Cochrane for Clinicians

Putting Evidence into Practice

Effectiveness of PPAR Gamma Agonists in Preventing Recurrent Stroke and Other Vascular Events

Madhavi Singh, MD; Kristen Grine, DO; and Amy Hays, MD, Penn State University College of Medicine, Hershey, Pennsylvania

Author disclosure: No relevant financial affiliations.

Clinical Question

Are peroxisome proliferator–activated receptor (PPAR) gamma agonists effective at preventing recurrent stroke and other serious vascular events in people with previous stroke or transient ischemic attack (TIA)?

Evidence-Based Answer

PPAR gamma agonists are probably effective in preventing recurrent stroke in people with previous stroke or TIA (absolute risk reduction [ARR] = 2.9%; 95% CI, 0.1% to 4.8%; number needed to treat [NNT] = 35; 95% CI, 21 to 1,000). (Strength of Recommendation [SOR]: B, based on inconsistent or limited-quality patient-oriented evidence.) PPAR gamma agonists also appear to be effective in preventing other serious vascular events (relative risk = 0.73; 95% CI, 0.54 to 0.99). (SOR: B, based on inconsistent or limited-quality patient-oriented evidence.) It is uncertain whether adverse effects are more common in those treated with PPAR gamma agonists vs. placebo.[1]

Practice Pointers

Cerebrovascular accidents, or strokes, are classified as ischemic (80%) or hemorrhagic. Stroke recurs in 30% of cases.[1] People who have a recurrent stroke have more than double the cumulative mortality rate vs. those with only a single episode of stroke.[2] Diabetes mellitus contributes to one in nine cases of stroke and TIA.[3] PPAR gamma agonists are insulin-sensitizing drugs used to treat hyperglycemia with insulin resistance and have been widely recommended for the treatment of type 2 diabetes.

This Cochrane review is an update of an initial review performed in January 2014. Five RCTs with 5,039 participants were identified; four evaluated pioglitazone (Actos) and one evaluated rosiglitazone (Avandia).[1] Three studies that included participants with recurrent stroke from the United States, Japan, and South Africa were ultimately included. They revealed that PPAR gamma agonists probably reduced the recurrence of stroke compared with placebo (ARR = 2.9%; 95% CI, 0.1% to 4.8%; NNT = 35; 95% CI, 21 to 1,000; 4,979 participants). The risk of bias was unclear because of the lack of information on randomization in one study, and a single large study with 3,876 participants influenced the outcome.

Common adverse effects associated with the use of PPAR gamma agonists include edema, anemia, liver dysfunction, and heart failure. In a 2010 trial, an increased risk of mortality and vascular events was found with rosiglitazone compared with pioglitazone in people with diabetes who were older than 65 years.[4] In the current review, the authors did not demonstrate that adverse effects occurred more often in participants treated with PPAR gamma agonists vs. placebo because of a wide CI and a high level of statistical heterogeneity. One study demonstrated that PPAR gamma agonists were associated with fewer serious vascular events, but there was a high risk of bias because of incomplete outcomes data. Data from this study were not part of the meta-analysis. Disability caused by vascular events or quality-of-life changes were not reported in any of the studies.

This is the first review of its kind; no other review articles have yet been published. PPAR gamma agonists are not considered first-line therapy, but they may be considered in combination with other therapy in patients with no compelling need to minimize hypoglycemia or if cost is a major issue. In patients who are at high risk for or have established atherosclerotic cardiovascular disease, chronic kidney disease, or heart failure, PPAR gamma agonists may be considered.[5] Because of the small number of included studies and level of quality of some of the studies, the conclusions of this review should be interpreted with caution.

The practice recommendations in this activity are available at http://www.cochrane.org/CD010693.

Editor's Note: The ARR, NNT, and related CIs reported in this Cochrane for Clinicians were calculated by the authors based on raw data provided in the original Cochrane review.

These are summaries of reviews from the Cochrane Library.

This series is coordinated by Corey D. Fogleman, MD, assistant medical editor.

A collection of Cochrane for Clinicians published in *AFP* is available at https://www.aafp.org/afp/cochrane.

CME **This clinical content** conforms to AAFP criteria for CME. See CME Quiz on page 267.

References

1. Liu J, Wang L. Peroxisome proliferator–activated receptor gamma agonists for preventing recurrent stroke and other vascular events in people with stroke or transient ischaemic attack. *Cochrane Database Syst Rev.* 2019;(10):CD010693.

2. Aarnio K, Haapaniemi E, Melkas S, et al. Long-term mortality after first-ever and recurrent stroke in young adults. *Stroke*. 2014;45(9):2670-2676.
3. Sarwar N, Gao P, Kondapally Seshasai SR, et al.; Emerging Risk Factors Collaboration. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies [published correction appears in *Lancet*. 2010;376(9745):958]. *Lancet*. 2010;375(9733):2215-2222.
4. Graham DJ, Ouellet-Hellstrom R, MaCurdy TE, et al. Risk of acute myocardial infarction, stroke, heart failure, and death in elderly Medicare patients treated with rosiglitazone or pioglitazone. *JAMA*. 2010;304(4):411-418.
5. American Diabetes Association. Addendum. 9. Pharmacologic approaches to glycemic treatment: *Standards of Medical Care in Diabetes—2020*. *Diabetes Care*. 2020;43(suppl 1):S98-S110.

Corticosteroids for Hospitalized Patients with Community-Acquired Pneumonia

William E. Cayley, Jr., MD, MDiv, University of Wisconsin School of Medicine and Public Health, Eau Claire, Wisconsin

Author disclosure: No relevant financial affiliations.

Clinical Question

Are corticosteroids safe and effective at reducing rates of mortality and clinical failure (i.e., death, worsening of imaging studies, or no clinical improvement) in adults and children hospitalized with community-acquired pneumonia (CAP)?

Evidence-Based Answer

For adults hospitalized with severe CAP, the use of corticosteroids may reduce the likelihood of mortality. (Strength of Recommendation [SOR]: B, based on inconsistent or limited-quality patient-oriented evidence.) For adults and children hospitalized with CAP, the use of corticosteroids may reduce the likelihood of early clinical failure. The risk of hyperglycemia is transient and of limited clinical significance.[1] (SOR: A, based on consistent, good-quality patient-oriented evidence.)

Practice Pointers

CAP is a significant cause of morbidity and mortality in the United States. There were 257,000 emergency department visits because of CAP in 2016 and 49,157 deaths (approximately 15.1 per 100,000 people) from CAP in 2017.[2,3] The authors of a previous Cochrane review found that "in most patients with pneumonia, corticosteroids are generally beneficial for accelerating the time to resolution of symptoms,"[4] but the evidence was not deemed strong enough to make firm recommendations. Subsequently, a 2015 systematic review found that corticosteroids for adults hospitalized with CAP might reduce mortality, use of mechanical ventilation, and length of hospital stay.[5] However, the most recent guidelines from the American Thoracic Society (ATS) and the Infectious Diseases Society of America (IDSA) do not recommend using corticosteroids for adults with nonsevere or severe CAP, and they endorse the use of corticosteroids only for patients with CAP and refractory septic shock.[6]

The authors of this review incorporated 17 randomized controlled trials (RCTs) with a total of 2,264 patients: 15 RCTs including 1,954 adults (mean age = 69.8 years) and two RCTs including 310 children (mean age = 5.6 years).[1] Although the authors searched broadly for studies examining all severities of pneumonia and all treatment settings, the only studies that met inclusion criteria were RCTs of corticosteroids used in the inpatient treatment of CAP. The included trials were conducted in Europe (eight studies), the Middle East (three studies), China (two studies), Japan (two studies), South Africa (one study), and Australia (one study). Thirteen of the 17 studies began in 2000 or later. For the main outcomes reported in the Cochrane review, the findings were generally consistent across the studies.

Definitions of pneumonia severity varied across studies, but for this review the authors defined severe CAP as a Pneumonia Severity Index (PSI) score of more than 4.[7] There was variation among trials in corticosteroid duration (one to 10 days) and dosing, but most trials in adults used intravenous corticosteroid dosages equivalent to 40 to 50 mg of prednisone per day for five to 10 days, whereas the trials in children used varied doses of prednisolone, methylprednisolone, or dexamethasone. The studies in this review were assessed as being at low risk of attrition bias; low or unclear risk of selection bias; low, unclear, or high risk of performance and detection bias; and overall high risk of reporting bias.

The reviewers found moderate-quality evidence that prescribing corticosteroids to 18 patients would prevent one death (with mortality measured within 30 days of randomization) and high-quality evidence that prescribing corticosteroids to four patients would prevent one episode of early clinical failure (e.g., death from any cause, radiographic progression, clinical instability at day 5 to 8). For adults with nonsevere CAP, the estimates of effect size for preventing mortality by treating with corticosteroids were too broad to allow for any firm conclusion of risk or benefit, but there was high-quality evidence that treating nine patients with corticosteroids would prevent one episode of early clinical failure. Hyperglycemia was more common with corticosteroid treatment, but no differences were noted between groups in rates of gastrointestinal bleeding, neuropsychiatric events, or adverse cardiac events.

The two studies of treatment in children did not report any deaths, but high-quality evidence showed that using corticosteroids to treat three children with CAP would prevent one episode of early clinical failure. The two studies also reported no adverse events, and one trial reported that there were no cases of hyperglycemia.

The previous Cochrane review addressing corticosteroid treatment for CAP found insufficient evidence to support clinical recommendations,[4] but subsequent meta-analyses

SUMMARY TABLE

Corticosteroids vs. Control for Hospitalized Patients with CAP

Outcomes	Risk with control	Risk with corticosteroids (95% CI)	NNT (95% CI)*	Participants (studies)	Quality of evidence (GRADE)
30-day mortality in adults	82 per 1,000	53 per 1,000 (38 to 74)	34 (24 to 125)	1,863 (11 RCTs)	Moderate
30-day mortality in adults with severe CAP (PSI > 4)[7]	131 per 1,000	76 per 1,000 (52 to 110)	18 (13 to 48)	995 (9 RCTs)	Moderate
30-day mortality in adults with nonsevere CAP	29 per 1,000	28 per 1,000 (13 to 58)	—	868 (4 RCTs)	Moderate
Early clinical failure in adults	373 per 1,000	149 per 1,000 (86 to 261)	5 (4 to 9)	1,324 (6 RCTs)	Moderate
Early clinical failure in adults with severe CAP (PSI > 4)[7]	422 per 1,000	135 per 1,000 (63 to 296)	4 (3 to 8)	419 (5 RCTs)	High
Early clinical failure in adults with nonsevere CAP	352 per 1,000	240 per 1,000 (197 to 292)	9 (7 to 17)	905 (2 RCTs)	High
Early clinical failure in children	659 per 1,000	270 per 1,000 (158 to 461)	3 (2 to 5)	88 (2 RCTs)	High

Note: The terms adults and children could not be uniformly defined because various age cutoffs were used across studies.

CAP = community-acquired pneumonia; NNT = number needed to treat; PSI = Pneumonia Severity Index; RCTs = randomized controlled trials.

*—The NNTs were calculated by the author based on raw data provided in the original Cochrane review.

Information from references 1 and 7.

have demonstrated improvements in morbidity[8-10] and mortality[5] when adjunctive corticosteroids are used in hospitalized patients with CAP. The recent ATS/IDSA guidelines[6] were published after this Cochrane review, focus only on adults, and cite the four previous meta-analyses[5,8-10]; however, they do not address the findings of this review. The ATS/IDSA guidelines do not support routine use of corticosteroids in adults with severe or nonsevere CAP, but they call for further research in this area.[6]

The practice recommendations in this activity are available at http://www.cochrane.org/CD007720.

Editor's Note: This review was completed prior to the onset of the coronavirus disease 2019 (COVID-19) pandemic and thus should not be seen as evidence that corticosteroids have a role in the treatment of COVID-19 pneumonia.

References

1. Stern A, Skalsky K, Avni T, et al. Corticosteroids for pneumonia. *Cochrane Database Syst Rev.* 2017;(12):CD007720.
2. Rui P, Kang K, Ashman JJ. National Hospital Ambulatory Medical Care Survey: 2016 emergency department summary tables. 2016. Accessed December 2, 2019. https://www.cdc.gov/nchs/data/ahcd/nhamcs_emergency/2016_ed_web_tables.pdf
3. Kochanek KD, Murphy SL, Xu J, et al. Deaths: final data for 2017. *Natl Vital Stat Rep.* 2019;68(9):1-77.
4. Chen Y, Li K, Pu H, et al. Corticosteroids for pneumonia. *Cochrane Database Syst Rev.* 2011;(3):CD007720.
5. Siemieniuk RAC, Meade MO, Alonso-Coello P, et al. Corticosteroid therapy for patients hospitalized with community-acquired pneumonia: a systematic review and meta-analysis. *Ann Intern Med.* 2015;163(7):519-528.
6. Metlay JP, Waterer GW, Long AC, et al. Diagnosis and treatment of adults with community-acquired pneumonia. An official clinical practice guideline of the American Thoracic Society and Infectious Diseases Society of America. *Am J Respir Crit Care Med.* 2019;200(7):e45-e67.
7. PSI/PORT Score: Pneumonia Severity Index for CAP. Accessed February 18, 2020. https://www.mdcalc.com/psi-port-score-pneumonia-severity-index-cap
8. Briel M, Spoorenberg SMC, Snijders D, et al.; Ovidius Study Group; Capisce Study Group; STEP Study Group. Corticosteroids in patients hospitalized with community-acquired pneumonia: systematic review and individual patient data metaanalysis. *Clin Infect Dis.* 2018;66(3):346-354.
9. Chen LP, Chen JH, Chen Y, et al. Efficacy and safety of glucocorticoids in the treatment of community-acquired pneumonia: a meta-analysis of randomized controlled trials. *World J Emerg Med.* 2015;6(3):172-178.
10. Horita N, Otsuka T, Haranaga S, et al. Adjunctive systemic corticosteroids for hospitalized community-acquired pneumonia: systematic review and meta-analysis 2015 update. *Sci Rep.* 2015;5:14061. ■