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

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## CEA vs. Stenting: Mixed Results, Mostly Bad

### Clinical Question

Is carotid artery stenting more effective than endarterectomy in patients with carotid artery stenosis?

### Bottom Line

These two randomized trials, one with short-term outcomes and the other with five-year outcomes, demonstrate that carotid artery stenting results in more frequent strokes (clinical and radiographically detected) than carotid endarterectomy (CEA). However, the rate of fatal and disabling strokes is comparable. (Level of Evidence = 2b–)

### Synopsis

These two studies, one from the Czech Republic (N = 150) and the other multinational (the International Carotid Stenting Study [ICSS]; N = 1,700), compared CEA with carotid artery stenting. The investigators used comparable methods (concealed allocation, only outcome assessors were blinded) and recruited adults with carotid stenosis. The Czech researchers evaluated patients with at least 70% stenosis before intervention, at 24 hours, and again 30 days later. The ICSS researchers, who evaluated patients with at least 50% stenosis, provided five-year outcome data. Although the authors of both studies report on functional outcomes (such as the modified Rankin scale), the Czech researchers report on magnetic resonance imaging–detected lesions and cognitive function, and the ICSS investigators report stroke rates.

In the Czech study, new infarcts were detected on magnetic resonance imaging in 49% of stented patients compared with 25% of the patients treated with CEA (number needed to treat to harm [NNTH] = 4). Most of these were silent as only two stented patients and one CEA-treated patient had symptoms. The authors reported no differences in any of the cognitive measures.

In the ICSS, the rate of fatal strokes was similar (6.4% vs. 6.5%) in each group. However, the rate of all strokes was 4.4% higher in the stented patients after the first year and 5.8% higher after the fifth year of follow-up (NNTH = 38 for the first year and 500 for the fifth year). Additionally, during the first year of follow-up, the stented group had 2.6% more deaths, but by five years, the death rate was similar for each group. The authors also report that the long-term functional outcomes were similar for each group.

**Study design:** Randomized controlled trial (nonblinded)

**Funding source:** Industry plus government

**Allocation:** Concealed

**Setting:** Inpatient (any location) with outpatient follow-up

**References:** Kuliha M, Roubec M, Procházka V, et al. Randomized clinical trial comparing neurological outcomes after carotid endarterectomy or stenting. *Br J Surg*. 2015;102(3):194-201.

Bonati LH, Dobson J, Featherstone RL, et al.; International Carotid Stenting Study investigators. Long-term outcomes after stenting versus endarterectomy for treatment of symptomatic carotid stenosis: the International Carotid Stenting Study (ICSS) randomized trial. *Lancet*. 2015;385(9967):529-538.

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## Are Some Antidepressants Safer Than Others Regarding Suicide Risk?

### Clinical Question

Are some antidepressants safer than others regarding suicide risk?

### Bottom Line

Mirtazapine (Remeron) and venlafaxine are associated with higher rates of completed suicide in primary care patients. Rates of suicide attempts and completion are similar with the use of selective serotonin reuptake ▶

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inhibitors (SSRIs) and tricyclic antidepressants. (Level of Evidence = 2b)

### Synopsis

These U.K.-based researchers used Qresearch, a large primary care database of more than 12 million patients from 600 general practices, to identify 238,963 patients with a new diagnosis of depression. Most patients (87.7%) received a prescription for an antidepressant and most of these prescriptions (71.3%) were for an SSRI. The mean duration of treatment was 221 days. During the first five years of follow-up, the authors identified 198 cases of suicide and 5,243 cases of attempted suicide or self-harm. Suicide rates were higher in the first 28 days of treatment. Absolute risks of suicide over one year ranged from 0.02% for amitriptyline to 0.19% for mirtazapine. There was no difference in suicide rates or rates of attempted suicide/self-harm between patients treated with SSRIs and tricyclic and related antidepressants. Compared with citalopram (Celexa), rates of suicide were significantly increased with mirtazapine (hazard ratio [HR] = 3.70; 95% confidence interval [CI], 2.00 to 6.84) and venlafaxine (HR = 2.23; 95% CI, 1.14 to 4.39). Other studies have shown similar suicide rates between SSRIs and tricyclic antidepressants (*Am J Psychiatry*. 2003;160(4):790-792).

**Study design:** Cohort (retrospective)

**Funding source:** Government

**Setting:** Outpatient (any)

**Reference:** Coupland C, Hill T, Morriss R, Arthur A, Moore M, Hippisley-Cox J. Antidepressant use and risk of suicide and attempted suicide or self harm in people aged 20 to 64: cohort study using a primary care database. *BMJ*. 2015;350:h517.

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## 9-Valent HPV Vaccine Offers Only Small Advantage Over Quadrivalent Vaccine

### Clinical Question

Is a 9-valent human papillomavirus (HPV) vaccine more effective than a quadrivalent vaccine?

### Bottom Line

A new 9-valent HPV vaccine is generally similar in effectiveness to the older quadrivalent vaccine. There is a small benefit of the new vaccine compared with the older vaccine for women who are initially uninfected (2.4 vs. 4.2 cases per 1,000 person-years), but you would have to immunize approximately 160 women with the

new vaccine to prevent one high-grade lesion over three years. It is possible that with additional follow-up, benefit would continue to accrue to the immunized women. (Level of Evidence = 1b)

### Synopsis

The current HPV vaccine is quadrivalent (qHPV), meaning it is active against the four oncogenic HPV subtypes (6, 11, 16, and 18) that cause approximately 70% of cervical cancers. This industry-funded study examines the effectiveness of a 9-valent vaccine (9vHPV), which theoretically extends protection to subtypes that cause an additional 20% of cervical cancers. This was an “adaptive design” clinical trial, something we are seeing more frequently these days. The first phase of the trial is used to establish the most effective dosage, and then the second phase evaluates its effectiveness. These researchers initially randomized 1,242 women to receive one of three doses of 9vHPV or qHPV as a control group, and then an additional 13,598 women were randomized to receive the selected dose of 9vHPV or qHPV. The average age of participants was 22 years, with a range of 16 to 26 years, and the women came from treatment centers all over the world.

The study was powered to find a difference in outcomes regarding the five subtypes not covered by the qHPV vaccine. Analysis was per protocol (including only those who got all three immunizations within one year, were HPV-free at the beginning of the study, and had no protocol violations), rather than the preferred intention-to-treat analysis. The authors did report results for a modified intention-to-treat population that included all patients who received at least one dose of the vaccine. This is important, because based on data from the Centers for Disease Control and Prevention, only approximately two-thirds of women complete the series (<http://www.cdc.gov/mmwr/preview/mmwrhtml/su6302a10.htm>). Women in the study were followed up for up to 60 months.

Approximately one-half the participants were HPV-positive by serology or polymerase chain reaction at baseline. The primary outcome was the rate of high-grade cervical, vulvar, or vaginal disease caused by one of the five HPV subtypes not in the older vaccine, and that rate was significantly lower with the 9vHPV vaccine in the per-protocol population (0.1 vs. 1.6 per 1,000 person-years). There was no difference between groups with respect to the four HPV subtypes shared by both vaccines. The 9vHPV vaccine stimulated similar degrees of immunogenicity for HPV types 6, 16, and 18, with a slightly lower titer for type 11. In the modified intention-to-treat analysis, there was no overall difference in the incidence of the primary outcome between groups ►

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(14.0 vs. 14.0 cases per 1,000 person-years). When considering only women who were uninfected at baseline, there was a significant reduction in the incidence of HPV (2.4 vs. 4.2 cases per 1,000 person-years), and in particular cases associated with one of the nine subtypes among those who were initially uninfected (0.0 vs. 1.2 cases per 1,000 person-years). The overall incidence of adverse events was similar between groups, but more patients reported moderate to severe pain or swelling with the 9vHPV vaccine. Serious events were similar between groups.

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

**Funding source:** Industry

**Allocation:** Uncertain

**Setting:** Population-based

**Reference:** Joura EA, Giuliano AR, Iversen OE, et al.; Broad Spectrum HPV Vaccine Study. A 9-valent HPV vaccine against infection and intraepithelial neoplasia in women. *N Engl J Med.* 2015;372(8):711-723.

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## NSAID Use Associated with Increased Risk of Serious Bleeding and CV Events After MI

### Clinical Question

Do nonsteroidal anti-inflammatory drugs (NSAIDs) increase the risk of bleeding and cardiovascular (CV) events in adults receiving antithrombotic therapy after myocardial infarction (MI)?

### Bottom Line

The use of concomitant NSAIDs in adults who receive antithrombotic therapy after MI increases the risk of serious bleeding complications and recurrent adverse CV events. This study found the highest risk among users of celecoxib (Celebrex) and diclofenac, and the lowest risk among users of ibuprofen and naproxen. The risk of bleeding significantly increased in as little as zero to three days after beginning NSAID treatment and persisted for at least 90 days. (Level of Evidence = 2b)

### Synopsis

These investigators linked information obtained from multiple databases in Denmark on hospital admissions, causes of death, and drug prescriptions to assess the

association of concomitant NSAID use with the risks of bleeding and CV events in patients receiving antithrombotic treatment after MI. During the study period, the only NSAID available over the counter in Denmark was ibuprofen, 200 mg. Study participants included adults 30 years or older admitted to the hospital with a first-time MI from 2002 to 2011 and who survived at least 30 days after discharge. Outcomes included bleeding episodes requiring hospital admission or causing death, gross bleeding from the respiratory or urinary tract, and anemia caused by bleeding, as well as the combined outcome of CV death, nonfatal recurrent MI, ischemic cerebrovascular event, or systemic arterial emboli.

A total of 61,971 patients (mean age of 67.7 years) met inclusion criteria; 20,931 (33.8%) filled at least one NSAID prescription after discharge. Incidence rates of bleeding were significantly increased in patients with concomitant NSAID treatment compared with those without (4.2 events vs. 2.2 events per 100 person-years, respectively). All types of NSAIDs were associated with an increased risk of bleeding, although celecoxib (hazard ratio [HR] = 2.59; 95% confidence interval [CI], 1.68 to 3.98) and diclofenac (HR = 3.09; 95% CI, 2.55 to 3.75) increased risk more than ibuprofen (HR = 1.65; 95% CI, 1.39 to 1.96) and naproxen (HR = 1.56; 95% CI, 0.84 to 2.90). The risk of bleeding significantly increased in as little as zero to three days after beginning NSAID treatment and persisted for at least 90 days. Similarly, concomitant NSAID treatment was significantly associated with an increased risk of adverse CV events compared with no use of NSAIDs, with the highest risk again being among users of celecoxib (HR = 1.46; 95% CI, 1.13 to 1.89) and diclofenac (HR = 1.65; 95% CI, 1.44 to 1.90) and lowest among those taking ibuprofen (HR = 1.42; 95% CI, 1.28 to 1.57) and naproxen (HR = 0.86; 95% CI, 0.52 to 1.36). A sensitivity analysis excluding patients with rheumatoid arthritis (which independently increases the risk of CV disease) did not change the results.

**Study design:** Cohort (prospective)

**Funding source:** Foundation

**Setting:** Inpatient (any location) with outpatient follow-up

**Reference:** Schjerning Olsen AM, Gislason GH, McGettigan P, et al. Association of NSAID use with risk of bleeding and cardiovascular events in patients receiving antithrombotic therapy after myocardial infarction. *JAMA.* 2015;313(8):805-814.

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