Annual zoledronic acid infusion lowers risk of fracture, death, *J Fam Pract* 2007; 56:1013–1016	
SECTION 1: IDENTIFYING INFORMATION	
1.1 Citation	Lyles KW, Colón-Emeric CS, Magaziner JS, et al. Zoledronic acid and clinical fractures and mortality after hip fracture. *N Engl J Med* 2007; 357:1799–1809. Epub 2007 Sep 17.
1.2 PubMed ID	17878149
1.3 Reviewer name	Sarah-Anne Schumann
1.4 Reviewer affiliation	University of Chicago
1.5 Date review due	09/20/2007
SECTION 2: DETAILED STUDY DESCRIPTION	
2.1 Number of patients starting each arm of the study?	1065 zoledronic acid, 1062 placebo
2.2 Main characteristics of study patients? (Inclusions, exclusions, demographics, settings, etc)	**Men and women age 50 or older, within 90 days after surgical repair of hip fracture; exclusion-hypersensitivity to bisphosphonate, creatinine clearance <30 mL/min; high or low calcium; active cancer, life expectancy <6 months; international; 91% white, 76% to 77% female; mean age 74.5 years**
2.3 Intervention(s) being investigated?	**Zoledronic acid within 90 days of surgery and every 12 months**
2.4 Comparisons of treatment(s), placebo, usual care, and/or no treatment?	Placebo
2.5 Length of follow up? (Note specified endpoints, eg, death, cure, etc)	Median 1.9 years; stopped early based on surpassing the prespecified efficacy boundaries
2.6 What outcome measures are used? (List all measures used to assess effectiveness)	Planned to have primary outcome as mean time to first fracture, but used hazard ratio for fracture due to low number of overall fractures; secondary = change in bone mineral density in non-fractured hip, new vertebral, nonvertebral, and hip fractures, prespecified safety endpoints, including death
2.7 What is the effect of the intervention(s)? (Include absolute risk, relative risk, NNT, CI, *P*-values, etc)	***Rate of new fractures:*** 8.6% intervention vs 13.9% placebo; absolute risk reduction=5.3%, relative risk reduction=35%; ***deaths:*** 13.3% placebo, 9.6% intervention; relative risk reduction in death=28%

SECTION 3: INTERNAL VALIDITY	
3.1 Study addresses an appropriate and clearly focused question	Adequately addressed
3.2 Random allocation to comparison groups	Well addressed
3.3 Concealed allocation to comparison groups	Well addressed
3.4 Subjects and investigators kept "blind" to comparison group allocation status	Well addressed
3.5 Comparison groups are similar at the start of the trial	Well addressed
3.6 Were there any differences between the groups/arms of the study other than the intervention under investigation? If yes, please indicate whether the differences are a potential source of bias	Well addressed
3.7 Were all relevant outcomes measured in a standardized, valid, and reliable way?	Adequately addressed
3.8 Are patient-oriented outcomes included? If yes, what are they?	Yes. Fracture, adverse outcomes, death
3.9 What percent dropped out and were lost to follow up? Could this bias the results? How?	28.7% did not complete trial, 3% lost to follow-up
3.10 Was there an intention-to-treat analysis? If not, could this bias the results? How?	Yes
3.11 If a multisite study, are results comparable for all sites?	Not addressed
3.12 Is the funding for the trial a potential source of bias? If yes, what measures, if any, were taken to insure scientific integrity?	Novartis: "the academic investigators initiated the concept of the study, which was jointly designed with the sponsor. . . . data analysis was performed by the sponsor and confirmed by independent statisticians at UCSF."

SECTION 4: EXTERNAL VALIDITY	
4.1 To which patients might the findings apply? (Include patients in the study and other patients to whom the findings may be generalized)	Patients with hip fracture who cannot tolerate or refuse to take an oral bisphosphonate
4.2 In what care settings might the findings apply, or not apply?	Primary care, orthopedics, endocrine
4.3 To which clinicians or policy-makers might the findings be relevant?	As above
SECTION 5: REVIEW OF SECONDARY LITERATURE	
5.1 DynaMed excerpts	Zoledronic acid: summary of May 2007 *NEJM* article on zoledronic acid for osteoporosis-reduced incidence fracture, but noted side effects flu-like symptoms and arrhythmias; cites a couple of other preliminary studies
5.2 DynaMed citation/access date	Dynamed editorial team. Osteoporosis. Updated 9/13/07. Available at: www.ebscohost.com/dynamed. Accessed on 9/19/07.
5.3 UpToDate excerpts	Zoledronic acid: mentions May 2007 *NEJM* study as above and says IV zoledronic acid is an option for people who can't tolerate oral bisphosphonates for osteoporosis (not specific to hip fracture secondary prevention)
5.4 UpToDate citation/access date	Rosen HN. Bisphosphonates in the management of osteoporosis in postmenopausal women. Available at: www.uptodate.com. Accessed on 9/19/07.
5.5 PEPID PCP excerpts	Not mentioned in PEPID under osteoporosis
5.6 PEPID citation/access data	Singh A (author); French L (ed). Osteoporosis: therapeutics. PepidPCP [database online]. Available at: www.pepidonline.com. Accessed on 9/19/07.
5.7 Other excerpts (USPSTF; other guidelines; etc)	None
5.8 Citations for other excerpts	

SECTION 6: CONCLUSIONS	
6.1 How well does the study minimize sources of internal bias and maximize internal validity? Give one number on a scale of 1 to 7 (1=extremely well;	**2**

4=neutral; 7=extremely poorly)	
6.2 If 6.1 was coded as 4 or below, please describe the potential bias and how it could affect the study results. Specifically, what is the likely direction in which potential sources of internal bias might affect the results?	
6.3 Are the results of this study relevant to the health care needs of patients cared for by "full scope" family physicians, general internists, general pediatricians, or general ob/gyns? Are they applicable without significant change in programs or policies such as the organization or financing of practice? Give one number of a scale of 1 to 7 (1=absolutely relevant; 4=neutral; 7=not at all relevant)	**2**; but most primary care practices can't administer the infusion so patients would need to be referred for that once a year
6.4 Please explain your response to item 6.3.	
6.5 What is the main recommendation for change in practice, if any? Include a description of the change in practice, the indications, and the target population.	For patients with a prior hip fracture and who are unable or unwilling to take an oral bisphosphonate, IV zoledronic acid once a year will reduce risk of fracture and death.
SECTION 7: EDITORIAL DECISION	
7.1 FPIN PURLs editorial decision	PURL
7.2 Editor (BE or JH)	Bernard Ewigman, MD, MSPH, Professor & Chairman, Department of Family Medicine, The University of Chicago
7.3 Date of decision	September 20, 2007
7.4 Brief summary of reason for decision	For patients who do not tolerate oral bisphosphonates, often because of esophageal complaints, for whom compliance may be a issue, this trial shows a clinical significant benefit. Cost ($1000 per annual injection) will be a barrier to implementation. Oral bisphosphonates would seem to remain the mainstay, but this offers an effective alternative for the subset of patients with osteoporosis who do not tolerate or cannot consistently take oral bisphosphonates.