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

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Tranexamic Acid Decreased Death from Bleeding but Not All-Cause Mortality in Women with Postpartum Hemorrhage

Clinical Question

Does tranexamic acid (Cyklokapron) decrease the rate of death and hysterectomy in women with postpartum hemorrhage?

Bottom Line

In this really large study, tranexamic acid did not decrease the frequency of the primary outcome of death or hysterectomy in women with postpartum hemorrhage. However, there was a very small reduction in the rate of death from bleeding in the women treated with tranexamic acid. (Level of Evidence = 1b)

Synopsis

In this multicenter international study, the research teams recruited 20,060 women, 16 years or older, with a clinical diagnosis of postpartum hemorrhage following a vaginal delivery or a cesarean delivery (clinically estimated blood loss of more than 500 mL after vaginal birth or 1,000 mL after cesarean delivery, or any blood loss associated with hemodynamic instability). With other routine interventions for bleeding, the researchers administered 1 g of tranexamic acid or placebo by slow intravenous injection (100 mg per mL intravenously at an approximate rate of 1 mL per minute). If bleeding continued after 30 minutes, or stopped and restarted within 24 hours of the first dose, a second dose of 1 g of tranexamic acid or placebo could be given.

The authors reported no difference in the rate of the primary outcome, a composite of death from all causes or hysterectomy within 42 days of randomization. However, the authors reported there was a very small, barely statistically significant reduction in death due to hemorrhage (1.5% vs. 1.9%; $P = .045$) in patients who received tranexamic acid. If it takes 20,000 patients to barely achieve statistical significance, the impact cannot be all that great (number needed to treat [NNT] = 274; 95% confidence interval, 137 to 18,923). This is fairly typical of intervention trials: Ignore that the primary outcome was the same in both groups and focus on a secondary end point, which then becomes the tail wagging the dog. In the group of women given tranexamic acid one to three hours after delivery, there was more significant decrease in death from bleeding (NNT = 100).

Study design: Randomized controlled trial (double-blinded)

Funding source: Industry plus foundation

Allocation: Concealed

Setting: Other

Reference: WOMAN Trial Collaborators. Effect of early tranexamic acid administration on mortality, hysterectomy, and other morbidities in women with post-partum haemorrhage (WOMAN): an international, randomised, double-blind, placebo-controlled trial. *Lancet*. 2017;389(10084):2105-2116.

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Newer Oral Hypoglycemics Do Not Increase or Decrease Mortality

Clinical Question

Do newer (incretin-based) treatments for type 2 diabetes mellitus increase mortality?

Bottom Line

This seems like a strange question considering that the goal is to decrease mortality with drug therapy. Nevertheless, this study showed that the new kids on the diabetes block—exenatide (Byetta), dulaglutide (Trulicity), sitagliptin (Januvia), saxagliptin (Onglyza), and others—do not increase mortality, even in patients with cardiovascular risk. This jury is still out as to whether these agents do what they are supposed to do: decrease mortality as well as blood glucose levels. (Level of Evidence = 1a)

POEMs

Synopsis

These researchers searched four databases, including Cochrane Central and clinicaltrials.gov, to identify randomized controlled trials that evaluated glucagon-like peptide-1 receptor agonists or dipeptidyl-peptidase-4 inhibitors with placebo or active treatment in patients with type 2 diabetes, including a large number of patients with cardiovascular disease. They included 112 studies in which at least one patient died. The studies comprised 151,614 total patients and ranged from 12 to 234 weeks in duration (median 24 weeks). Two researchers independently selected studies for inclusion and evaluated the research for bias, which was generally low. There was no difference in all-cause mortality between incretin drugs vs. control agents (odds ratio = 0.96; 95% confidence interval, 0.90 to 1.02). There was also no increased mortality in patients at risk of cardiovascular disease. There was little heterogeneity among the studies and no evidence of publication bias.

Study design: Meta-analysis (randomized controlled trials)

Funding source: Foundation

Setting: Various (meta-analysis)

Reference: Liu J, Li L, Deng K, et al. Incretin based treatments and mortality in patients with type 2 diabetes: systematic review and meta-analysis. *BMJ*. 2017;357:j2499.

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Treatment of Subclinical Hypothyroidism Ineffective in Older Adults

Clinical Question

Is there a clinical benefit to treating subclinical hypothyroidism in older adults?

Bottom Line

Treatment of patients with a minimally elevated thyrotropin (thyroid-stimulating hormone) level did not result in any improvement in symptoms. If patients present with a thyrotropin level between 4.6 and 10 mIU per L, repeat the test because the levels often normalize (this occurred in 60% of the patients initially referred for the study). Only consider treatment if levels increase to above 10.0 mIU per L. (Level of Evidence = 1b)

Synopsis

Whether to treat patients with subclinical hypothyroidism (slightly elevated thyrotropin level, normal thyroxine [T₄] level, and no or minimal symptoms) remains controversial. The authors of this study recruited 737 adults with subclinical hypothyroidism, 65 years and older, and randomized them to receive thyroid replacement or matching placebo. The mean baseline thyrotropin level was 6.4 mIU per L (normal range = 0.4 to 4.59 mIU per L), and few patients had a value greater than 10.0 mIU per L. The groups were balanced, allocation was appropriately concealed, and analysis was by intention to treat. Patients were followed for one year, and the primary outcomes were the four-item ThyPRO thyroid symptom score and a seven-item Tiredness score.

The treatment dosage of levothyroxine was started at 50 mcg daily for most patients, and gradually increased until the thyrotropin was in the normal range (the placebo group had sham titration of their dosage). The final achieved average thyrotropin level was just greater than 3.0 mIU per L, which is a bit higher than the target 2.5 mIU per L recommended by some guidelines (*Eur Thyroid J*. 2013;2(4):215-228). At the end of the study period, there was no difference in any clinical outcomes. A subset of slightly more than one-half of the patients in each group had extended follow-up for a median of two years, and at that time there was a slightly greater improvement in the Tiredness score in the levothyroxine group, but this was of marginal clinical and statistical significance. There was no difference in harms, including cardiovascular events, although the study was not powered to detect a difference if there was one.

Study design: Randomized controlled trial (double-blinded)

Funding source: Government

Allocation: Concealed

Setting: Outpatient (any)

Reference: Stott DJ, Rodondi N, Kearney PM, et al.; TRUST Study Group. Thyroid hormone therapy for older adults with subclinical hypothyroidism. *N Engl J Med*. 2017;376(26):2534-2544.

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