0.00
Yes	0.63	(0.15, 2.52)	0.81 (0.65)	0.74
Standard plus aspirin				
No (ref)	1.00	(1.00, 1.00)	1.00 (0.00)	0.00
Yes	1.55	(0.27, 8.75)	2.31 (2.43)	0.31
Therapeutic				
No (ref)	1.00	(1.00, 1.00)	1.00 (0.00)	0.00
Yes	0.68	(0.11, 4.11)	1.04 (1.15)	0.66

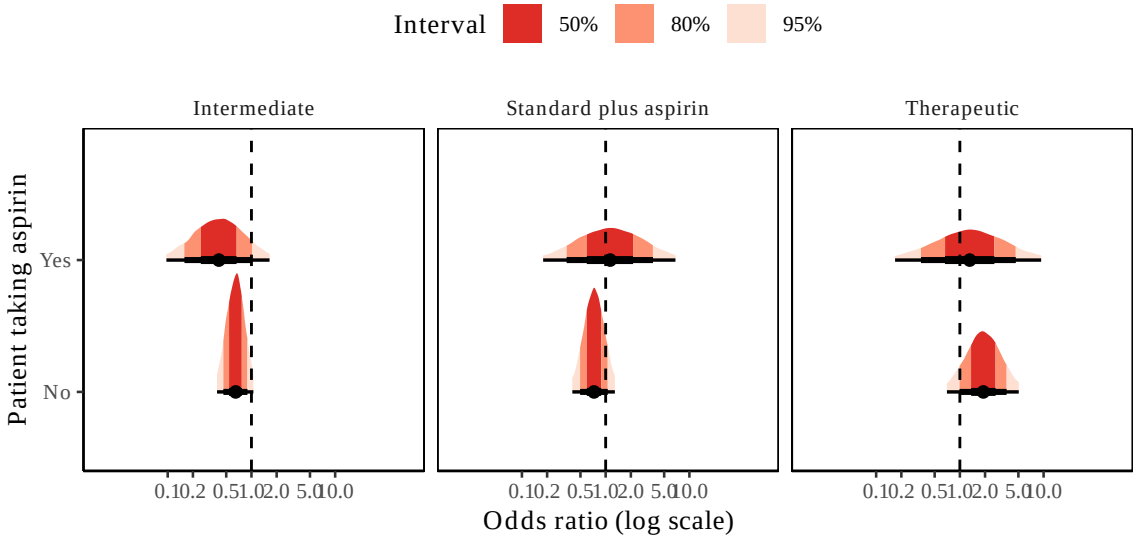

Figure 2.19: Posterior densities of odds ratio for anticoagulation interventions relative to standard dose by whether patient taking aspirin using ACS-ITT set.

2.2.3.10 Joint Model

2.2.4 Per-Protocol Analysis

The primary model was re-analysed using the ACS-PP set.

Table 2.37: Summary of primary composite outcome by treatment group for participants in ACS-PP.

n (%)	Standard dose	Intermediate dose	Standard dose plus aspirin	Therapeutic dose	Overall
Randomised	599	603	274	46	1522
Outcome missing	13 (2.2)	11 (1.8)	3 (1.1)	0 (0.0)	27 (1.8)
Outcome observed	586 (97.8)	592 (98.2)	271 (98.9)	46 (100.0)	1495 (98.2)
Met primary outcome	45 (7.7)	30 (5.1)	20 (7.4)	7 (15.2)	102 (6.8)

Table 2.38: Summary of model parameters (fixed-effects odds-ratios) for primary outcome model fit to the ACS-PP set.

Parameter	Median	95% CrI	Mean (SD)	Pr(OR < 1)
Intermediate	0.63	(0.38, 1.04)	0.65 (0.17)	0.96
Standard plus aspirin	0.69	(0.38, 1.25)	0.73 (0.23)	0.89
Therapeutic	2.19	(0.74, 6.00)	2.50 (1.42)	0.07
Ineligible aspirin	3.92	(1.22, 12.09)	4.62 (2.91)	0.01
Age 60+	1.94	(1.21, 3.08)	2.00 (0.48)	0.00
Australia/New Zealand	1.00	(0.21, 4.26)	1.31 (1.12)	0.50
Nepal	1.42	(0.37, 4.96)	1.74 (1.26)	0.30

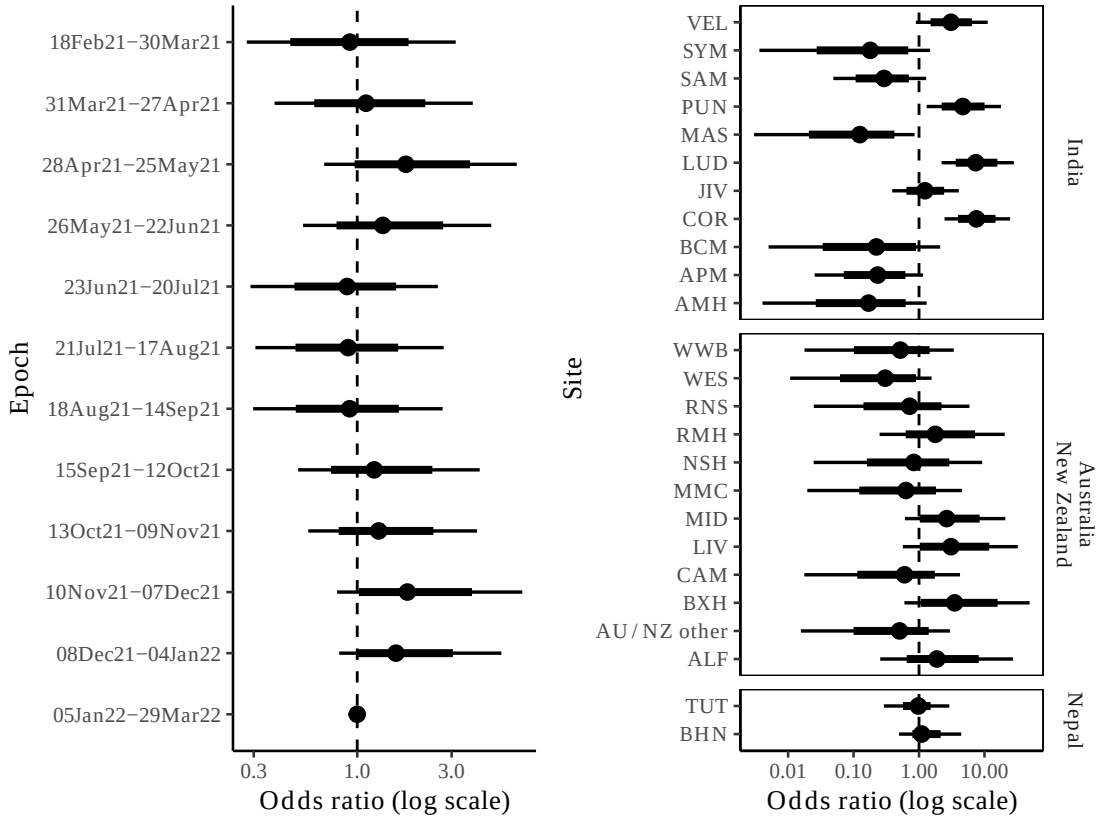

Figure 2.20: Posterior Summaries (point - median, block - 75% CrI, line - 95% CrI) of odds ratio for epoch and site effects for the primary outcome model fit to the ACS-PP set.

2.2.5 Sensitivity Analyses

2.2.5.1 Sensitivity: FAS-ITT

The primary model was fit to the expanded FAS-ITT set. The model treatment effects were similar to those obtained under the ACS-ITT set.

Table 2.39: Summary of model parameters (fixed-effects odds-ratios) for primary outcome model fit to the FAS-ITT set.

Parameter	Median	95% CrI	Mean (SD)	Pr(OR < 1)
Intermediate	0.63	(0.38, 1.05)	0.65 (0.17)	0.96
Standard plus aspirin	0.73	(0.40, 1.31)	0.77 (0.23)	0.85
Therapeutic	1.87	(0.68, 4.96)	2.11 (1.14)	0.11
Intermediate vs Therapeutic	0.34	(0.12, 0.95)	0.39 (0.22)	0.98
Ineligible aspirin	3.45	(1.11, 10.19)	4.00 (2.39)	0.02
Age 60+	1.95	(1.24, 3.08)	2.01 (0.47)	0.00
Australia/New Zealand	1.01	(0.23, 4.08)	1.30 (1.05)	0.49
Nepal	1.54	(0.38, 5.42)	1.89 (1.42)	0.26

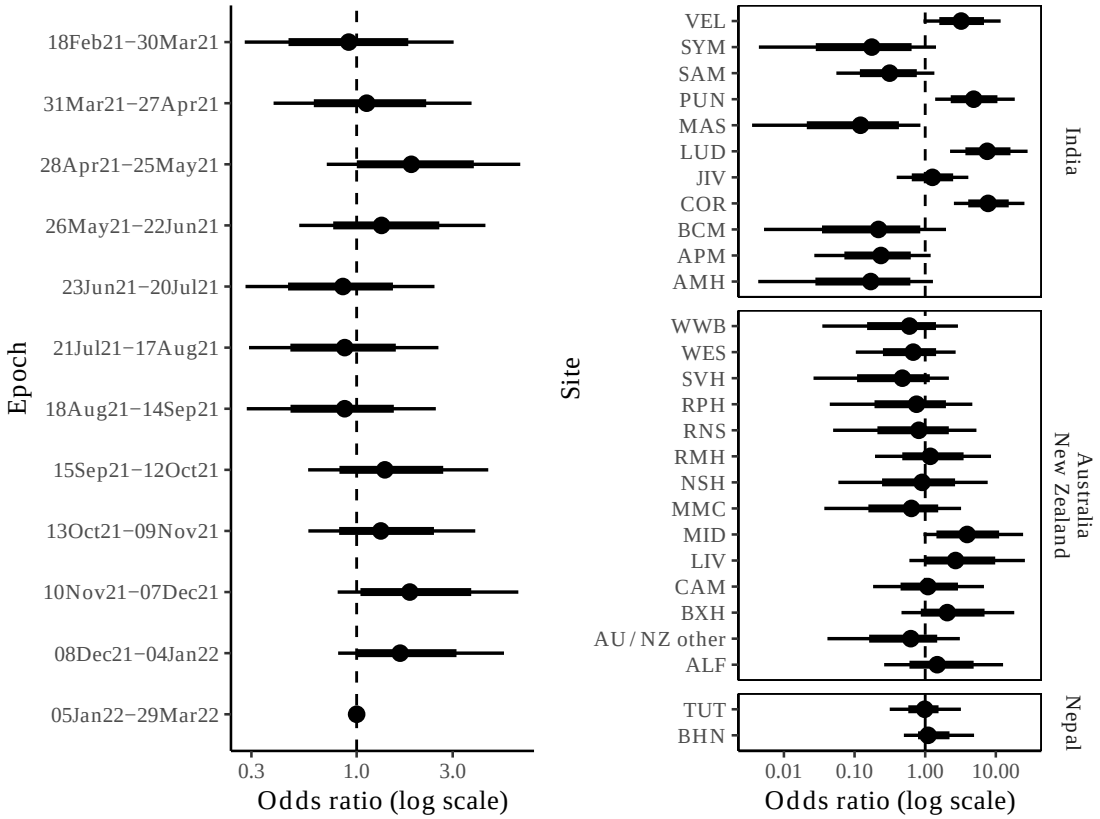

Figure 2.21: Posterior Summaries (point - median, block - 75% CrI, line - 95% CrI) of odds ratio for epoch and site effects for the primary outcome model fit to the FAS-ITT set.

2.2.5.2 Sensitivity: Concurrent Randomisations

In the following section, analyses are undertaken where the analysis set is restricted to participants who were randomised concurrently amongst the interventions of interest. Three sets are considered, one for each intervention. Given that the intermediate and standard dose interventions were available the entire time the anticoagulation domain was open, that analysis set is restricted to only participants randomised to one of those interventions. The other sets are determined by either a patients calendar time of randomisation or the protocol version under which they were enrolled. Given that RAR was not activated in the domain, the epoch terms are removed from these models as the intervention availability is the only factor varying the allocation probabilities. Additionally, due to smaller sample sizes, site terms and antiviral intervention terms have been dropped from the models. For the definitions of the analysis sets, refer to Section 2.1.2.

2.2.5.2.1 Intermediate dose

- **Model**: logistic regression
- **Terms**: anticoagulation intervention, age group, country
- **Set**: ACS-ITT-intermediate

Table 2.40: Summary of primary composite outcome by treatment group for participants in ACS-ITT-intermediate

n (%)	Standard dose	Intermediate dose	Overall
Randomised	610	613	1223
Outcome missing	14 (2.3)	12 (2.0)	26 (2.1)
Outcome observed	596 (97.7)	601 (98.0)	1197 (97.9)
Met primary outcome	45 (7.6)	30 (5.0)	75 (6.3)

Table 2.41: Summary of model parameters (fixed-effects odds-ratios) for primary outcome model fit to the ACS-ITT-intermediate set.

Parameter	Median	95% CrI	Mean (SD)	Pr(OR < 1)
Intermediate dose	0.63	(0.39, 1.01)	0.65 (0.16)	0.97
Age 60+	2.27	(1.41, 3.65)	2.34 (0.57)	0.00
Australia/New Zealand	1.09	(0.50, 2.13)	1.15 (0.42)	0.41
Nepal	0.83	(0.33, 1.81)	0.89 (0.39)	0.67

2.2.5.2.2 Standard dose plus aspirin

- **Model**: logistic regression
- **Terms**: anticoagulation intervention, age group, country
- **Set**: ACS-ITT-aspirin

A summary of the number of participants randomised and the number meeting the primary outcome are reported in Table 2.42, noting that 35 participants were ineligible for the standard dose plus aspirin intervention. The model parameter summaries are reported in Table 2.43.

Table 2.42: Summary of primary composite outcome by treatment group for participants in ACS-ITT-aspirin.

n (%)	Standard dose	Intermediate dose	Standard dose plus aspirin	Overall
Randomised	299	298	283	880
Outcome missing	7 (2.3)	5 (1.7)	4 (1.4)	16 (1.8)
Outcome observed	292 (97.7)	293 (98.3)	279 (98.6)	864 (98.2)
Met primary outcome	24 (8.2)	18 (6.1)	21 (7.5)	63 (7.3)

Table 2.43: Summary of model parameters (fixed-effects odds-ratios) for primary outcome model fit to the ACS-ITT-aspirin set.

Parameter	Median	95% CrI	Mean (SD)	Pr(OR < 1)
Intermediate dose	0.74	(0.39, 1.37)	0.77 (0.25)	0.83
Standard dose plus aspirin	0.85	(0.46, 1.54)	0.89 (0.28)	0.70
Age 60+	1.73	(1.01, 2.91)	1.79 (0.49)	0.02
Australia/New Zealand	0.29	(0.06, 0.99)	0.35 (0.25)	0.98

2.2.5.2.3 Therapeutic dose

- **Model**: logistic regression
- **Terms**: anticoagulation intervention, age group, country
- **Set**: ACS-ITT-therapeutic

Table 2.44: Summary of primary composite outcome by treatment group for participants in ACS-ITT-therapeutic.

n (%)	Standard dose	Intermediate dose	Therapeutic dose	Overall
Randomised	79	65	50	194
Outcome missing	4 (5.1)	3 (4.6)	0 (0.0)	7 (3.6)
Outcome observed	75 (94.9)	62 (95.4)	50 (100.0)	187 (96.4)
Met primary outcome	6 (8.0)	3 (4.8)	7 (14.0)	16 (8.6)

Table 2.45: Summary of model parameters (fixed-effects odds-ratios) for primary outcome model fit to the ACS-ITT-therapeutic set.

Parameter	Median	95% CrI	Mean (SD)	Pr(OR < 1)
Intermediate dose	0.65	(0.18, 2.25)	0.80 (0.57)	0.75
Therapeutic dose	1.63	(0.54, 5.07)	1.93 (1.20)	0.19
Age 60+	1.88	(0.66, 5.45)	2.18 (1.27)	0.12
India	0.39	(0.08, 1.62)	0.51 (0.41)	0.90
Australia/New Zealand	1.05	(0.37, 2.84)	1.19 (0.65)	0.46

2.2.5.3 Sensitivity: Missing meet primary outcome

In this analysis, patients with missing primary outcome data were assumed to have satisfied the primary outcome.

Table 2.46: Summary of primary composite outcome by treatment group for participants in ACS-ITT set assuming patients with missing outcomes met the primary outcome.

n (%)	Standard dose	Intermediate dose	Standard dose plus aspirin	Therapeutic dose	Overall
Randomised	610	613	283	50	1556
Outcome missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Outcome observed	610 (100.0)	613 (100.0)	283 (100.0)	50 (100.0)	1556 (100.0)
Met primary outcome	59 (9.7)	42 (6.9)	25 (8.8)	7 (14.0)	133 (8.5)

Table 2.47: Summary of model parameters (fixed-effects odds-ratios) for primary outcome model fit to the ACS-ITT set assuming patients with missing data met the primary outcome.

Parameter	Median	95% CrI	Mean (SD)	Pr(OR < 1)
Intermediate	0.65	(0.42, 1.01)	0.67 (0.15)	0.97
Standard plus aspirin	0.69	(0.40, 1.17)	0.72 (0.20)	0.91
Therapeutic	1.23	(0.48, 3.09)	1.38 (0.69)	0.33
Intermediate vs Therapeutic	0.53	(0.20, 1.41)	0.60 (0.32)	0.90
Ineligible aspirin	2.01	(0.66, 5.70)	2.31 (1.35)	0.11
Age 60+	1.74	(1.14, 2.63)	1.78 (0.38)	0.00
Australia/New Zealand	2.15	(0.50, 8.22)	2.72 (2.13)	0.14
Nepal	1.46	(0.37, 5.01)	1.78 (1.26)	0.27

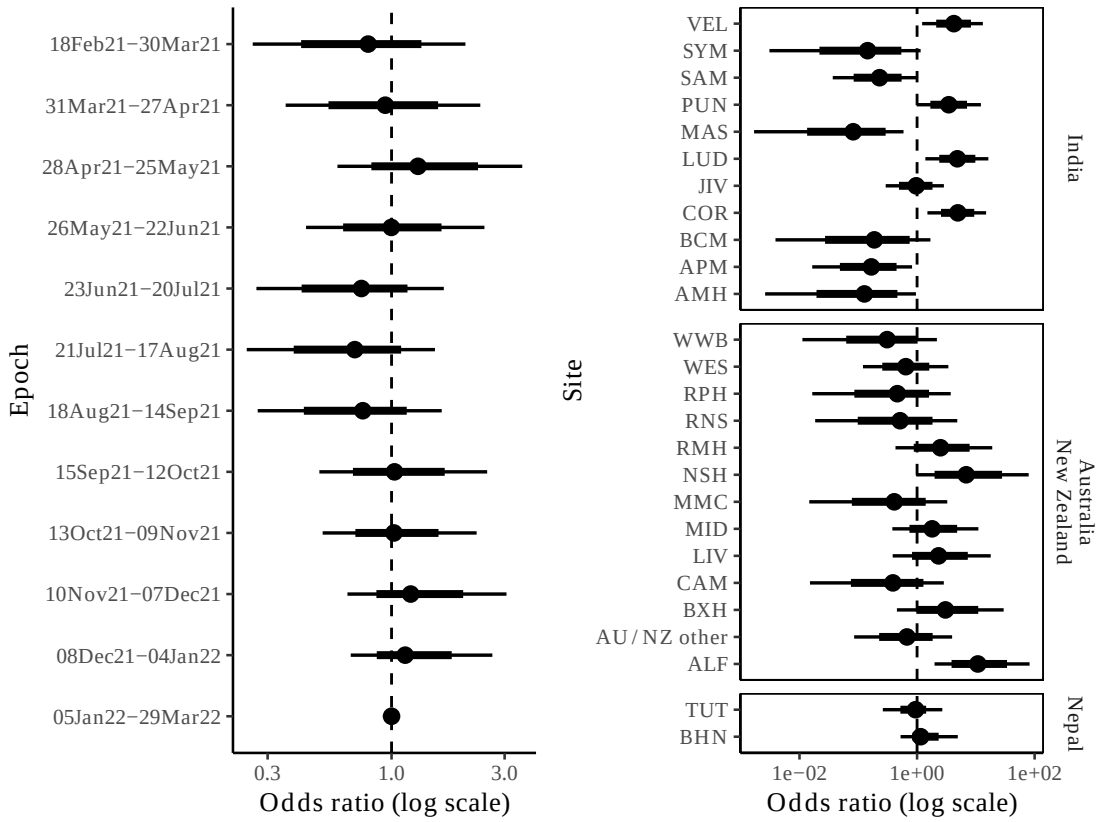

Figure 2.22: Posterior Summaries (point - median, block - 75% CrI, line - 95% CrI) of odds ratio for epoch and site effects for the primary model fit to the ACS-ITT set assuming patients with missing data met the primary outcome.

2.2.5.4 Sensitivity: Missing do not meet primary outcome

In this analysis, patients with missing primary outcome data were assumed to have not satisfied the primary outcome conditions.

Table 2.48: Summary of primary composite outcome by treatment group for participants in ACS-ITT set assuming patients with missing outcomes did not meet the primary outcome.

n (%)	Standard dose	Intermediate dose	Standard dose plus aspirin	Therapeutic dose	Overall
Randomised	610	613	283	50	1556
Outcome missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Outcome observed	610 (100.0)	613 (100.0)	283 (100.0)	50 (100.0)	1556 (100.0)
Met primary outcome	45 (7.4)	30 (4.9)	21 (7.4)	7 (14.0)	103 (6.6)

Table 2.49: Summary of model parameters (fixed-effects odds-ratios) for primary model fit to the ACS-ITT set assuming patients with missing data did not meet the primary outcome.

Parameter	Median	95% CrI	Mean (SD)	Pr(OR < 1)
Intermediate	0.64	(0.38, 1.07)	0.66 (0.17)	0.96
Standard plus aspirin	0.75	(0.41, 1.35)	0.78 (0.24)	0.83
Therapeutic	2.02	(0.72, 5.43)	2.30 (1.26)	0.09
Intermediate vs Therapeutic	0.32	(0.11, 0.91)	0.37 (0.21)	0.98
Ineligible aspirin	4.56	(1.41, 13.62)	5.30 (3.28)	0.01
Age 60+	1.94	(1.21, 3.07)	1.99 (0.48)	0.00
Australia/New Zealand	0.89	(0.20, 3.64)	1.15 (0.96)	0.56
Nepal	1.52	(0.39, 5.25)	1.85 (1.37)	0.27

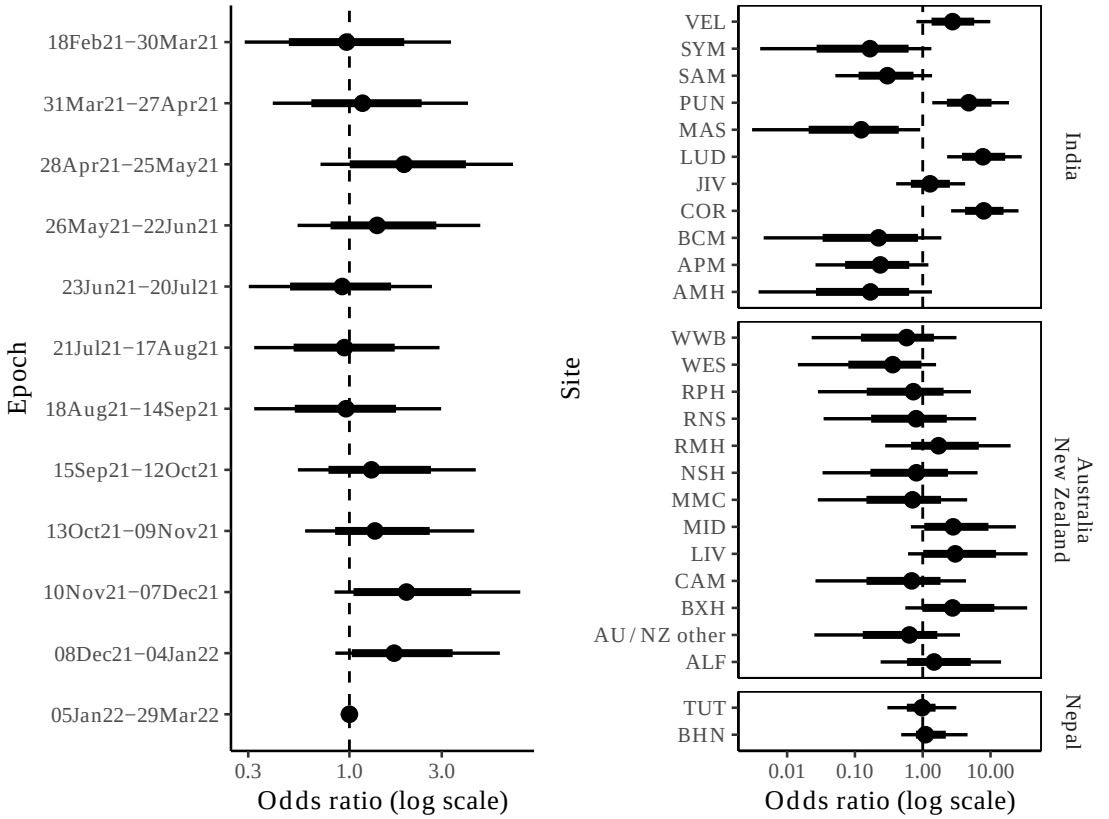

Figure 2.23: Posterior Summaries (point - median, block - 75% CrI, line - 95% CrI) of odds ratio for epoch and site effects for the primary outcome model fit to the ACS-ITT set assuming patients with missing data did not meet the primary outcome.

2.2.6 Post-hoc Sensitivity Analyses

The following sections report on other post-hoc analyses which were undertaken, but not explicitly specified in the SAP. These include simplifications of the model by dropping the site and epoch terms, and alteration of the model priors.

2.2.6.1 Prior Sensitivity - Treatment Contrasts

The primary analysis model encodes the prior in terms of orthonormal contrasts. As a check of prior sensitivity, the primary model was re-fit with priors specified in terms of the more usual treatment contrasts.

Table 2.50: Summary of model parameters (fixed-effects odds-ratios) for primary model fit to the ACS-ITT set with priors on treatment conrasts.

Parameter	Median	95% CrI	Mean (SD)	Pr(OR < 1)
Intermediate	0.62	(0.38, 1.01)	0.64 (0.16)	0.97
Standard plus aspirin	0.72	(0.40, 1.27)	0.75 (0.22)	0.87
Therapeutic	1.82	(0.69, 4.73)	2.05 (1.06)	0.11
Intermediate vs Therapeutic	0.34	(0.12, 0.93)	0.39 (0.22)	0.98
Ineligible aspirin	3.89	(1.27, 11.71)	4.55 (2.78)	0.01
Age 60+	1.96	(1.23, 3.13)	2.02 (0.49)	0.00
Australia/New Zealand	1.08	(0.24, 4.41)	1.40 (1.20)	0.46
Nepal	1.47	(0.37, 5.21)	1.81 (1.36)	0.28

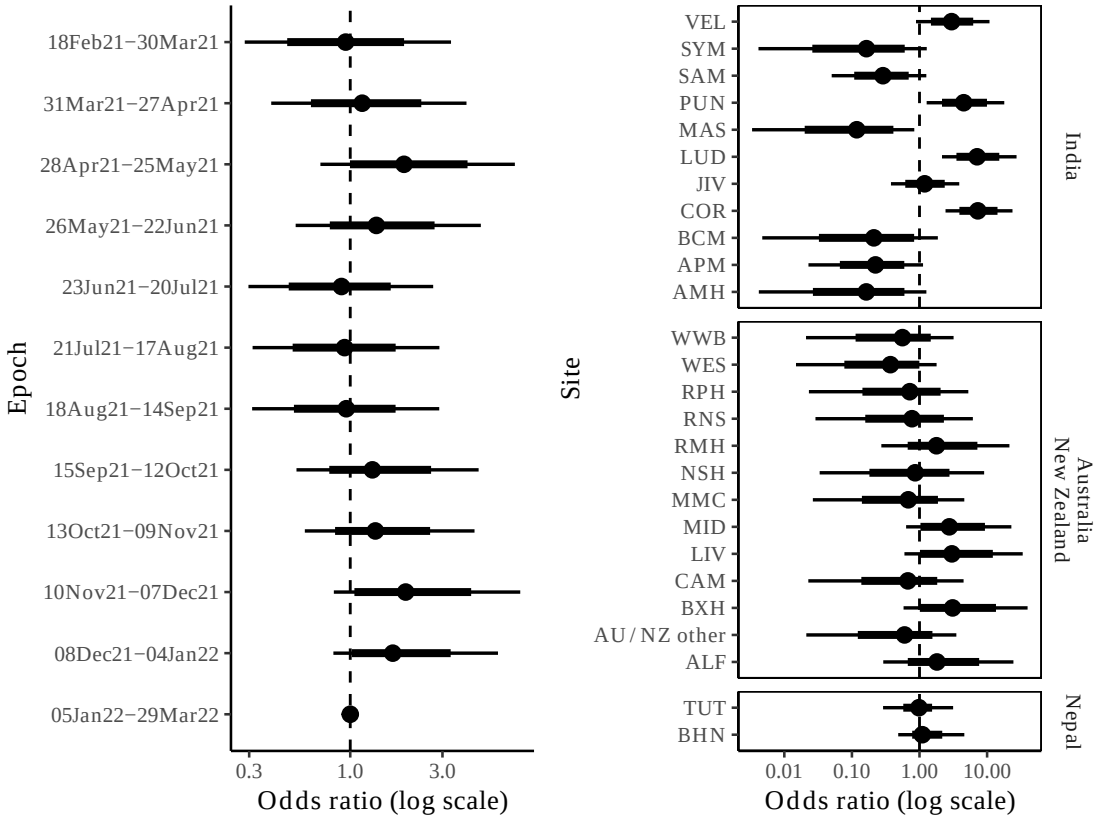

Figure 2.24: Posterior Summaries (point - median, block - 0.75 CrI, line - 0.95 CrI) of odds ratio for epoch and site effects for the primary model fit to the ACS-ITT set with priors on treatment conrasts.

2.3 Secondary Outcomes

For all secondary outcomes, the primary model (adjusting for interventions, age group, country, site, and epoch using the relevant outcome model) was fit to the ACS-ITT set. The only sensitivity analysis conducted was to repeat the analyses restricted to contemporaneous controls using a reduced model.

2.3.1 Time to clinical recovery to day 28

This section reports on the analysis for time to clinical recovery. Time to clinical recovery was taken as the first day from the index admission at which the patient had a WHO outcome score of 3 or less. For participants whose WHO outcome score was greater than 3 on the day of discharge, their day of recovery was counted as the first day after discharge, e.g. if discharged on day 7 with a daily WHO score of 4, then time to recovery was quantified as 8. Death was treated as a competing-risk to recovery. If recovery and death reportedly occurred on the same day (e.g. daily status WHO scale < 4 but discharge outcome of death on same day), then the patient was considered to have died on that day without recovery. No adjustment was made for participants who recovered but then subsequently died (i.e. only the first event was considered; any such patients were just counted as recovered on the relevant day). No allowance was made for participants who discharged against medical advice (treated as recovered following discharge).

The analysis of the time to clinical recovery to day 28 outcome used a discrete-time competing risk time-to-event model (multinomial logistic regression). The events of interest were death or recovery. Baseline cause-specific hazards were modelled separately for death and recovery with some smoothing enforced across adjacent time points via a first order random walk prior on the logit intercept terms.

- **Model**: multinomial logistic regression
- **Terms**: anticoagulation intervention, antiviral intervention, aspirin eligibility, age group, region, epoch
- **Set**: ACS-ITT

Table 2.51: Summary for time to recovery or death to day 28, ACS-ITT

Intervention	Randomised	Known	Died	Recovered	Unrecovered	TTR, Median (Q1, Q3)
Standard	610	610	15 (2.5)	592 (97.0)	3 (0.5)	6 (4.00, 7.00)
Intermediate	613	613	10 (1.6)	598 (97.6)	5 (0.8)	6 (4.00, 7.00)
Standard plus aspirin	283	283	9 (3.2)	271 (95.8)	3 (1.1)	6 (4.00, 8.00)
Therapeutic	50	50	4 (8.0)	46 (92.0)	0 (0.0)	6 (4.25, 9.00)

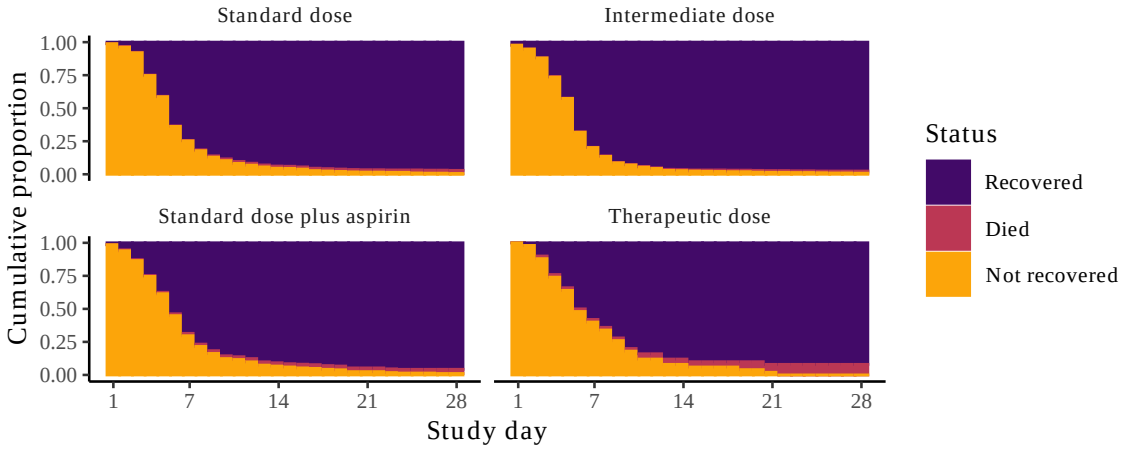

Figure 2.25: Observed progression of patients with respect to death and recovery, ACS-ITT.

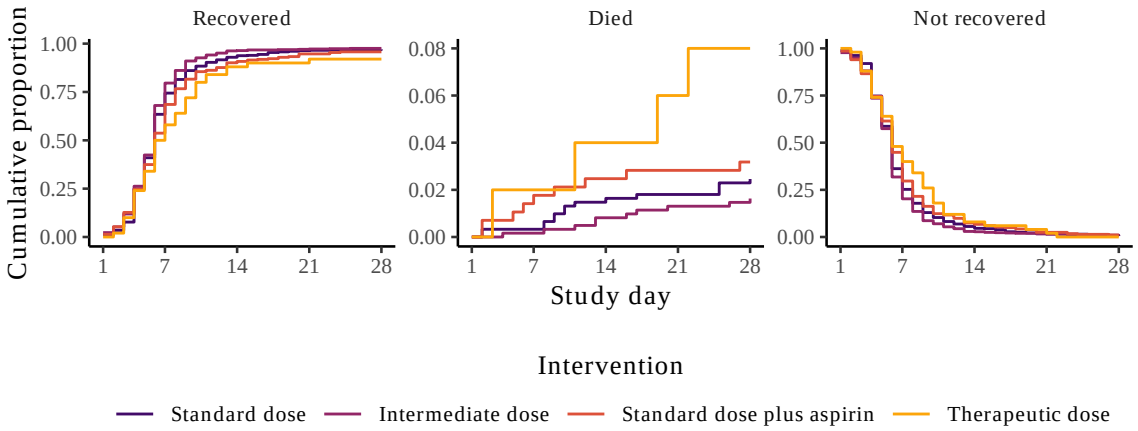

Figure 2.26: Observed progression of patients with respect to death and recovery, ACS-ITT.

Table 2.52: Posterior summary of cause-specific odds ratios for recovery or death to day 28, ACS-ITT.

Factor	Median	95% CrI	Mean (SD)	Pr(OR > 1)
Recovery				
Intermediate	1.13	(0.98, 1.29)	1.13 (0.08)	0.95
Standard plus aspirin	1.00	(0.84, 1.19)	1.00 (0.09)	0.50
Therapeutic	0.89	(0.61, 1.29)	0.90 (0.18)	0.27
Ineligible aspirin	0.77	(0.49, 1.17)	0.78 (0.17)	0.11
Age 60+	0.64	(0.56, 0.74)	0.65 (0.05)	0.00
Australia/New Zealand	0.72	(0.40, 1.27)	0.75 (0.23)	0.13
Nepal	0.68	(0.23, 2.54)	0.85 (0.68)	0.24
Death				
Intermediate	0.62	(0.26, 1.47)	0.69 (0.31)	0.14
Standard plus aspirin	0.92	(0.37, 2.18)	1.01 (0.47)	0.42
Therapeutic	2.96	(0.75, 11.08)	3.71 (2.82)	0.94
Ineligible aspirin	4.28	(1.06, 15.46)	5.32 (4.07)	0.98
Age 60+	0.89	(0.41, 1.91)	0.96 (0.39)	0.38
Australia/New Zealand	0.57	(0.12, 2.66)	0.77 (0.69)	0.23
Nepal	1.78	(0.38, 7.88)	2.37 (2.07)	0.78

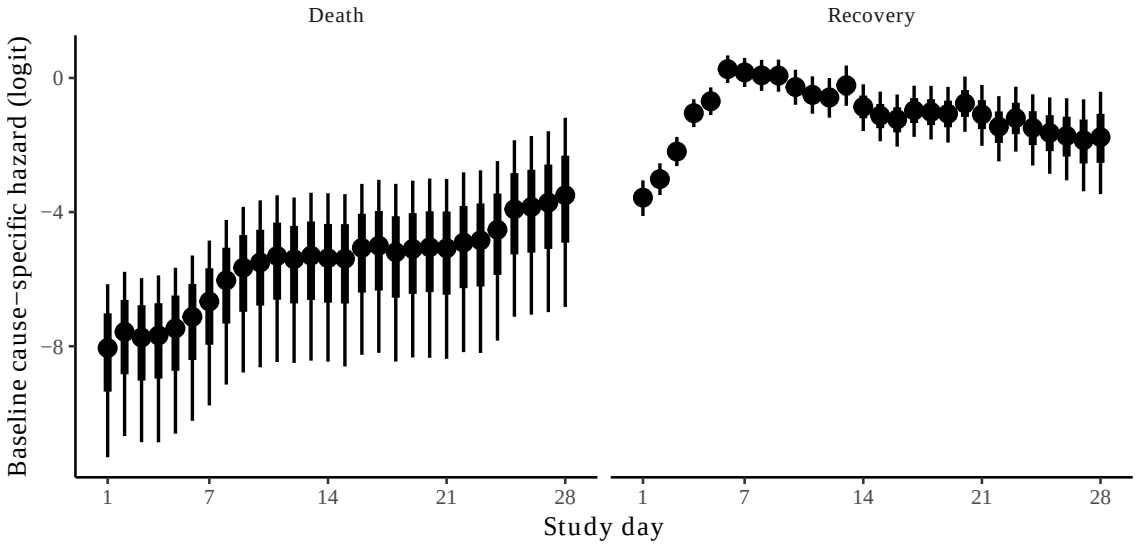

Figure 2.27: Cause-specific baseline hazard posterior summaries, ACS-ITT.

2.3.1.1 Sensitivity: Concurrent Enrolments

2.3.1.1.1 Intermediate dose

- **Model**: multinomial logistic regression
- **Terms**: anticoagulation intervention, age group, region
- **Set**: ACS-ITT-intermediate

Table 2.53: Summary for time to recovery or death to day 28, ACS-ITT-intermediate

Intervention	Randomised	Known	Died	Recovered	Unrecovered	TTR, Median (Q1, Q3)
Standard	610	610	15 (2.5)	592 (97.0)	3 (0.5)	6 (4.00, 7.00)
Intermediate	613	613	10 (1.6)	598 (97.6)	5 (0.8)	6 (4.00, 7.00)

Table 2.54: Posterior summary of cause-specific odds ratios for recovery or death to day 28, ACS-ITT-intermediate

Factor	Median	95% CrI	Mean (SD)	Pr(OR > 1)
Recovery				
Intermediate	1.14	(0.98, 1.32)	1.14 (0.09)	0.96
Age 60+	0.67	(0.57, 0.78)	0.67 (0.05)	0.00
Australia/New Zealand	0.70	(0.58, 0.86)	0.71 (0.08)	0.00
Nepal	0.68	(0.54, 0.85)	0.69 (0.08)	0.00
Death				
Intermediate	0.86	(0.38, 1.88)	0.91 (0.37)	0.34
Age 60+	1.07	(0.47, 2.44)	1.15 (0.51)	0.55
Australia/New Zealand	0.34	(0.09, 0.99)	0.39 (0.24)	0.02
Nepal	0.60	(0.18, 1.59)	0.68 (0.39)	0.18

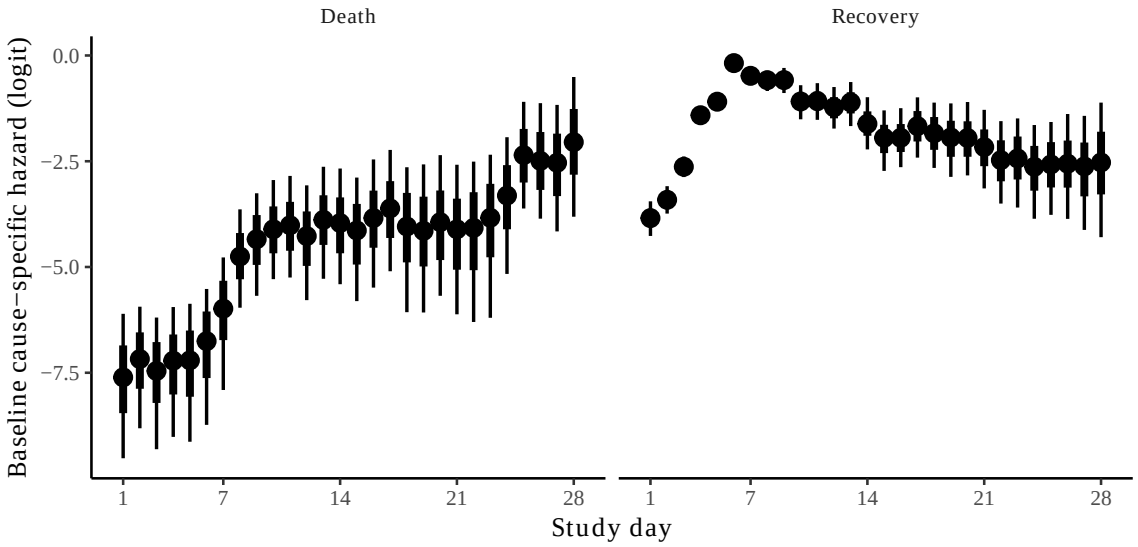

Figure 2.28: Cause-specific baseline hazard posterior summaries, ACS-ITT-intermediate.

2.3.1.1.2 Standard plus aspirin

- **Model**: multinomial logistic regression
- **Terms**: anticoagulation intervention, age group, region
- **Set**: ACS-ITT-aspirin

Table 2.55: Summary for recovery or death to day 28, ACS-ITT-aspirin

Intervention	Randomised	Known	Died	Recovered	Unrecovered	TTR, Median (Q1, Q3)
Standard	299	299	10 (3.3)	286 (95.7)	3 (1.0)	6 (4.00, 8.00)
Intermediate	298	298	7 (2.3)	288 (96.6)	3 (1.0)	6 (4.00, 7.00)
Standard plus aspirin	283	283	9 (3.2)	271 (95.8)	3 (1.1)	6 (4.00, 8.00)

Table 2.56: Posterior summary of cause-specific odds ratios for recovery or death to day 28, ACS-ITT-aspirin.

Factor	Median	95% CrI	Mean (SD)	Pr(OR > 1)
Recovery				
Intermediate	1.22	(1.01, 1.47)	1.22 (0.12)	0.98
Standard plus aspirin	1.02	(0.85, 1.23)	1.03 (0.10)	0.60
Age 60+	0.75	(0.63, 0.89)	0.75 (0.07)	0.00
Australia/New Zealand	1.04	(0.75, 1.42)	1.05 (0.17)	0.58
Death				
Intermediate	1.00	(0.38, 2.49)	1.11 (0.55)	0.50
Standard plus aspirin	0.93	(0.38, 2.24)	1.02 (0.48)	0.43
Age 60+	1.40	(0.63, 3.16)	1.53 (0.66)	0.79
Australia/New Zealand	0.54	(0.10, 2.30)	0.71 (0.60)	0.22

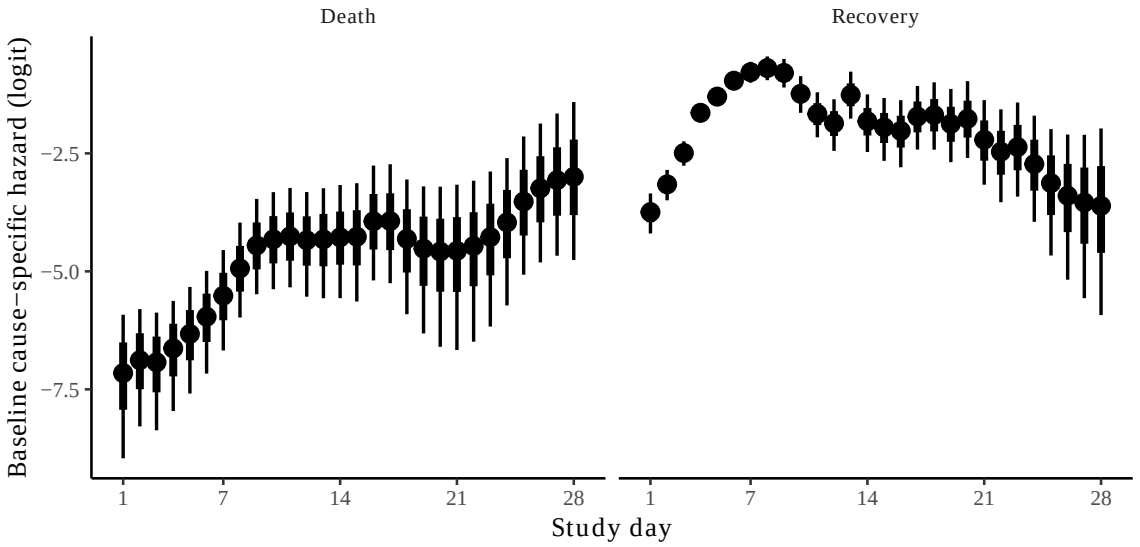

Figure 2.29: Cause-specific baseline hazard posterior summaries, ACS-ITT-aspirin.

2.3.1.1.3 Therapeutic

- **Model**: multinomial logistic regression
- **Terms**: anticoagulation intervention, age group, region
- **Set**: ACS-ITT-therapeutic

Table 2.57: Summary for recovery or death to day 28, ACS-ITT-therapeutic.

Intervention	Randomised	Known	Died	Recovered	Unrecovered	TTR, Median (Q1, Q3)
Standard	79	79	1 (1.3)	78 (98.7)	0 (0.0)	6 (4.25, 9.00)
Intermediate	65	65	1 (1.5)	63 (96.9)	1 (1.5)	6 (4.00, 9.00)
Therapeutic	50	50	4 (8.0)	46 (92.0)	0 (0.0)	6 (4.25, 9.00)

Table 2.58: Posterior summary of cause-specific odds ratios for recovery or death to day28, ACS-ITT-therapeutic

Factor	Median	95% CrI	Mean (SD)	Pr(OR > 1)
Recovery				
Intermediate	0.99	(0.67, 1.45)	1.01 (0.20)	0.47
Therapeutic	0.99	(0.65, 1.49)	1.01 (0.21)	0.47
Age 60+	0.47	(0.32, 0.68)	0.48 (0.09)	0.00
India	2.37	(1.27, 4.31)	2.47 (0.78)	1.00
Australia/New Zealand	1.22	(0.84, 1.76)	1.24 (0.23)	0.86
Death				
Intermediate	1.71	(0.24, 11.60)	2.76 (3.46)	0.70
Therapeutic	7.75	(1.36, 51.10)	12.26 (14.77)	0.99
Age 60+	0.10	(0.01, 0.95)	0.19 (0.35)	0.02
India	0.91	(0.13, 5.90)	1.43 (1.69)	0.46
Australia/New Zealand	0.33	(0.07, 1.43)	0.44 (0.38)	0.08

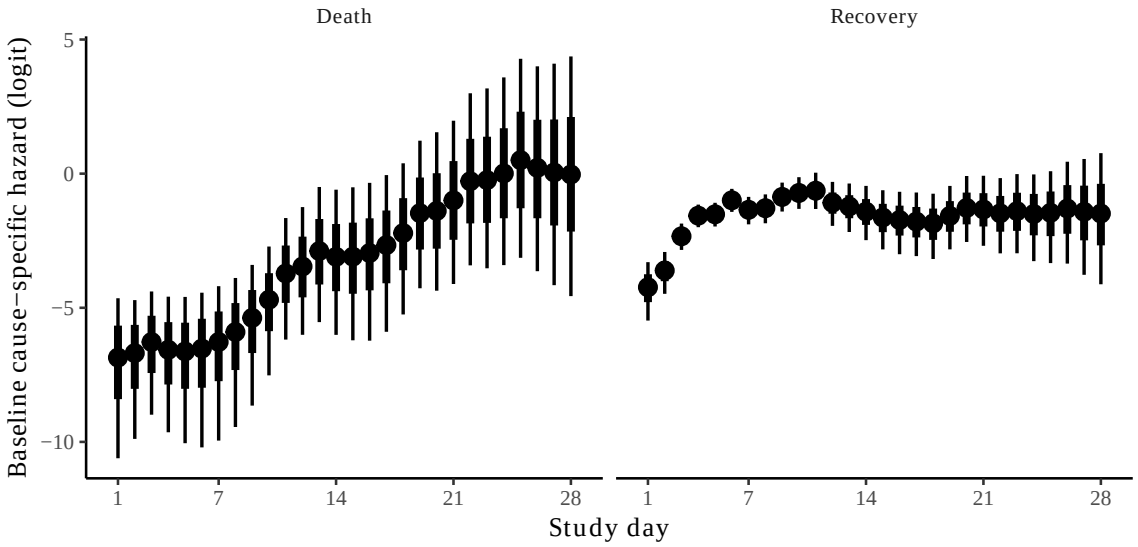

Figure 2.30: Cause-specific baseline hazard posterior summaries, ACS-ITT-therapeutic

2.3.2 WHO 8-point ordinal outcome scale at day 28

This section reports on the analysis of the secondary outcome: WHO outcome scale at day 28. The model is coded so that an odds ratio less than 1 implies a benefit (reduction in odds of having a higher WHO score at day 28).

- **Model**: cumulative logistic (ordinal) regression assuming proportional odds
- **Terms**: anticoagulation intervention, antiviral intervention, aspirin eligibility, age group, region, site nested within region, and epoch.
- **Set**: ACS-ITT

Table 2.59 presents the number of participants where the outcome was observed by the allocated anticoagulation arm. The model parameters (odds ratios) are summarised in Table 2.60 for the fixed-effect terms and in Figure 2.32 for the site and epoch specific terms.

Table 2.59: Summary of WHO scale at 28 by treatment group, ACS-ITT.

Anticoagulation intervention	Patients	Known	Deaths	Hospitalised	WHO, Median (Q1, Q3)
Standard dose	610	596	19 (3%)	15 (3%)	1 (1, 2)
Intermediate dose	613	603	15 (2%)	8 (1%)	1 (1, 2)
Standard dose plus aspirin	283	281	10 (4%)	9 (3%)	1 (1, 2)
Therapeutic dose	50	50	6 (12%)	2 (4%)	1 (1, 2)
Overall	**1556**	**1530**	**50 (3%)**	**34 (2%)**	**1 (1, 2)**

Table 2.60: Summary of model parameters (fixed-effects odds-ratios) for WHO outcome scale at day 28 outcome model fit to the ACS-ITT set.

Parameter	Median	95% CrI	Mean (SD)	Pr(OR < 1)
Intermediate	0.77	(0.59, 1.02)	0.78 (0.11)	0.97
Standard plus aspirin	0.79	(0.55, 1.11)	0.80 (0.14)	0.91
Therapeutic	1.55	(0.77, 3.10)	1.65 (0.60)	0.11
Ineligible aspirin	1.66	(0.76, 3.51)	1.78 (0.72)	0.10
Age 60+	2.31	(1.78, 3.01)	2.33 (0.31)	0.00
Australia/New Zealand	1.29	(0.43, 3.65)	1.48 (0.85)	0.32
Nepal	0.69	(0.23, 2.23)	0.82 (0.57)	0.75

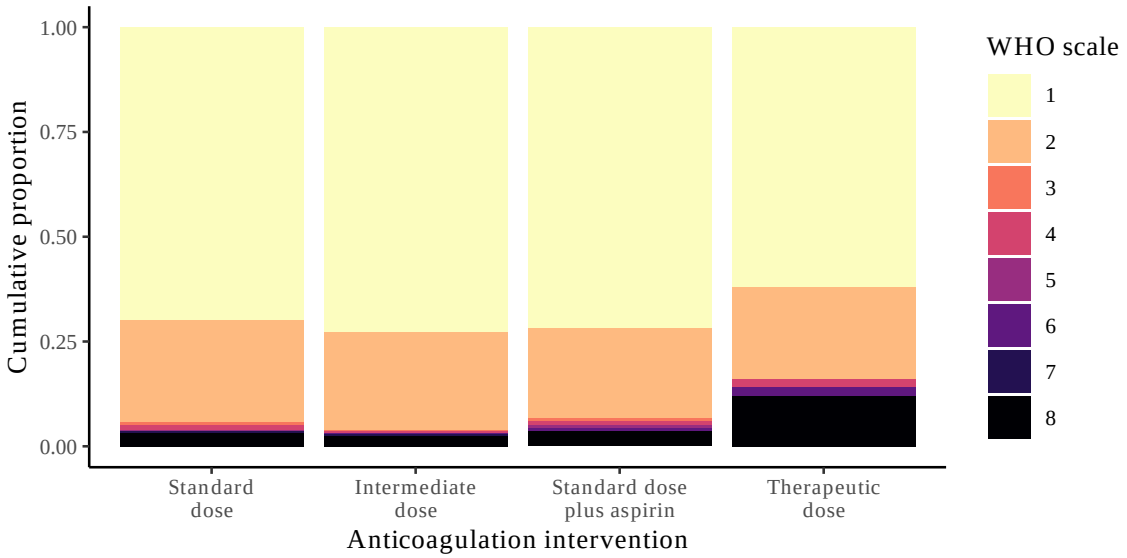

Figure 2.31: Observed distribution of WHO outcome scale at day 28 by treatment group, ACS-ITT.

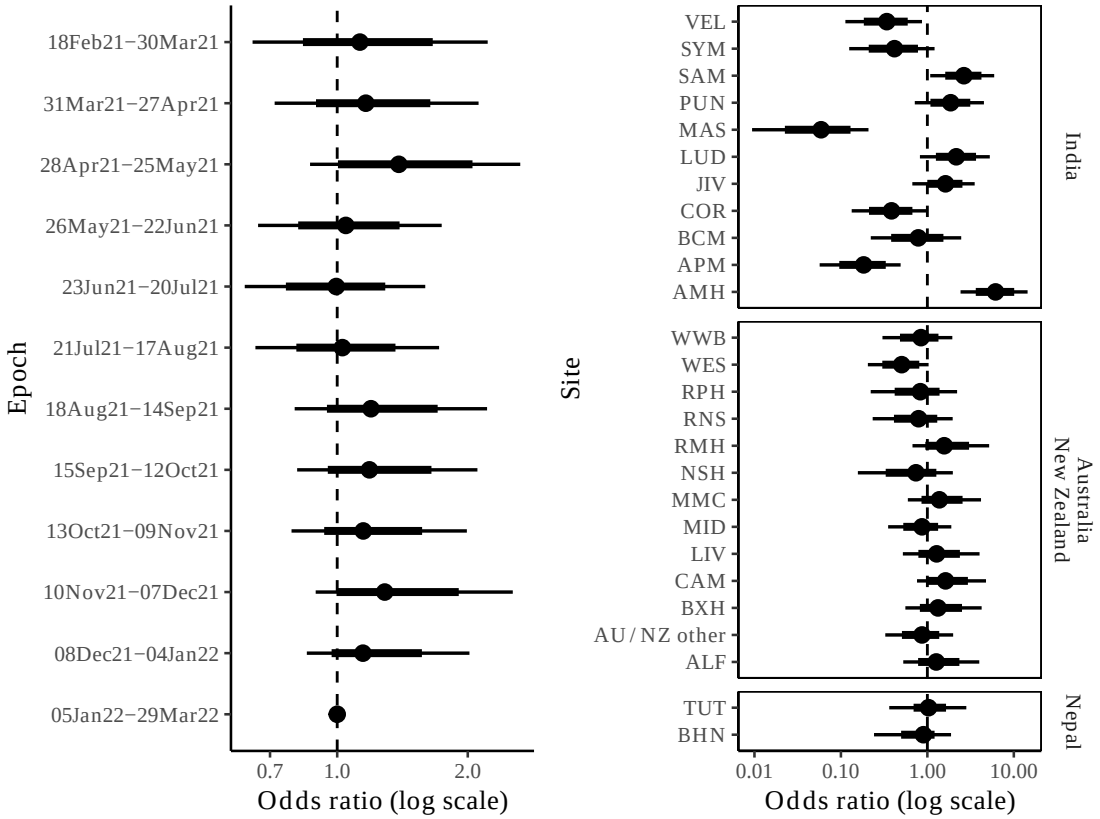

Figure 2.32: Posterior Summaries (point - median, block - 75% CrI, line - 95% CrI) of odds ratio for epoch and site effects on WHO outcome scale at day 28 for the outcome model fit to the ACS-ITT set.

2.3.2.1 Sensitivity: Concurrent Enrolments

2.3.2.1.1 Intermediate dose

- **Model**: cumulative logistic (ordinal) regression assuming proportional odds
- **Terms**: anticoagulation intervention, age group, region
- **Set**: ACS-ITT-intermediate

Table 2.61: Summary of WHO outcome scale at day 28 by treatment group, ACS-ITT-intermediate.

Anticoagulation intervention	Patients	Known	Deaths	Hospitalised	WHO, Median (Q1, Q3)
Standard dose	610	596	19 (3%)	15 (3%)	1 (1, 2)
Intermediate dose	613	603	15 (2%)	8 (1%)	1 (1, 2)
Overall	**1223**	**1199**	**34 (3%)**	**23 (2%)**	**1 (1, 2)**

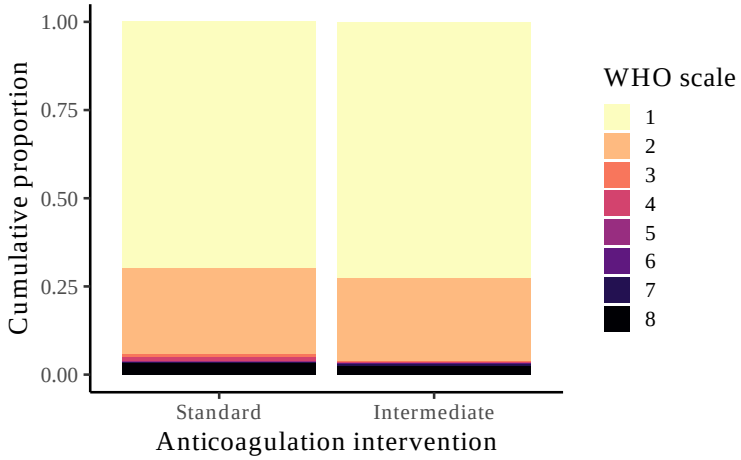

Figure 2.33: Observed distribution of WHO outcome scale at day 28 by treatment group, ACS-ITT-intermediate.

Table 2.62: Summary of model posterior odds ratios for WHO outcome scale at day 28 by treatment group, ACS-ITT-intermediate.

Parameter	Median	95% CrI	Mean (SD)	Pr(OR < 1)
Intermediate	0.80	(0.62, 1.03)	0.81 (0.10)	0.96
Age 60+	2.57	(1.97, 3.35)	2.60 (0.36)	0.00
Australia/New Zealand	2.05	(1.41, 2.96)	2.08 (0.40)	0.00
Nepal	0.54	(0.30, 0.93)	0.56 (0.16)	0.99

2.3.2.1.2 Standard dose plus aspirin

- **Model**: cumulative logistic (ordinal) regression assuming proportional odds
- **Terms**: anticoagulation intervention, age group, region
- **Set**: ACS-ITT-aspirin

Table 2.63: Summary of WHO outcome scale at day 28 by treatment group, ACS-ITT-aspirin.

Anticoagulation intervention	Patients	Known	Deaths	Hospitalised	WHO, Median (Q1, Q3)
Standard dose	299	291	11 (4%)	8 (3%)	1 (1, 2)
Intermediate dose	298	293	12 (4%)	4 (1%)	1 (1, 2)
Standard dose plus aspirin	283	281	10 (4%)	9 (3%)	1 (1, 2)
Overall	**880**	**865**	**33 (4%)**	**21 (2%)**	**1 (1, 2)**

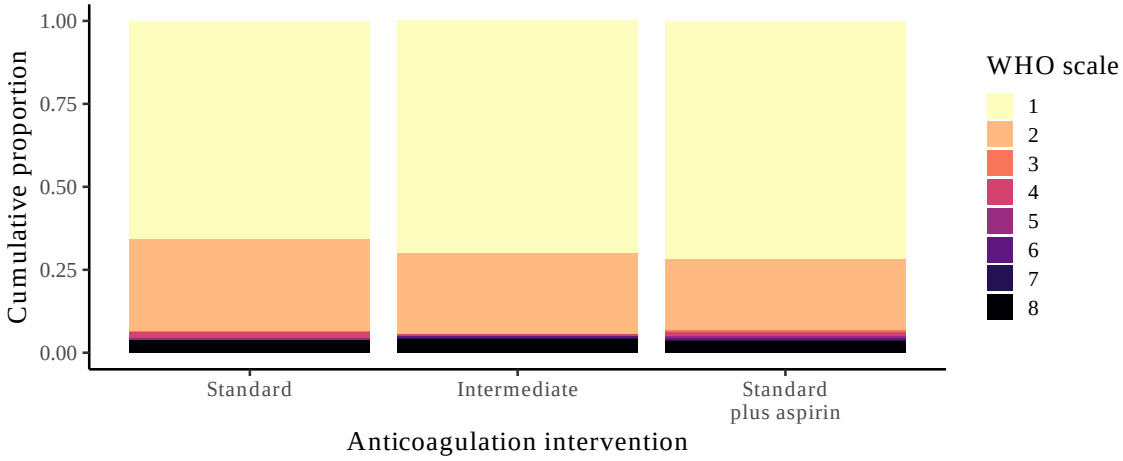

Figure 2.34: Observed distribution of WHO outcome scale at day 28 by treatment group, ACS-ITT-aspirin.

Table 2.64: Summary of model posterior odds ratios for WHO outcome scale at day 28 by treatment group, ACS-ITT-aspirin.

Parameter	Median	95% CrI	Mean (SD)	Pr(OR < 1)
Intermediate	0.85	(0.60, 1.20)	0.86 (0.15)	0.83
Standard plus aspirin	0.75	(0.53, 1.07)	0.76 (0.14)	0.94
Age 60+	2.06	(1.50, 2.81)	2.08 (0.33)	0.00
Australia/New Zealand	0.92	(0.49, 1.63)	0.96 (0.29)	0.61

2.3.2.1.3 Therapeutic dose

- **Model**: cumulative logistic (ordinal) regression assuming proportional odds
- **Terms**: anticoagulation intervention, age group, region
- **Set**: ACS-ITT-therapeutic

Note: the reference region was switched to Nepal for this model due to small numbers in India.

Table 2.65: Summary of WHO outcome scale at day 28 by treatment group, ACS-ITT-therapeutic.

Anticoagulation intervention	Patients	Known	Deaths	Hospitalised	WHO, Median (Q1, Q3)
Standard dose	79	75	3 (4%)	1 (1%)	1 (1, 2)
Intermediate dose	65	63	1 (2%)	1 (2%)	1 (1, 2)
Therapeutic dose	50	50	6 (12%)	2 (4%)	1 (1, 2)
Overall	**194**	**188**	**10 (5%)**	**4 (2%)**	**1 (1, 2)**

Table 2.66: Summary of model posterior odds ratios for WHO outcome scale at day 28 by treatment group, ACS-ITT-therapeutic.

Parameter	Median	95% CrI	Mean (SD)	Pr(OR < 1)
Intermediate	0.49	(0.23, 1.03)	0.53 (0.21)	0.97
Therapeutic	1.11	(0.52, 2.35)	1.20 (0.47)	0.39
Age 60+	3.20	(1.66, 6.36)	3.40 (1.21)	0.00
India	1.00	(0.36, 2.56)	1.11 (0.58)	0.50
Australia/New Zealand	3.90	(2.02, 7.57)	4.14 (1.44)	0.00

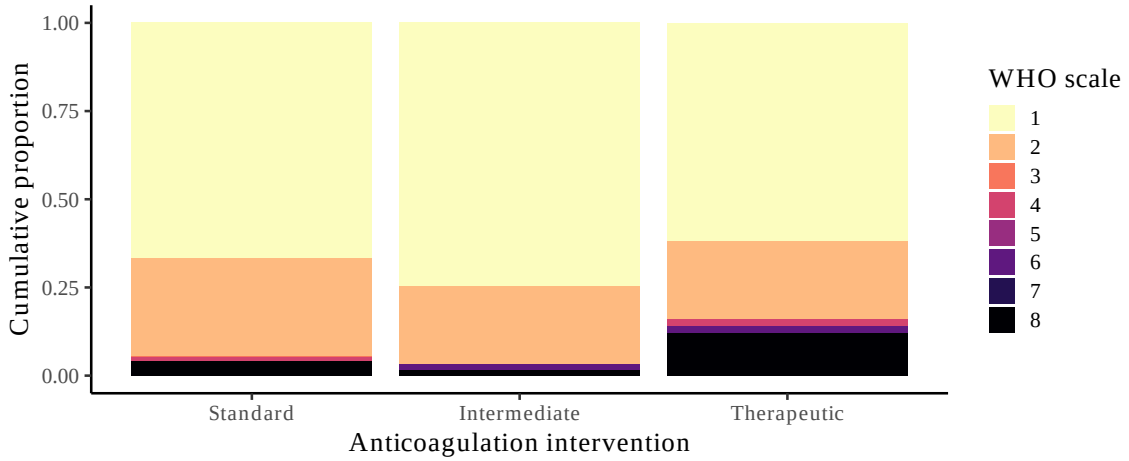

Figure 2.35: Observed distribution of WHO outcome scale at day 28 by treatment group, ACS-ITT-therapeutic.

2.3.3 All-cause mortality to day 28

This section reports on the analysis of the secondary outcome: all-cause mortality to day 28. For this outcome, participants who died within 28 days were coded to have a value of 1, and those who did not, to have a value of 0. The model is coded so that an odds ratio less than 1 implies a benefit (reduction in odds of death by day 28).

- **Model**: logistic regression
- **Terms**: anticoagulation intervention, antiviral intervention, aspirin eligibility, age group, region, site nested within region, and epoch.
- **Set**: ACS-ITT

Table 2.67 presents the number of participants where the outcome was observed by the allocated anticoagulation arm. The model parameters (odds ratios) are summarised in Table 2.68 for the fixed-effect terms and in Figure 2.36 for the site and epoch specific terms.

The proportion who had died by day 28 was 3.3% (50 / 1530) amongst all randomised participants. Compared with standard dose, the median adjusted odds ratios (95% CrI) from the primary model were: 0.84 (0.41, 1.67) for intermediate dose, 0.82 (0.36, 1.81) for standard dose plus aspirin, and 3.16 (0.95, 10.5) for therapeutic dose. The corresponding posterior probabilities for effectiveness were 0.69, 0.69 and 0.03 respectively.

Table 2.67: Summary of mortality by day 28 by treatment group, ACS-ITT.

n (%)	Patients	Known	Missing	Died by day 28
Low dose	610	596 (97.7)	14 (2.3)	19 (3.2)
Intermediate dose	613	603 (98.4)	10 (1.6)	15 (2.5)
Low dose with aspirin	283	281 (99.3)	2 (0.7)	10 (3.6)
Therapeutic dose	50	50 (100.0)	0 (0.0)	6 (12.0)
Overall	**1556**	**1530 (98.3)**	**26 (1.7)**	**50 (3.3)**

Table 2.68: Summary of model parameters (fixed-effects odds-ratios) for mortality by day 28 primary model fit to the ACS-ITT set.

Parameter	Median	95% CrI	Mean (SD)	Pr(OR < 1)
Intermediate	0.84	(0.42, 1.70)	0.89 (0.33)	0.69
Low with aspirin	0.82	(0.35, 1.84)	0.89 (0.39)	0.69
Therapeutic	3.17	(0.96, 10.05)	3.77 (2.43)	0.03
Ineligible aspirin	4.73	(1.23, 16.96)	5.82 (4.21)	0.01
Age 60+	2.08	(1.12, 3.86)	2.19 (0.72)	0.01
Australia/New Zealand	0.62	(0.13, 2.75)	0.82 (0.73)	0.73
Nepal	2.85	(0.57, 11.08)	3.61 (2.87)	0.09

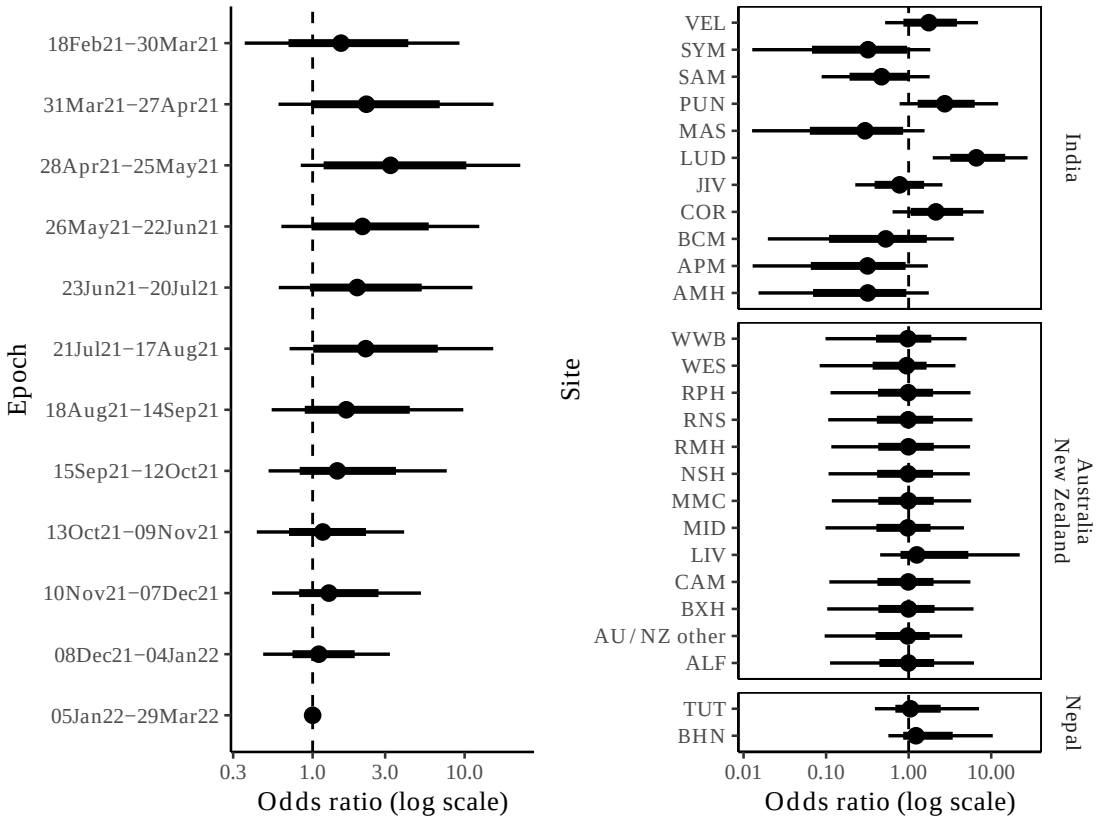

Figure 2.36: Posterior Summaries (point - median, block - 75% CrI, line - 95% CrI) of odds ratio for epoch and site effects on day 28 mortality for the primary model fit to the ACS-ITT set.

2.3.3.1 Sensitivity: Concurrent Enrolments

2.3.3.1.1 Intermediate dose

- **Model**: logistic regression
- **Terms**: anticoagulation intervention, age group, region
- **Set**: ACS-ITT-intermediate

Table 2.69: Summary of mortality to day 28 by treatment group, ACS-ITT-intermediate.

n (%)	Patients	Known	Missing	Died by day 28
Low dose	610	596 (97.7)	14 (2.3)	19 (3.2)
Intermediate dose	613	603 (98.4)	10 (1.6)	15 (2.5)
Overall	**1223**	**1199 (98.0)**	**24 (2.0)**	**34 (2.8)**

Table 2.70: Summary of posterior odds ratios for ACS-ITT-intermediate set.

Parameter	Median	95% CrI	Mean (SD)	Pr(OR < 1)
Intermediate	0.78	(0.40, 1.53)	0.83 (0.29)	0.76
Age 60+	2.83	(1.43, 5.60)	3.00 (1.07)	0.00
Australia/New Zealand	0.46	(0.12, 1.40)	0.54 (0.34)	0.90
Nepal	1.31	(0.45, 3.21)	1.44 (0.71)	0.29

2.3.3.1.2 Standard dose plus aspirin

- **Model**: logistic regression
- **Terms**: anticoagulation intervention, age group, region
- **Set**: ACS-ITT-aspirin

Table 2.71: Summary of mortality to day 28 by treatment group, ACS-ITT-aspirin.

n (%)	Patients	Known	Missing	Died by day 28
Low dose	299	291 (97.3)	8 (2.7)	11 (3.8)
Intermediate dose	298	293 (98.3)	5 (1.7)	12 (4.1)
Low dose with aspirin	283	281 (99.3)	2 (0.7)	10 (3.6)
Overall	**880**	**865 (98.3)**	**15 (1.7)**	**33 (3.8)**

Table 2.72: Summary of posterior odds ratios for ACS-ITT-aspirin set.

Parameter	Median	95% CrI	Mean (SD)	Pr(OR < 1)
Intermediate	1.09	(0.48, 2.48)	1.19 (0.53)	0.42
Low with aspirin	0.89	(0.38, 2.07)	0.97 (0.44)	0.61
Age 60+	2.45	(1.22, 4.87)	2.60 (0.95)	0.01
Australia/New Zealand	0.41	(0.08, 1.58)	0.52 (0.40)	0.89

2.3.3.1.3 Therapeutic dose

- **Model**: logistic regression
- **Terms**: anticoagulation intervention, age group, region
- **Set**: ACS-ITT-therapeutic

Note: the reference region was switched to Nepal for this model due to small numbers in India.

Table 2.73: Summary of mortality to day 28 by treatment group, ACS-ITT-therapeutic.

n (%)	Patients	Known	Missing	Died by day 28
Low dose	79	75 (94.9)	4 (5.1)	3 (4.0)
Intermediate dose	65	63 (96.9)	2 (3.1)	1 (1.6)
Therapeutic dose	50	50 (100.0)	0 (0.0)	6 (12.0)
Overall	**194**	**188 (96.9)**	**6 (3.1)**	**10 (5.3)**

Table 2.74: Summary of posterior odds ratios for ACS-ITT-therapeutic. set.

Parameter	Median	95% CrI	Mean (SD)	Pr(OR < 1)
Intermediate	0.66	(0.13, 3.11)	0.91 (0.86)	0.69
Therapeutic	2.64	(0.70, 10.68)	3.38 (2.75)	0.07
Age 60+	2.80	(0.78, 11.41)	3.60 (3.05)	0.06
India	0.42	(0.08, 1.81)	0.55 (0.46)	0.87
Australia/New Zealand	0.28	(0.06, 1.02)	0.35 (0.26)	0.97

2.3.4 Days alive and free of hospital to day 28

This section reports on the analysis of the secondary outcome: days alive and free of hospital (DAFH) to day 28. For this outcome, participants who died within 28 days were coded to have 0 DAFH. The model is coded so that an odds ratio greater than 1 implies a benefit (increased odds of more days alive and free of hospital).

- **Model**: cumulative logistic (ordinal) regression assuming proportional odds
- **Terms**: anticoagulation intervention, antiviral intervention, aspirin eligibility, age group, region, site nested within region, and epoch.
- **Set**: ACS-ITT

Table 2.75 presents the number of participants where the outcome was observed by the allocated anticoagulation arm. The observed distribution of DAFH by arm is shown in Figure 2.37, Figure 2.38, and Figure 2.39. The model parameters (odds ratios) are summarised in Table 2.76 for the fixed-effect terms and in Figure 2.40 for the site and epoch specific terms.

Table 2.75: Summary of days alive and free of hospital to day 28 by treatment group, ACS-ITT.

Anticoagulation intervention	Patients	Known	Deaths	DAFH, Median (Q1, Q3)
Low-dose	610	596	19 (3%)	23 (21, 24)
Intermediate-dose	613	603	15 (2%)	23 (21, 24)
Low-dose with aspirin	283	281	10 (4%)	22 (20, 24)
Therapeutic-dose	50	50	6 (12%)	22 (19, 24)
Overall	**1556**	**1530**	**50 (3%)**	**23 (21, 24)**

Table 2.76: Summary of model parameters (fixed-effects odds-ratios) for days alive and free of hospital to day 28 outcome model fit to the ACS-ITT set.

Parameter	Median	95% CrI	Mean (SD)	Pr(OR > 1)
Intermediate	1.14	(0.93, 1.39)	1.15 (0.12)	0.90
Low with aspirin	1.07	(0.82, 1.41)	1.08 (0.15)	0.69
Therapeutic	0.73	(0.40, 1.31)	0.76 (0.23)	0.14
Ineligible aspirin	1.07	(0.56, 2.04)	1.13 (0.39)	0.58
Age 60+	0.59	(0.48, 0.72)	0.59 (0.06)	0.00
AU/NZ	0.82	(0.36, 1.87)	0.89 (0.40)	0.31
NP	0.68	(0.22, 2.67)	0.87 (0.76)	0.26

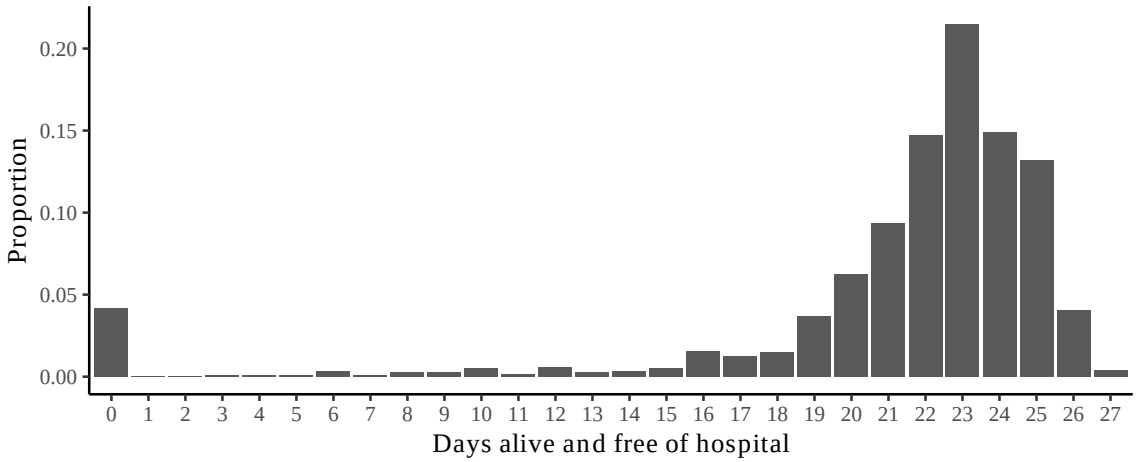

Figure 2.37: Observed overall distribution of days alive and free of hospital at day 28, ACS-ITT.

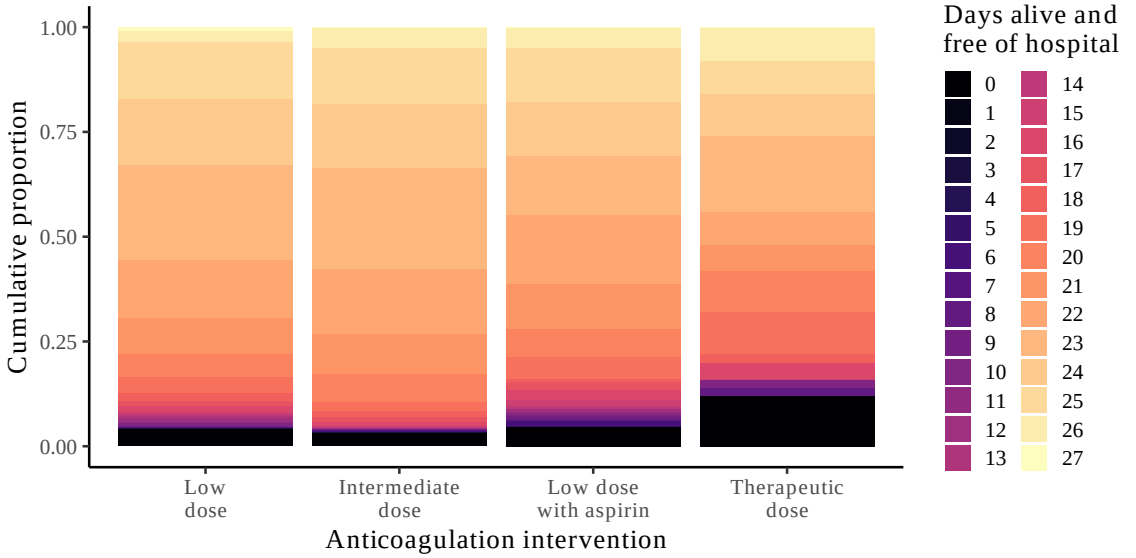

Figure 2.38: Observed distribution of days alive and free of hospital at day 28 by treatment group, ACS-ITT.

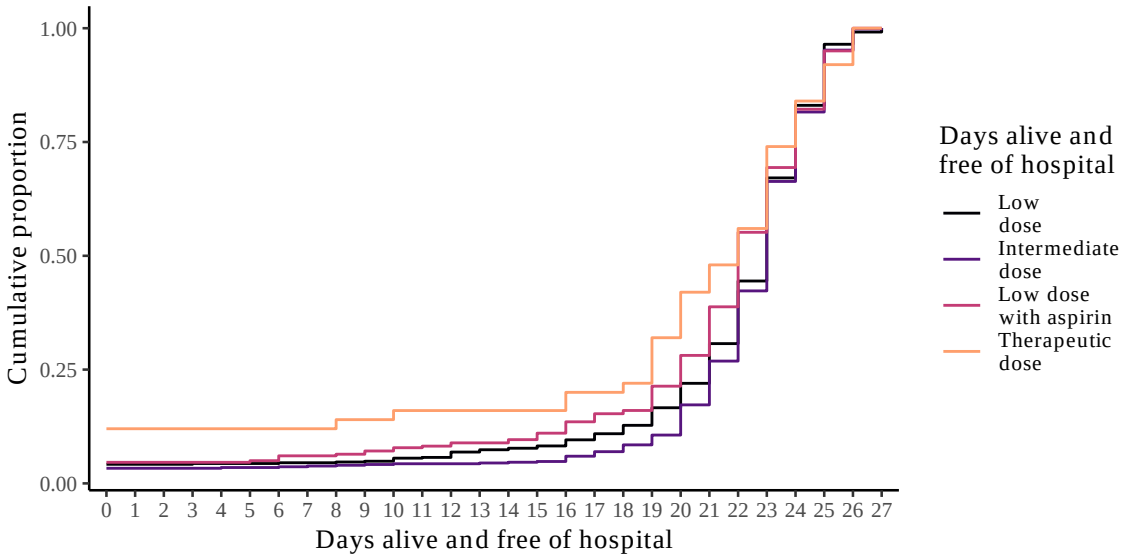

Figure 2.39: Observed cumulative distribution of days alive and free of hospital at day 28 by treatment group, ACS-ITT.

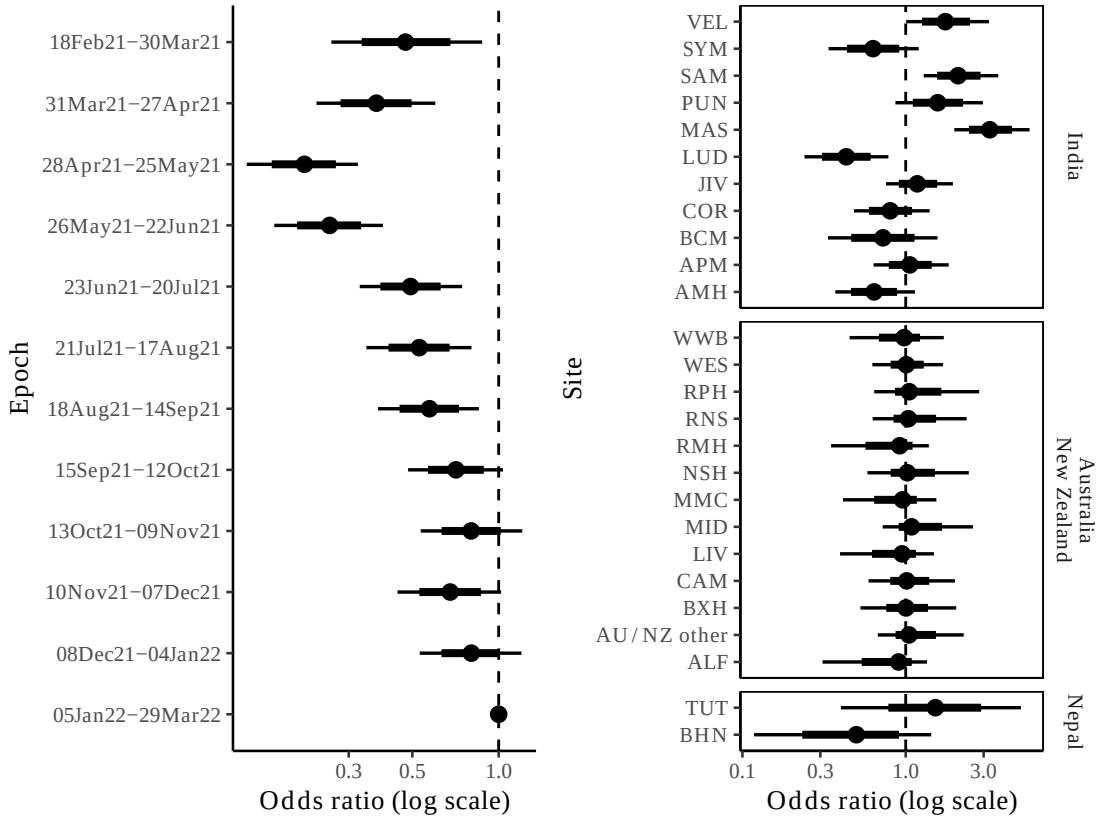

Figure 2.40: Posterior Summaries (point - median, block - 75% CrI, line - 95% CrI) of odds ratio for epoch and site effects on days alive and free of hospital to day 28 for the outcome model fit to the ACS-ITT set.

2.3.4.1 Sensitivity: Concurrent Enrolments

2.3.4.1.1 Intermediate dose

- **Model**: cumulative logistic (ordinal) regression assuming proportional odds
- **Terms**: anticoagulation intervention, age group, region
- **Set**: ACS-ITT-intermediate

Table 2.77: Summary of days alive and free of hospital to day 28 by treatment group, ACS-ITT-intermediate.

Anticoagulation intervention	Patients	Known	Deaths	DAFH, Median (Q1, Q3)
Low-dose	610	596	19 (3%)	23 (21, 24)
Intermediate-dose	613	603	15 (2%)	23 (21, 24)
Overall	**1223**	**1199**	**34 (3%)**	**23 (21, 24)**

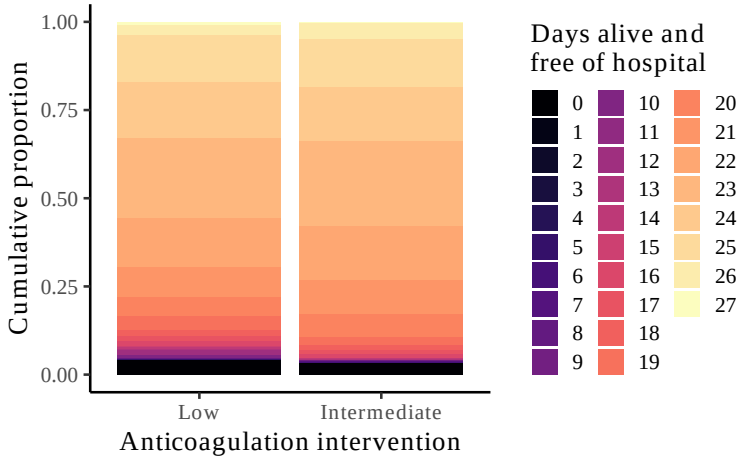

Figure 2.41: Observed distribution of days alive and free of hospital at day 28 by treatment group, ACS-ITT-intermediate.

Table 2.78: Summary of days alive and free of hospital to day 28 by treatment group, ACS-ITT-intermediate.

Parameter	Median	95% CrI	Mean (SD)	Pr(OR > 1)
Intermediate	0.72	(0.41, 1.27)	0.75 (0.22)	0.13
Low with aspirin	0.94	(0.58, 1.53)	0.97 (0.24)	0.40
Therapeutic	1.13	(0.79, 1.63)	1.15 (0.22)	0.74
Ineligible aspirin	1.07	(0.56, 2.05)	1.13 (0.39)	0.59
Age 60+	0.59	(0.48, 0.72)	0.59 (0.06)	0.00
AU/NZ	0.83	(0.36, 1.93)	0.91 (0.41)	0.33
NP	0.68	(0.22, 2.62)	0.86 (0.71)	0.26

2.3.4.1.2 Standard dose plus aspirin

- **Model**: cumulative logistic (ordinal) regression assuming proportional odds
- **Terms**: anticoagulation intervention, age group, region
- **Set**: ACS-ITT-aspirin

Table 2.79: Summary of days alive and free of hospital to day 28 by treatment group, ACS-ITT-aspirin.

Anticoagulation intervention	Patients	Known	Deaths	DAFH, Median (Q1, Q3)
Low-dose	299	291	11 (4%)	22 (20, 24)
Intermediate-dose	298	293	12 (4%)	22 (21, 24)
Low-dose with aspirin	283	281	10 (4%)	22 (20, 24)
Overall	**880**	**865**	**33 (4%)**	**22 (20, 24)**

Table 2.80: Summary of days alive and free of hospital to day 28 by treatment group, ACS-ITT-aspirin.

Parameter	Median	95% CrI	Mean (SD)	Pr(OR > 1)
Intermediate	1.28	(0.97, 1.71)	1.30 (0.19)	0.96
Low with aspirin	1.13	(0.85, 1.51)	1.14 (0.17)	0.79
Age 60+	0.58	(0.44, 0.75)	0.58 (0.08)	0.00
Australia/New Zealand	0.92	(0.57, 1.49)	0.95 (0.24)	0.38

2.3.4.1.3 Therapeutic dose

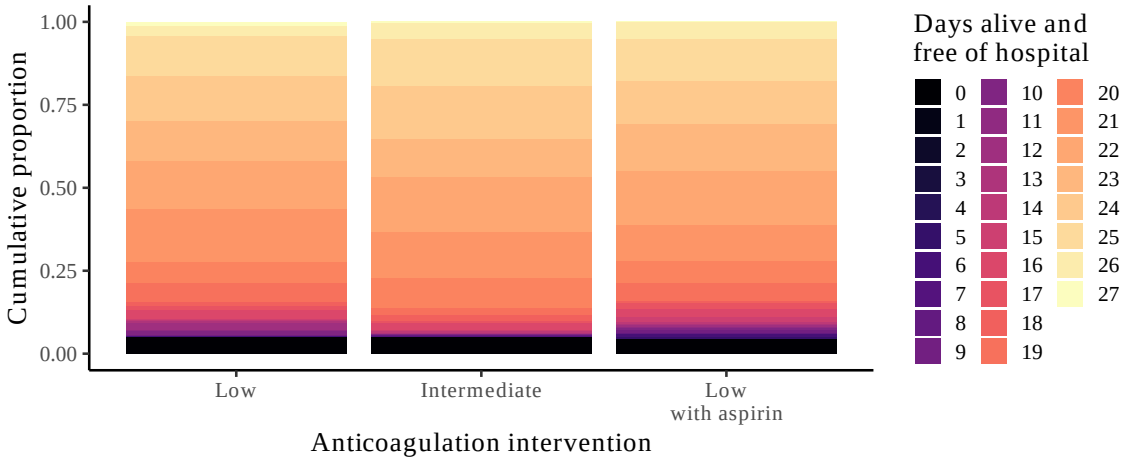

Figure 2.42: Observed distribution of days alive and free of hospital at day 28 by treatment group, ACS-ITT-aspirin.

- **Model**: cumulative logistic (ordinal) regression assuming proportional odds
- **Terms**: anticoagulation intervention, age group, region
- **Set**: ACS-ITT-therapeutic

Note: the reference region was switched to Nepal for this model due to small numbers in India.

Table 2.81: Summary of days alive and free of hospital to day 28 by treatment group, ACS-ITT-therapeutic

Anticoagulation intervention	Patients	Known	Deaths	DAFH, Median (Q1, Q3)
Low-dose	79	75	3 (4%)	22 (20, 24)
Intermediate-dose	65	63	1 (2%)	22 (20, 24)
Therapeutic-dose	50	50	6 (12%)	22 (19, 24)
Overall	**194**	**188**	**10 (5%)**	**22 (19, 24)**

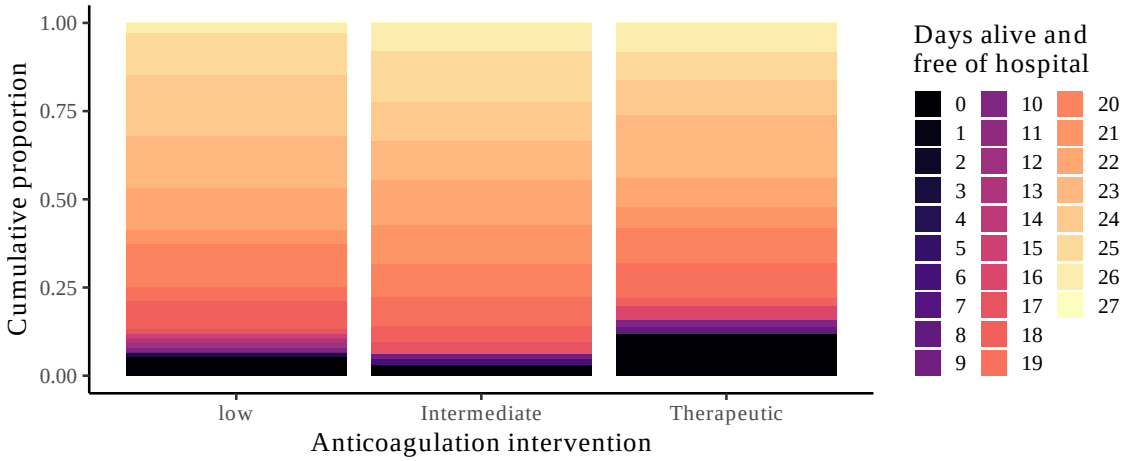

Figure 2.43: Observed distribution of days alive and free of hospital at day 28 by treatment group, ACS-ITT-therapeutic

Table 2.82: Summary of days alive and free of hospital to day 28 by treatment group, ACS-ITT-therapeutic

Parameter	Median	95% CrI	Mean (SD)	Pr(OR > 1)
Intermediate	1.19	(0.66, 2.19)	1.25 (0.39)	0.72
Therapeutic	0.85	(0.46, 1.60)	0.89 (0.29)	0.30
Age 60+	0.45	(0.26, 0.76)	0.46 (0.13)	0.00
India	1.58	(0.73, 3.47)	1.71 (0.71)	0.88
Australia/New Zealand	1.27	(0.73, 2.22)	1.33 (0.38)	0.81

2.3.5 Days alive and free of invasive or non-invasive ventilation to day 28

This section reports on the analysis of the secondary outcome: days alive and free invasive or non-invasive ventilation (DAFV) to day 28. For this outcome, participants who died within 28 days were coded to have 0 DAFV.

- **Model**: cumulative logistic (ordinal) regression assuming proportional odds
- **Terms**: anticoagulation intervention, antiviral intervention, aspirin eligibility, age group, region, site nested within region, and epoch.
- **Set**: ACS-ITT

Table 2.83 presents the number of participants where the outcome was observed by the allocated anticoagulation arm. The observed distribution of DAFV by arm is shown in Figure 2.44.

Table 2.83: Summary of days alive and free of ventilation to day 28 by treatment group.

Anticoagulation intervention	Patients	Known	Deaths	Any ventilation	DAFV, Median (Q1, Q3)
Low-dose	610	596	19 (3%)	34 (6%)	28 (28, 28)
Intermediate-dose	613	603	15 (2%)	23 (4%)	28 (28, 28)
Low-dose with aspirin	283	281	10 (4%)	17 (6%)	28 (28, 28)
Therapeutic-dose	50	50	6 (12%)	7 (14%)	28 (28, 28)
Overall	**1556**	**1530**	**50 (3%)**	**81 (5%)**	**28 (28, 28)**

Table 2.84: Summary of model parameters (fixed-effects odds-ratios) for days alive and free of ventilation to day 28 primary model fit to the ACS-ITT set.

Parameter	Median	95% CrI	Mean (SD)	Pr(OR > 1)
Intermediate	1.35	(0.78, 2.34)	1.41 (0.41)	0.85
Standard plus aspirin	1.23	(0.65, 2.33)	1.29 (0.43)	0.73
Therapeutic	0.35	(0.13, 0.95)	0.40 (0.22)	0.02
Ineligible aspirin	0.27	(0.08, 0.98)	0.33 (0.25)	0.02
Age 60+	0.52	(0.32, 0.85)	0.54 (0.14)	0.00
AU/NZ	1.04	(0.26, 4.51)	1.38 (1.22)	0.52
NP	0.59	(0.16, 2.52)	0.78 (0.69)	0.23

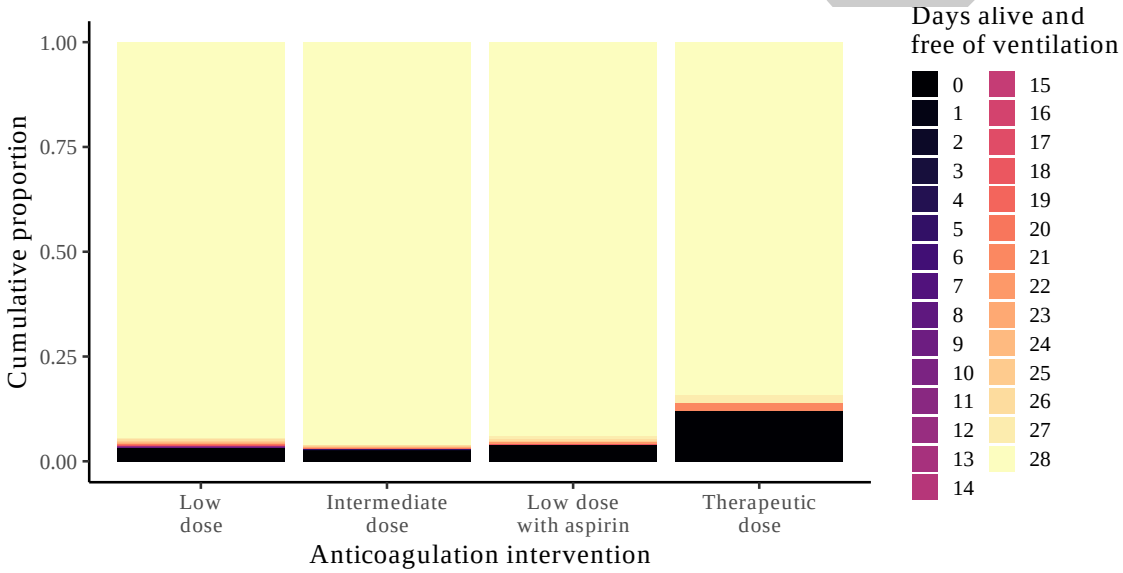

Figure 2.44: Observed distribution of days alive and free of ventilation at day 28 by treatment group.

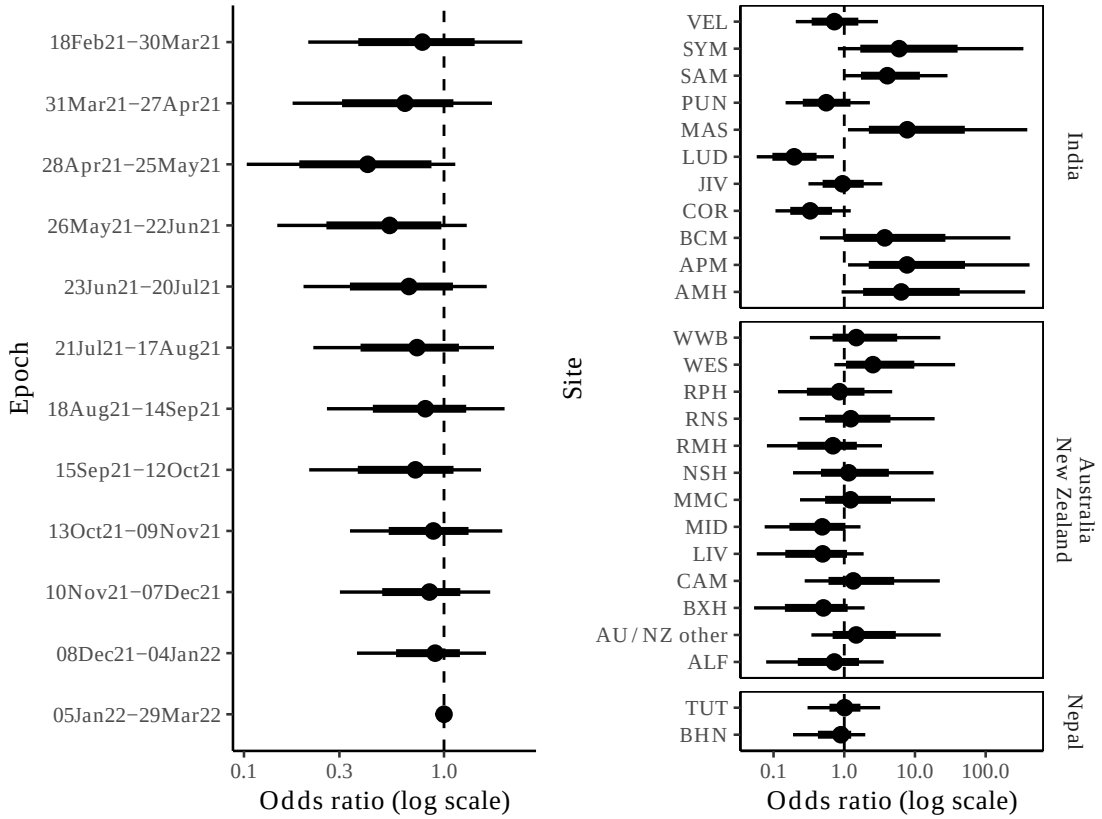

Figure 2.45: Posterior Summaries (point - median, block - 75% CrI, line - 95% CrI) of odds ratio for epoch and site effects on days alive and free of ventilation to day 28 for the primary model fit to the ACS-ITT set.

2.3.5.1 Sensitivity: Concurrent Enrolments

2.3.5.1.1 Intermediate dose

- **Model**: cumulative logistic (ordinal) regression assuming proportional odds
- **Terms**: anticoagulation intervention, age group, region
- **Set**: ACS-ITT-intermediate

Table 2.85: Summary of days alive and free of ventilation to day 28 by treatment group, ACS-ITT-intermediate.

Anticoagulation intervention	Patients	Known	Deaths	Any ventilation	DAFV, Median (Q1, Q3)
Low-dose	610	596	19 (3%)	34 (6%)	28 (28, 28)
Intermediate-dose	613	603	15 (2%)	23 (4%)	28 (28, 28)
Overall	**1223**	**1199**	**34 (3%)**	**57 (5%)**	**28 (28, 28)**

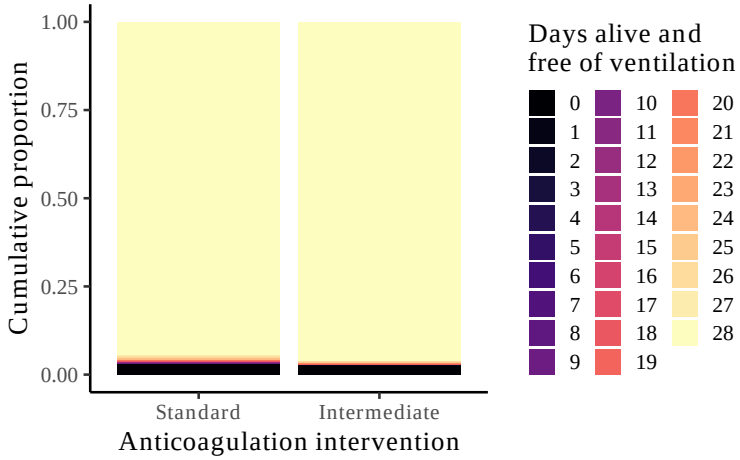

Figure 2.46: Observed distribution of days alive and free of ventilation at day 28 by treatment group, ACS-ITT-intermediate.

Table 2.86: Summary of days alive and free of ventilation to day 28 by treatment group, ACS-ITT-intermediate.

Parameter	Median	95% CrI	Mean (SD)	Pr(OR > 1)
Intermediate	1.45	(0.86, 2.46)	1.50 (0.41)	0.92
Age 60+	0.44	(0.26, 0.76)	0.46 (0.13)	0.00
Australia/New Zealand	0.75	(0.37, 1.63)	0.81 (0.33)	0.23
Nepal	0.93	(0.41, 2.38)	1.05 (0.54)	0.43

2.3.5.1.2 Standard dose plus aspirin

- **Model**: cumulative logistic (ordinal) regression assuming proportional odds
- **Terms**: anticoagulation intervention, age group, region
- **Set**: ACS-ITT-aspirin

Table 2.87: Summary of days alive and free of ventilation to day 28 by treatment group, ACS-ITT-aspirin.

Anticoagulation intervention	Patients	Known	Deaths	Any ventilation	DAFV, Median (Q1, Q3)
Low-dose	299	291	11 (4%)	20 (7%)	28 (28, 28)
Intermediate-dose	298	293	12 (4%)	15 (5%)	28 (28, 28)
Low-dose with aspirin	283	281	10 (4%)	17 (6%)	28 (28, 28)
Overall	**880**	**865**	**33 (4%)**	**52 (6%)**	**28 (28, 28)**

Table 2.88: Summary of days alive and free of ventilation to day 28 by treatment group, ACS-ITT-aspirin.

Parameter	Median	95% CrI	Mean (SD)	Pr(OR > 1)
Intermediate	1.24	(0.65, 2.41)	1.32 (0.46)	0.74
Standard plus aspirin	1.20	(0.63, 2.28)	1.26 (0.43)	0.71
Age 60+	0.55	(0.32, 0.97)	0.57 (0.17)	0.02
Australia/New Zealand	3.19	(0.92, 14.28)	4.30 (3.83)	0.97

2.3.5.1.3 Therapeutic dose

- **Model**: cumulative logistic (ordinal) regression assuming proportional odds
- **Terms**: anticoagulation intervention, age group, region

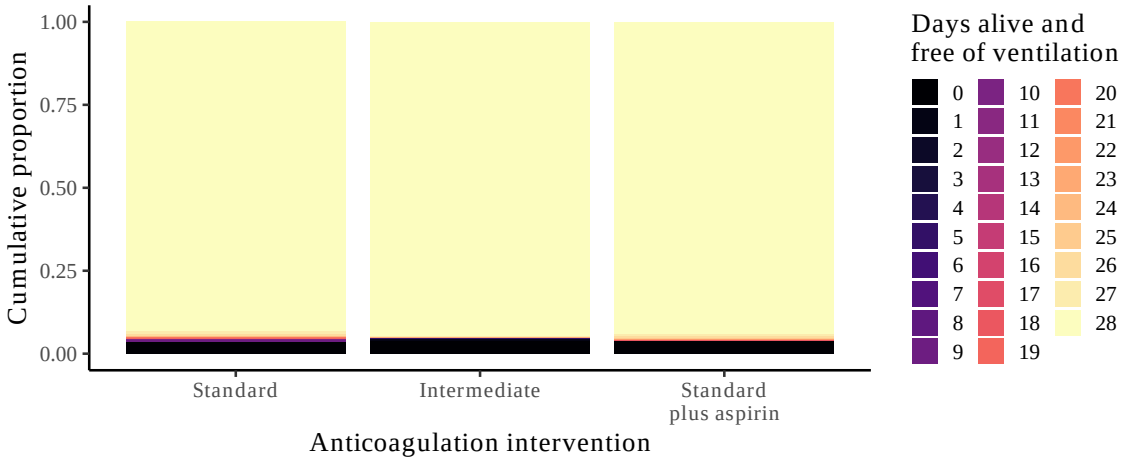

Figure 2.47: Observed distribution of days alive and free of ventilation at day 28 by treatment group, ACS-ITT-aspirin.

- **Set**: ACS-ITT-therapeutic

Note: the reference region was switched to Nepal for this model due to small numbers in India.

Table 2.89: Summary of days alive and free of ventilation to day 28 by treatment group, ACS-ITT-therapeutic.

Anticoagulation intervention	Patients	Known	Deaths	Any ventilation	DAFV, Median (Q1, Q3)
Low-dose	79	75	3 (4%)	6 (8%)	28 (28, 28)
Intermediate-dose	65	63	1 (2%)	3 (5%)	28 (28, 28)
Therapeutic-dose	50	50	6 (12%)	7 (14%)	28 (28, 28)
Overall	**194**	**188**	**10 (5%)**	**16 (8%)**	**28 (28, 28)**

Table 2.90: Summary of days alive and free of ventilation to day 28 by treatment group, ACS-ITT-therapeutic.

Parameter	Median	95% CrI	Mean (SD)	Pr(OR > 1)
Intermediate	1.51	(0.46, 5.43)	1.87 (1.37)	0.75
Therapeutic	0.51	(0.18, 1.50)	0.59 (0.35)	0.11
Age 60+	0.52	(0.19, 1.37)	0.59 (0.31)	0.09
India	2.71	(0.69, 13.46)	3.82 (4.33)	0.92
Australia/New Zealand	0.97	(0.38, 2.59)	1.10 (0.58)	0.47

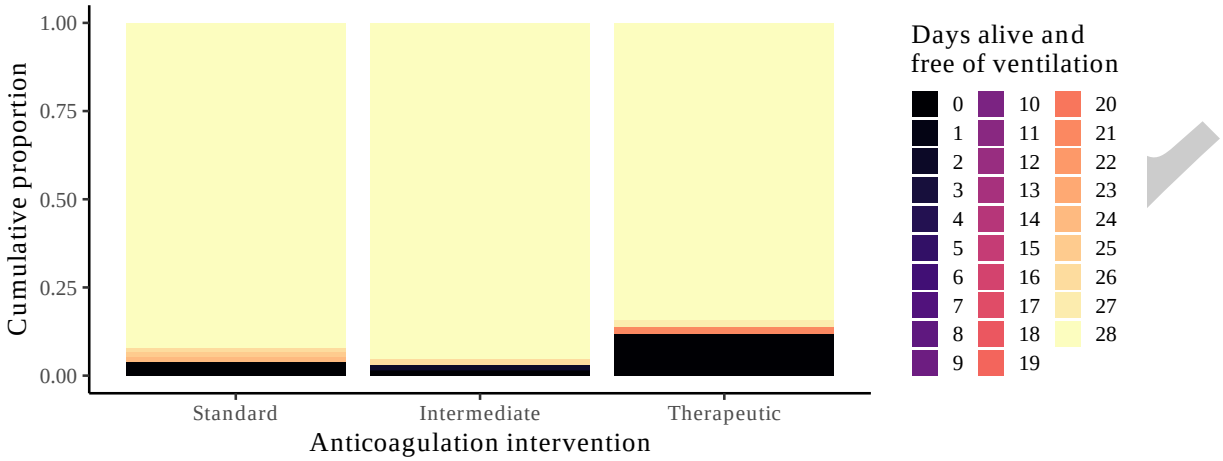

Figure 2.48: Observed distribution of days alive and free of ventilation at day 28 by treatment group, ACS-ITT-therapeutic.

2.3.6 Presence of patient reported shortness of breath at day 28

This section reports on the analysis of the secondary outcome: patient reported shortness of breath at day 28. For this outcome, participants who died within 28 days were coded to have a missing value, so this outcome reflects shortness of breath at day 28 amongst patients who survived to at least day 28. The model is coded so that an odds ratio less than 1 implies a benefit (reduction in odds of shortness of breath at day 28).

- **Model**: logistic regression
- **Terms**: anticoagulation intervention, antiviral intervention, aspirin eligibility, age group, region, site nested within region, and epoch.
- **Set**: ACS-ITT

Table 2.91 presents the number of participants where the outcome was observed by the allocated anticoagulation arm. The model parameters (odds ratios) are summarised in Table 2.92 for the fixed-effect terms and in Figure 2.49 for the site and epoch specific terms.

Table 2.91: Summary of patient reported shortness of breath at day 28 by treatment group.

n (%)	Patients	Known	Missing	Shortness of breath day 28
Standard dose	610	577 (94.6)	33 (5.4)	115 (19.9)
Intermediate dose	613	584 (95.3)	29 (4.7)	110 (18.8)
Standard dose plus aspirin	283	271 (95.8)	12 (4.2)	59 (21.8)
Therapeutic dose	50	44 (88.0)	6 (12.0)	11 (25.0)
Overall	**1556**	**1476 (94.9)**	**80 (5.1)**	**295 (20.0)**

Table 2.92: Summary of model parameters (fixed-effects odds-ratios) for shortness of breath at day 28 primary model fit to the ACS-ITT set.

Parameter	Median	95% CrI	Mean (SD)	Pr(OR < 1)
Intermediate	0.77	(0.55, 1.09)	0.79 (0.14)	0.93
Standard plus aspirin	1.19	(0.77, 1.84)	1.22 (0.28)	0.22
Therapeutic	0.93	(0.35, 2.30)	1.02 (0.50)	0.57
Ineligible aspirin	1.19	(0.40, 3.31)	1.36 (0.77)	0.38
Age 60+	2.09	(1.48, 2.94)	2.12 (0.37)	0.00
Australia/New Zealand	2.32	(0.59, 8.49)	2.89 (2.20)	0.11
Nepal	0.52	(0.13, 2.52)	0.72 (0.71)	0.81

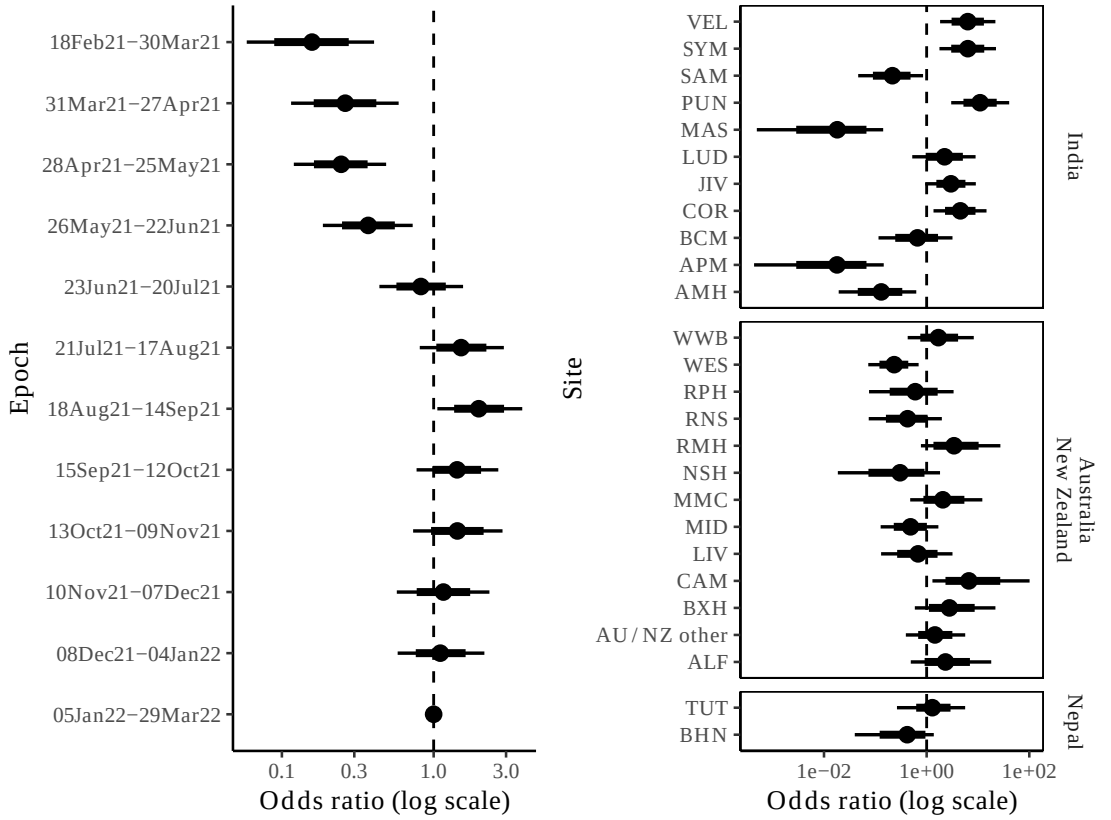

Figure 2.49: Posterior Summaries (point - median, block - 75% CrI, line - 95% CrI) of odds ratio for epoch and site effects on day 28 shortness of breath for the primary model fit to the ACS-ITT set.

2.3.6.1 Sensitivity: Concurrent Enrolments

2.3.6.1.1 Intermediate dose

- **Model**: logistic regression
- **Terms**: anticoagulation intervention, age group, region
- **Set**: ACS-ITT-intermediate

Table 2.93: Summary of shortness of breath at day 28 by treatment group, ACS-ITT-intermediate.

n (%)	Patients	Known	Missing	Shortness of breath day 28
Standard dose	610	577 (94.6)	33 (5.4)	115 (19.9)
Intermediate dose	613	584 (95.3)	29 (4.7)	110 (18.8)
Overall	**1223**	**1161 (94.9)**	**62 (5.1)**	**225 (19.4)**

Table 2.94: Summary of posterior odds ratios, ACS-ITT-intermediate.

Parameter	Median	95% CrI	Mean (SD)	Pr(OR < 1)
Intermediate	0.91	(0.67, 1.23)	0.92 (0.14)	0.74
Age 60+	1.64	(1.19, 2.24)	1.66 (0.27)	0.00
Australia/New Zealand	3.91	(2.62, 5.82)	4.00 (0.82)	0.00
Nepal	0.47	(0.22, 0.92)	0.50 (0.18)	0.99

2.3.6.1.2 Standard dose plus aspirin

- **Model**: logistic regression
- **Terms**: anticoagulation intervention, age group, region
- **Set**: ACS-ITT-aspirin

Table 2.95: Summary of shortness of breath at day 28 by treatment group, ACS-ITT-aspirin.

n (%)	Patients	Known	Missing	Shortness of breath day 28
Standard dose	299	280 (93.6)	19 (6.4)	55 (19.6)
Intermediate dose	298	280 (94.0)	18 (6.0)	52 (18.6)
Standard dose plus aspirin	283	271 (95.8)	12 (4.2)	59 (21.8)
Overall	**880**	**831 (94.4)**	**49 (5.6)**	**166 (20.0)**

Table 2.96: Summary of posterior odds ratios, ACS-ITT-aspirin.

Parameter	Median	95% CrI	Mean (SD)	Pr(OR < 1)
Intermediate	0.96	(0.64, 1.46)	0.99 (0.21)	0.57
Standard plus aspirin	1.17	(0.78, 1.77)	1.20 (0.26)	0.22
Age 60+	1.54	(1.05, 2.23)	1.56 (0.30)	0.01
Australia/New Zealand	2.17	(1.17, 3.91)	2.26 (0.70)	0.01

2.3.6.1.3 Therapeutic dose

- **Model**: logistic regression
- **Terms**: anticoagulation intervention, age group, region
- **Set**: ACS-ITT-therapeutic

Note: the reference region was switched to Nepal for this model due to small numbers in India.

Table 2.97: Summary of shortness of breath at day 28 by treatment group, ACS-ITT-therapeutic.

n (%)	Patients	Known	Missing	Shortness of breath day 28
Standard dose	79	72 (91.1)	7 (8.9)	18 (25.0)
Intermediate dose	65	61 (93.8)	4 (6.2)	13 (21.3)
Therapeutic dose	50	44 (88.0)	6 (12.0)	11 (25.0)
Overall	**194**	**177 (91.2)**	**17 (8.8)**	**42 (23.7)**

Table 2.98: Summary of posterior odds ratios, ACS-ITT-therapeutic.

Parameter	Median	95% CrI	Mean (SD)	Pr(OR < 1)
Intermediate	0.46	(0.18, 1.13)	0.51 (0.25)	0.95
Therapeutic	0.66	(0.25, 1.68)	0.74 (0.38)	0.80
Age 60+	1.89	(0.84, 4.34)	2.07 (0.93)	0.06
India	1.25	(0.36, 4.03)	1.49 (0.96)	0.36
Australia/New Zealand	12.28	(5.66, 28.30)	13.51 (5.93)	0.00

2.3.7 Modified Medical Research Council (mMRC) breathlessness scale at day 28

The mMRC scale was only asked of participants who responded "yes" to the question of new or worsening breathlessness since COVID. Therefore, the distribution of this outcome scale is conditional on the patient responding that they were experiencing new or worse breathlessness since having COVID. In the following tables "Not asked" refers to participants who responded "no" the question of breathlessness.

Table 2.99: mMRC breathlessness scale by anticoagulation intervention (day 28).

mMRC breathlessness scale (day 28)	Standard	Intermediate	Standard plus aspirin	Therapeutic	Overall
Only breathless with strenuous exercise	40 (7)	50 (8)	26 (9)	2 (4)	118 (8)
Short of breath up a slight hill	47 (8)	39 (6)	16 (6)	4 (8)	106 (7)
Walks slower than most people of the same age	12 (2)	11 (2)	15 (5)	3 (6)	41 (3)
Stops for breath after walking about 100 metres	14 (2)	8 (1)	1 (0)	2 (4)	25 (2)
Too breathless to leave the house	2 (0)	2 (0)	1 (0)	0 (0)	5 (0)
Not asked	462 (76)	474 (77)	212 (75)	33 (66)	1181 (76)
(Missing)	33 (5)	29 (5)	12 (4)	6 (12)	80 (5)

Table 2.100: Summary of model parameters (fixed-effects odds-ratios) for the mMRC scale at day 28 primary model fit to the ACS-ITT set.

Parameter	Median	95% CrI	Mean (SD)	Pr(OR < 1)
Intermediate	0.71	(0.42, 1.19)	0.73 (0.20)	0.91
Low with aspirin	1.09	(0.57, 2.11)	1.16 (0.40)	0.40
Therapeutic	0.73	(0.24, 2.25)	0.86 (0.54)	0.71
Ineligible aspirin	1.02	(0.24, 4.02)	1.30 (1.06)	0.49
Age 60+	1.47	(0.92, 2.39)	1.52 (0.38)	0.05
AU/NZ	2.65	(0.72, 9.65)	3.30 (2.44)	0.07
NP	1.36	(0.31, 5.39)	1.73 (1.39)	0.33

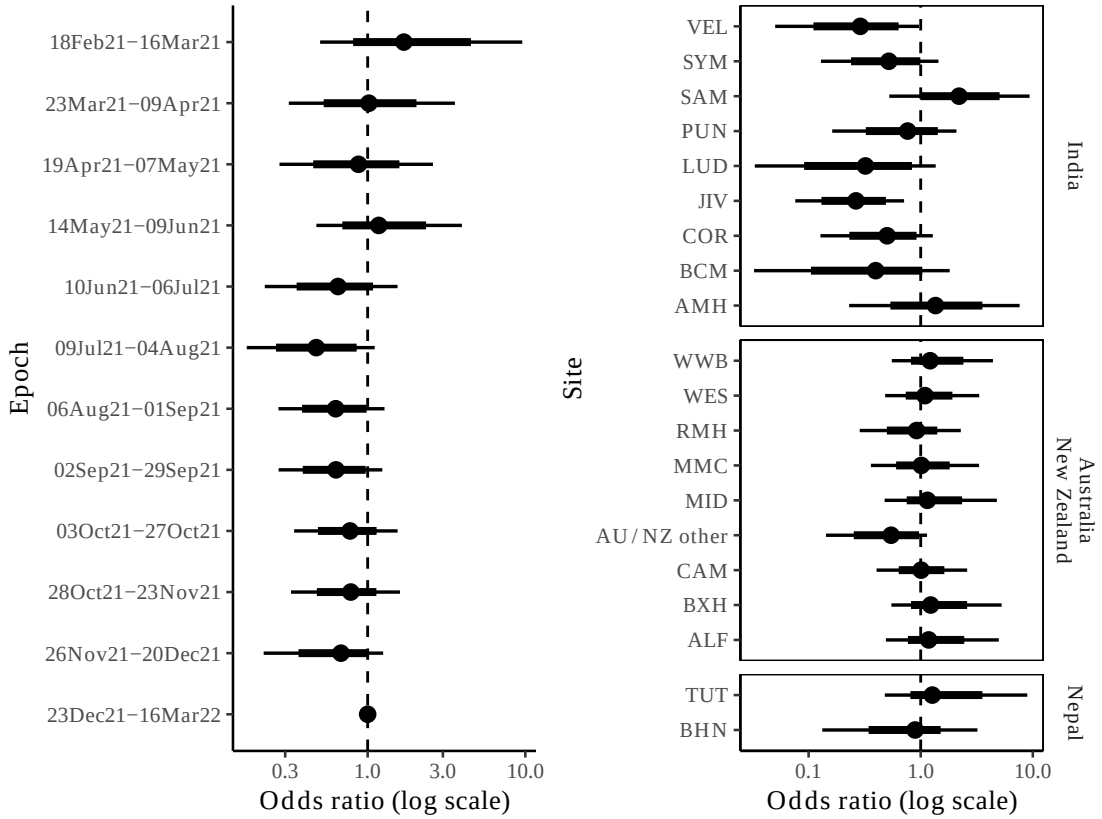

Figure 2.50: Posterior Summaries (point - median, block - 75% CrI, line - 95% CrI) of odds ratio for epoch and site effects on the mMRC scale at day 28 for the primary model fit to the ACS-ITT set.

2.3.7.1 Sensitivity: Concurrent Enrolments

2.3.8 Quality of life as measured by EQ-5D-5L questionnaire at day 28

The EQ-5D-5L responses are described.

Table 2.101: Prevelance of 10 most frequent, and worst, reported EQ-5D-5L profiles by treatment (day 28).

	Frequency		Cumulative	
Health state	n	%	n	%
Standard				
11111	279	48.4	279	48.4
11121	36	6.2	315	54.7
11221	22	3.8	337	58.5
22211	18	3.1	355	61.6
11112	17	3	372	64.6
21111	16	2.8	388	67.4
11211	15	2.6	403	70
21121	15	2.6	418	72.6
21221	14	2.4	432	75
21211	13	2.3	445	77.3
...				
55533	1	0.2	576	100
Intermediate				
11111	304	52.1	304	52.1
11121	47	8	351	60.1
11221	24	4.1	375	64.2
22211	20	3.4	395	67.6
21121	17	2.9	412	70.5
21111	11	1.9	423	72.4
21211	11	1.9	434	74.3
11112	9	1.5	443	75.9
11211	9	1.5	452	77.4
11212	9	1.5	461	78.9
...				
55555	1	0.2	584	100
Standard plus aspirin				
11111	126	46.5	126	46.5
11121	27	10	153	56.5
11221	13	4.8	166	61.3
21111	11	4.1	177	65.3
22211	11	4.1	188	69.4
21121	9	3.3	197	72.7

11112	8	3	205	75.6
22221	5	1.8	210	77.5
11211	4	1.5	214	79
21221	4	1.5	218	80.4
...				
55555	1	0.4	271	100
Therapeutic				
11111	24	54.5	24	54.5
21111	3	6.8	27	61.4
22211	2	4.5	29	65.9
22232	2	4.5	31	70.5
11112	1	2.3	32	72.7
11121	1	2.3	33	75
11211	1	2.3	34	77.3
11213	1	2.3	35	79.5
11221	1	2.3	36	81.8
21213	1	2.3	37	84.1
...				
32223	1	2.3	44	100

Table 2.102: Distribution of responses on the EQ-5D-5L (day 28).

EQ-5D-5L	Standard	Intermediate	Standard plus aspirin	Therapeutic	Overall
Mobility					
1	413 (56)	438 (60)	194 (56)	29 (49)	1074 (57)
2	130 (18)	124 (17)	63 (18)	11 (19)	328 (17)
3	27 (4)	16 (2)	8 (2)	4 (7)	55 (3)
4	4 (1)	5 (1)	5 (1)	0 (0)	14 (1)
5	2 (0)	1 (0)	1 (0)	0 (0)	4 (0)
Any mobility problem	163 (22)	146 (20)	77 (22)	15 (25)	401 (21)
Self care					
1	482 (72)	493 (73)	223 (70)	38 (76)	1236 (72)
2	79 (12)	79 (12)	39 (12)	6 (12)	203 (12)
3	10 (1)	7 (1)	7 (2)	0 (0)	24 (1)
4	2 (0)	3 (0)	0 (0)	0 (0)	5 (0)
5	3 (0)	2 (0)	2 (1)	0 (0)	7 (0)
Any self care problem	94 (14)	91 (13)	48 (15)	6 (12)	239 (14)
Usual activities					
1	396 (52)	426 (57)	192 (55)	29 (49)	1043 (55)
2	150 (20)	135 (18)	64 (18)	11 (19)	360 (19)
3	25 (3)	17 (2)	12 (3)	3 (5)	57 (3)
4	2 (0)	4 (1)	0 (0)	1 (2)	7 (0)

5	3 (0)	2 (0)	3 (1)	0 (0)	8 (0)
Any usual activities problem	180 (24)	158 (21)	79 (23)	15 (25)	432 (23)
Pain/discomfort					
1	394 (52)	396 (51)	174 (47)	33 (60)	997 (51)
2	139 (18)	154 (20)	82 (22)	5 (9)	380 (19)
3	38 (5)	28 (4)	9 (2)	6 (11)	81 (4)
4	4 (1)	5 (1)	5 (1)	0 (0)	14 (1)
5	1 (0)	1 (0)	1 (0)	0 (0)	3 (0)
Any pain/discomfort problem	182 (24)	188 (24)	97 (26)	11 (20)	478 (24)
Anxiety/depression					
1	475 (70)	495 (74)	230 (74)	32 (57)	1232 (72)
2	80 (12)	73 (11)	34 (11)	7 (12)	194 (11)
3	15 (2)	10 (1)	3 (1)	4 (7)	32 (2)
4	6 (1)	5 (1)	3 (1)	1 (2)	15 (1)
5	0 (0)	1 (0)	1 (0)	0 (0)	2 (0)
Any anxiety/depression problem	101 (15)	89 (13)	41 (13)	12 (21)	243 (14)

Table 2.103: Descriptive summary of EQ-5D VAS (day 28).

	Standard	Intermediate	Standard plus aspirin	Therapeutic
n	610	613	283	50
Mean	85.1	85.8	85.2	86.1
SD	11.8	11.4	11.1	13.7
Median	90	90	90	90
Mode	90	90	90	90
Min	9	10	30	50
Max	100	100	100	100
Missing, n (%)	36 (5.9)	33 (5.38)	12 (4.24)	7 (14)

2.4 Domain Specific Outcomes

The anticoagulation domain-specific outcomes are reported in Table 2.104. The number of thrombotic and bleeding events were low across all interventions and overall.

Table 2.104: Descriptive summary of anticoagulation-specific outcomes (thrombotic and bleeding events).

Outcome, n (%)	Standard dose (n = 610)	Intermediate dose (n = 613)	Standard dose plus aspirin (n = 283)	Therapeutic dose (n = 50)	Overall (n = 1556)
Mortality					
Died by day 28	19 (3)	15 (2)	10 (4)	6 (12)	50 (3)
Unknown	14 (2)	10 (2)	2 (1)	0 (0)	26 (2)
Thrombotic events					
Unknown	18 (3)	14 (2)	5 (2)	2 (4)	39 (3)
Deep vein thrombosis	1 (0)	0 (0)	0 (0)	0 (0)	1 (0)
Pulmonary embolus	0 (0)	1 (0)	1 (0)	0 (0)	2 (0)
Acute myocardial infarction	1 (0)	1 (0)	0 (0)	0 (0)	2 (0)
Ischemic cerebrovascular event	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Other confirmed thrombotic event	1 (0)	0 (0)	0 (0)	0 (0)	1 (0)
Any thrombotic event	3 (1)	2 (0)	1 (0)	0 (0)	6 (0)
Any thrombotic event or death	21 (4)	17 (3)	11 (4)	6 (12)	55 (4)
Bleeding					
Unknown	15 (2)	13 (2)	4 (1)	2 (4)	34 (2)
Major bleeding (as defined by ISTH)	1 (0)	2 (0)	3 (1)	0 (0)	6 (0)
Clinically relevant non-major bleeding	1 (0)	2 (0)	2 (1)	1 (2)	6 (0)
Any clinically relevant bleeding	2 (0)	4 (1)	3 (1)	1 (2)	10 (1)
Heparin-induced thrombocytopenia	0 (0)	1 (0)	0 (0)	0 (0)	1 (0)

The SAP described a formal analysis of the two composite outcomes: any thrombotic event (or death), and any clinical relevant bleeding. Due to the small number of bleeding events (10 of 1,521 known outcomes) this analysis was not undertaken. Similarly, for any thrombotic event or death, due to the majority of the events being due to death, the results were expected to be similar to those for all-cause mortality to day 28. Despite this, the analysis *was* performed for any thrombotic event or death and the results reported below.

2.4.1 Any thrombotic event (or death) to day 28

Table 2.105: Summary of model parameters (fixed-effects odds-ratios) for any thrombotic event or death to day 28 for primary model fit to the ACS-ITT set.

Parameter	Median	95% CrI	Mean (SD)	Pr(OR < 1)
Standard (ref)	1.00	(1.00, 1.00)	1.00 (0.00)	0.00
Intermediate	0.85	(0.44, 1.65)	0.90 (0.31)	0.68
Standard plus aspirin	0.87	(0.39, 1.90)	0.94 (0.39)	0.64
Therapeutic	2.47	(0.82, 7.47)	2.91 (1.84)	0.06
Eligible aspirin (ref)	1.00	(1.00, 1.00)	1.00 (0.00)	0.00
Ineligible aspirin	4.66	(1.18, 15.91)	5.65 (3.94)	0.01
Age < 60 (ref)	1.00	(1.00, 1.00)	1.00 (0.00)	0.00
Age 60+	2.06	(1.14, 3.75)	2.15 (0.66)	0.01
India (ref)	1.00	(1.00, 1.00)	1.00 (0.00)	0.00
Australia/NZ	0.96	(0.22, 3.94)	1.25 (1.03)	0.52
Nepal	2.51	(0.56, 9.18)	3.11 (2.41)	0.10

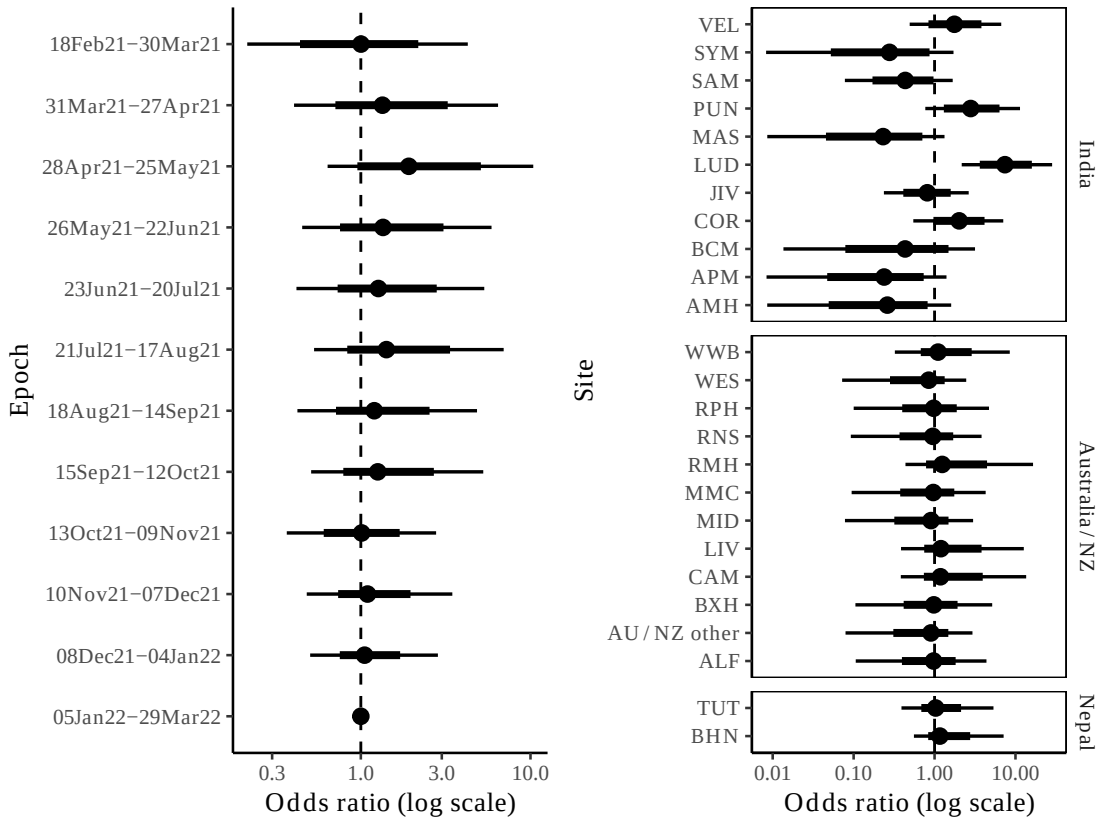

Figure 2.51: Posterior Summaries (point - median, block - 75% CrI, line - 95% CrI) of odds ratio for epoch and site effects for any thrombotic event or death to day 28 for the primary model fit to the ACS-ITT set.

3 Appendix

3.1 Primary Outcome by Model Covariates (ACS-ITT)

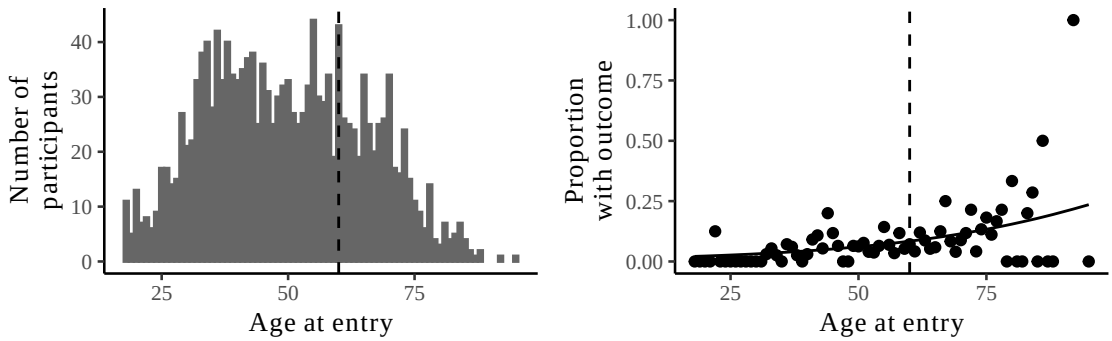

Figure 3.1: Proportion of participants satisfying primary outcome criteria by age at randomisation, ACS-ITT. Vertical dashed line indicates the pre-specified cut-point of 60 years of age.

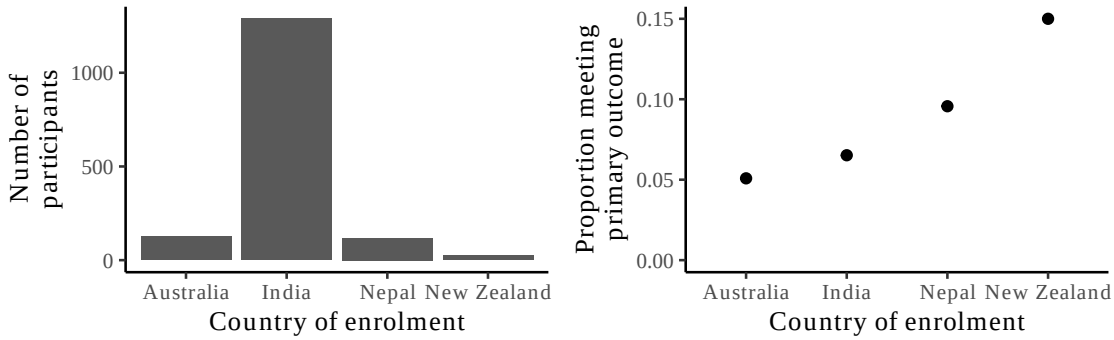

Figure 3.2: Proportion of participants satisfying primary outcome criteria by country of randomisation, ACS-ITT.

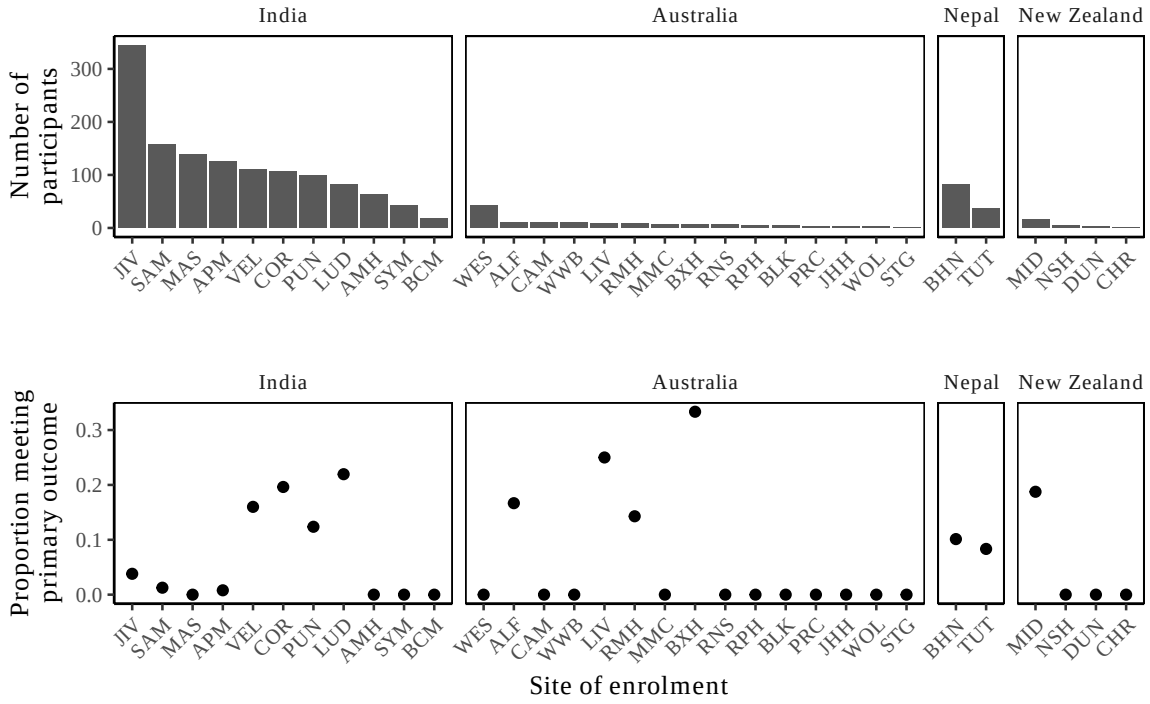

Figure 3.3: Proportion of participants satisfying primary outcome criteria by country and site of randomisation, ACS-ITT.

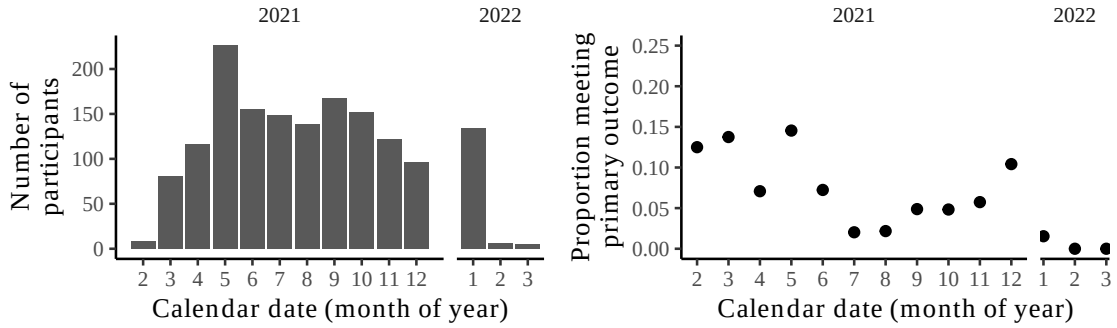

Figure 3.4: Proportion of participants satisfying primary outcome criteria by calendar time (month) of randomisation, ACS-ITT.

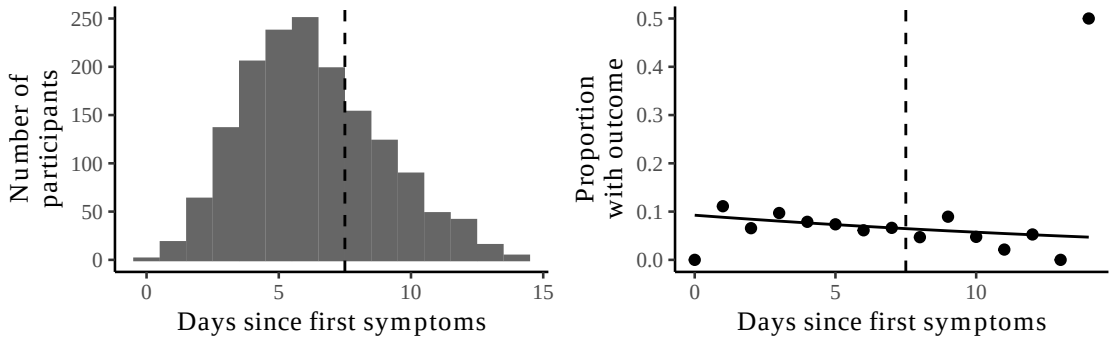

Figure 3.5: Proportion of participants satisfying primary outcome criteria by days since first symptoms at randomisation, ACS-ITT. Vertical dashed line indicates the pre-specified cut-point of 7 days.

3.2 Time to recovery to day 28 by model covariates (ACS-ITT)

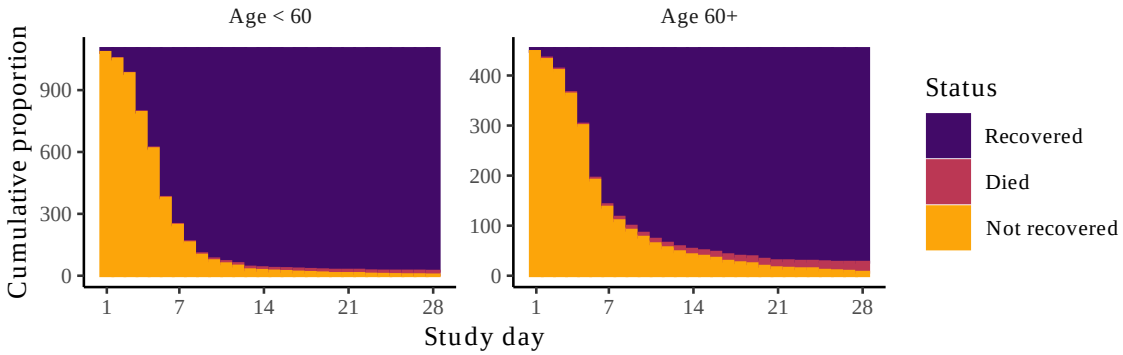

Figure 3.6: Time to clinical recovery to day 28 by age group at randomisation, ACS-ITT.

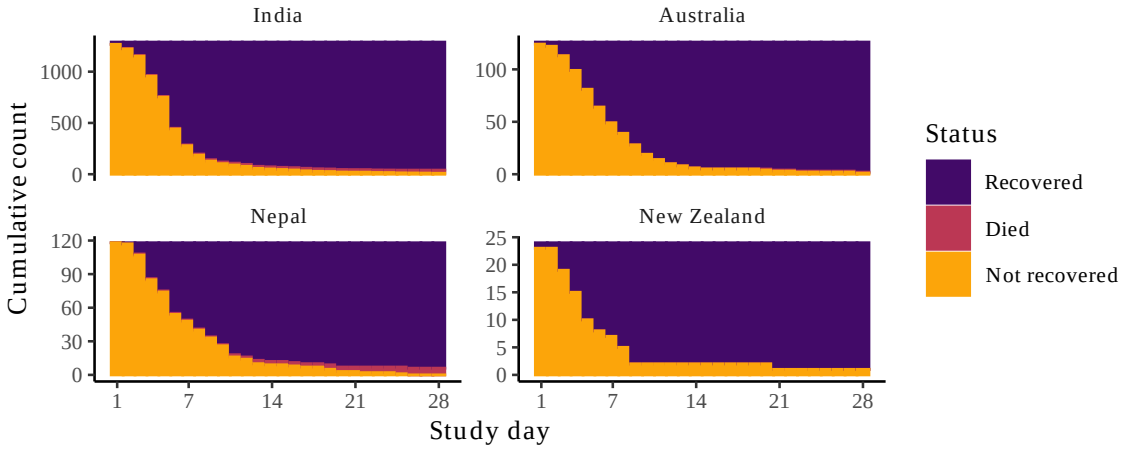

Figure 3.7: Time to clinical recovery to day 28 by country of randomisation, ACS-ITT.

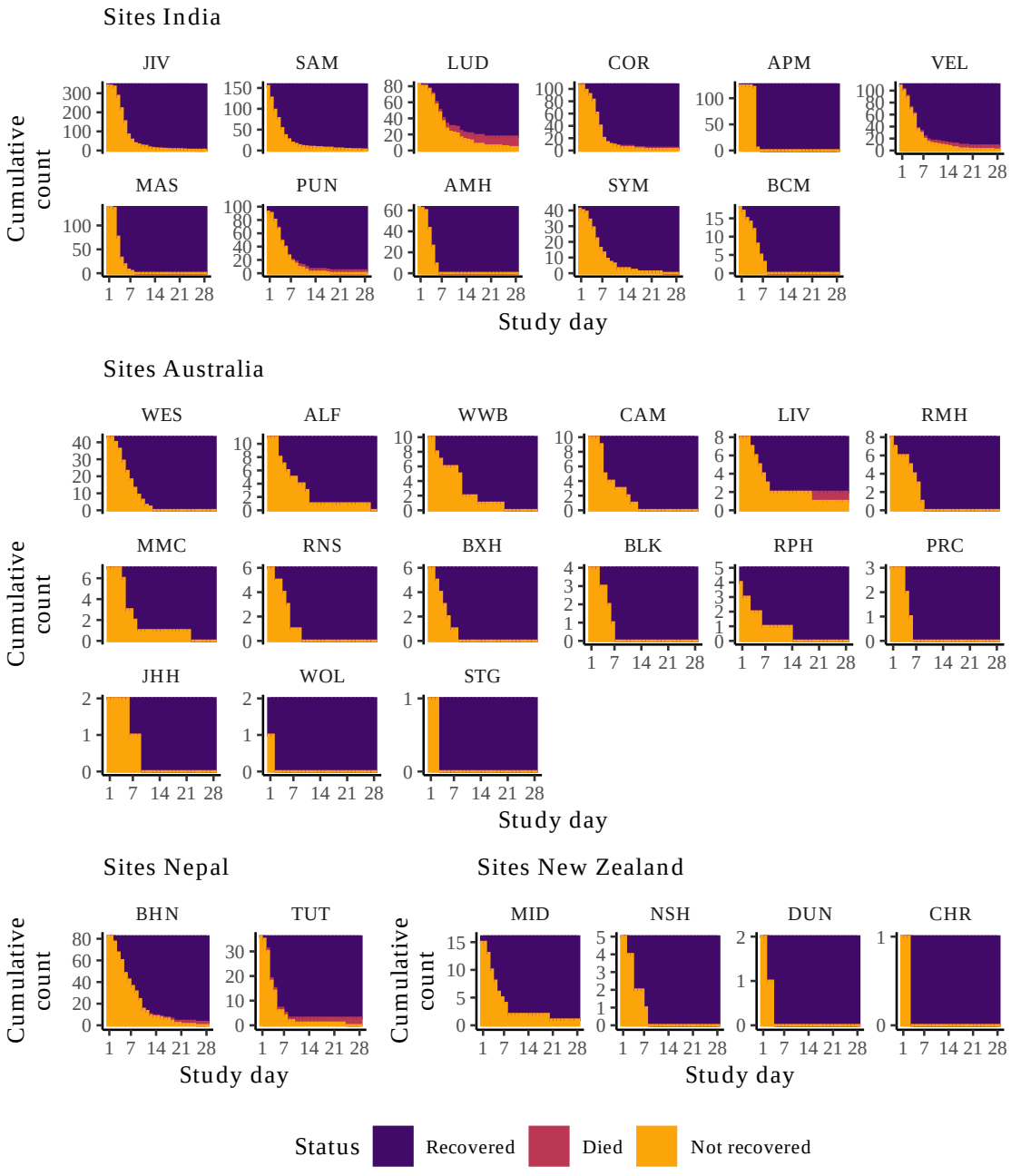

Figure 3.8: Time to clinical recovery to day 28 by country and site of randomisation, ACS-ITT.

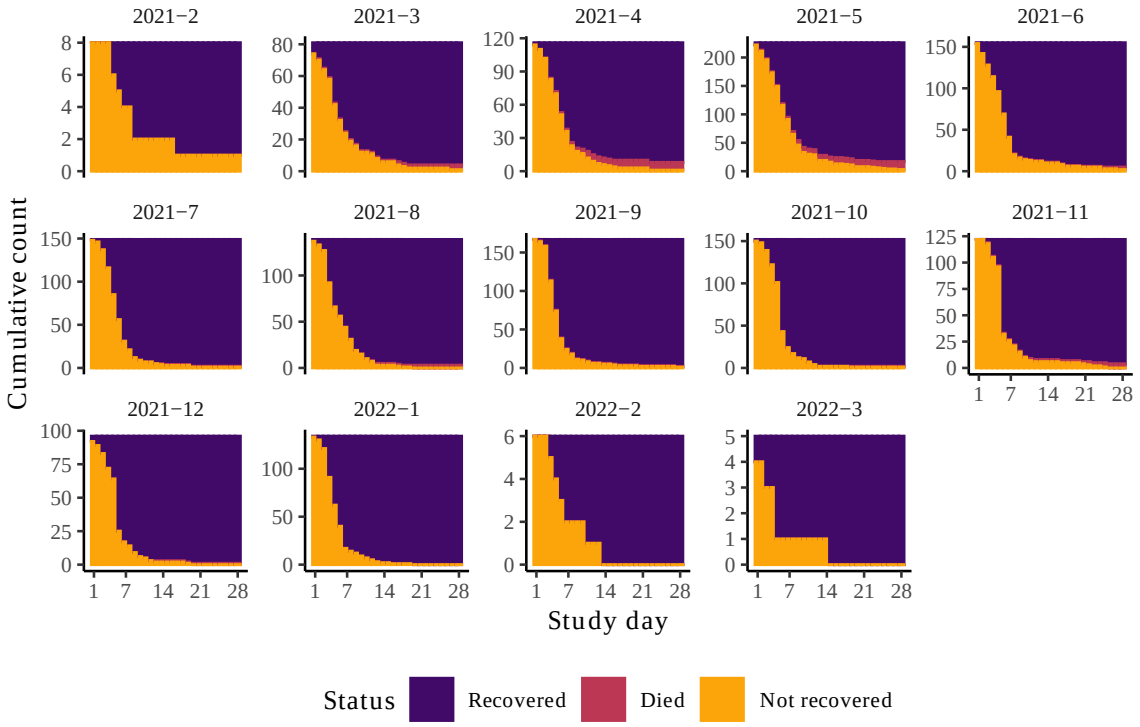

Figure 3.9: Time to clinical recovery to day 28 by calendar time (month) of randomisation, ACS-ITT.

3.3 WHO outcome scale at day 28 by model covariates (ACS-ITT)

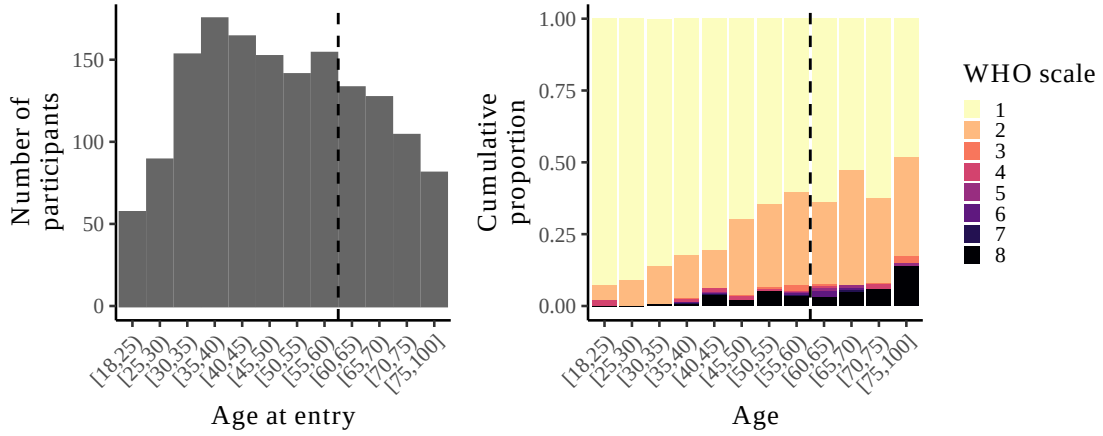

Figure 3.10: Distribution of WHO outcome scale day 28 by age at randomisation, ACS-ITT. Vertical dashed line indicates the pre-specified cut-point of 60 years of age.

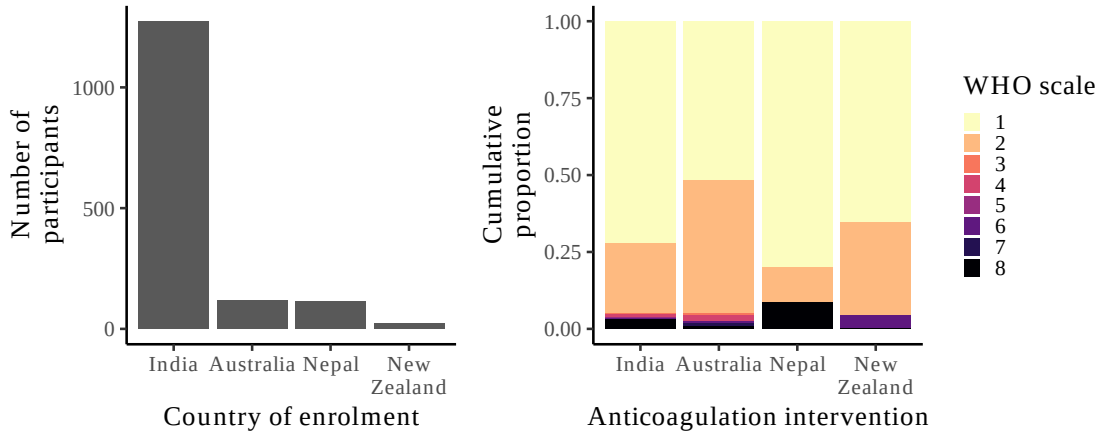

Figure 3.11: Distribution of WHO scale at day 28 by country of randomisation, ACS-ITT.

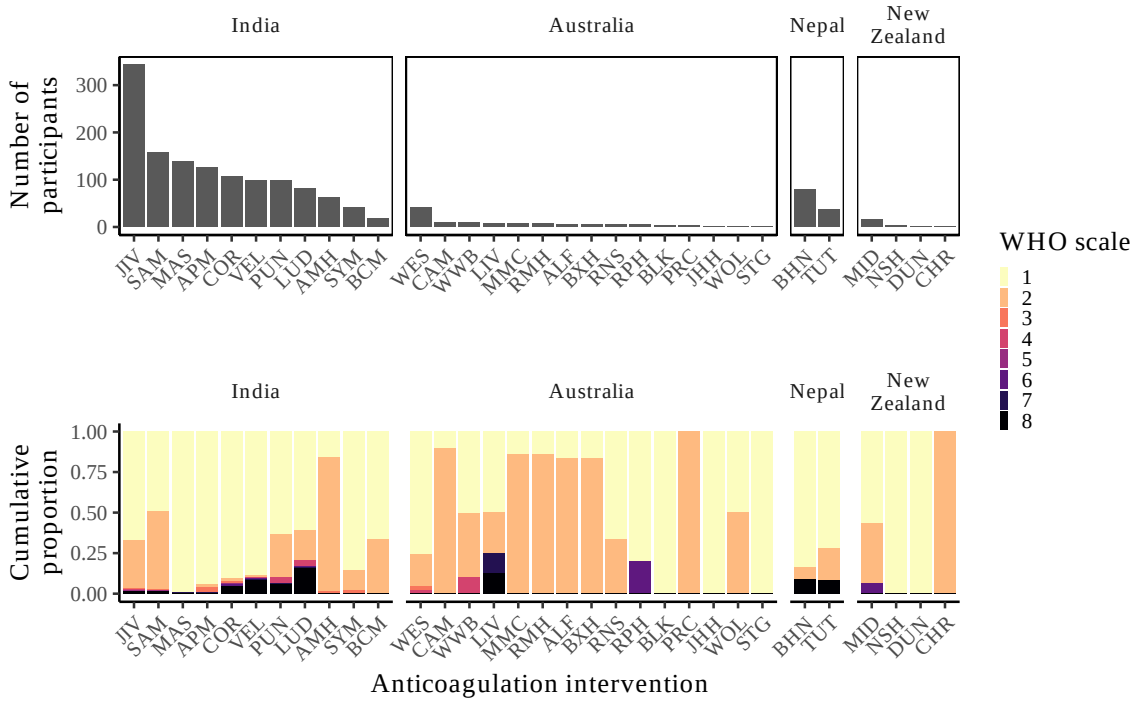

Figure 3.12: Distribution of WHO scale at day 28 by country and site of randomisation, ACS-ITT.

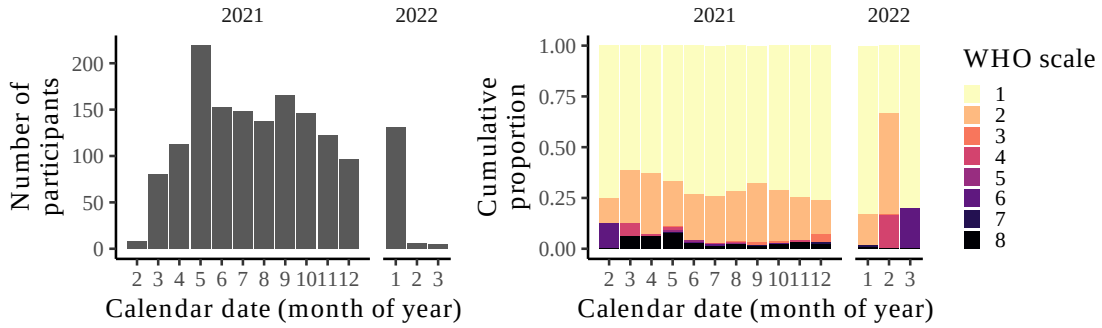

Figure 3.13: Distribution of WHO scale at day 28 by calendar time (month) of randomisation, ACS-ITT.

3.4 Mortality to day 28 by Model Covariates (ACS-ITT)

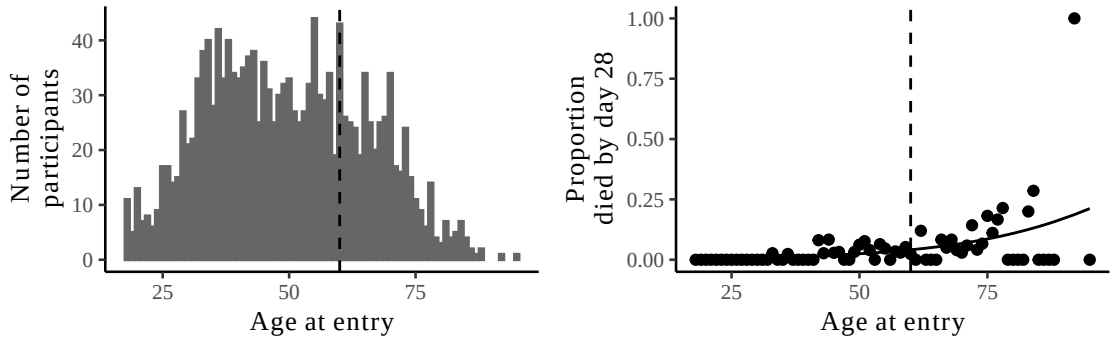

Figure 3.14: Proportion of participants who died by day 28 by age at randomisation, ACS-ITT. Vertical dashed line indicates the pre-specified cut-point of 60 years of age.

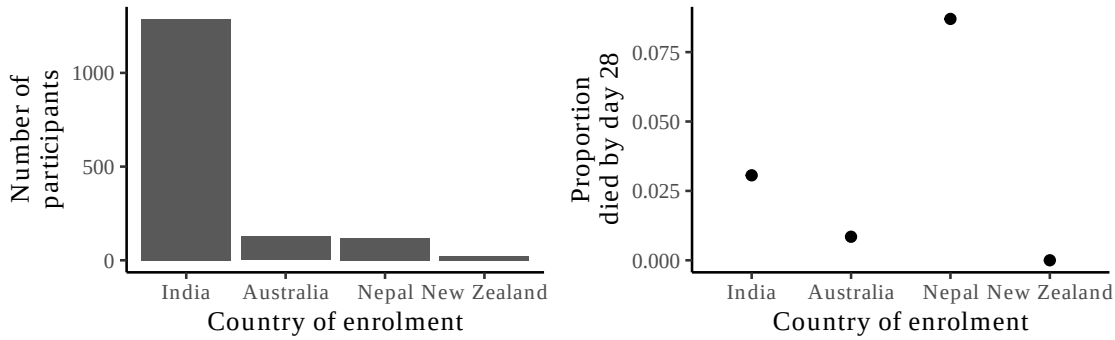

Figure 3.15: Proportion of participants who died by day 28 by country of randomisation, ACS-ITT.

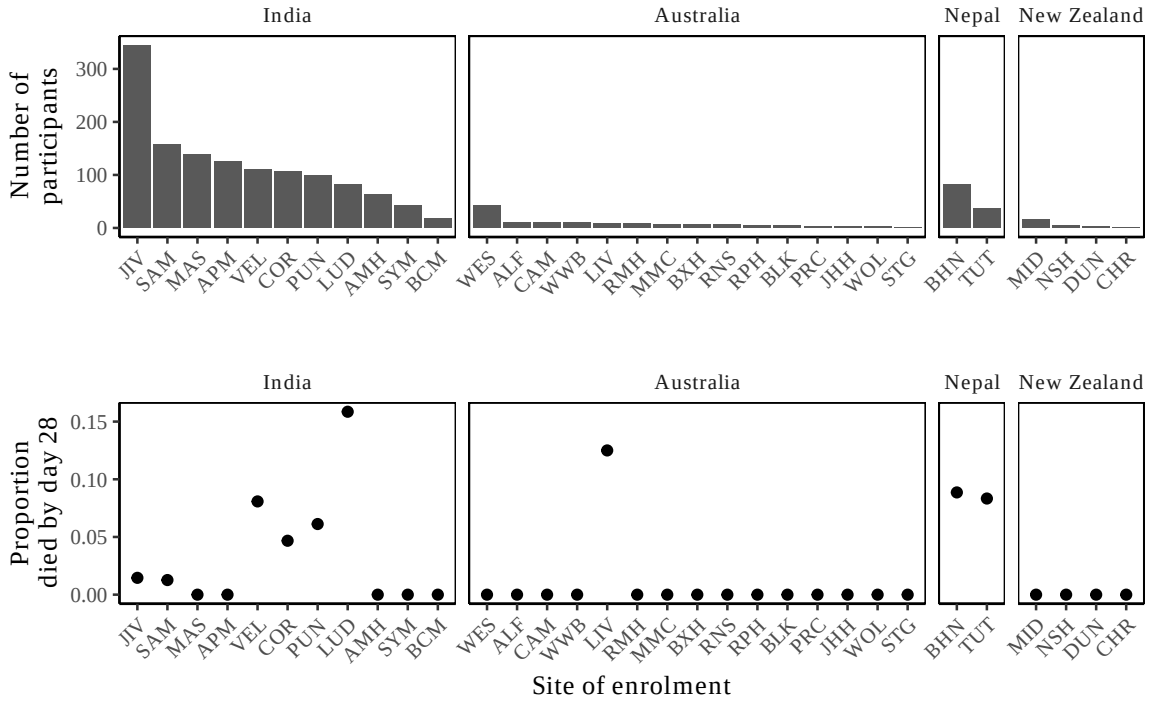

Figure 3.16: Proportion of participants who died by day 28 by country and site of randomisation, ACS-ITT.

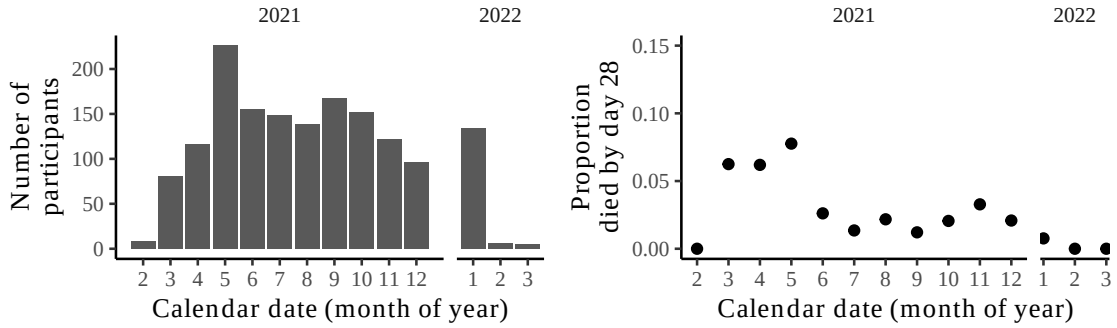

Figure 3.17: Proportion of participants who died by day 28 by calendar time (month) of randomisation, ACS-ITT.

3.5 Days alive and free of hospital to day 28 by Model Covariates (ACS-ITT)

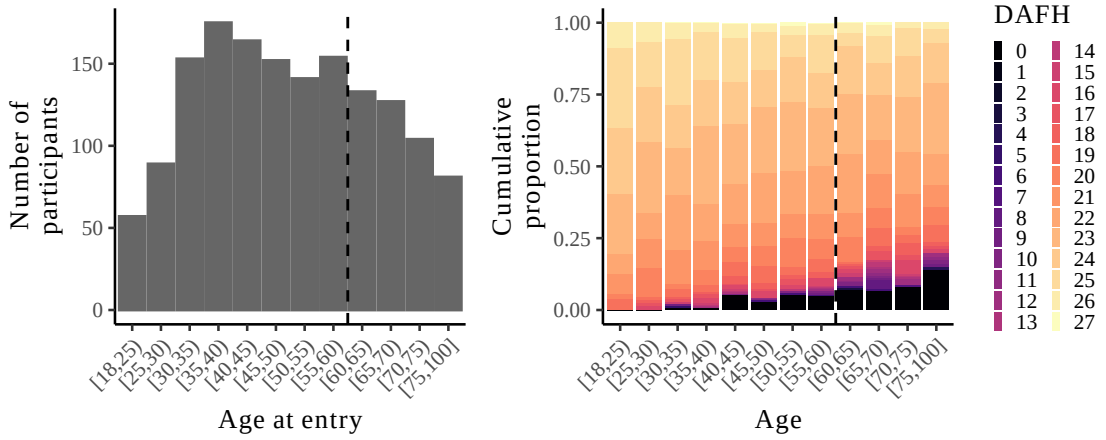

Figure 3.18: Distribution of days alive and free of hospital to day 28 by age groups, ACS-ITT.

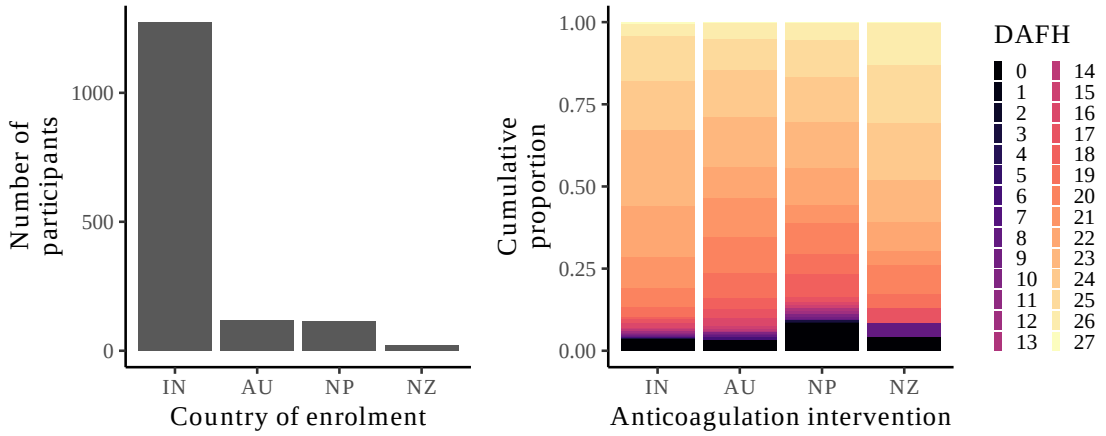

Figure 3.19: Distribution of days alive and free of hospital to day 28 by country of randomisation, ACS-ITT.

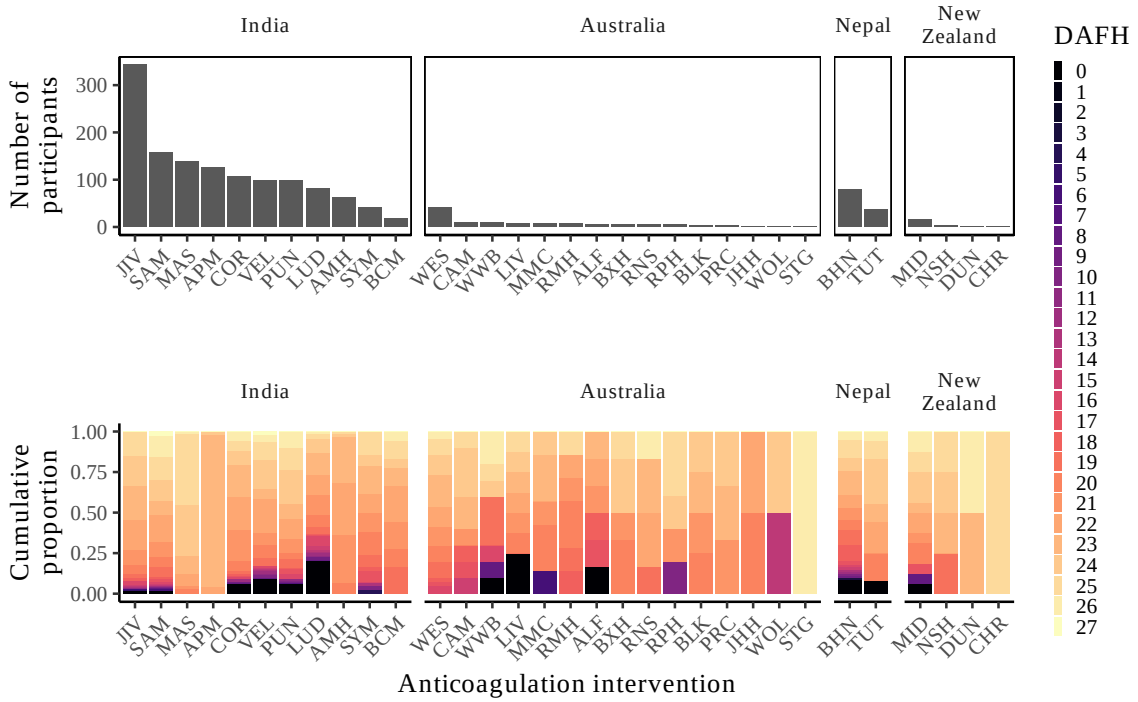

Figure 3.20: Distribution of days alive and free of hospital to day 28 by country and site of randomisation, ACS-ITT.

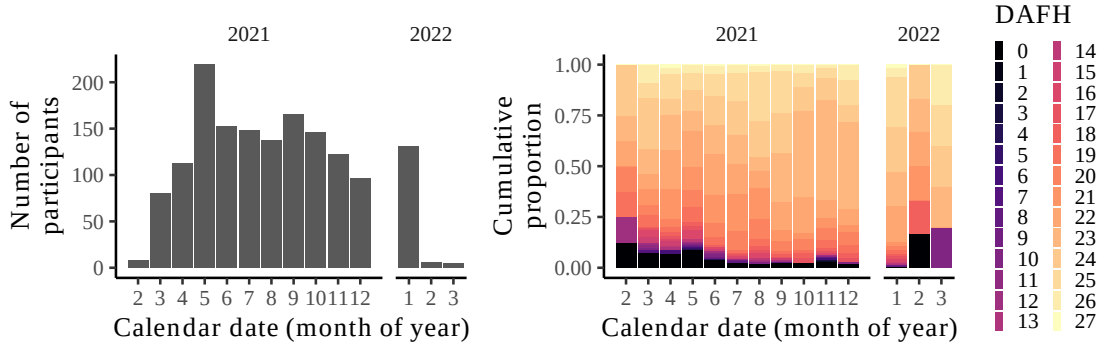

Figure 3.21: Distribution of days alive and free of hospital to day 28 by calendar time (month) of randomisation, ACS-ITT.

3.6 Days alive and free of ventilation to day 28 by Model Covariates (ACS-ITT)

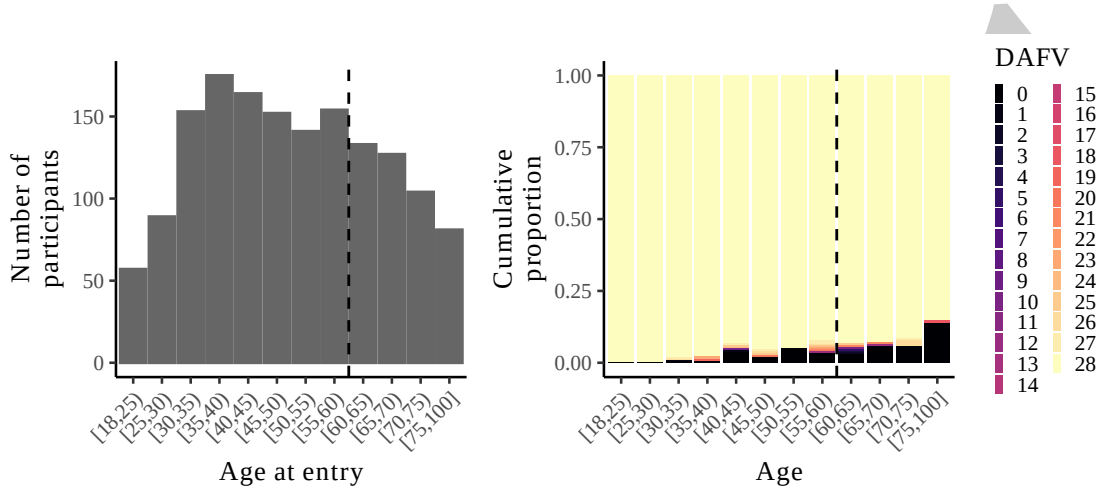

Figure 3.22: Distribution of days alive and free of ventilation to day 28 by age groups, ACS-ITT.

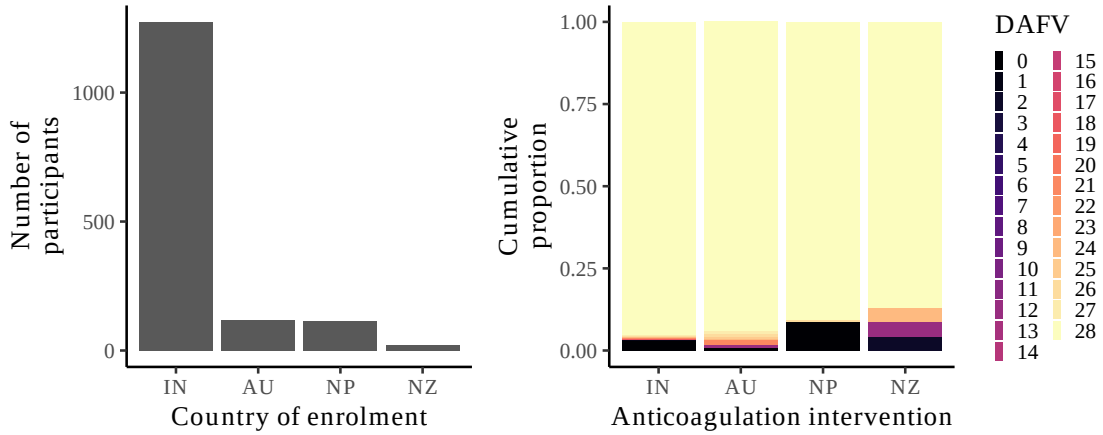

Figure 3.23: Distribution of days alive and free of ventilation to day 28 by country of randomisation, ACS-ITT.

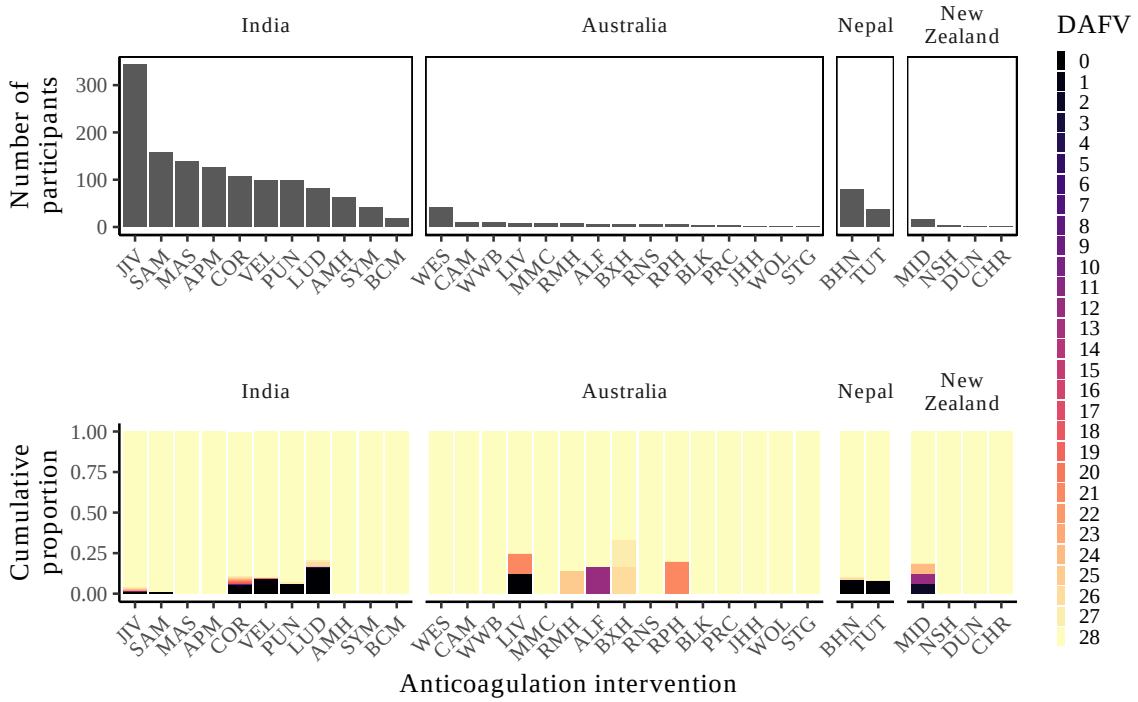

Figure 3.24: Distribution of days alive and free of ventilation to day 28 by country and site of randomisation, ACS-ITT.

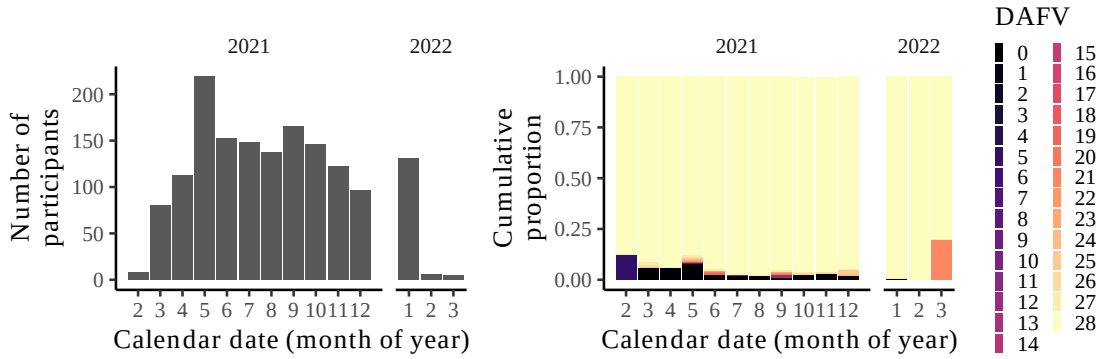

Figure 3.25: Distribution of days alive and free of ventilation to day 28 by calendar time (month) of randomisation, ACS-ITT.

3.7 Presence of patient reported shortness of breath at day 28 by model covariates (ACS-ITT)

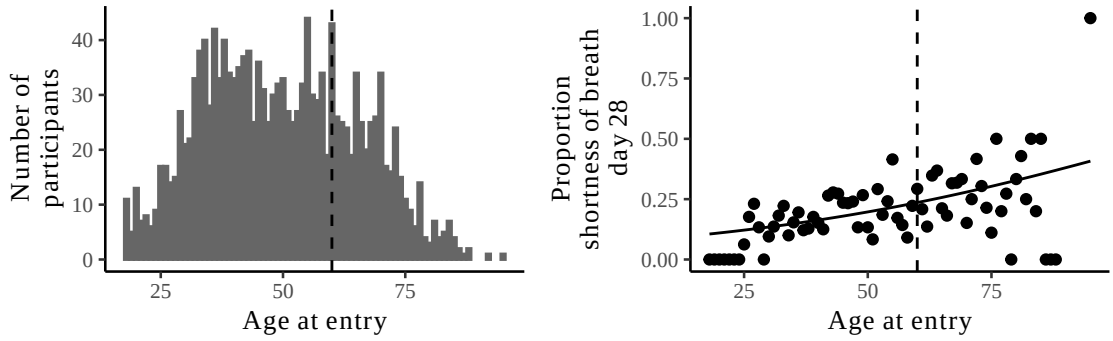

Figure 3.26: Proportion with patient reported shortness of breath at day 28 by age groups.

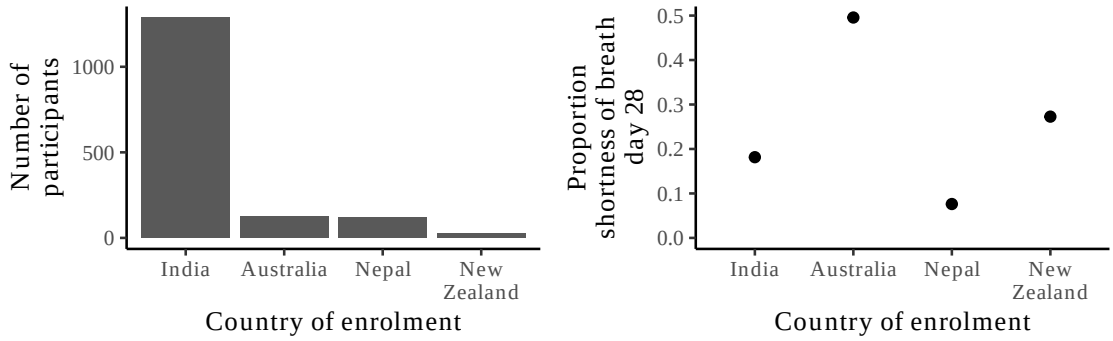

Figure 3.27: Proportion with patient reported shortness of breath at day 28 by country of randomisation.

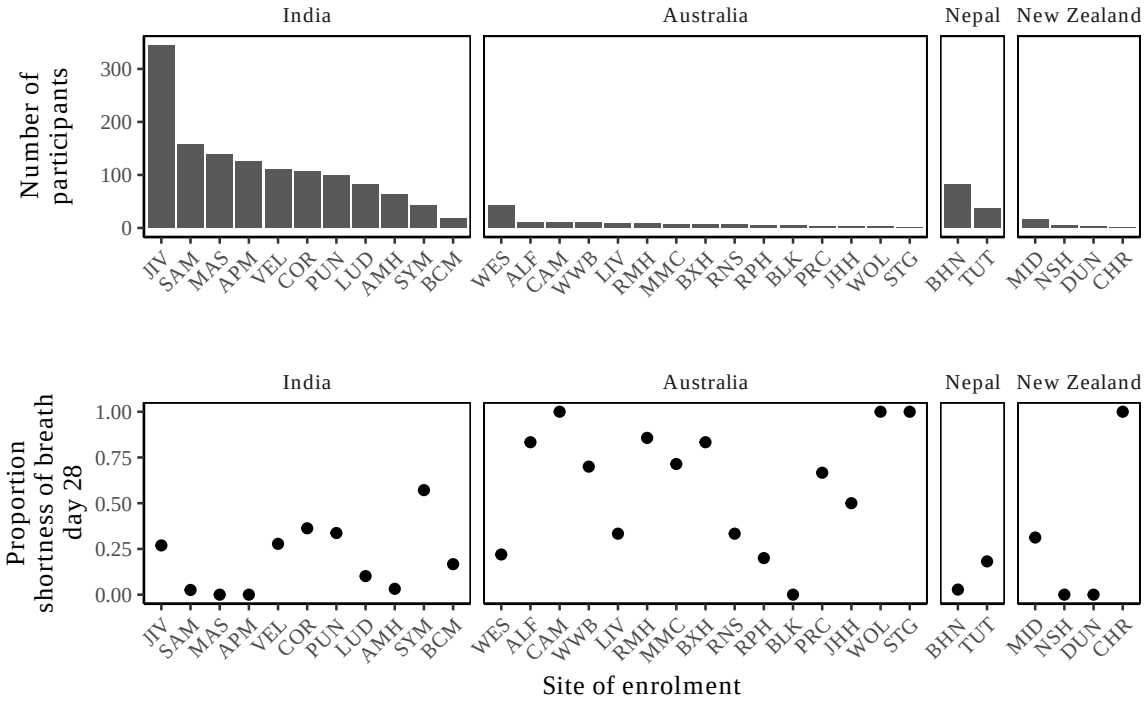

Figure 3.28: Proportion with patient reported shortness of breath at day 28 by country and site of randomisation.

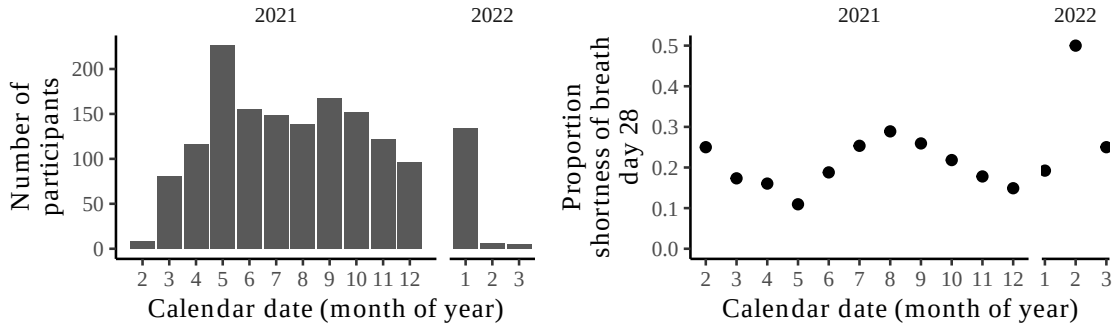

Figure 3.29: Proportion with patient reported shortness of breath at day 28 by calendar time (month) of randomisation.

3.8 Primary Model Posterior Predictive Summary

3.8.1 Primary Outcome

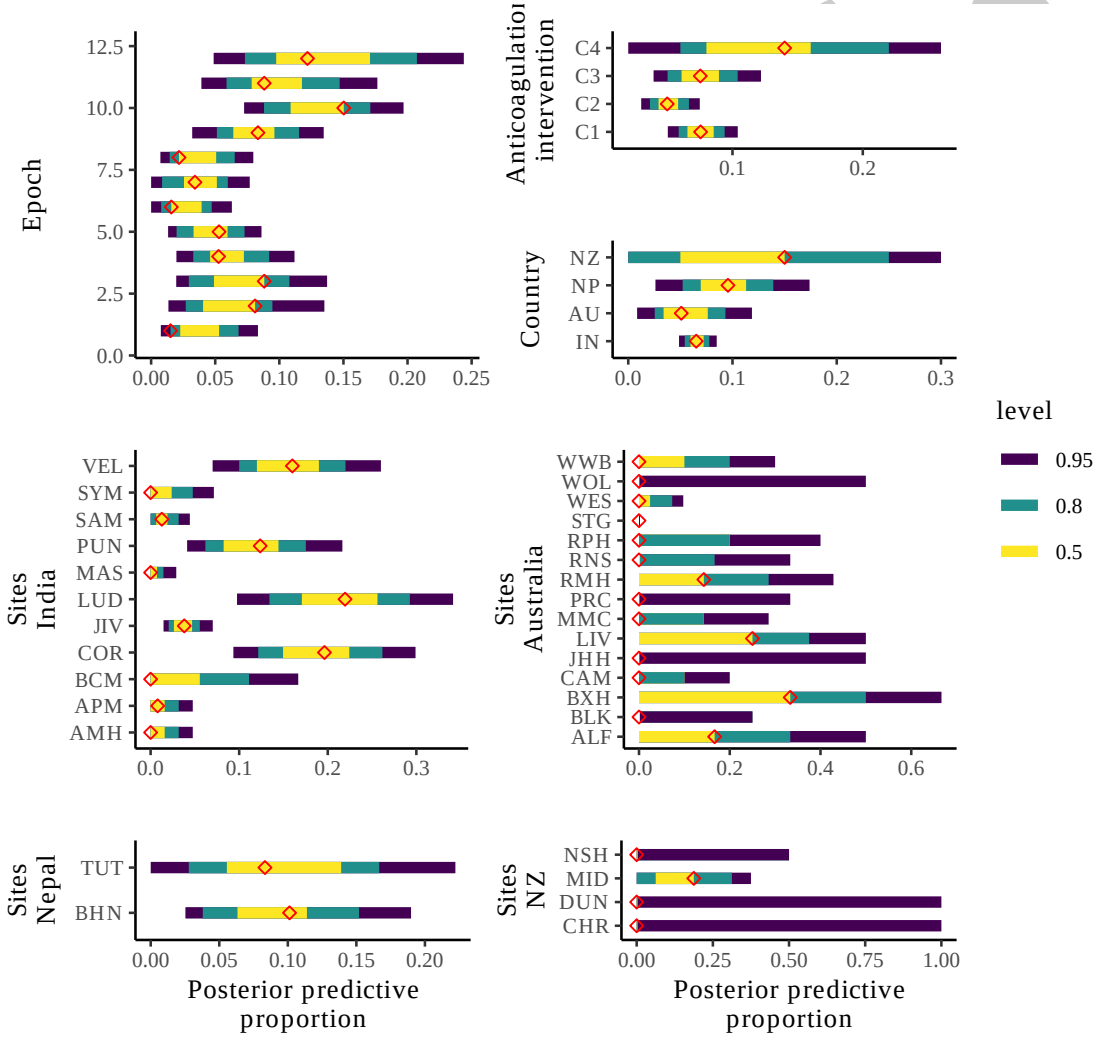

Figure 3.30: Posterior predictive distribution for primary outcome by model covariates for primary model using ACS-ITT. Red diamond indicates observed proportions.

3.8.2 WHO outcome scale dat day 28

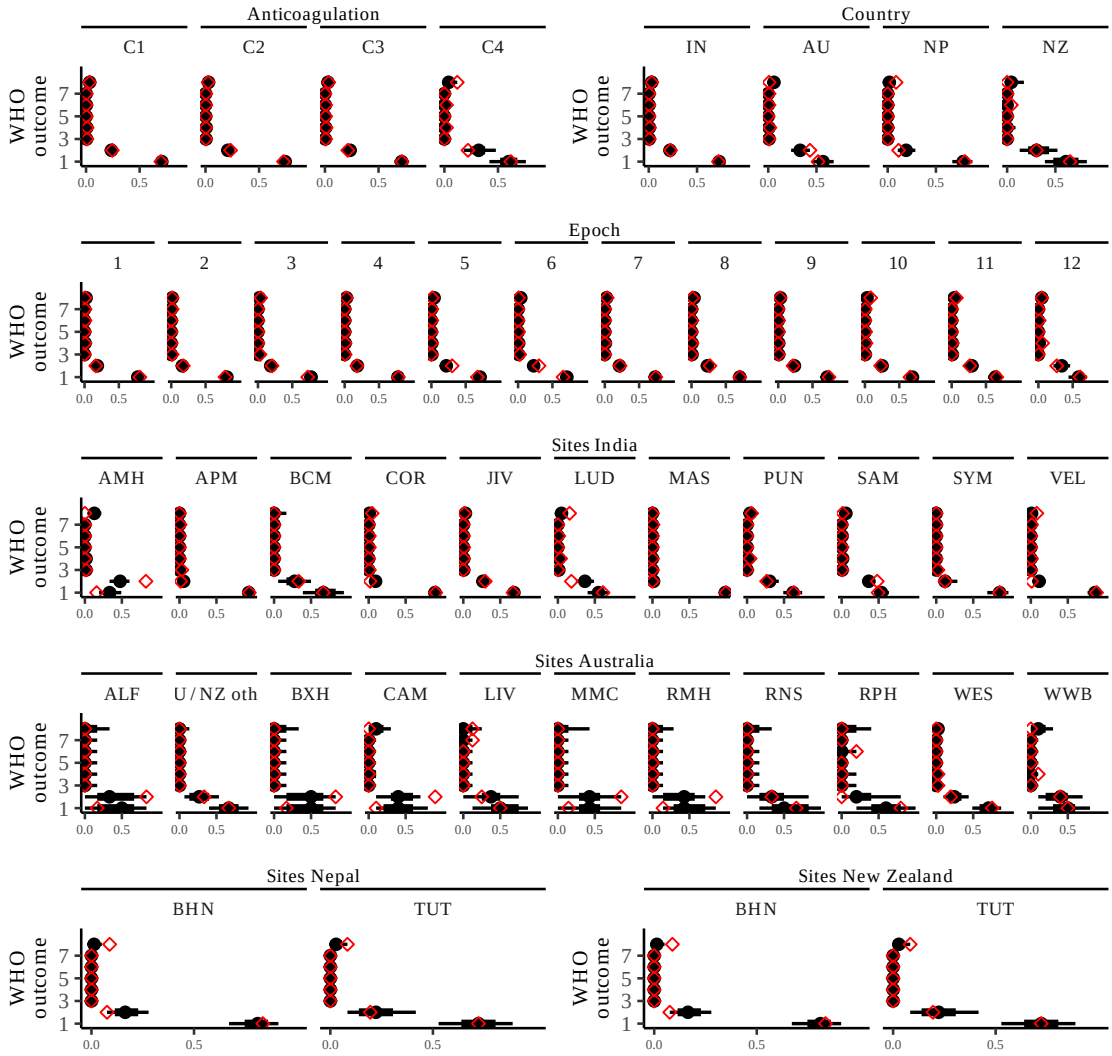

Figure 3.31: Posterior predictive distribution for WHO scale by model covariates for primary model using ACS-ITT. Red diamond indicates observed proportions.

3.8.3 Mortality to day 28

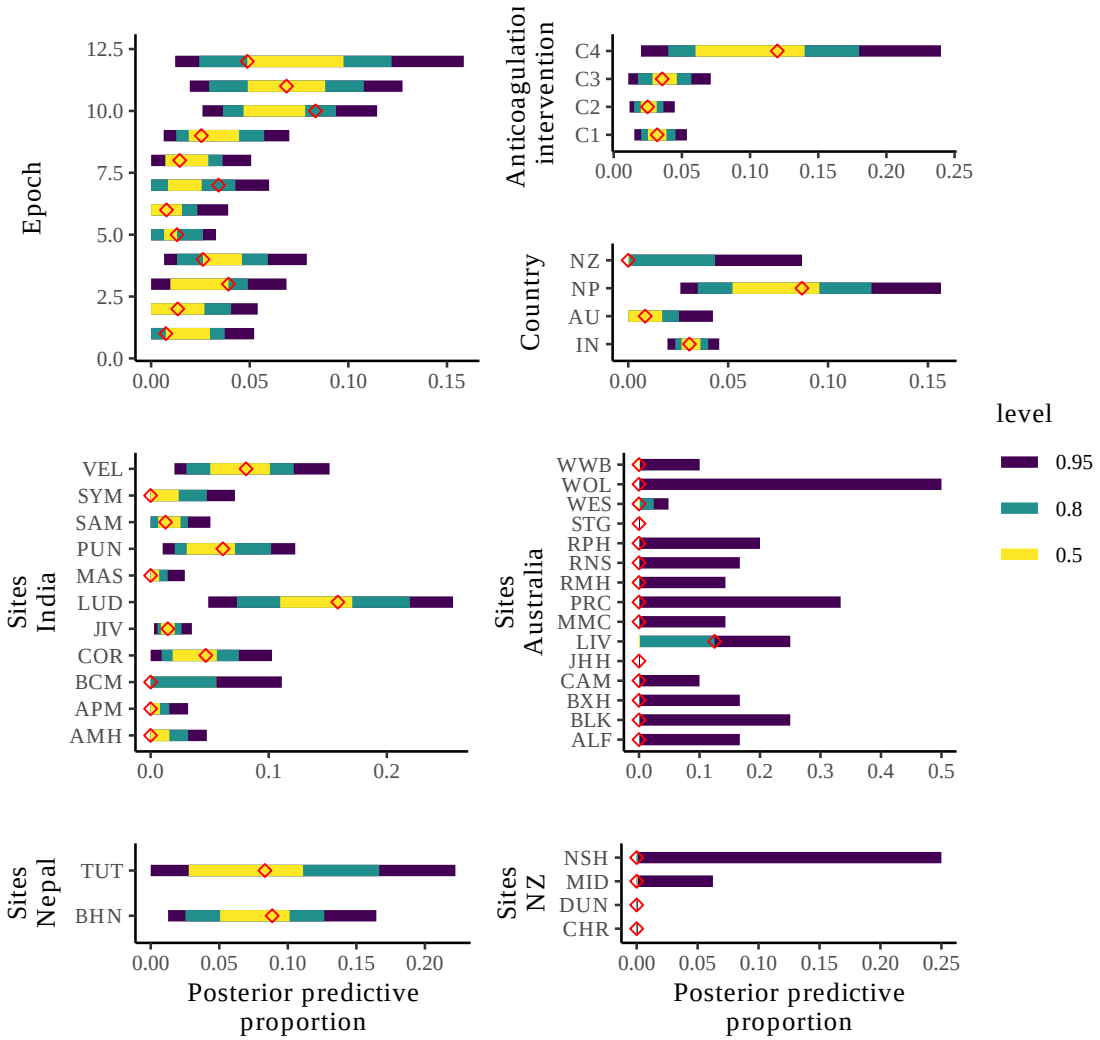

Figure 3.32: Posterior predictive distribution for mortality to day 28 by model covariates for primary model using ACS-ITT. Red diamond indicates observed proportions.

3.8.4 Days alive and free of hospital to day 28

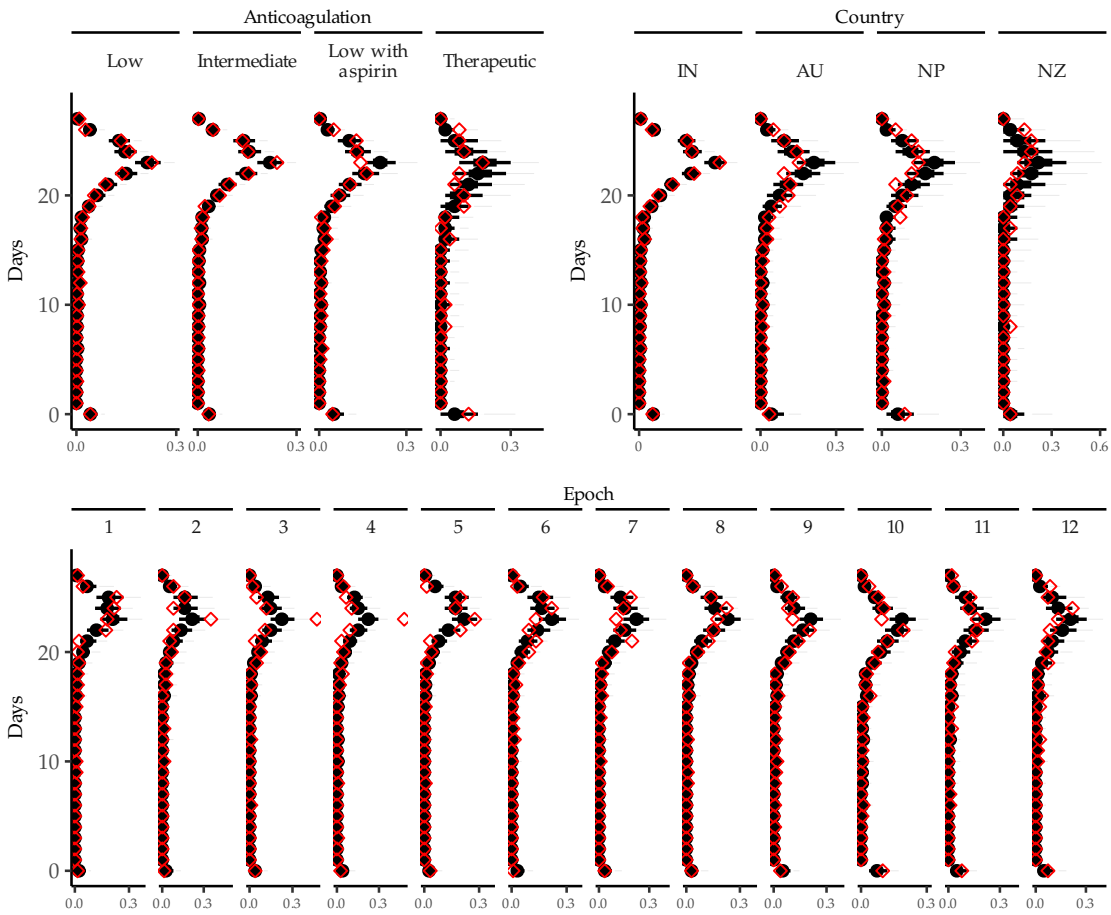

Figure 3.33: Posterior predictive distribution for days alive and free of hospital to day 28 by model covariates (intervention, country, and epoch) for primary model using ACS-ITT. Red diamond indicates observed proportions.

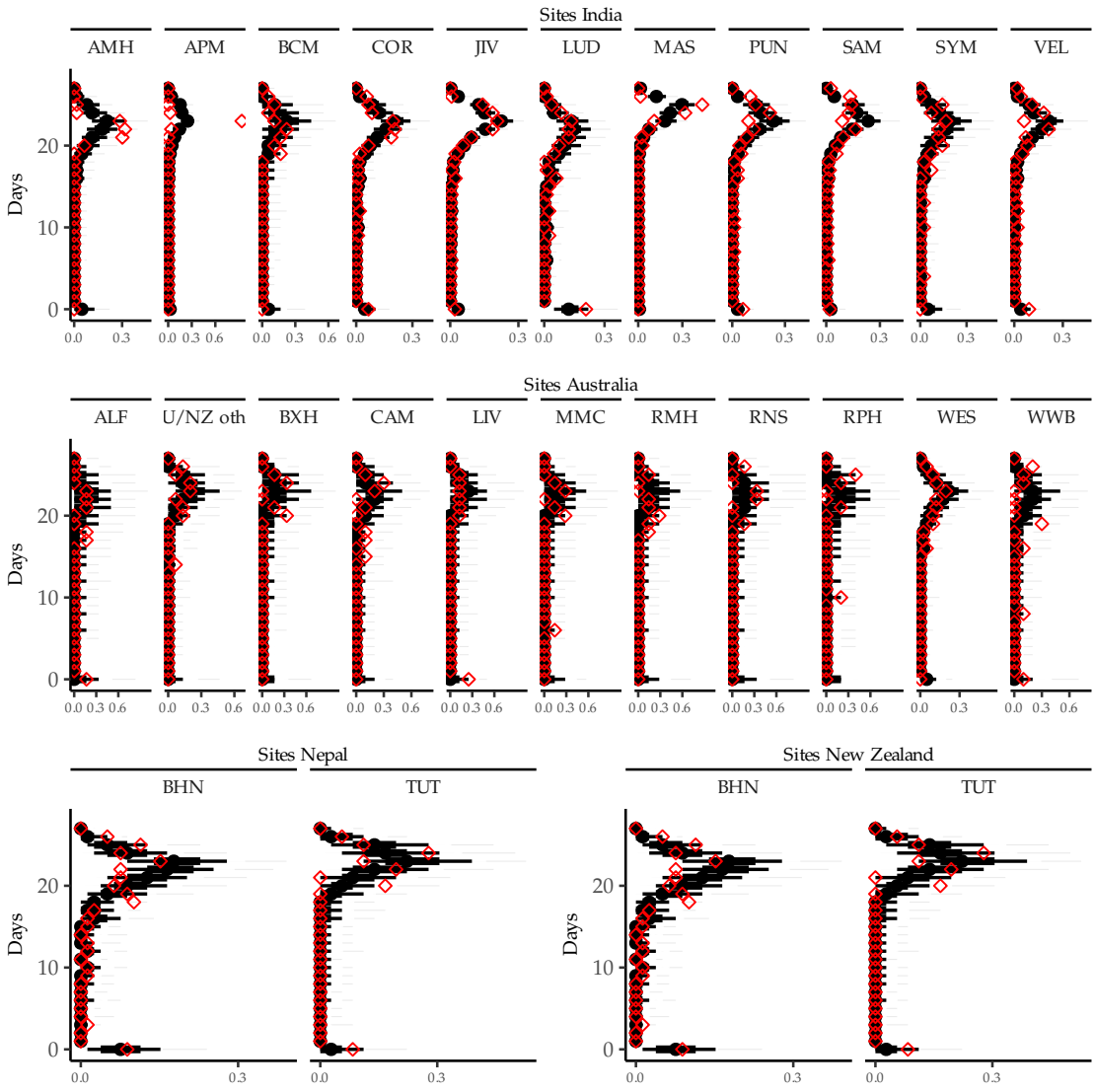

Figure 3.34: Posterior predictive distribution for days alive and free of hospital to day 28 by model covariates (site) for primary model using ACS-ITT. Red diamond indicates observed proportions.

3.8.5 Days alive and free of ventilation to day 28

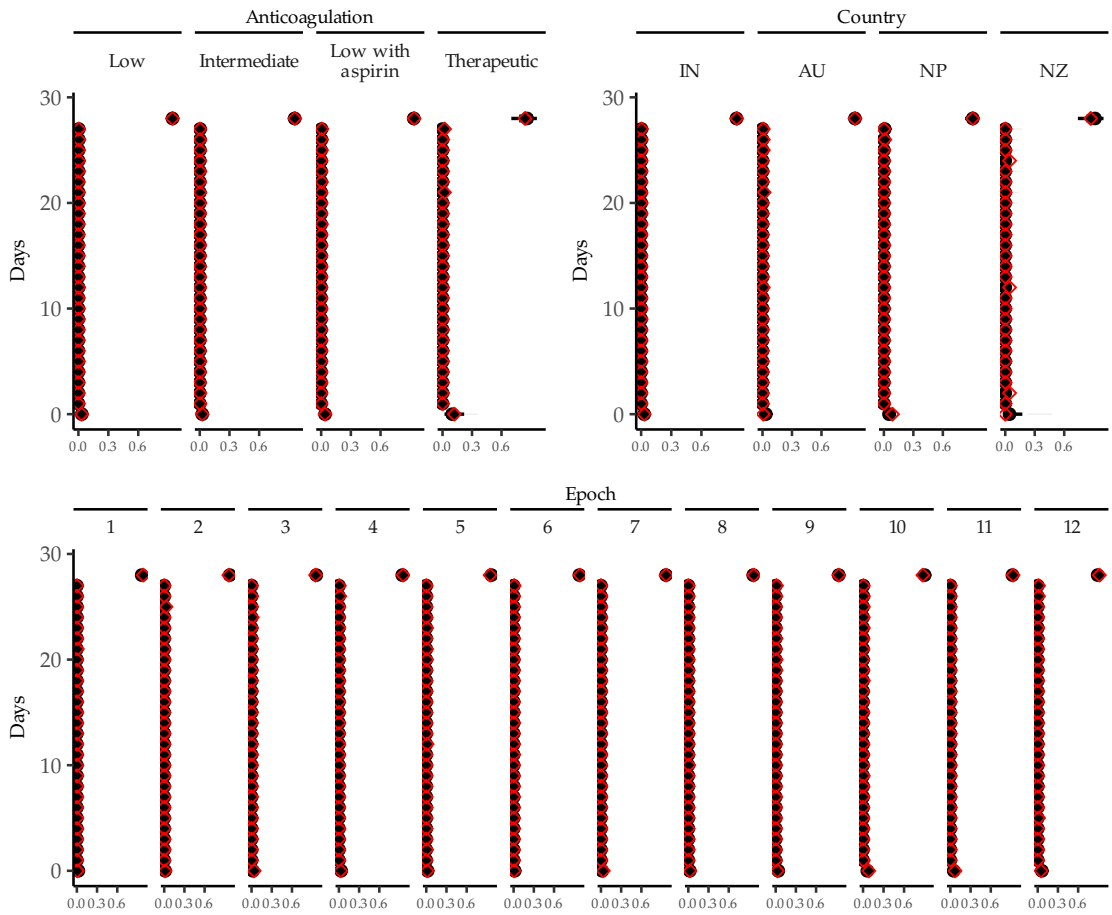

Figure 3.35: Posterior predictive distribution for days alive and free of ventilation to day 28 by model covariates (intervention, country, and epoch) for primary model using ACS-ITT. Red diamond indicates observed proportions.

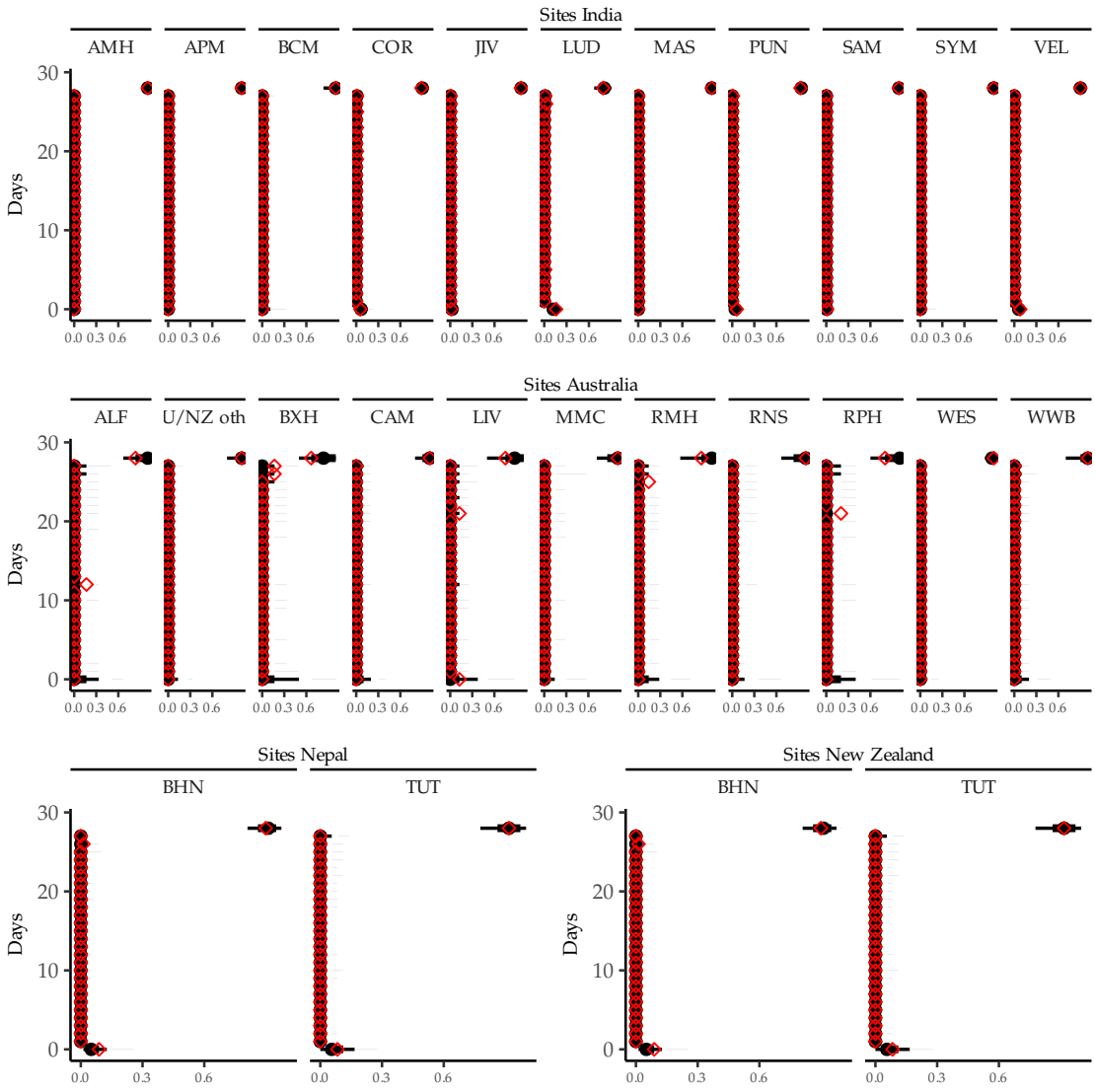

Figure 3.36: Posterior predictive distribution for days alive and free of ventilation to day 28 by model covariates (site) for primary model using ACS-ITT. Red diamond indicates observed proportions.

3.8.6 Presence of patient reported shortness of breath at day 28

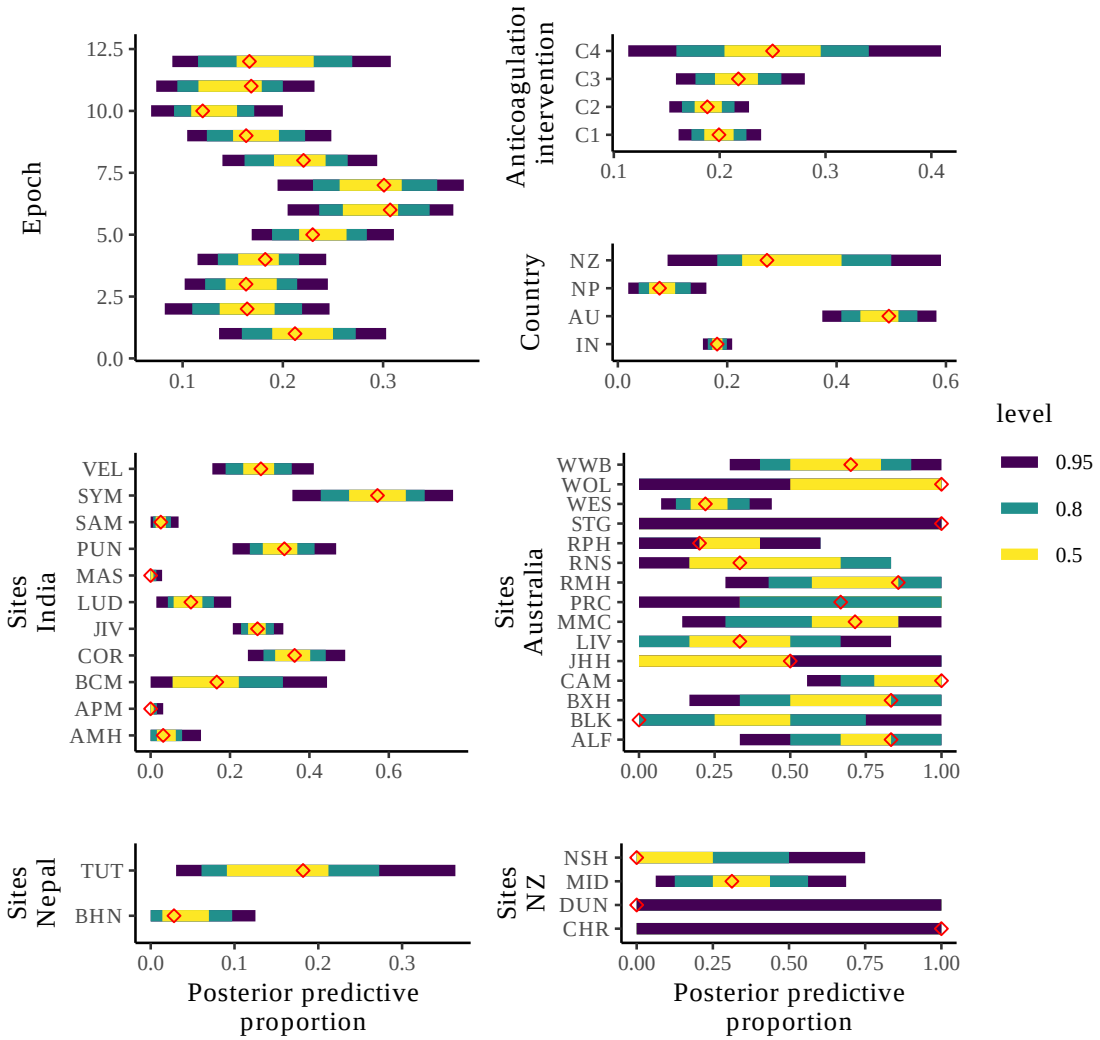

Figure 3.37: Posterior predictive distribution for shortness of breath at day 28 by model covariates for primary model using ACS-ITT. Red diamond indicates observed proportions.

3.8.7 mMRC Breathlessness Scale

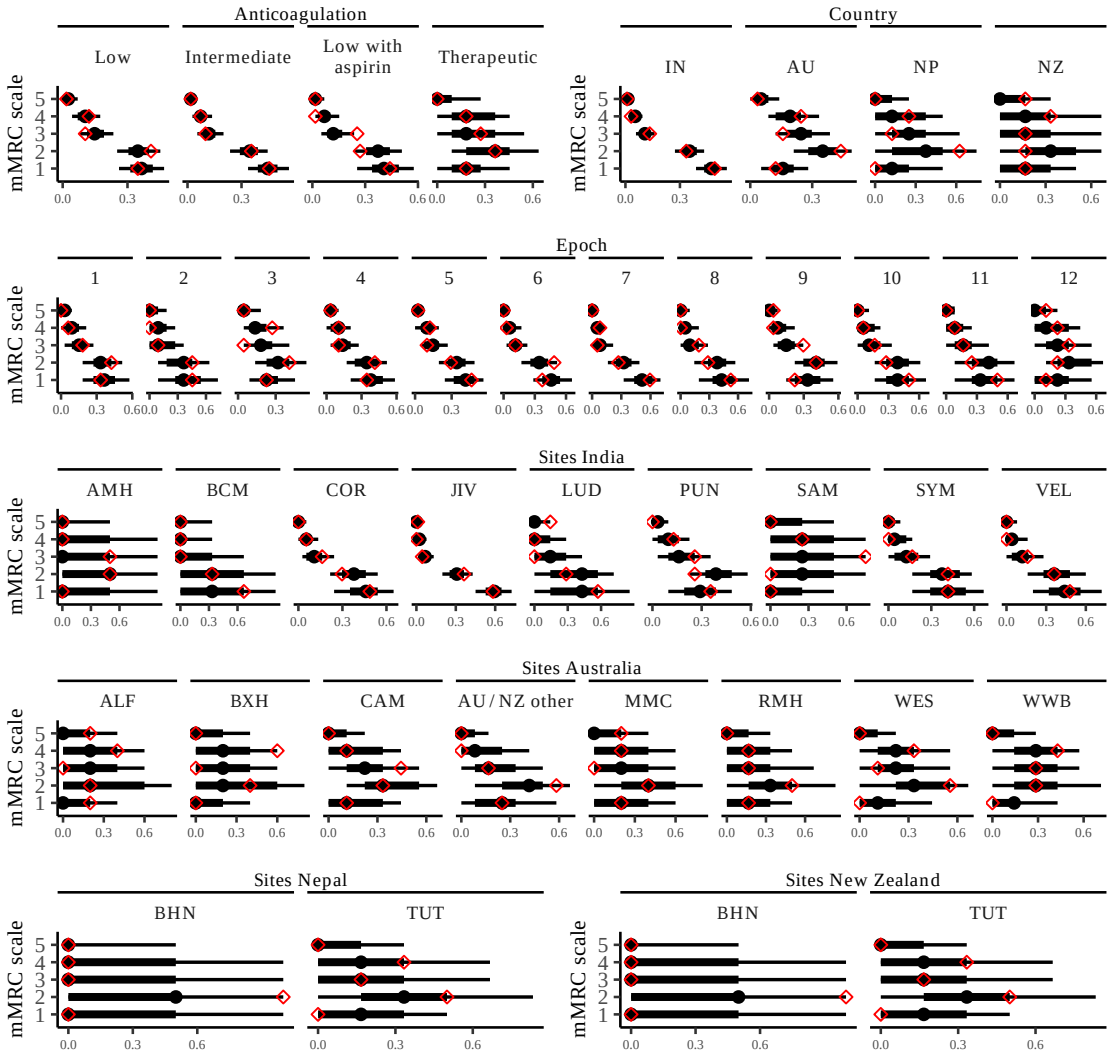

Figure 3.38: Posterior predictive distribution for mMRC scale by model covariates for primary model using ACS-ITT. Red diamond indicates observed proportions.