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Clarithromycin for improved clinical outcomes in community-acquired pneumonia: A subgroup analysis of the ACCESS trial ☆

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ABSTRACT

Background: In the ACCESS trial, the addition of clarithromycin to standard-of-care antibiotics (SoC) enhanced early clinical response and attenuated the inflammatory burden in adults with community-acquired pneumonia (CAP) requiring hospitalisation. A post-hoc analysis was performed to investigate the benefit in specific subgroups.

Methods: The primary endpoint comprised two conditions to be met during the first 72 h: ≥50% decrease in respiratory symptom severity score; and any of ≥30% decrease in sequential organ failure assessment score and favourable change in the kinetics of procalcitonin (PCT, defined as ≥80% PCT decrease or PCT <0.25 ng/mL). In this exploratory post-hoc analysis, achievement of the study composite primary endpoint was compared between the two treatment groups within subsets differentiated by demographic characteristics, comorbidities, CAP severity, baseline laboratory findings and corticosteroid co-

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administration. The impact of clarithromycin treatment on the need for mechanical ventilation (MV) in all subgroups was also analysed.

Results: The addition of clarithromycin significantly increased the proportion of patients achieving the primary endpoint across all subgroups and decreased the need for MV in 19 out of the 37 subgroups studied. For instance, the primary endpoint was attained in 32.7% of placebo-treated patients and in 67% of clarithromycin-treated patients with CURB-65 score ≥2 (P<0.0001), whereas MV was required in 18.8% and 7.4% of patients, respectively (P=0.022). The addition of corticosteroids alone was not as clinically advantageous as the use of clarithromycin alone, when added to SoC.

Conclusion: Adding clarithromycin to SoC in the ACCESS trial achieved early clinical anti-inflammatory responses and decreased the need for MV in subgroups of hospitalised patients with CAP.

Introduction

Several meta-analyses of observational trials have demonstrated survival benefit with the addition of macrolides to the antibiotic regimen for patients with severe community-acquired pneumonia (CAP) [1–7]. The combination of β-lactams and macrolides is recommended as first-line treatment for severe CAP in the guidelines of the Infectious Diseases Society of America/America Thoracic Society (IDSA/ATS), European Society of Clinical Microbiology and Infectious Diseases, European Respiratory Society European Society of Intensive Care Medicine, and American Latin Thoracic Society [8,9]. The selection of the most appropriate antibiotic in the IDSA/ATS guidelines is strongly shaped by patient comorbidities and pneumonia severity [8].

The efficacy of macrolides in the management of CAP has recently been illustrated by the principal findings of ACCESS, a randomised, double-blind placebo-controlled trial to examine the effect of adding oral clarithromycin to standard-of-care antibiotics (SoC) in hospitalised patients with CAP, which showed that addition of clarithromycin to SoC was associated with significant early clinical improvement [10]. The primary endpoint of the ACCESS trial integrated early clinical response (ECR), a requirement of both the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA) [11], with changes in sequential organ failure assessment (SOFA) score and blood procalcitonin (PCT) levels. Early reductions in SOFA score and PCT levels are considered indices of an early clinical anti-inflammatory response. Addition of clarithromycin to SoC was associated with significant decreases in the incidence of CAP-associated organ dysfunction and secondary sepsis and with earlier hospital discharge [10].

The favourable principal results of the ACCESS trial invite consideration of whether the macrolide treatment benefit in CAP is general or if this is restricted to patients with specific demographic features or specific degrees of CAP severity. To investigate this, a post-hoc analysis of the primary endpoint was performed among subgroups of patients defined by the presence of comorbidities and a range of laboratory markers. This analysis also provided a timely opportunity to examine the interplay between clarithromycin use and corticosteroid therapy, an important consideration in light of recently published recommendations by a panel of experts for the use of corticosteroids in severe CAP [12].

Methods

Study design

Details of the design and conduct of the ACCESS trial have been published [10]. Enrolled patients were adults with radiologically-confirmed pneumonia; at least two of cough, expectoration, dyspnoea or pleuritic pain; at least two of the signs of the systemic inflammatory response syndrome; SOFA score ≥2; and PCT ≥0.25 ng/mL. Participating patients were randomised 1:1 to SoC plus placebo or SoC plus clarithromycin.

The primary endpoint of the ACCESS trial was composite and required patients to meet two criteria: (i) ≥50% decrease in the respiratory symptom severity (RSS) score compared with baseline, without the need for a change in SoC; (ii) ≥30% decrease in the baseline SOFA score and/or favourable changes in PCT kinetics (defined as ≥80% decrease in PCT compared with baseline or absolute PCT >0.25 ng/mL) [10].

Subgrouping of patients and statistical analysis

For this exploratory analysis, patients were categorised according to age and sex, comorbidities, CAP severity and baseline laboratory findings. The comorbidities selected were those identified in the IDSA/ATS guidelines: age, chronic obstructive pulmonary disease (COPD), chronic heart failure/chronic coronary disease, type 2 diabetes mellitus, atrial fibrillation and obesity [8]. The analysis was limited to subgroups with at least 50 patients as this was considered the minimum number for robust analysis, assuming a 30% difference in the achievement of the primary endpoint between placebo- and clarithromycin-treated patients in each subgroup.

Subgrouping for CAP severity was specified by the CURB-65 score, in which a score ≥2 is the threshold for hospital admission [13], and by the Pneumonia Severity Index (PSI), in which values ≥91 indicate severe CAP [14]. Subgrouping for laboratory metrics at hospital admission involved the absolute counts of neutrophils and lymphocytes, C-reactive protein (CRP), PCT, pO_2/FiO_2 and creatinine. For all these indices except CRP, patients were stratified according to the median of the total enrolled patients; for CRP the expert-endorsed [15,16] cut-off of 150 mg/L was used. Finally, patients were split into subgroups according to whether or not they were co-administered intravenous methylprednisolone or dexamethasone, delivering at least 400 mg equivalent hydrocortisone daily, a cut-off advocated in the recent guidelines [12]. In this subgrouping, patients who were on intravenous methylprednisolone or dexamethasone before the start of the study drug and patients who received intravenous methylprednisolone or dexamethasone after the start of the study drug were analysed together.

Quantitative variables were expressed as means and standard deviations and compared using the Student's t-test. Comparisons of the achievement of the primary endpoint between the placebo group and the clarithromycin group in each subgroup were done using the Fisher's exact test. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. In a separate analysis, the OR for death at the end of the 90-day follow-up among patients achieving the primary endpoint was calculated separately for each group of treatment with comparisons by the Breslow-Day test. Any P-value less than 0.05 was considered statistically significant.

Results

Among patients stratified for baseline characteristics and/or comorbidities, the addition of clarithromycin significantly increased the proportion of patients achieving the primary endpoint in each stratum of every subgroup. For example, among patients with no documented comorbidities, the primary endpoint was achieved in 13 of 41 (31.7%; 95%CIs 19.6 to 46.9) placebo-treated patients and 36 of 54 (66.7%; 95%CIs 53.4 to 77.8) clarithromycin-treated patients; among patients with one comorbidity the corresponding numbers were 23 of 53 (43.4%; 95%CIs 30.9 to 56.7) vs. 34 of 49 (69.4%; 95%CIs 55.5 to 80.5), and among patients with two or more comorbidities, the numbers of patients were 15 of 39 (38.5%; 95%CIs 24.9 to 54.1) vs. 21 of 31 (67.7%; 95%CIs 50.1 to 80.4) (Fig. 1A; subgroup analyses for age and COPD status have already been reported [10] but are retained in Fig. 1 for completeness and the convenience of readers). Baseline severity between the two treatment groups did not differ for any of these subgroups (Supplementary Tables 1 to 8).

Clinical benefit with the addition of clarithromycin to SoC was also apparent among subgroups of CAP patients stratified for severity according to baseline CURB-65 score (<2 and ≥2) or baseline PSI (≤90 and ≥91) or the combination of these scores with comorbidities (Fig. 1B). Baseline severity between the two treatment groups did not differ for any of these subgroups (Supplementary Tables 9 to 12).

Subgroup analysis of baseline laboratory values considered indicative of the intensity of the inflammatory reaction of the host demonstrated benefit with clarithromycin in all subgroups and across all indices examined (Fig. 1C). Baseline severity between the two treatment groups did not differ for any of these subgroups (Supplementary Tables 13 to 18). The primary endpoint was achieved in 18 of 66 (27.3%; 95%CIs 18.0 to 39.0) placebo-treated patients vs. 51 of 77 (66.2%; 95%CIs 55.1 to 75.8) clarithromycin-treated patients with CRP <150 mg/L; and in 33 of 67 (49.3%; 95%CIs 37.7 to 60.9) and 40 of 57 (70.2%; 95%CIs 57.3 to 80.5) patients with CRP ≥150 mg/L, respectively.

The primary endpoint was met in 11 of 31 patients with documented infections by Gram-positive cocci in the SoC plus placebo group (35.5%; 95%CIs 21.1 to 53.0) and in 29 of 40 patients with documented infections by Gram-positive cocci in the SoC plus clarithromycin group (72.5%; 95%CIs 57.2 to 83.9) (P=0.003). The primary endpoint was met in 20 of 50 patients with documented infections by Gram-negative bacteria in the SoC plus placebo group (40.0%; 95%CIs 27.6 to 50.8) and in 27 of 39 patients with documented infections by Gram-negative bacteria in the SoC plus clarithromycin group (69.3%; 95%CIs 53.6 to 81.4) (P=0.010). The primary endpoint was met in 7 of 16 patients with documented viral infections in the SoC plus placebo group (43.8%; 95%CIs 23.1 to 66.8) and in 12 of 16 patients with documented viral infections in the SoC plus clarithromycin group (80.0%; 95%CIs 54.8 to 92.9) (P=0.066).

Subgroup analysis with respect to the incidence of mechanical ventilation showed that the benefit with clarithromycin was most pronounced for patients aged ≥65 years; patients without medical history of diabetes mellitus; patients without medical history of chronic heart failure/coronary heart disease; patients with medical history of atrial fibrillation; non-obese patients; and patients with medical history of COPD (Fig. 2A). A beneficial effect of clarithromycin was also found for patients with CURB-65 score ≥2; PSI ≥91; ≥8880 neutrophils/mm^3; <1000 lymphocytes/mm^3; blood CRP either <150 mg/L or ≥150 mg/L; blood PCT ≥1.04 ng/mL; pO_2/FiO_2 ≥235; and blood creatinine ≥1.2 mg/dL (Fig. 2B and 2C).

Before the start of treatment with the study drug, 31 patients in the placebo group and 33 patients in the clarithromycin group were receiving intravenous methylprednisolone or dexamethasone; another 23 and 15 patients, respectively, started intravenous methylprednisolone or dexamethasone after the start of treatment with the study drug. Baseline severity did not differ between treatment assignments for these subgroups (Supplementary Table 19). The odds for achieving the primary endpoint were similar for the subgroups of patients co-administered and not co-administered corticosteroids (Fig. 3A).The primary endpoint was achieved in 62 of 86 patients (72.1%; 95%CIs 61.8 to 80.55) treated with SoC plus clarithromycin but no corticosteroids compared with 19 of 53 patients (35.8%; 95%CIs 24.3 to 49.3) treated with SoC plus placebo and corticosteroids (P<0.0001). The respective results for the need for MV were 6 of 86 patients (7.0%; 95%CIs 3.2 to 14.4) treated with SoC, clarithromycin and no corticosteroids and 11 of 53 patients (20.8%; 95%CIs 12 to 33.5) treated with SoC, placebo and corticosteroids (P=0.030) (Fig. 3B).

Published results of the ACCESS trial showed that clarithromycin treatment was associated with earlier discharge alive from hospital after 90 days [10]. This led us to consider if achievement of the primary endpoint in the clarithromycin group increased the likelihood of survival at the end of the 90-day follow-up period. This analysis showed that the odds of death by day 90 in patients who attained the early primary endpoint were significantly lower in patients who received clarithromycin than in those who received placebo (Table 1).

Discussion

A subgroup analysis of the ACCESS trial primary endpoints was performed by defining post-hoc subgroups according to comorbidities, severity scores of CAP and baseline laboratory values. In all examined subgroups, the primary endpoint was consistently achieved by significantly larger proportions of the patients treated with SoC plus clarithromycin vs. SoC plus placebo. This post-hoc analysis also affirmed that the benefit of adding clarithromycin to SoC was independent of the co-administration of corticosteroids. The addition of corticosteroids did not enhance the benefit of clarithromycin, and the use of steroids alone was not as effective as the use of clarithromycin alone, when added to SoC therapy.

Table 1
Comparative odds for death by day 90 in each treatment group following achievement of the primary endpoint.

	No attainment of the primary endpoint, n (%)	Attainment of the primary endpoint, n (%)	OR (95%CIs), P-value	P of comparison of the ORs*
	SoC + placebo			
Survival	47 (57.3)	36 (70.6)	0.56 (0.27-1.18); P=0.143	0.043
Death	35 (42.7)	15 (29.4)		
Total	82	51		
	SoC + clarithromycin			
Survival	17 (39.5)	71 (78.0)	0.18 (0.08-0.41); P<0.0001	
Death	26 (60.5)	20 (22.0)		
Total	43	91		

* by the Breslow-Day's test.
Abbreviations CI: confidence interval; n: number of patients; OR: odds ratio; SoC: standard-of-care.

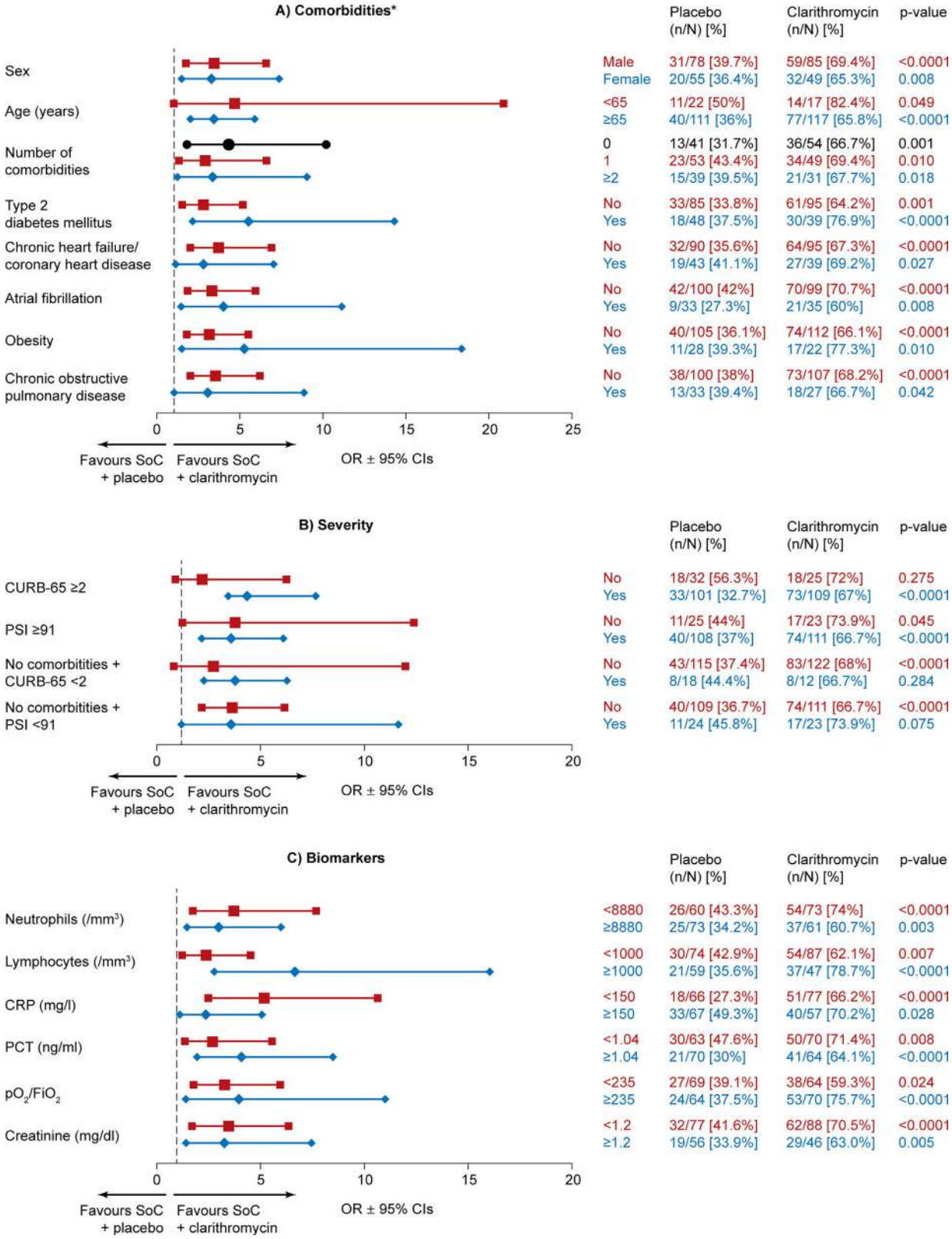

Fig. 1. Attainment of the primary endpoint in the patient subgroups.
For these analyses patients were split into subgroups according to comorbidities (panel A), severity scores without/with comorbidities (panel B), and blood biomarkers (panel C).
The attainment of the primary endpoint is compared between patients treated with SoC plus placebo and patients treated with SoC plus clarithromycin in each subgroup and is provided as the OR and 95%CIs; as frequencies and percentages; and as *P*-values of comparisons using red or blue or black colour similar to the respective subgroup. *P*-values for comparisons are derived from the Fisher's exact test after Bonferroni correction for multiple comparisons.
*Comorbidities included are those reported as significant for the management of community-acquired pneumonia in the 2019 IDSA/ATS guidelines
Abbreviations ATS: American Thoracic Society; CI: confidence interval; IDSA: Infectious Diseases Society of America; n: number of patients meeting the primary endpoint; N: number of patients in the indicated subgroup; OR: odds ratio; SoC: standard-of-care.

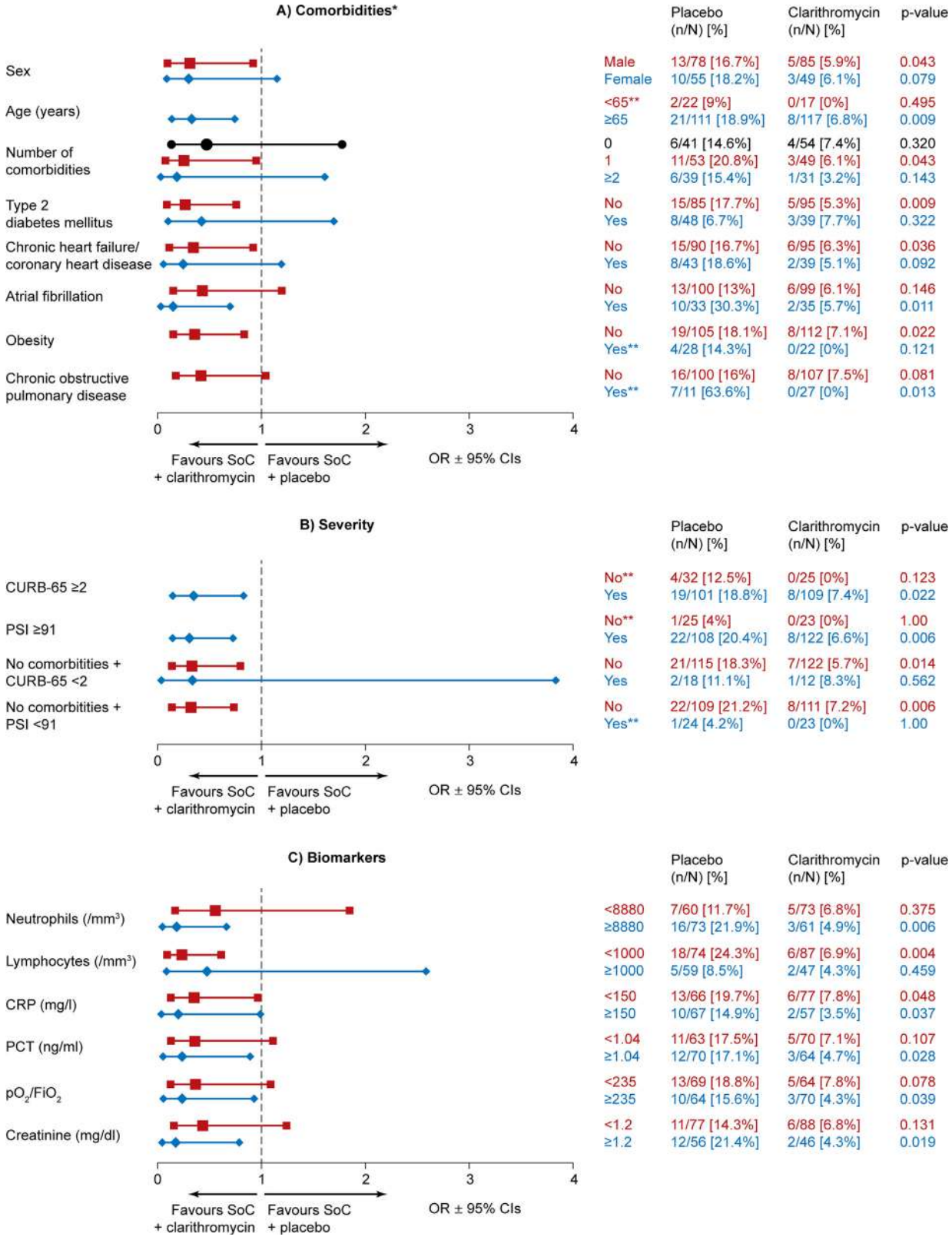

Fig. 2. Need for mechanical ventilation in the patient subgroups For these analyses patients were split into subgroups according to comorbidities (panel A), severity scores without/with comorbidities (panel B), and blood biomarkers (panel C).

The need for mechanical ventilation was compared between patients treated with SoC plus placebo and patients treated with SoC plus clarithromycin in each subgroup and is provided as the OR and 95% CIs; as frequencies and percentages; and as *P*-values of comparisons using red or blue or black colour similar to the respective subgroup. *P*-values for comparisons are derived from the Fisher's exact test after Bonferroni correction for multiple comparisons.

*Comorbidities included are those reported as significant for the management of community-acquired pneumonia in the 2019 IDSA/ATS guidelines.

**Subgroups for which the OR cannot be calculated because one value is zero.

Abbreviations ATS: American Thoracic Society; CI: confidence interval; IDSA: Infectious Diseases Society of America; n: number of patients meeting the primary endpoint; N: number of patients in the indicated subgroup; OR: odds ratio; SoC: standard-of-care.

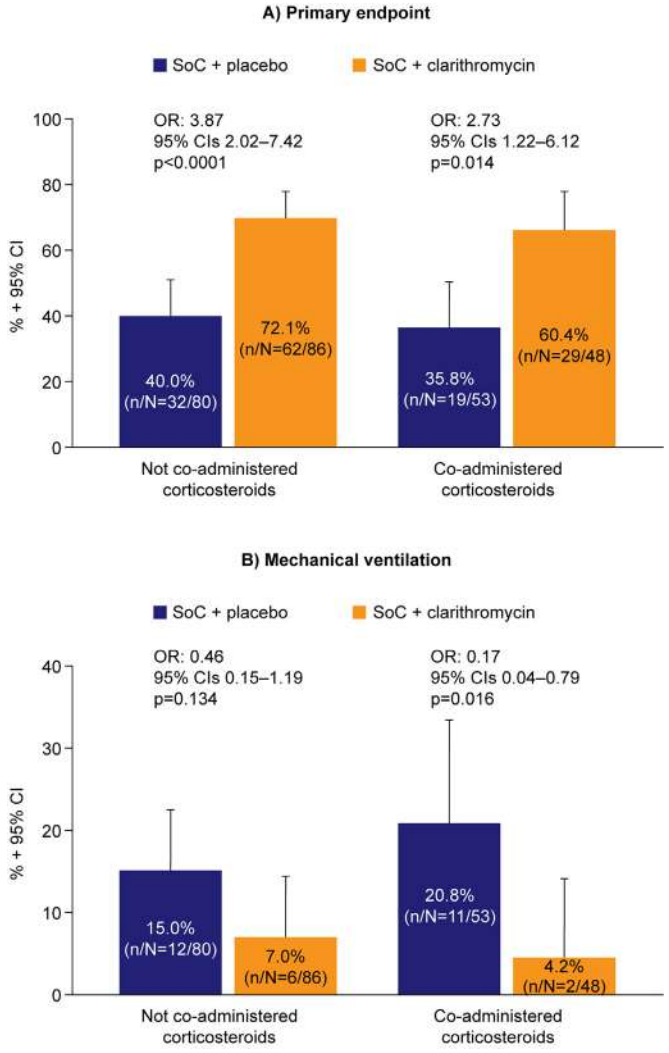

Fig. 3. The effect of adding clarithromycin to corticosteroids on the attainment of the primary endpoint (panel A) and the need for mechanical ventilation (panel B). The *P*-values of comparisons are shown separately for patients co-administered corticosteroids or not co-administered corticosteroids. The *P*-values for comparisons are derived from the Fisher's exact test after Bonferroni correction for multiple comparisons.
Abbreviations CI: confidence interval; n: number of patients meeting the primary endpoint; N: number of patients in the indicated subgroup; OR: odds ratio; SoC: standard-of-care.

This analysis reinforces the findings of previous studies showing a survival benefit of macrolide treatment among patients with severe CAP [7,17,18]. Questions of whether this is a class effect or an effect particular to clarithromycin remain to be elucidated but some lines of evidence favour the possibility of a unique and specific drug effect. Specifically, in a prospective registration of patients with severe CAP (PSI >130) by the Hellenic Sepsis Study Group, addition of clarithromycin to β-lactams substantially decreased the risk for death during the first 28 days. The benefit of adding clarithromycin was greater than in propensity-matched patients treated with a combination of azithromycin and β-lactam [18]. Similarly, a recent meta-analysis including 58 759 patients and 47 publications published between 1994 and 2022 demonstrated that incorporating a macrolide into the treatment regimen reduced the risk of death after 30 days by approximately 35% and enhanced the chances of CAP resolution by a factor of 1.23 [7]. Four of the included studies expressly stated the macrolide used (azithromycin vs. clarithromycin). The overall mortality rate for azithromycin was 22.2% (806/3630 patients), compared with 8.8% (37/419 patients) for clarithromycin, a statistically significant difference in favour of clarithromycin ($P<0.0001$ by Fisher's exact test, OR 0.34, 95%CIs 0.24 to 0.48). Post-hoc analysis of mortality in ACCESS by the end-of-treatment visit day 8 revealed a 55% relative reduction in mortality in the clarithromycin group (OR 0.45; $P=0.042$) [10]. There was also a 30% relative reduction of 28-day mortality (OR 0.70; $P=0.25$), a difference that was not significant [10]. These findings are concordant with the benefits of macrolides described in the meta-analyses outlined above, although the ACCESS trial was not powered principally to explore a treatment effect on mortality.

Published guidelines suggest that macrolide benefit occurs through an effect on immune function [8,9]. In three previous randomised controlled trials (RCTs), clinical benefit was shown with the addition of clarithromycin to SoC in critically ill patients with Gram-negative infections [19–22]. Some of these patients had marked hyper-inflammation, whereas others were in a state of sepsis-induced immunoparalysis. In the present subgroup analysis of the ACCESS trial, benefit from clarithromycin was discernible in patients with both high or low circulating levels of inflammatory markers, in patients with decreased lymphocytes and in patients with or without hypoxia. Despite the favourable effect of clarithromycin in the immune dysregulation of CAP, it should always be noted that clarithromycin is an antibiotic and that injudicious use may induce antimicrobial resistance. This consideration is supported by the results of an RCT in healthy volunteers, where a single course of oral clarithromycin or oral azithromycin induced the emergence of resistance in the oral flora lasting for at least 42 days [23].

The main limitation of the presented analysis is the lack of stratifying randomisation for each of the studied subgroups, including the subgroups of patients treated with or without corticosteroids. The decision to initiate corticosteroid treatment was at the discretion of the attending physicians and this may introduce bias for the interpretation of the findings. However, no statistically significant differences were found between patients of each subgroup allocated to placebo or to clarithromycin at baseline, which provides some mitigation of this concern.

The ACCESS trial has provided the first evidence from a prospective RCT of clinical benefit from the addition of clarithromycin to β-lactams in CAP with at least moderate features of sepsis [10]. Supplementation of SoC with clarithromycin resulted in enhanced ECR and attenuated inflammatory burden of the host and was associated with clear clinical benefit on secondary endpoints, including progression to organ dysfunction, development of new sepsis, and shorter hospital stay [10]. This exploratory analysis demonstrated that the overall primary endpoint findings of the ACCESS trial apply to all examined subgroups. Enhanced attainment of the composite primary endpoint of ECR and early attenuation of inflammation in the first 72 h appear to underpin a survival benefit from clarithromycin after 90 days.

Contributors

KA drafted the manuscript, revised the manuscript for intellectual content and approved the final version for submission.

KL, ET, NK, GN, SD, LS, KI, AP, PK, VR, GC, TS, SG, AM, SG, ICP, HM, SK, SG, TK and VT contributed to data acquisition, revised the manuscript for intellectual content and approved the final version for submission.

KD performed statistical analysis, revised the manuscript for intellectual content and approved the final version for submission.

AT and MSN analysed the data, revised the manuscript for intellectual content and approved the final version for submission.

EJG-B conceptualised the study, analysed the data, drafted the manuscript, revised the manuscript for intellectual content and approved the final version for submission. EJG-B accessed and verified the data, and is responsible for the decision to submit the manuscript.

Data sharing

Data are available upon application to the corresponding author in conjunction with a signed data access agreement.

Declarations

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Competing Interests: K. Akinosoglou reports receiving honoraria and consulting fees from healthcare companies, including MSD, Pfizer, 3M Hellas, GSK/ViiV and Gilead.

I. Papanikolaou has received honoraria or served as PI for studies from Boehringer-ingelheim, GlaxoSmithKline and AstraZeneca.

H. Milionis reports receiving honoraria, consulting fees and non-financial support from healthcare companies, including Amgen, Angelini, Bayer, Mylan, MSD, Pfizer and Servier.

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The other authors do not declare any conflict of interest.

Ethical Approval: The study was approved by the National Ethics Committee of Greece. Approvals are provided in the Methods section.

Sequence Information: Not applicable

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijantimicag.2024.107406.

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