Colchicine and aspirin in community patients with COVID-19 (ACT): an open-label, factorial, randomised, controlled trial

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For the Spanish translation of the abstract see Online for appendix 3

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Summary

Background The large number of patients worldwide infected with the SARS-CoV-2 virus has overwhelmed health-care systems globally. The Anti-Coronavirus Therapies (ACT) outpatient trial aimed to evaluate anti-inflammatory therapy with colchicine and antithrombotic therapy with aspirin for prevention of disease progression in community patients with COVID-19.

Methods The ACT outpatient, open-label, 2×2 factorial, randomised, controlled trial, was done at 48 clinical sites in 11 countries. Patients in the community aged 30 years and older with symptomatic, laboratory confirmed COVID-19 who were within 7 days of diagnosis and at high risk of disease progression were randomly assigned (1:1) to receive colchicine 0·6 mg twice daily for 3 days and then 0·6 mg once daily for 25 days versus usual care, and in a second (1:1) randomisation to receive aspirin 100 mg once daily for 28 days versus usual care. Investigators and patients were not masked to treatment allocation. The primary outcome was assessed at 45 days in the intention-to-treat population; for the colchicine randomisation it was hospitalisation or death, and for the aspirin randomisation it was major thrombosis, hospitalisation, or death. The ACT outpatient trial is registered at ClinicalTrials.gov, NCT04324463 and is ongoing.

Findings Between Aug 27, 2020, and Feb 10, 2022, 3917 patients were randomly assigned to colchicine or control and to aspirin or control; after excluding 36 patients due to administrative reasons 3881 individuals were included in the analysis (n=1939 colchicine *vs* n=1942 control; n=1945 aspirin *vs* 1936 control). Follow-up was more than 99% complete. Overall event rates were 5 (0·1%) of 3881 for major thrombosis, 123 (3·2%) of 3881 for hospitalisation, and 23 (0·6%) of 3881 for death; 66 (3·4%) of 1939 patients allocated to colchicine and 65 (3·3%) of 1942 patients allocated to control experienced hospitalisation or death (hazard ratio [HR] 1·02, 95% CI 0·72–1·43, p=0·93); and 59 (3·0%) of 1945 of patients allocated to aspirin and 73 (3·8%) of 1936 patients allocated to control experienced major thrombosis, hospitalisation, or death (HR 0·80, 95% CI 0·57–1·13, p=0·21). Results for the primary outcome were consistent in all prespecified subgroups, including according to baseline vaccination status, timing of randomisation in relation to onset of symptoms (post-hoc analysis), and timing of enrolment according to the phase of the pandemic (post-hoc analysis). There were more serious adverse events with colchicine than with control (34 patients [1·8%] of 1939 *vs* 27 [1·4%] of 1942) but none in either group that led to discontinuation of study interventions. There was no increase in serious adverse events with aspirin versus control (31 [1·6%] *vs* 31 [1·6%]) and none that led to discontinuation of study interventions.

Interpretation The results provide no support for the use of colchicine or aspirin to prevent disease progression or death in outpatients with COVID-19.

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Introduction

It is estimated that 3·8 billion people worldwide have been infected with the SARS-CoV-2 virus, which causes COVID-19, by the end of 2021.[1] Although only a minority of those infected develop moderate or severe disease, the large number of patients requiring hospital admission has overwhelmed many health-care systems, and an estimated 18 million people died by the end of 2021.[2] Vaccination is the most effective way to prevent disease progression and thereby reduce morbidity due to COVID-19, but is not accessible for many people[3] and hesitancy has limited uptake.[4] Additional affordable, efficacious, safe, and readily available treatments that prevent disease progression and death are needed.

COVID-19 disease progression is characterised by dysregulated inflammation and coagulation activation.[5,6] Treatments that target these pathways could help to reduce the need for hospitalisation and prevent complications, including respiratory failure and death. Colchicine is a simple, inexpensive, and widely available

Research in context

Evidence before this study

We did a search of PubMed from Jan 1, 2020, to May 31, 2022, in English language only using the terms "colchicine" AND "coronavirus" OR "COVID" OR "coronavirus disease-2019" OR "coronavirus 2019" OR "COVID19" OR "covid-19 " AND "clinical trial" OR "randomized controlled trial". Meta-analyses did not indicate a benefit of colchicine in outpatients or inpatients with COVID-19, but the estimate obtained from the only large trial in outpatients suggested a reduction in hospitalisation or death. One randomised trial of aspirin in outpatients with COVID-19 was stopped early because of low event rates and therefore the potential benefit was unknown.

Added value of this study

The ACT outpatient trial testing colchicine and aspirin in 3881 outpatients with COVID-19 found lower than expected rates of hospitalisation and no evidence that either colchicine or aspirin prevented disease progression.

Implications of all the available evidence

The results of the ACT study taken together with the results of our updated meta-analysis, suggest that there is no evidence to support the use of either colchicine or aspirin to prevent disease progression or death in outpatients with COVID-19. The lower-than-expected event rates in the ACT outpatient trial might reflect lower virulence of emerging COVID-19 variants, increasing immunity in the population due to infection and use of vaccination, the increasing use of effective treatments, and changing patterns of medical care.

oral therapy that targets inflammation.[7] Aspirin is effective for prevention and treatment of venous and arterial thrombosis.[8–10] In outpatients with COVID-19, one large randomised trial suggested that colchicine might be effective for preventing disease progression.[11] Aspirin and oral anticoagulants have undergone randomised evaluation in outpatients with COVID-19 but the trials were stopped early owing to low event rates and provided no evidence of benefit.[12–15]

The Anti-Coronavirus Therapy (ACT) trials are a 2 × 2 factorial design studies that evaluated anti-inflammatory and antithrombotic therapy in inpatients and outpatients with COVID-19.[16] Here we report the results of the ACT outpatient trial, which aimed to test colchicine and aspirin in community patients with COVID-19. The results of the ACT inpatient trial are reported separately.[17]

Methods

Study design

The ACT outpatient trial was an open-label, factorial, randomised, controlled trial done at 48 sites (community practices and hospital outpatient sites) in 11 countries, with the first patient enrolled on Aug 27, 2020, and the last on Feb 10, 2022.

In brief, this is a 2×2 factorial trial in which community patients with COVID-19 were randomly assigned to colchicine or control (1:1 ratio) as well as to aspirin or control (1:1 ratio). All participating trial centres obtained ethics approval before commencing recruitment and all patients provided informed consent.

The Population Health Research Institute, McMaster University, Ontario, Canada, coordinated the ACT trials and was responsible for all aspects of trial conduct. A trial steering committee designed the study and approved the protocol. The steering committee met regularly to assess study progress and to discuss necessary interventions or protocol amendments as needed. During the trial, the protocol was amended by the steering committee to restrict inclusion to patients older than 30 years and increase the sample size from 2500 to 3500.[16] 334 patients were aged 18–30 years (inclusive) before July 15, 2021, the date of protocol amendment. At that point, 1507 outpatients were enrolled.

The design of the ACT outpatient trial has been published previously,[16] and the protocol is available online. The statistical analysis plan was finalised before any investigator was made aware of the trial results.

Participants

Patients were eligible for inclusion in the ACT outpatient trial if they were symptomatic with laboratory-confirmed COVID-19 disease, at least 30 years old and within 7 days (ideally 72 h) of diagnosis or worsening clinically (but not requiring hospitalisation). To be included, patients younger than 70 years had to have at least one additional risk factor for disease progression, including male sex, body-mass index of at least 30 kg/m², chronic cardiovascular, respiratory, or renal disease, active cancer, or diabetes. Patients were excluded if they had advanced kidney or advanced liver disease that would preclude them from receiving study interventions, were pregnant or lactating, or had a medical indication, were already using or had a contraindication to the trial interventions. Detailed eligibility criteria are summarised in appendix 4 (p 1).

Randomisation and masking

Patients were randomly assigned (1:1) to receive colchicine or control, and in a second random assignment (1:1) to aspirin once daily or control. Following informed consent, randomisation was done by means of a centralised computer system, which used block randomisation with stratification according to centre. Investigators, patients, and those doing the analyses were not masked to treatment allocation.

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See **Online** for appendix 4

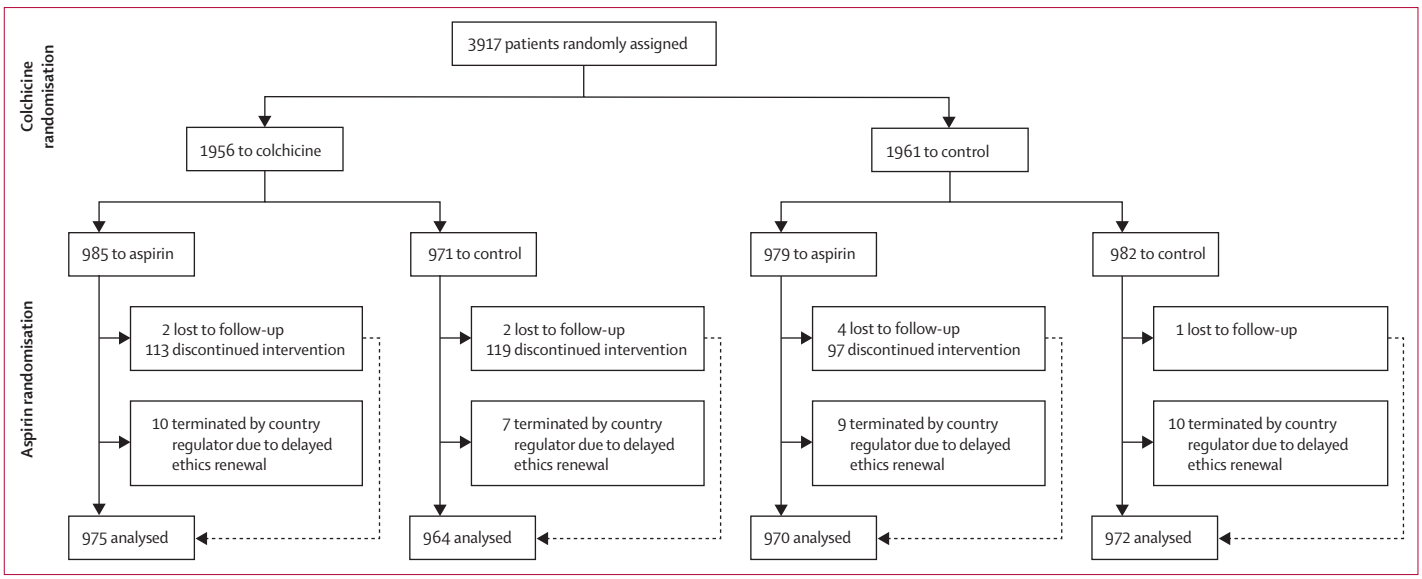

Figure 1: **Trial profile**

	Colchicine versus control group (n=3881)		Aspirin versus control group (n=3881)	
	Colchicine	Control	Aspirin	Control
Randomised	1939	1942	1945	1936
Age in years	45·0 (13·7)	45·0 (13·3)	45·2 (13·5)	44·8 (13·4)
<50	1225 (63·2%)	1234 (63·5%)	1223 (62·9%)	1236 (63·8%)
50–69	632 (32·6%)	634 (32·6%)	642 (33·0%)	624 (32·2%)
≥70	82 (4·2%)	74 (3·8%)	80 (4·1%)	76 (3·9%)
Female	766 (39·5%)	765 (39·4%)	750 (38·6%)	781 (40·3%)
Male	1173 (60·5%)	1177 (60·6%)	1195 (61·4%)	1155 (59·7%)
Ethnicity				
Arab	1014 (52·3%)	1024 (52·7%)	1021 (52·5%)	1017 (52·5%)
White European	429 (22·1%)	426 (21·9%)	424 (21·8%)	431 (22·3%)
Latin American	163 (8·4%)	157 (8·1%)	164 (8·4%)	156 (8·1%)
South Asian	239 (12·3%)	230 (11·8%)	241 (12·4%)	228 (11·8%)
Other Asian	49 (2·5%)	60 (3·1%)	51 (2·6%)	58 (3·0%)
Other	45 (2·3%)	44 (2·3%)	44 (2·3%)	45 (2·3%)
Smoking or vaping				
Current	397 (20·5%)	390 (20·1%)	403 (20·7%)	384 (19·8%)
Former	185 (9·5%)	191 (9·8%)	195 (10·0%)	181 (9·3%)
Never	1357 (70·0%)	1360 (70·0%)	1347 (69·3%)	1370 (70·8%)
Body-mass index (kg/m²)	29·7 (5·8)	30·2 (6·0)	29·9 (5·8)	30·1 (6·0)
Diabetes	256 (13·2%)	264 (13·6%)	247 (12·7%)	273 (14·1%)
Hypertension	435 (22·4%)	422 (21·7%)	440 (22·6%)	417 (21·5%)
Dyslipidaemia	163 (8·4%)	166 (8·5%)	173 (8·9%)	156 (8·1%)
Cardiovascular disease	98 (5·1%)	89 (4·6%)	100 (5·1%)	87 (4·5%)
Coronary disease or myocardial infarction	68 (3·5%)	73 (3·8%)	75 (3·9%)	66 (3·4%)
Stroke	5 (0·3%)	1 (0·1%)	2 (0·1%)	4 (0·2%)
Peripheral artery disease	20 (1·0%)	14 (0·7%)	21 (1·1%)	13 (0·7%)
Chronic lung disease	151 (7·8%)	149 (7·7%)	139 (7·1%)	161 (8·3%)

(Table 1 continues on next page)

Procedures

Patients received either oral colchicine 0·6 mg twice daily for 3 days and then 0.6 mg once daily for 25 days or control, and in a second randomisation received oral aspirin 100 mg once daily as a tablet or control. Treatments were continued for 28 days. Additional details of the dosing regimens of the interventions are provided in appendix 4 (p 2). The control groups received usual care, as established by the local investigator. Remote monitoring using a combination of telephone and video was used to assess site enrolment procedures, data management, safety reporting, adherence to the protocol, and regulatory compliance. Patients were contacted at day 8 and day 45 to evaluate adherence and to collect information on adverse events and outcomes.

Outcomes

Outcomes are detailed in appendix 4 (p 3). The primary outcome for the comparison between colchicine and control was a composite of hospitalisation or death. The primary outcome for the comparison between aspirin and control was a composite of major thrombosis (includes pulmonary embolism, acute limb ischaemia, stroke, and myocardial infarction), hospitalisation or death. The secondary outcome for the aspirin vs control comparison was any thrombosis (major thrombosis plus venous thromboembolism). Additional exploratory outcomes were the composite of hospitalisation or respiratory death and individual components of composites. Analyses on the effect of treatments were done in prespecified and post-hoc subgroups.

Statistical analysis

All analyses were done according to the intention-to-treat principle and included all patients from the time of

randomisation. Continuous data were presented as means (SD) or medians (IQR) (depending on their distribution) and categorical data were presented as n (%). Kaplan-Meier curves were used for survival analysis and stratified Cox proportional hazard models with treatment group as a predictive variable and stratified by the other group of the factorial design were used to estimate the hazard ratio (HR) and the 95% CIs. We prespecified subgroup analyses to explore whether the effect of treatment was modified by age, sex, comorbidities at baseline, and by vaccination status at time of enrolment. Analyses of timing of randomisation in relation to the onset of symptoms and timing of enrolment in relation to the phase of the pandemic were done post-hoc. The ACT outpatient trial aimed to enroll 3500 patients which would provide at least 80% power with a two-sided α of 0·05 to detect a 30% relative risk reduction for each intervention versus control assuming an overall incidence rate of the primary outcome of 7·5% at 45 days and allowing for up to 2% loss to follow-up. There was no adjustment for multiplicity of testing because there was only one primary outcome for each randomisation. We prespecified that other outcomes would be considered supportive if the results were consistent with the primary outcome. All analyses were done by means of SAS version 9.4.

An independent data and safety monitoring committee (DSMC) oversaw the ACT trials and did a formal interim analysis when approximately two-thirds of the target sample size had been enrolled. The interim analysis was guided by the Haybittle-Peto boundary of three standard deviations to indicate benefit. If this boundary was crossed it had to be confirmed at a subsequent analysis done at least 1 month later for the trial to be stopped for efficacy. The DSMC also examined the consistency of results across the inpatient and outpatient trials. No modification to the level of significance of the primary outcome was needed because of the extreme boundaries applied.

In order to contextualise our results, we did a literature search of electronic databases (PubMed) to identify major trials of colchicine in outpatients and inpatients with COVID-19. We restricted inclusion to randomised trials involving at least 100 adults that reported mortality, which was the main outcome of interest. The data for the primary outcome in each trial of colchicine in outpatients and inpatients with COVID-19 as well as for mortality were pooled by means of a fixed effects Mantel-Haenszel model and are reported as risk ratios and 95% CIs with a p value for heterogeneity. These pooled analyses were not prespecified. The ACT outpatient trial is registered at ClinicalTrials.gov, NCT04324463.

Role of the funding source

The funders of the study had no role in study design, patient recruitment, data collection, data analysis, data interpretation, writing of the report.

	Colchicine versus control group (n=3881)		Aspirin versus control group (n=3881)	
	Colchicine	Control	Aspirin	Control
(Continued from previous page)				
Chronic kidney disease	46 (2·4%)	51 (2·6%)	54 (2·8%)	43 (2·2%)
Immunosuppressed	40 (2·1%)	45 (2·3%)	45 (2·3%)	40 (2·1%)
Active cancer	13 (0·7%)	7 (0·4%)	6 (0·3%)	14 (0·7%)
Vaccination status				
Nil	1388 (71·6%)	1421 (73·2%)	1390 (71·5%)	1419 (73·3%)
Partial	118 (6·1%)	103 (5·3%)	114 (5·9%)	107 (5·5%)
Full	419 (21·6%)	402 (20·7%)	425 (21·9%)	396 (20·5%)
Unknown	14 (0·7%)	16 (0·8%)	16 (0·8%)	14 (0·7%)
Symptoms				
Fever	1042 (53·7%)	1057 (54·4%)	1053 (54·1%)	1046 (54·0%)
Cough	1578 (81·4%)	1544 (79·5%)	1554 (79·9%)	1568 (81·0%)
Muscle pain	1240 (64·0%)	1249 (64·3%)	1253 (64·4%)	1236 (63·8%)
Breathlessness	576 (29·7%)	583 (30·0%)	576 (29·6%)	583 (30·1%)
Loss of smell or taste	1097 (56·6%)	1106 (57·0%)	1098 (56·5%)	1105 (57·1%)
Diarrhoea	537 (27·7%)	567 (29·2%)	571 (29·4%)	533 (27·5%)
Fatigue	1214 (62·6%)	1238 (63·7%)	1235 (63·5%)	1217 (62·9%)
Headaches	1039 (53·6%)	1035 (53·3%)	1020 (52·4%)	1054 (54·4%)
Symptom onset to randomisation, days	5·4 (3·1)	5·4 (3·3)	5·4 (3·2)	5·4 (3·2)
Tertile 1 (0–4 days)	787 (40·6%)	789 (40·6%)	771 (39·6%)	805 (41·6%)
Tertile 2 (5–6 days)	586 (30·2%)	571 (29·4%)	590 (30·3%)	567 (29·3%)
Tertile 3 (7–28 days)	564 (29·1%)	579 (29·8%)	581 (29·9%)	562 (29%)
Diagnosis to randomisation, days	1·6 (1·8)	1·6 (1·9)	1·6 (1·8)	1·6 (1·9)

Data are n (%) or mean (SD).

Table 1: **Baseline characteristics**

	Colchicine group (n=1939)	Control group (n=1942)	Hazard ratio (95% CI)	p value
Hospitalisation or death†	66 (3·4%)	65 (3·3%)	1·02 (0·72–1·43)	0·93
Hospitalisation or respiratory death	65 (3·4%)	65 (3·3%)	1·00 (0·71–1·41)	0·99
Hospitalisation	62 (3·2%)	61 (3·1%)	1·02 (0·71–1·45)	0·92
Death	12 (0·6%)	11 (0·6%)	1·09 (0·48–2·47)	0·84
Respiratory death	10 (0·5%)	7 (0·4%)	1·43 (0·54–3·75)	0·47

Data are n (%) unless stated otherwise. *Any thrombosis occurred in three patients randomly assigned to colchicine and four randomly assigned to control. Pulmonary embolism occurred in one patient randomly assigned to colchicine and two randomly assigned to control. †Primary outcome.

Table 2: **Colchicine versus control—outcomes***

Results

The ACT outpatient trial was done at 48 sites in 11 countries, with the first patient enrolled on Aug 27, 2020, and the last on Feb 10, 2022.

Patient flow is presented in figure 1. After screening patients for eligibility, in the 2×2 factorial study design, 3917 patients were randomly allocated to receive colchicine versus control and then randomly allocated to receive aspirin versus control. After exclusion for administrative reasons of 36 patients enrolled in Ecuador (as required by the regulator due to delayed application

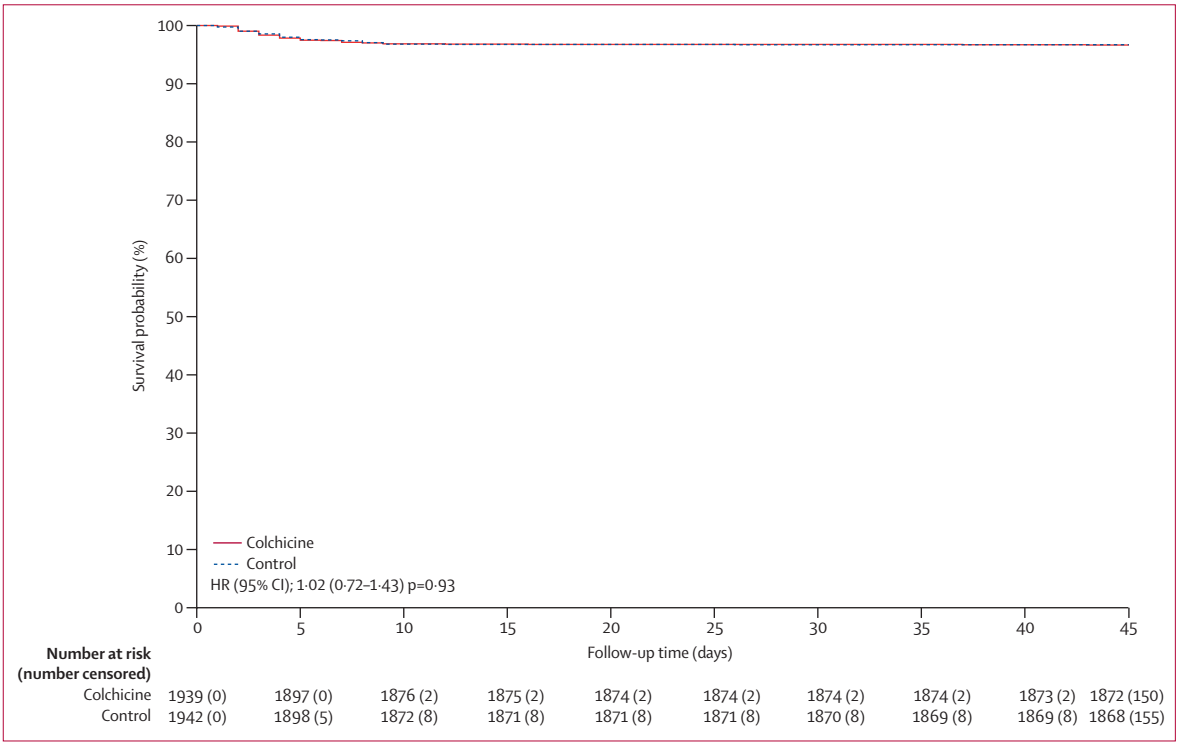

Figure 2: **Kaplan-Meier curve showing the effect of colchicine compared with control on the primary outcome of hospitalisation or death**

	Aspirin (n=1945)	Control (n=1936)	HR (95% CI)	p value
Major thrombosis, hospitalisation, or death*	59 (3·0%)	73 (3·8%)	0·80 (0·57–1·13)	0·21
Any thrombosis†‡	2 (0·1%)	5 (0·3%)	0·40 (0·08–2·06)	0·27
Any thrombosis, hospitalisation, or respiratory death	59 (3·0%)	73 (3·8%)	0·80 (0·57–1·13)	0·21
Major thrombosis§	1 (0·1%)	4 (0·2%)	0·25 (0·03–2·23)	0·21
Any venous thromboembolism	1 (0·1%)	4 (0·2%)	0·25 (0·03–2·24)	0·22
Death	12 (0·6%)	11 (0·6%)	1·09 (0·48–2·46)	0·84
Respiratory death	10 (0·5%)	7 (0·4%)	1·42 (0·54–3·73)	0·48
Hospitalisation	56 (2·9%)	67 (3·5%)	0·83 (0·58–1·19)	0·31

Data are n (%) unless stated otherwise. *Primary outcome. †Includes stroke, myocardial infarction, acute limb ischaemia, and pulmonary embolism. ‡Secondary outcome. §Includes major thrombosis plus deep vein thrombosis.

Table 3: **Aspirin versus control outcomes**

for ethics renewal), 3881 patients enrolled between December 2021 and Feb 10, 2022 were included in the final analyses.

There were 83 protocol deviations, including 24 patients in whom eligibility criteria were not met, 45 for use of prohibited medications, 6 for incorrect product administration, 2 for informed consent irregularities; appendix 4 p 4). Among patients who completed day 45 follow-up, adherence, defined by taking at least 80% of study drug, was 1708 [89·1%] of 1925 for the comparison of colchicine versus control and 1732 [90·0%] of 1925 for aspirin versus control.

Table 1 presents baseline characteristics, clinical features of patients randomly assigned to colchicine versus control and separately for those randomly assigned to aspirin versus control. Baseline characteristics were well matched between groups. Among 3881 patients randomly assigned, mean age was 45·0 years (SD 13·5), 2350 (60·6%) were male, and 2038 (52·5%) were Arab, 855 (22·0%) White European, 469 (12·1%) South Asian, and 320 (8·2%) Latin American. Most patients were not vaccinated: 2809 (72·4%) were confirmed unvaccinated and vaccinated status was unknown in 30 (0·8%) patients, whereas 221 (5·7%) were partially vaccinated and 821 (21·2%) were fully vaccinated (two doses of mRNA vaccine or a single dose of Johnson and Johnson vaccine). Time from symptom onset to randomisation was a mean of 5·4 (SD 3·2) days and the most common symptoms at baseline were cough (3122 [80·4%]), muscle pain (2489 [64·1%]), fatigue (2452 [63·2%]), loss of sense of taste or smell (2203 [56·8%]), and headaches (2074 [53·4%]).

Overall event rates were five [0·1%] of 3881 for major thrombosis, 123 [3·2%] of 3881 for hospitalisation, and 23 [0·6%] of 3881 for death. Event rates for hospitalisation or death in each of the four treatment cells are presented in appendix 4 (p 5). There was no statistical evidence of an interaction between the two randomised treatments for the primary or secondary outcomes.

Event rates for hospitalisation or death fell progressively during the trial (appendix 4 p 12).

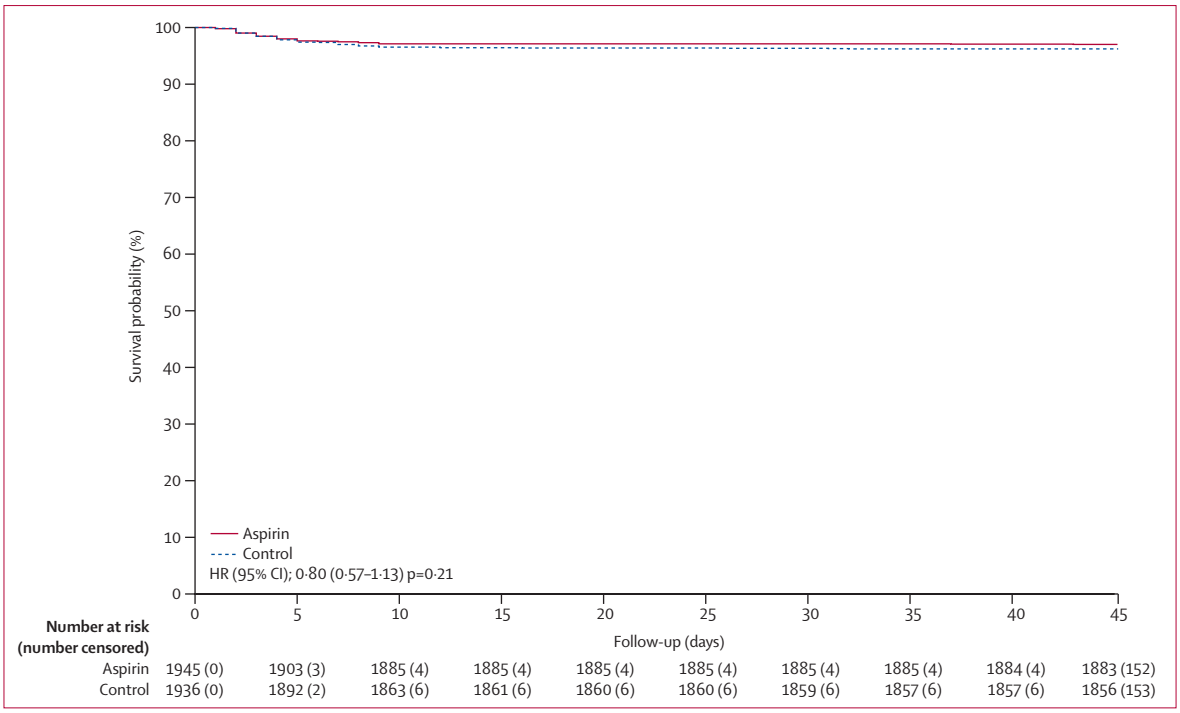

Figure 3: **Kaplan-Meier curve showing the effect of aspirin compared with control on the primary outcome of major thrombosis, hospitalisation, or death**

Outcomes for colchicine versus control are summarised in table 2 and a Kaplan-Meier curve for the primary outcome is shown in figure 2. Follow-up for the primary outcome at day 45 was 99·7% complete. Colchicine compared with control did not significantly reduce the primary outcome of hospitalisation or death (66 [3·4%] events in 1939 participants versus 65 [3·3%] events in 1942 participants; HR 1·02, 95% CI 0·72–1·43; p=0·93), the exploratory outcomes of hospitalisation or respiratory death (65 [3·4%] *vs* 65 [3·3%] events; HR 1·00, 0·71–1·41; p=0·99), or individual components of these outcomes. There was no evidence of benefit of colchicine in prespecified subgroups or in a subgroup defined post hoc according to timing of enrolment according to the phase of the pandemic (all p values for interaction were non-significant; appendix 4 p 13).

Outcomes for aspirin versus control are summarised in table 3 and a Kaplan-Meier curve for the primary outcome is shown in figure 3. Follow-up for the primary outcome at day 45 was 99·7% complete. Aspirin versus control did not significantly reduce the primary outcome of major thrombosis, hospitalisation, or death (59 [3·0%] events in 1945 participants *vs* 73 [3·8%] events in 1936 participants; HR 0·80, 95% CI 0·57–1·13, p=0·21), the secondary exploratory, post-hoc outcomes of any thrombosis, hospitalisation, or respiratory death (59 [3·0%] *vs* 73 [3·8%] events; HR 0·80, 0·57–1·13, p=0·21), or individual components of these outcomes. There was no evidence of benefit of aspirin in prespecified subgroups or in a subgroup defined post hoc including according to timing of enrolment according to the phase of the pandemic (all p values for interaction were non-significant; appendix 4 p 14). Patients randomly assigned to colchicine had more serious adverse events than those randomly assigned to control (34 patients [1·8%] of 1939 *vs* 27 [1·4%] of 1942) but there were no serious adverse events in either group that led to discontinuation of study interventions. A similar number of patients randomly assigned to aspirin versus control had a serious adverse event (31 [1·6%] *vs* 31 [1·6%]) but no serious adverse events led to discontinuation of study interventions. A listing of serious adverse events is provided in appendix 4 (colchicine versus control p 6–8; aspirin versus control p 9–11.

Figure 4 presents the results of a meta-analysis of the effects of colchicine compared with control on the reported primary outcome and the outcome of mortality in outpatients and inpatients with COVID-19.[11,16,18–21] In two outpatient trials (including our results) involving a combined total of 8369 patients, colchicine compared with control did not significantly reduce the primary outcome (170 *vs* 196 events, risk ratio 0·87, 95% CI 0·71–1·07; p=0·26) or mortality (17 *vs* 20 deaths; risk ratio 0·85, 0·45–1·63; p=0·34). In four inpatient trials (including the results of the ACT inpatient trial) involving a combined total of 15 335 patients, colchicine compared with control did not reduce the primary outcome (1702 *vs* 1737 events; RR 0·99, 0·94–1·05; p=0·10), and in five inpatient trials (including the results of the ACT inpatient trial) involving a combined total of 15 495 patients did not have a

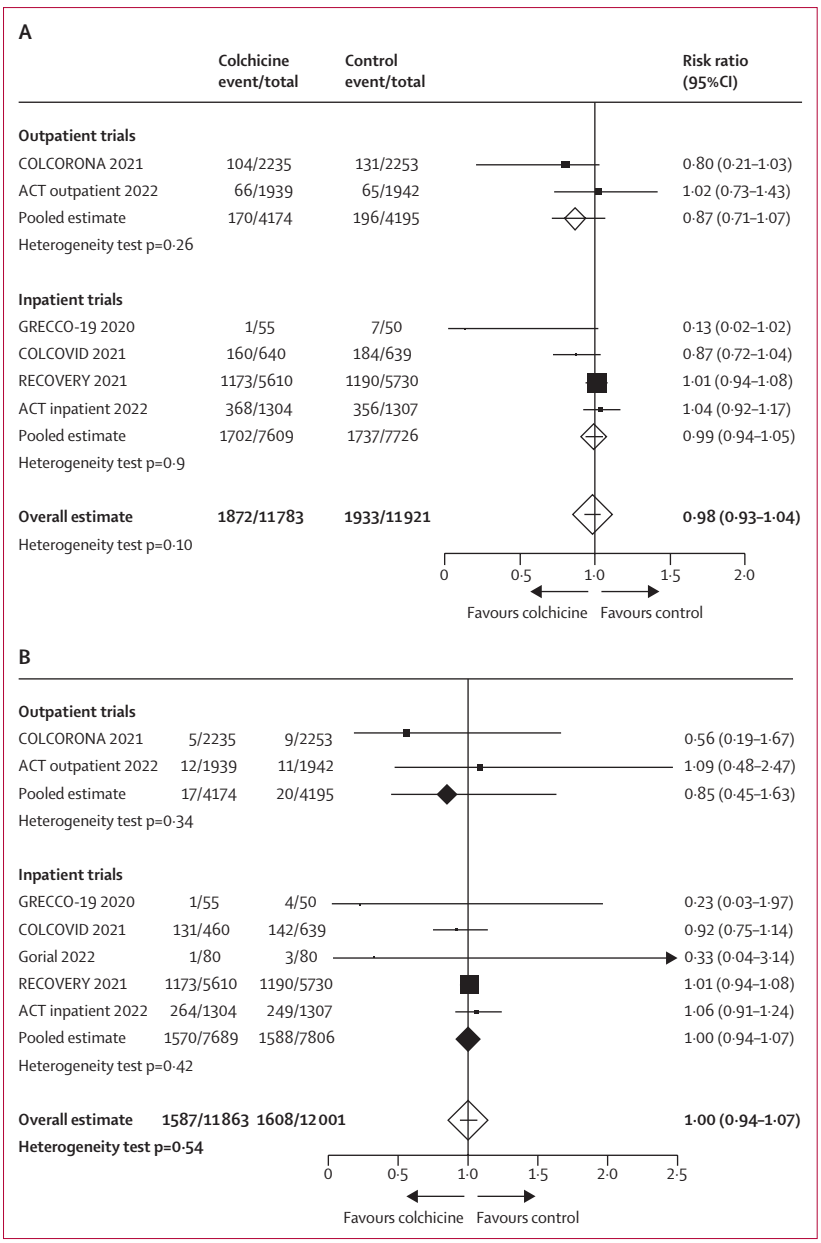

Figure 4: **Meta-analysis of randomised trials of colchicine versus control on the trial primary outcome as reported in the trials (A) and mortality (B)**

significantly reduced mortality (1570 *vs* 1588 deaths; RR 1·00, 0·94–1·07; p=0·42). The estimates for all trials combined was similar to those for the inpatient trials because of the relatively few events in the outpatient trials.

Discussion

The ACT outpatient trial provides no evidence for a benefit of either colchicine or aspirin for the prevention of disease progression or death in community patients with COVID-19. Results were consistent for the primary and secondary outcomes, as well as in all subgroups examined, including baseline vaccination status, and timing from onset of COVID-19 symptoms to randomisation.

The event rate for the primary outcome in the ACT outpatient trial was substantially lower than originally projected and continued to fall substantially during the trial. When this first became evident during the first half of the trial, the steering committee modified the protocol to increase the sample size, enrich the risk profile of the study population by restricting recruitment to patients aged at least 30 years (previously ≥18 years), and expanded the primary outcome to include thrombotic events.[16] The overall mortality event rate at the end of the ACT outpatient trial was 0·6%, which is not dissimilar to that observed in the COLCORONA trial (0·2% colchicine *vs* 0·4% in placebo), which tested colchicine in outpatients with COVID-19.[11] However, the overall hospitalisation rate in the ACT outpatient trial was 3·2%, which is substantially lower than the approximately 5% rate seen in COLCORONA, and only seven patients in ACT had a thrombotic event. It is unclear whether the emergence of less virulent COVID-19 variants, vaccination, use of effective cointerventions, or changing patterns of hospitalisation might have contributed to these findings.

The ACT outpatient trial results appear to be inconsistent with those of the COLCORONA trial in outpatients[11] and the COLCOVID trial in inpatients,[19] both of which suggested that colchicine might have benefits for prevention of disease progression in patients with COVID-19. However, the CIs are substantially overlapping and our results provide no support for the hypothesis that the lack of benefit of colchicine in the RECOVERY trial[18] is explained by an inadequate duration of colchicine treatment for 10 days or until discharge. Our conclusions regarding the lack of benefit of colchicine are supported by the results of our updated meta-analysis of randomised trials of colchicine, which provides no evidence that colchicine improves outcomes in outpatients or inpatients with COVID-19.

Coagulation activation and clinical thrombosis have been reported to be a prominent feature of disease progression in patients with COVID-19.[22] The ACTIV-4B trial evaluated the use of anticoagulant and antiplatelet therapies in outpatients with COVID-19 but enrolled only 657 patients before it was discontinued at the recommendation of the data and safety and monitoring board because of low event rates.[12] We did not do a meta-analysis of trials comparing aspirin with placebo in patients with COVID-19 because only two of the 338 patients who were randomly assigned to aspirin versus placebo in ACTIV-4B had a primary outcome and we did not identify any other trials evaluating aspirin in outpatients with COVID-19. Several other randomised trials have evaluated the use of prophylactic dose anticoagulants in outpatients with COVID-19, but all were stopped early owing to futility.[13–15] To date, no antithrombotic therapies have been shown to be beneficial in outpatients with COVID-19.

The strengths of the ACT outpatient trial include the recruitment of almost 4000 patients and high levels of adherence and follow-up. The study also has limitations. First, the trial was open label which raises the possibility for ascertainment and reporting biases. For example, investigators might have had heightened suspicion for a diagnosis of venous thromboembolism in patients not receiving investigational treatment with aspirin leading to increased use of diagnostic testing. However, venous thromboembolism was uncommon, and it is unlikely that this potential bias extends to other outcomes including the need for hospitalisation or death. Second, there was no adjudication of outcome events. Although there is a belief that adjudication improves the accuracy and precision of estimates of treatment effect in randomised trials, this remains unproven.[23] Third, we expect that background treatment differed according to local practice and availability of other therapies, but we did not collect information on the use of monoclonal antibodies or antiviral therapies for COVID-19. Finally, the low event rate substantially limited power to reliably detect important benefits of the interventions under evaluation. However, our results are supported by an updated meta-analysis of trials in inpatients with COVID-19 and previous trials of antithrombotic therapy in outpatients with COVID-19.

In conclusion, the ACT outpatient trial provides no support for the use of colchicine or aspirin to prevent disease progression or death in community adults with symptomatic, laboratory confirmed COVID-19.

Contributors

JWE, SSJ, EPB-C, RPW, SR, WH, SSA, JB, SC, MEF, ML, and SY conceived the study. LX and LH accessed and validated the raw data. LX, LH, and SIB did the formal analysis. JWE, SSJ, EPB-C, RPW, PL-J, ALD, AA, CF, SSA, SC, MEF, ML and SY acquired the funding. All authors were involved in the investigation. JWE, SSJ, EPB-C, RPW, SR, LX, LH, SIB, WH, SSA, JB, SC, MEF, ML, and SY were responsible for the methodology. JWE, SSJ, SR and SY were responsible for project administration and supervision. JWE wrote the original draft. The Steering Committee vouches for the accuracy and completeness of the data and for the adherence to the trial protocol. All authors were responsible for the writing review and editing and the decision to submit the manuscript. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Data sharing

Study materials including the protocol and statistical analysis plan are available online. Individual participant data will not be made available. After completion and publication of the results of long-term follow-up, the ACT Trials Steering Committee will consider reasonable requests for specific additional analyses on a cost recovery basis (waived for low-income and middle-income countries).

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Declaration of interests

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