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A Pragmatic Trial of Glucocorticoids for Community-Acquired Pneumonia

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ABSTRACT

BACKGROUND

Adjunctive glucocorticoids may reduce mortality among patients with severe community-acquired pneumonia (CAP) in well-resourced settings. Whether these drugs are beneficial in low-resource settings with limited diagnostic and treatment facilities is unclear.

METHODS

In this pragmatic, open-label, randomized, controlled trial conducted in 18 public hospitals in Kenya, we assigned adult patients who had received a diagnosis of CAP and who did not have a clear indication for glucocorticoids to receive either standard care for CAP or oral low-dose glucocorticoids for 10 days in addition to standard care. The primary outcome was death from any cause at 30 days after enrollment.

RESULTS

A total of 2180 patients underwent randomization (1089 assigned to the glucocorticoid group and 1091 to the standard-care group). The median age of the patients was 53 years (interquartile range, 38 to 72); 46% were women. At day 30, deaths were reported in 530 patients (24.3%): 246 patients (22.6%) in the glucocorticoid group and 284 patients (26.0%) in the standard-care group (hazard ratio, 0.84; 95% confidence interval, 0.73 to 0.97; P=0.02). The frequencies of adverse events and serious adverse events were similar in the two trial groups. Serious adverse events that were considered to be related to glucocorticoid administration occurred in 5 patients (0.5%).

CONCLUSIONS

In patients with CAP in a low-resource setting, adjunctive glucocorticoid therapy was associated with a lower risk of death than standard care. (Funded by Wellcome Trust and others; SONIA PACTR number, PACTR202111481740832; ISRCTN number, ISRCTN36138594.)

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CME

Community-acquired pneumonia (CAP) is a leading cause of complications and death worldwide.[1] The case-fatality rate from CAP in sub-Saharan Africa is three to five times the rate in high-income settings despite a markedly younger average age of the patients.[1,2]

A Quick Take is available at NEJM.org

Glucocorticoids have been proposed as adjunctive therapy for CAP owing to their immunomodulatory effects.[3] Data from two recent trials[4,5] and systematic reviews of adjunctive hydrocortisone in patients who had been admitted to an intensive care unit (ICU) for CAP[6-8] indicate reduced mortality among these patients. However, uncertainty remains because no benefit was shown in other studies.[4,9,10] Some[3] but not all[11] guidelines have been updated to recommend the use of glucocorticoids in selected groups with CAP, but it is unclear what the risks and benefits would be for patients in low-resource settings such as sub-Saharan Africa.

First, previous trials involved patients who were considerably older than those in sub-Saharan Africa and excluded patients with coexisting illnesses that are common among patients with CAP in sub-Saharan Africa, such as human immunodeficiency virus (HIV) infection and pulmonary tuberculosis. Second, delayed presentation to a hospital, which is common in sub-Saharan Africa, could compromise the effectiveness of adjunctive glucocorticoids for CAP, because evidence suggests that glucocorticoids should be given early in the course of the disease.[4,5] Third, limitations in diagnostic capacity in low-resource settings make it difficult to stratify patients according to the severity of CAP, which appears to influence measures of glucocorticoid efficacy. Finally, most of the evidence showing mortality reduction with use of adjunctive glucocorticoids is derived from studies conducted in ICUs, but studies that were not based in ICUs did not have mortality as a primary end point.[12,13] The limited availability of ICUs in sub-Saharan Africa[14] constrains the ability to identify and treat severely ill patients and manage any adverse events that may result from glucocorticoid administration.

We conducted a pragmatic, randomized, controlled trial — Steroids in Pneumonia (SONIA) — to evaluate the effectiveness and safety of adjunctive low-dose glucocorticoids in adult patients hospitalized with CAP in Kenya.

Methods

Trial Design and Patients

The trial[15] was conducted in 18 first-level referral hospitals that are part of a clinical information network in Kenya (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).[16] Access to ICUs was either very limited or nonexistent in these hospitals (Table S4), and patients were recruited from the general medical wards.

Eligible patients were adults (≥18 years of age) who had received a diagnosis of CAP and who did not have a clear indication for glucocorticoids to be included as part of their treatment. CAP was defined as the presence of at least two of the following signs and symptoms for less than 14 days: cough, fever, dyspnea, hemoptysis, chest pain, or crackles on chest examination. The patients were enrolled within the first 48 hours after hospital admission. Patients were excluded if they had a contraindication to the receipt of glucocorticoids, were pregnant or breast-feeding, had hospital-acquired pneumonia, or had a known or suspected condition warranting the use of glucocorticoids (e.g., asthma or coronavirus disease 2019 [Covid-19]). The assessment of the cause of CAP through imaging or laboratory tests and the use of standard severity scoring are frequently unavailable at the participating centers and were not a prerequisite for enrollment in the trial.

Oversight

We obtained ethical approval from the Kenyan Medical Research Institute Scientific and Ethics Review Unit, the Kenya Pharmacy and Poisons Board, and the Tropical Research Ethics Committee at the University of Oxford. Additional approvals were received from the institutional review boards and hospital administration at all 18 trial sites. Written informed consent was obtained from all the patients or their legally acceptable representative. An independent trial steering committee and data and safety monitoring board provided trial and safety oversight.

The data and safety monitoring board, which reviewed the results of an interim analysis that was conducted after approximately half the targeted number of primary events had occurred (with stopping guidelines based on the Haybittle–

Peto rules[17]), recommended continuation of the trial. Details regarding the interim analysis are provided in the Supplementary Appendix.

The first and last authors had access to all the trial data and vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol (available at NEJM.org). The trial funders had no role in the trial design; in the collection, analysis, or interpretation of the data; or in the writing of the manuscript.

TRIAL PROCEDURES AND FOLLOW-UP

The patients in this open-label trial were randomly assigned in a 1:1 ratio to receive either low-dose glucocorticoids plus standard care (glucocorticoid group) or standard care alone (standard-care group). Before the recruitment of patients, an independent trial statistician at a central location sealed randomization cards into opaque envelopes. Sites received batches of these sealed envelopes, which were securely stored and opened sequentially only after confirming the eligibility of patients and their enrollment in the trial.

The elements of standard care were determined by the attending physicians and included the administration of a beta-lactam (such as benzylpenicillin or a cephalosporin) and a macrolide (typically, erythromycin or azithromycin), according to the guidelines of the World Health Organization.[18]

The patients in the glucocorticoid group underwent additional randomization to receive a single daily dose of one of five locally available glucocorticoids in bioequivalent doses for a total of 10 days (including after discharge) in addition to standard care. The five dose groups received 6 mg of dexamethasone, 160 mg of hydrocortisone, 30 mg of methylprednisolone, 50 mg of prednisolone, or 50 mg of prednisone (Table S5). The dose and duration of glucocorticoid therapy was informed by the findings in the RECOVERY trial.[19] If oral administration of glucocorticoids was not possible at enrollment, intravenous formulations were administered until it was clinically possible to revert to oral formulations (Table S11). Because of the high pill burden imposed by locally available formulations of hydrocortisone and prednisone (Table S5), these formulations were discontinued after the second month of recruitment. There was no tapering of glucocorticoid dose at the end of treatment.[20]

The trial team provided glucocorticoids free of charge but did not influence any other aspects of patient treatment. During hospitalization, the patients received in-person daily follow-up by the trial team. Follow-up after discharge from the hospital was performed through telephone calls made to the patients or their next of kin on days 14 and 30 after enrollment. A local clinical officer (nonphysician clinician[21]) was employed at each hospital to conduct trial roles, including recruitment and follow-up. This clinician had no role in patient treatment, which was performed by the local hospital medical teams led by a consulting physician.

OUTCOMES

The primary outcome was death from any cause within 30 days after enrollment. Secondary outcomes included death at days 7, 14, and 21 and death during hospitalization and after discharge up to 30 days after enrollment. Safety outcomes consisted of adverse events and serious adverse events. Data regarding an additional prespecified secondary outcome of immune response were collected during the trial but are not included in this report.

STATISTICAL ANALYSIS

We estimated that the enrollment of 2180 patients would provide the trial with 85% power to detect a 25% lower mortality in the glucocorticoid group than in the standard-care group at day 30, assuming 20% mortality in the standard-care group and 15% in the glucocorticoid group and allowing for 5% loss to follow-up.[1,2,15] The statistical analysis plan was approved by the trial data and safety monitoring board.

The primary analysis was a comparison of 30-day mortality in the glucocorticoid and standard-care groups in the intention-to-treat population, which included all the patients who had undergone randomization. We used a Cox regression model that incorporated the trial site as a stratification variable to estimate the hazard ratio for death and its associated 95% confidence interval. The proportional-hazards assumption was assessed by plotting Schoenfeld residuals (Fig. S3) and was confirmed to be valid. We used a stratified log-rank test to compare survival curves for the two trial groups.

We performed prespecified subgroup analyses (according to age, sex, glucocorticoid type, trial region, and oxygen saturation at admission) by including interaction terms in the regression models. Secondary outcome analyses included a comparison of mortality at days 7, 14, and 21 both during hospitalization and after discharge according to trial group. Statistical analyses for secondary end points were not adjusted for multiple testing, so the widths of the confidence intervals should not be used to replace hypothesis testing.

Safety analyses included patients who had received at least one dose of any trial treatment. Frequencies of adverse events were presented according to severity and relationship to treatment for patients in the glucocorticoid group.

After we performed extensive exploration of missing data, we assumed that data were missing at random.[22] We conducted two post hoc sensitivity analyses in populations that were defined as follows: a complete-case population (which excluded patients with missing outcome data at 30 days) and a modified intention-to-treat population (which excluded patients who had received glucocorticoids before randomization).

RESULTS

PATIENTS

Recruitment took place from April 26, 2022, to June 30, 2024. A total of 46,224 patients who had been admitted to the adult medical wards of the participating hospitals were screened (Fig. 1 and Table S6). Of the 2180 patients who underwent randomization, 1089 were assigned to receive standard care plus glucocorticoids and 1091 to receive standard care alone. Vital status was known for 2107 of these patients (96.7%) at day 14 and for 2082 patients (95.5%) at day 30. Of the 98 patients (4.5%) with missing day 30 data, 75 patients (3.4%) had been withdrawn from the trial and 23 patients (1.1%) had been lost to follow-up (Fig. 1).

The median age at enrollment was 53 years (interquartile range, 38 to 72); 1009 patients (46.3%) were women, and 808 (37.1%) had low oxygen saturation (<90%) at admission. The characteristics of the patients at enrollment (Table 1), antibiotics received (Table S7), and adherence to prescribed medications (Table S12) were similar in the two trial groups. The patients were considered to be representative of the general adult population with CAP at the trial sites (Table S9). The most common coexisting illnesses at admission were HIV infection in 344 patients (15.8%) and hypertension in 300 patients (13.8%) (Table 1 and Table S10). Of the 1089 patients who were assigned to receive glucocorticoids, 352 (32.3%) were assigned to receive methylprednisolone, 343 (31.5%) to receive prednisolone, 371 (34.1%) to receive dexamethasone, and 23 (2.1%) to receive either hydrocortisone or prednisone (Table S11). The median duration of glucocorticoid treatment during the in-hospital period was 4 days (interquartile range, 2 to 8) (Table S7). Overall, 5 patients (0.2%) were transferred to an ICU during their hospital stay.

PRIMARY OUTCOME

Of the 2180 patients who were included in the intention-to-treat analyses, death was reported in 530 patients (24.3%; 95% confidence interval [CI], 22.5 to 26.1) within the 30-day follow-up period. Of these deaths, 246 of 1089 (22.6%; 95% CI, 20.2 to 25.2) occurred in the glucocorticoid group and 284 of 1091 (26.0%; 95% CI, 23.5 to 28.7) in the standard-care group. The patients who were receiving glucocorticoids had a lower 30-day mortality than those who were receiving standard care alone (hazard ratio for death, 0.84; 95% CI, 0.73 to 0.97; P=0.02) (Fig. 2).

SECONDARY OUTCOMES

The risk of death at 7 days, 14 days, and 21 days after enrollment was consistent with the results for the primary outcome (Table S13). In the glucocorticoid group, deaths were reported in 196 of 1089 patients (18.0%) during hospitalization and in 50 of 1089 patients (4.6%) outside the hospital; in the standard-care group, deaths occurred in 223 of 1091 patients (20.4%) and in 61 of 1091 patients (5.6%), respectively (Table S14). Deaths that were stratified according to prespecified subgroups are presented in Figure 3.

In a post hoc sensitivity analysis, the hazard ratio for death in the complete-case analysis involving 2082 patients was 0.84 (95% CI, 0.73 to 0.96) and the hazard ratio in the modified intention-to-treat analysis involving 2142 patients was 0.83 (95% CI, 0.72 to 0.97) (Table S15).

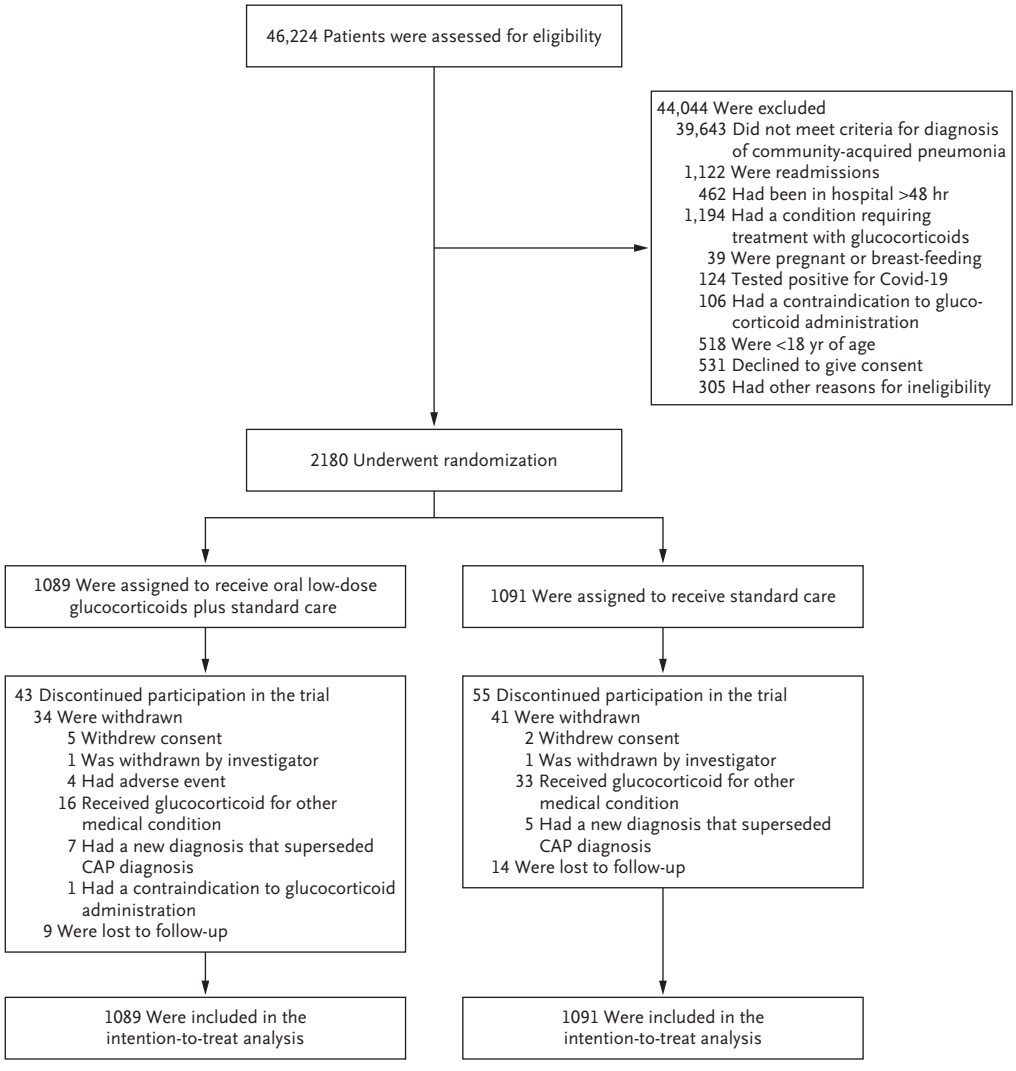

Figure 1. Enrollment and Outcomes.

Of the 2180 patients with community-acquired pneumonia who were assigned to receive either standard care or oral low-dose glucocorticoids in addition to standard care, reasons for withdrawal from the trial included a lack of consent, adverse events, and receipt of a glucocorticoid for other medical conditions. Investigator-led withdrawals of one patient in each group were due to the recommendation of a hospital physician to allow the patient to receive glucocorticoids as part of their treatment. Covid-19 denotes coronavirus disease 2019.

SAFETY

A total of 385 adverse events in 338 patients were reported by day 30 after baseline. Of these events, 18 (4.7%) were severe adverse events, 200 (51.9%) were mild events, and 167 (43.4%) were moderate events. Of the 211 adverse events that were reported in the glucocorticoid group, 62 (29.4%) were determined by the investigator to be related to glucocorticoid administration. The most common adverse events were pulmonary tuberculosis (34 events [16.1%]) and hyperglycemia (35 events [16.6%]) among the 211 events reported in the glucocorticoid group and pulmonary tuberculosis (35 events [20.1%]) and acute kidney injury (14 events [8.0%]) among the 174 events reported in the standard-care group (Table S17).

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Glucocorticoid Group (N=1089)	Standard-Care Group (N=1091)
Median age (IQR) — yr	52 (38–72)	53 (38–72)
Sex — no. (%)		
Male	578 (53.1)	593 (54.4)
Female	511 (46.9)	498 (45.6)
Body-mass index†	24.1±12.9	24.0±7.6
Chest radiograph available — no. (%)‡	423 (38.8)	425 (39.0)
Oxygen saturation at admission — no. (%)		
<90%	404 (37.1)	404 (37.0)
≥90%	650 (59.7)	659 (60.4)
Missing data	35 (3.2)	28 (2.6)
Altered mental state — no. (%)	24 (2.2)	26 (2.4)
Systolic blood pressure — no. (%)		
<90 mm Hg	92 (8.4)	86 (7.9)
≥90 mm Hg	995 (91.4)	1003 (91.9)
Missing data	2 (0.2)	2 (0.2)
Respiratory rate — no. (%)		
<30/min	996 (91.5)	1016 (93.1)
≥30/min	52 (4.8)	45 (4.1)
Missing data	41 (3.8)	30 (2.7)
Temperature — no. (%)		
35.0°C to 39.9°C	1008 (92.6)	1019 (93.4)
<35°C or ≥40°C	7 (0.6)	7 (0.6)
Missing data	74 (6.8)	65 (6.0)
Pulse rate — no. (%)		
<125/min	930 (85.4)	978 (89.6)
≥125/min	154 (14.1)	109 (10.0)
Missing data	5 (0.5)	4 (0.4)
Blood glucose — no. (%)		
<252 mg/dl	993 (91.2)	975 (89.4)
≥252 mg/dl	31 (2.8)	51 (4.7)
Missing data	65 (6.0)	65 (6.0)
HIV infection status — no. (%)		
Positive	178 (16.3)	166 (15.2)
Negative	411 (37.7)	431 (39.5)
Unknown	500 (45.9)	494 (45.3)
Chronic illness — no. (%)§	390 (35.8)	398 (36.5)
Hypertension	143 (13.1)	157 (14.4)
Diabetes mellitus	50 (4.6)	70 (6.4)
Congestive cardiac failure	17 (1.6)	21 (1.9)
Pulmonary tuberculosis	21 (1.9)	10 (0.9)
Other	42 (3.9)	47 (4.3)

* Plus–minus values are means ±SD. IQR denotes interquartile range. To convert the values for glucose to millimoles per liter, multiply by 0.05551.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ Chest radiographs were not reviewed by radiologists, and no formal clinical reports were available.
§ Additional details regarding chronic illnesses are provided in Table S10 in the Supplementary Appendix. Some participants reported more than one chronic illness at enrollment.

A total of 96 serious adverse events were reported throughout the study. Such events that were deemed by the investigator to be possibly related to glucocorticoid administration were reported in 5 of 1089 participants (0.5%) in the glucocorticoid group (Table 2). Among the patients with serious adverse events, the most common event in the two groups was progression to severe CAP, which occurred in 9 of 45 patients (20.0%) in the glucocorticoid group and in 5 of 51 patients (9.8%) in the standard-care group (Table S18).

DISCUSSION

In this trial conducted under pragmatic conditions in Kenya, we found a lower risk of death from any cause among patients with CAP who were assigned to receive glucocorticoids along with standard care within 48 hours after hospital admission than among those assigned to receive standard care alone. Although the effect size (hazard ratio, 0.84) was smaller than that in previous reports from France (hazard ratio, 0.53),[5] Egypt (hazard ratio, 0.22),[23] and a meta-analysis of 12 trials (hazard ratio, 0.62),[8] our results are consistent in identifying a beneficial effect of glucocorticoids in the management of CAP.

Our trial differs from several other trials that have evaluated adjunctive glucocorticoids in that we selected a non-ICU setting to investigate mortality among patients with CAP. In previous trials of glucocorticoids in non-ICU settings conducted in Europe, investigators reported a reduced time to clinical stability[12] and reduced length of stay and likelihood of ICU admission[13] but did not have mortality as a primary outcome. Of the 18 studies informing the current guidelines of the Society of Critical Care Medicine that recommend the use of glucocorticoids in patients with severe CAP,[3] only 3 were conducted in Africa with a total enrollment of 194 patients, all of whom had non-Black ancestry.[23-25] As compared with the CAPE-COD trial conducted in French ICUs (a large trial that reported a beneficial effect of hydrocortisone in reducing mortality among patients with CAP),[5] the patients in our trial were younger (median age, 53 years vs. 67 years), included more women (46.3% vs. 30.6%), had more patients with coexisting illnesses causing immunosuppression at enrollment (16.3% vs. 6.4%), and had higher overall mortality (24.3% vs. 9.1%).

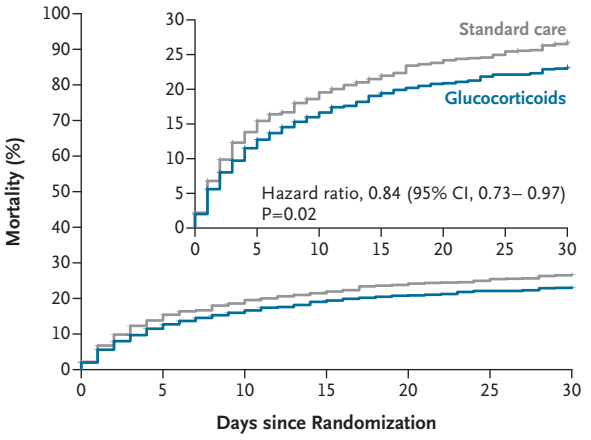

Figure 2. Cumulative Risk of Death from Any Cause.

Shown is the risk of death among the patients with community-acquired pneumonia who were assigned to receive either standard care or oral low-dose glucocorticoids at 30 days (the primary outcome). The inset graph shows the same data on an expanded y axis. The hazard ratio was derived from Cox regression after adjustment for the trial site. The log-rank P value for the comparison of the two survival curves was 0.049.

Overall mortality was higher in our trial than the estimate we had used in our pretrial power calculations. However, the trial was not powered to assess differences in outcomes according to disease severity or glucocorticoid type. Therefore, potential differential effects according to disease severity or glucocorticoid type in low-resource settings remain uncertain. In addition, the availability of cost-efficient and patient-friendly (according to pill burden) oral and intravenous formulations will need consideration if specific glucocorticoids are to be recommended for the treatment of CAP in our region.[1]

Glucocorticoids have been reported to be safe when used in the management of severe CAP, with reversible hyperglycemia being the main side effect.[7,8,26] As has been reported elsewhere,[5,27,28] hyperglycemia was a common adverse event in our trial. However, the percentage of serious adverse events caused by hyperglycemia in the glucocorticoid group was low (8.9%) (Table S18). Even so, safety concerns remain and may need further investigation. We recommend accounting for the capacity to monitor blood glucose regularly if glucocorticoids are to be recom-

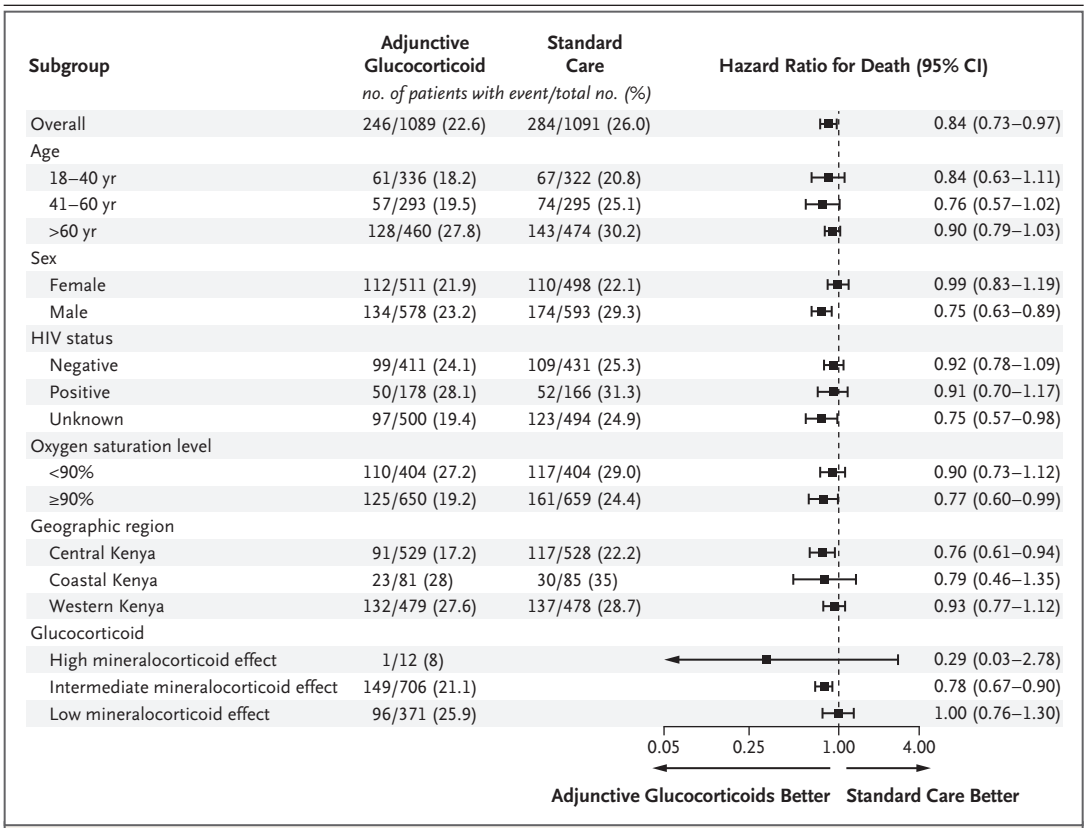

Figure 3. Primary Outcome, According to Subgroup.

The forest plot shows the risk of death (primary outcome) in subgroups of patients with community-acquired pneumonia who were assigned to receive either standard care or oral low-dose glucocorticoids in addition to standard care. The confidence intervals have not been adjusted for multiplicity and should not be used in place of hypothesis testing. The glucocorticoid subgroup has been categorized according to mineralocorticoid potency as high effect (hydrocortisone), intermediate effect (methylprednisolone, prednisolone, or prednisone), and low effect (dexamethasone).

mended for use in the management of CAP in sub-Saharan Africa.

A major strength of our trial is the large sample size and large number of primary outcome events that occurred in patients who were recruited from multiple sites representing diverse populations across the country. The pragmatic nature of the trial, which was designed to reflect real-world conditions in low-resource settings, means that the results are likely to be more relevant to patients in sub-Saharan Africa than to those in high-resource settings. On the basis of our findings, adjunctive glucocorticoids could represent a low-cost intervention to reduce the high case fatality associated with CAP in sub-Saharan Africa.

The main limitation of the trial is the enrollment of a heterogenous patient population because of limited diagnostic and treatment capabilities. This factor constrained our ability to compare the trial patients with those in previous studies or to identify which patients benefited from the intervention. It is possible that the results were affected by the inclusion of patients with conditions for which glucocorticoids have proven benefit (e.g., pneumocystis pneumonia and septic shock). However, the studies that showed benefit in these patients were conducted in markedly different settings and used different doses of glucocorticoids. Our broad eligibility criteria that did not take into consideration pneumonia severity and other baseline prognostic factors (e.g., functional status) may have biased our results toward the

Table 2. Summary of Safety Analysis.

Adverse Event	Glucocorticoid Group (N=1089)	Standard-Care Group (N=1091)	Total (N=2180)
Any adverse event			
No. of events reported	211	174	385
Patients with adverse event — no. (%)*	184 (16.9)	154 (14.1)	338 (15.5)
Serious adverse event†			
No. of events reported	45	51	96
Patients with serious adverse event — no. (%)*	44 (4.0)	48 (4.4)	92 (4.2)
Severity of adverse event‡			
No. of events/total no. of reported adverse events (%)			
Mild	117/211 (55.5)	83/174 (47.7)	200/385 (51.9)
Moderate	85/211 (40.3)	82/174 (47.1)	167/385 (43.4)
Severe	9/211 (4.3)	9/174 (5.2)	18/385 (4.7)
No. of patients with event/no. in safety population (%)			
Mild	104/1089 (9.6)	79/1091 (7.2)	183/2180 (8.4)
Moderate	79/1089 (7.3)	77/1091 (7.1)	156/2180 (7.2)
Severe	8/1089 (0.7)	9/1091 (0.8)	17/2180 (0.8)
Adverse event related to glucocorticoid treatment — no. of events/total no. of reported adverse events§			
Related	62/211 (29.4)	—	—
Probably related	15/211 (7.1)	—	—
Not related	134/211 (63.5)	—	—

* Patients who had one or more adverse events or serious adverse events were counted only once.
† Serious adverse events included death, life-threatening events, hospitalization, disability or permanent damage, or events warranting intervention to prevent permanent impairment.
‡ Severe adverse events included safety events that did not fall under the definition of serious adverse events. In this category, events were classified as mild, moderate, or severe according to the intensity of symptoms. Events were counted only once within each severity grade or relatedness category.
§ The relatedness of an adverse event to glucocorticoid treatment was assessed by the site investigators. Relatedness was not assessed in patients in the standard-care group because they did not receive any randomized trial intervention.

null, given that glucocorticoids appear to have a larger effect in patients with severe disease. We did not monitor cointerventions that were provided, and the open-label nature of the trial could also have influenced the result — factors that are mitigated by our use of a mortality end point.

In addition, although patients underwent randomization within 48 hours after hospital admission, we did not record the number of hours until the initiation of glucocorticoids, which could have affected outcomes. Providing glucocorticoids free of charge may have limited our ability to assess their effect under conditions in which drug costs may influence treatment choices. Another limitation is that we primarily used oral formulations of glucocorticoids, which limits comparisons with studies that used intravenous formulations with better treatment adherence.

In our trial involving patients who were hospitalized with CAP in a low-resource setting, the adjunctive use of glucocorticoids was associated with a lower risk of death from any cause than standard care.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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