# POEMs



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This series is coordinated by Sumi Sexton, MD, Associate Medical Editor.

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## CIN Treatment May Increase Miscarriages but Does Not Affect Fertility

### Clinical Question

What is the effect of treatment for cervical intraepithelial neoplasia (CIN) on fertility and early pregnancy outcomes?

### Bottom Line

In this analysis of 15 observational studies (it would be difficult and unethical to do randomized research on this topic), excision using any method for CIN did not affect fertility, although second trimester miscarriages were more likely. A study published at the same time found the risk of preterm birth doubled with excisions of a depth of at least 15 mm. (Level of Evidence = 2a)

### Synopsis

To conduct this meta-analysis, the authors used Medline and Embase to identify all studies that compared fertility and early pregnancy (< 24 weeks' gestation) outcomes in women with or without treatment for CIN. They included all types of treatment, both ablative and excisional. Two investigators independently performed the literature searches and data extraction. The authors included 15 cohort studies that used any method to assemble women who did and did not undergo treatment, and evaluated fertility and early pregnancy outcomes. Regardless of type of treatment, pregnancy rates or time to conception in women trying to conceive was not affected by treatment of CIN in four studies of 38,050 women. Total miscarriage rates also were not different in 10 studies of 39,504 women. However, second semester miscarriage rates were higher (1.6% vs. 0.4%) in women who underwent treatment (risk ratio = 2.60; 95% confidence interval, 1.45 to 4.67). The numbers of ectopic pregnancies (1.6% vs. 0.8%) and pregnancy terminations (12.2% vs. 7.4%) were also higher in treated women. In a separate case-control study that evaluated 1,313 women who underwent colposcopy with 1,313 matched control patients, the risk of preterm birth was not affected by a small excision, but larger lesions (15 mm or more) were associated with a doubling of the risk of preterm and very preterm births, independent of the time since the excision (*BMJ.* 2014;349:g6223).

**Study design:** Meta-analysis

**Funding source:** Government

**Setting:** Various (meta-analysis)

**Reference:** *Kyrgiou M, Mitra A, Arbyn M, et al. Fertility and early pregnancy outcomes after treatment for cervical intraepithelial neoplasia: systematic review and meta-analysis.* BMJ. *2014;349:g6192.*

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## Valsartan/Sacubitril Reduces Mortality More Than Enalapril 10 mg Twice Daily in Patients with Heart Failure

### Clinical Question

Does inhibition of angiotensin and neprilysin offer benefits beyond those of angiotensin inhibition alone?

### Bottom Line

The combination of an angiotensin receptor blocker (valsartan) and neprilysin inhibitor (sacubitril) reduces cardiovascular mortality more than an angiotensin-converting ▶

enzyme (ACE) inhibitor (enalapril [Vasotec]) alone, with an acceptable safety and tolerability profile. The choice of dosage is concerning, however, because the study compared a fairly high dose of valsartan with a moderate dose of enalapril. (Level of Evidence = 1b)

### Synopsis

Neprilysin is an endopeptidase that breaks down vasoactive peptides such as natriuretic peptide, bradykinin, and adrenomedullin. Sacubitril inhibits this compound's activity, which has the effect of blocking the vasoconstriction, sodium retention, and cardiac remodeling that accompany more advanced stages of heart failure. A previous trial compared sacubitril with an ACE inhibitor, but angioedema was a problem. In the current trial, patients were randomized to receive the combination of sacubitril and the angiotensin receptor blocker valsartan or to receive enalapril, an older ACE inhibitor. All patients were adults with New York Heart Association (NYHA) class II, III, or IV heart failure; an ejection fraction no greater than 40% (later changed to 35%); and an elevated B-type natriuretic peptide level. The authors excluded those with hypotension, a glomerular filtration rate of less than 30 mL per minute per 1.73 $m^2$, a serum potassium level greater than 5.2 mEq per L (5.2 mmol per L), or a history of angioedema or other adverse effects of ACE inhibitors or angiotensin receptor blockers.

The authors ultimately enrolled 10,513 patients. They then had to run a gauntlet of two separate run-in phases: 1,102 patients left the study because they did not tolerate enalapril, 977 left because they did not tolerate the valsartan/sacubitril combination, and another 43 left primarily because of protocol violations. This meant a total of 8,399 patients were randomized to receive valsartan/sacubitril, 200 mg, or enalapril, 10 mg, each given twice daily. The dosage of valsartan is near the top of the recommended dosing range, whereas the dosage of enalapril is closer to the middle of the recommended range (10 to 40 mg per day) for that drug. Groups were balanced at the start of the study, with an average age of 63 years, 22% women, and the majority with NYHA class II (70%) or class III (24%) heart failure. Patients were followed for a median of 27 months, at which time an independent data monitoring committee halted the trial.

The primary outcome was a cardiovascular death or hospitalization for worsening heart failure. Obviously, this is an inappropriate composite, because they are very different outcomes. Looking at each outcome individually, however, there were fewer cardiovascular deaths in the intervention group (13.3% vs. 16.5%; $P < .001$; number needed to treat [NNT] = 31) and fewer hospitalizations in the intervention group (12.8% vs. 15.6%; $P < .001$; NNT = 36). All-cause mortality was also significantly lower in the intervention group (17.0% vs. 19.8%; NNT = 36), as was a validated symptom score. There were no significant differences in rates of renal function decline or new onset atrial fibrillation. Subgroup analyses showed similar benefits by age, sex, race, and comorbidities. Significant hypotension was more common in the valsartan/sacubitril group (14.0% vs. 9.2%; $P < .001$; number needed to treat to harm = 21), whereas cough and elevated serum creatinine levels were more common in the enalapril group. The valsartan/sacubitril group had lower mean blood pressures, supporting concerns of a "straw man" comparison with the selected dose of enalapril.

**Study design:** Randomized controlled trial (double-blinded)

**Funding source:** Industry

**Allocation:** Concealed

**Setting:** Outpatient (any)

**Reference:** *McMurray JJ, Packer M, Desai AS, et al.; PARADIGM-HF Investigators and Committees. Angiotensin-neprilysin inhibition versus enalapril in heart failure.* N Engl J Med. *2014;371(11):993-1004.*

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## Optimal Treatment of Acute Venous Thromboembolism

### Clinical Question

What is the optimal treatment strategy for acute venous thromboembolism?

### Bottom Line

This complex network meta-analysis of eight treatment regimens for acute venous thromboembolism found that a combination of unfractionated heparin and vitamin K antagonists is associated with the least effective strategy with the highest risk of recurrent events. Oral rivaroxaban (Xarelto) and apixaban (Eliquis) may be associated with the lowest risk of bleeding, but no overall significant differences occurred for effectiveness and safety compared with the combination of low-molecular-weight heparin (LMWH; Lovenox) and vitamin K antagonists. Rivaroxaban and apixaban have been compared head-to-head only with the traditional LMWH–vitamin K antagonist combination in three manufacturer-sponsored clinical trials (two of rivaroxaban; one of apixaban). (Level of Evidence = 1a)

### Synopsis

These investigators performed a meta-analysis comparing the clinical outcomes and safety associated with ▶

eight different treatment regimens for acute venous thromboembolism, including deep venous thrombosis or pulmonary embolism. Multiple databases were searched, including Medline, Embase, the Cochrane Registry, the Health Technology Assessment, and references of included studies, for randomized trials that compared at least two of any of the eight various regimens with each other, but not with placebo. No language restrictions were applied. Two individuals independently evaluated potential studies for inclusion and assessed methodologic quality using a standard risk-of-bias scoring tool. Differences were resolved by consensus agreement. The primary outcomes measured included recurrent venous thromboembolism events and major bleeding episodes of clinical significance.

A total of 45 articles (N = 44,989 patients) met study inclusion criteria, including 22 trials that compared an unfractionated heparin–vitamin K antagonist combination with an LMWH–vitamin K antagonist combination; 12 that compared an unfractionated heparin–vitamin K antagonist combination with LMWH alone; three that compared an LMWH–vitamin K antagonist combination with LMWH alone; two that compared a fondaparinux (Arixtra)–vitamin K antagonist combination with an LMWH–vitamin K antagonist combination or an unfractionated heparin–vitamin K antagonist combination; and six that compared an LMWH–vitamin K antagonist combination with one of the direct oral anticoagulants: two with dabigatran (Pradaxa), one with apixaban, one with edoxaban, and two with rivaroxaban.

Follow-up occurred for a median of three months. Compared with an LMWH–vitamin K antagonist combination, all treatment strategies except an unfractionated heparin–vitamin K antagonist combination resulted in a similarly lower rate of recurrent venous thromboembolism events. The unfractionated heparin–vitamin K antagonist combination was associated with a significantly increased rate of recurrent venous thromboembolism events (number needed to treat to harm = 188) compared with an LMWH–vitamin K antagonist combination. Compared with an LMWH–vitamin K antagonist combination, the risk of a major bleeding episode was statistically lower with rivaroxaban (number needed to treat = 258) and apixaban (number needed to treat = 165). All of the other treatment regimens were associated with a similar risk of adverse bleeding events compared with an LMWH–vitamin K antagonist combination. Apixaban was associated with the greatest overall probability of being the least harmful therapy, although it was evaluated in only one manufacturer-sponsored trial.

**Study design:** Meta-analysis (randomized controlled trials)

**Funding source:** Foundation

**Setting:** Various (meta-analysis)

**Reference:** *Castellucci LA, Cameron C, Le Gal G, et al. Clinical and safety outcomes associated with treatment of acute venous thromboembolism: a systematic review and meta-analysis.* JAMA. *2014;312(11):1122-1135.*

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