note that 38.7% of patients in this group received an additional agent during their hospital stay that provided atypical coverage for an average of 4.5 days. The addition of a macrolide, a fluoroquinolone, or doxycycline was accepted as strategy-compliant if the agent was added for medical reasons. Since the study assessed empirical antibiotics only, atypical coverage could be added after the first day of the hospital stay without deviating from the protocol, even in the subgroup referred to as "antibiotic-adherent." The benefit of beta-lactam monotherapy versus other guideline-recommended regimens has historically centered on the question of whether atypical coverage is beneficial.[1] It would therefore be useful to know the difference in mortality between those in the beta-lactam monotherapy group who did not receive additional antibiotics against atypical pathogens and those who received beta-lactam–macrolide or fluoroquinolone.

Jolanta Piszczek, Pharm.D.
Eric Partlow, M.D.

Island Health
Victoria, BC, Canada
jolanta.piszczek@viha.ca

No potential conflict of interest relevant to this letter was reported.

1. Nie W, Li B, Xiu Q. β-Lactam/macrolide dual therapy versus β-lactam monotherapy for the treatment of community-acquired pneumonia in adults: a systematic review and meta-analysis. J Antimicrob Chemother 2014;69:1441-6.

DOI: 10.1056/NEJMc1506892

TO THE EDITOR: In this study, the noninferiority margin was 3 percentage points and the expected mortality was 5%. No clinical rationale for the large noninferiority margin was given. The study ran from February 2011 to September 2013. An article detailing the rationale for the study, but not the noninferiority margin, was published in April 2014, after the study was completed.[1] The original protocol, dated May 20, 2010, had specified a noninferiority margin of 2 percentage points at 28 days, and a final protocol, dated September 21, 2011, which was 7 months after the study had started, amended the margin to 3 percentage points at 90 days. The large noninferiority margin reported in the study is not clinically justified, the statistical rationale was published only after the trial had been completed, and the noninferiority margin and primary end point were changed once the study was under way. This study should be therefore interpreted with caution.

John Kinsella, M.D.
Rachel J. Kearns. M.B.

University of Glasgow
Glasgow, United Kingdom
john.kinsella@glasgow.ac.uk

No potential conflict of interest relevant to this letter was reported.

1. van Werkhoven CH, Postma DF, Oosterheert JJ, Bonten MJ. Antibiotic treatment of moderate-severe community-acquired pneumonia: design and rationale of a multicentre cluster-randomised cross-over trial. Neth J Med 2014;72:170-8.

DOI: 10.1056/NEJMc1506892

TO THE EDITOR: Postma et al. report that beta-lactam monotherapy is noninferior to beta-lactam–macrolide combination therapy in patients for whom there is a clinical suspicion of CAP and even in patients for whom CAP has been radiologically confirmed. In a recent clinical trial, Garin et al.[1] suggested that patients with severe pneumonia (Pneumonia Severity Index [PSI] risk class IV or score on CURB-65 [confusion, urea, respiratory rate, blood pressure, age ≥65 years] of ≥2) seemed to benefit from combination therapy.

In a previous systematic review and meta-analysis, we found that beta-lactam–macrolide combination therapy was associated with a decreased risk of death among patients with more severe (high-severity) CAP.[2] However, Postma et al. do not indicate the effects of beta-lactam–macrolide combination therapy and beta-lactam monotherapy in patients with high-severity CAP. Can the authors report the numbers of deaths in these two groups in different PSI and CURB-65 categories?

Wei Nie, M.D.
Bing Li, M.D.

Shanghai Changzheng Hospital
Shanghai, China
bing_li1962@163.com

No potential conflict of interest relevant to this letter was reported.

1. Garin N, Genné D, Carballo S, et al. β-Lactam monotherapy vs β-lactam-macrolide combination treatment in moderately severe community-acquired pneumonia: a randomized noninferiority trial. JAMA Intern Med 2014;174:1894-901.
2. Nie W, Li B, Xiu Q. β-Lactam/macrolide dual therapy versus β-lactam monotherapy for the treatment of community-acquired pneumonia in adults: a systematic review and meta-analysis. J Antimicrob Chemother 2014;69:1441-6.

DOI: 10.1056/NEJMc1506892

THE AUTHORS REPLY: Van der Eerden and Piszczek and Partlow mention that 38.7% of patients assigned to the beta-lactam strategy also received non–beta-lactam antibiotics at some time during the beta-lactam–strategy period. The protocol al-