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Most Likely to Change Clinical Practice

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CARDIOLOGY

In Women With Coronary Artery Disease, Newer Generation Drug-Eluting Stents Associated With Reduced Risks of Myocardial Infarction and Target Vessel Revascularization Compared to Bare Metal and Early Generation Drug-Eluting Stents

A Cochrane review has demonstrated that compared to bare metal stents, drug-eluting stents reduce the risk of target lesion revascularization [*Cochrane Database Syst Rev* 2010 May 12;(5):CD004587], but the large majority of patients with coronary artery disease recruited for clinical studies are male, and these trials may not have been adequately powered to draw similar conclusions in women. A recent pooled analysis of individual patient data has evaluated the long-term safety and efficacy of drug-eluting stents compared to bare-metal stents in a subgroup of female patients with coronary artery disease [*Lancet* 2013 Dec 7;382(9908):1879].

A systematic review identified 26 randomized trials comparing drug-eluting stents to bare-metal stents in 43,904 patients with coronary artery disease. Individual data from 11,557 women (26.3% of randomized patients) with a mean age of 67 years and a mean follow-up time of 2.9 years were included in the analysis. Drug-eluting stents were classified as either newer generation stents (including everolimus-eluting Xience and Promus stents, zotarolimus-eluting Endeavor and Resolute stents, biolimus-eluting BioMatrix and Nobori stents, and sirolimus-eluting Yukon stents) or early generation stents (sirolimus-eluting CYPHER stents and paclitaxel-eluting TAXUS stents). At baseline, women receiving drug-eluting stents had lower rates of diabetes and higher rates of previous myocardial infarction compared to those receiving bare metal stents. The minimum duration of dual antiplatelet therapy ranged from 2 to 12 months.

The cumulative incidence of myocardial infarction over 3 years was 4.8% in 6,278 women who received newer generation drug-eluting stents, significantly lower than the rates in the other groups (6% of 4,171 women with early generation drug-eluting stents and 7.7% of 1,108 women with bare metal stents) (level 2 [mid-level] evidence). Similarly, the cumulative incidence of target lesion revascularization over 3 years was significantly reduced in the newer generation drug-eluting stent group (6.3%) compared to the other groups (7.8% with early generation and 18.6% with bare metal stents). Newer generation drug-eluting stents were also associated with significantly lower rates of definite or probable stent thrombosis. The mortality rate was 5.7% overall, with no significant differences among treatment groups.

Collectively, these data support the use of newer generation drug-eluting stents compared to early generation drug-eluting stents or bare metal stents in women with coronary artery syndrome having percutaneous coronary intervention. However, drug-eluting stents are not the preferred option in patients unable to take dual antiplatelet therapy reliably for 12 months [*Circulation* 2011 Dec 6;124(23):e574-e651].

Testosterone Therapy Associated With Increased Cardiovascular Events in Men With Low Testosterone Levels and High Cardiovascular Risk

Testosterone replacement therapy has become increasingly common in recent years and has shown efficacy for improving sexual dysfunction, bone mineral density, exercise capacity, and metabolic parameters in men with androgen deficiency or chronic conditions including heart failure and diabetes. However, the relatively short duration of efficacy trials may limit the ability to assess potential harms.

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A recent 6-month randomized trial evaluating testosterone gel in frail elderly men was terminated early because of increased rates of cardiovascular events in the testosterone group [*N Engl J Med* 2010 Jul 8;363(2):109], raising concerns about whether these findings were specific to the trial or reflected a larger problem. A new retrospective cohort study has assessed long-term risks of testosterone therapy in men with low testosterone levels and high cardiovascular risk [*JAMA* 2013 Nov 6;310(17):1829].

A total of 8,709 men who visited a Veterans Administration facility for coronary angiography from 2005 to 2011 and who had serum testosterone $<$300 ng/dL ($<$10.4 nmol/L) were followed for a mean 27.5 months. At the time of angiography, 20% had had a previous myocardial infarction (MI) and 50% had diabetes. More than 80% had at least 20% stenosis in $\geq$1 epicardial vessel. Following angiography, 14% began testosterone therapy during the follow-up period (63.3% had testosterone patch, 35.7% had injection, and 1.1% had gel). The median time from angiography to the beginning of therapy was 531 days. The primary outcome was a composite of all-cause mortality, MI, and ischemic stroke.

There were a number of baseline differences between the men who received testosterone therapy and men who did not. The no-testosterone group was older (mean difference 3 years) and had significantly higher rates of coronary artery obstruction, hypertension, hyperlipidemia, heart failure, previous MI, chronic obstructive pulmonary disease, peripheral vascular disease, and cerebrovascular disease. In an analysis weighted by the probability of treatment with testosterone and adjusted for comorbidities, testosterone therapy was associated with an increased risk of primary outcome events (adjusted hazard ratio 1.29, 95% confidence interval 1.04-1.58). At 3 years, the cumulative event rates were 25.7% in the testosterone group vs 19.9% in the no-testosterone group (level 2 [mid-level] evidence). These data are consistent with the results of a recent systematic review assessing the effects of testosterone therapy in 2,994 men with low testosterone or chronic diseases (*BMC Med* 2013 Apr 18;11:108).

While it may be difficult to minimize bias in an observational study of this type, results from studies like this will often prompt longer follow-up in subsequent randomized trials. Until such data are available, this information and its limitations should be part of the discussion for men considering testosterone replacement therapy.

Multivessel Preventive Percutaneous Coronary Intervention (PCI) May Improve Cardiovascular Outcomes Compared to Culprit-Vessel-Only PCI Following ST-Elevation Myocardial Infarction

Current guidelines from the American College of Cardiology Foundation and the American Heart Association recommend primary percutaneous coronary intervention (PCI) of the culprit vessel only for most patients with ST-elevation myocardial infarction (STEMI). Performing PCI in noninfarct arteries at the same time as the infarct artery is discouraged except in cases of hemodynamic compromise [*Circulation* 2013 Jan 29;127(4):e362]. The recent Preventive Angioplasty in Acute Myocardial Infarction (PRAMI) randomized trial compared multivessel PCI vs culprit-vessel-only PCI in 465 patients with STEMI [*N Engl J Med* 2013 Sep 19;369(12):1115].

Following successful PCI on the culprit vessel, patients were randomized while in the catheterization laboratory to immediate PCI of noninfarct arteries with $>$50% stenosis (multivessel PCI) vs no further PCI procedure. Patients were excluded for previous coronary artery bypass graft (CABG) or for new indication for CABG. Subsequent PCI for angina was recommended only for patients with a confirmed diagnosis of refractory angina (symptoms uncontrolled by medical therapy plus objective evidence of ischemia). Otherwise, any follow-up PCI was discouraged. The primary outcome was a composite of cardiovascular death, nonfatal myocardial infarction, and refractory angina.

The trial was terminated early after an unplanned interim analysis showed a significant reduction in the rate of the primary outcome in the multivessel PCI group (level 2 [mid-level] evidence). At the time of the analysis, the mean follow-up was 23 months. The primary outcome occurred in 8.8% of patients with multivessel PCI vs 22.9% of patients with culprit-vessel-only PCI ($P<0.001$). Multivessel PCI was associated with reduced risks of nonfatal myocardial infarction (3% vs 8.7%, $P=0.009$, number needed to treat [NNT] 18), refractory angina (5.1% vs 13%, $P=0.002$, NNT 13), and repeat revascularization procedures (6.8% vs 19.9%, $P<0.001$, NNT 8). The decrease in cardiovascular mortality with multivessel PCI was not significant (1.7% vs 4.3%, $P=0.07$) and no significant difference occurred in noncardiac mortality (3.4% vs 2.6%).

While the absolute risk difference favoring multivessel intervention was substantial, only 74 patients had the primary outcome. The relatively low total number of events in a trial stopped early, especially with an unplanned interim analysis, carries a risk of

bias for magnifying the amount of benefit from the intervention.

NEPHROLOGY

Clarithromycin Might Increase All-Cause Mortality and Hospitalization for Acute Kidney Injury Compared to Azithromycin in Older Adults Receiving Calcium Channel Blockers

Calcium channel blockers are metabolized by the cytochrome P450 3A4 (CYP3A4) enzyme. The macrolide antibiotic clarithromycin is an inhibitor of CYP3A4, potentially leading to a drug-drug interaction when coprescribed with calcium channel blockers, whereas azithromycin is not. In an observational study with elderly patients, coprescription of calcium channel blockers with either clarithromycin or erythromycin (also a CYP3A4 inhibitor) was associated with increased risk of hospitalization for hypotension but azithromycin did not significantly increase risk [*CMAJ* 2011 Feb 22;183(3):303]. Hospitalization for hypotension soon after coadministration of a CYP3A4 inhibitor and a calcium channel blocker has also been described in several case reports. Nevertheless, clarithromycin is often prescribed to patients who are chronically on calcium channel blockers, despite a warning that serious adverse reactions may occur. A new study assessed the risk of mortality or hospitalization for acute kidney injury or hypotension in a large cohort of older adults being treated with calcium channel blockers who received either clarithromycin or azithromycin.

A total of 190,309 older adults (mean age 76 years) receiving a calcium channel blocker plus newly prescribed clarithromycin or azithromycin were retrospectively assessed for 30 days from the date of antibiotic prescription. Approximately 40% of clarithromycin prescriptions and 38% of azithromycin prescriptions were for treatment of respiratory infections. Calcium channel blockers evaluated in the study included amlodipine (53% of patients), diltiazem (22% of patients), nifedipine (17% of patients), verapamil (4% of patients), and felodipine (4% of patients) [*JAMA* 2013 Nov 9 early online].

Clarithromycin was associated with an increased risk of all-cause mortality compared to azithromycin (1.02% vs 0.59%, $P<0.05$, with a number needed to harm [NNH] of 232) (level 2 [mid-level] evidence). Clarithromycin was also associated with an increased risk of hospitalization for acute kidney injury (0.44% vs 0.22%, $P<0.05$, NNH 454) and hospitalization for hypotension (0.12% vs 0.07%, $P<0.05$, NNH 2,000). The risk of acute kidney injury was significantly greater in patients receiving nifedipine (NNH 160) compared to those receiving amlodipine (NNH 663).

Azithromycin is not without its own concerns. In March 2013, the FDA issued a warning that azithromycin can cause abnormal changes in the electrical activity of the heart that may lead to a potentially fatal irregular heart rhythm. Patients at particular risk for developing this condition include those with known risk factors such as existing QT interval prolongation, hypophosphatemia or hypomagnesemia, bradycardia, or use of antiarrhythmic drugs.

OBSTETRICS

In Twin Pregnancy With Cephalic Presentation of First Twin, Planned Vaginal Delivery Does Not Increase Neonatal Risks Compared to Planned Cesarean Delivery

Some observational data have suggested that vaginal delivery of twins may increase adverse outcomes compared to elective cesarean, but no strong evidence exists to recommend a policy of planned cesarean delivery in pregnancies without specific indications. A recent large randomized trial compared the delivery strategies of planned vaginal delivery and planned cesarean section in 2,804 twin pregnancies in which the first twin was presenting cephalically [*N Engl J Med* 2013 Oct 3;369(14):1295].

Women with twin pregnancy (gestational age 32 weeks to 38 weeks and 6 days) were randomized to planned vaginal delivery (with cesarean section only if indicated) vs planned cesarean section. Inclusion criteria included first twin in cephalic presentation and expected birth weight of both twins of 1,500-4,000 g (3.3-8.8 lbs) confirmed by ultrasound <7 days before randomization. In cases of noncephalic presentation of the second twin in the planned vaginal delivery group, the delivery method was at the discretion of the obstetrician and could include total breech extraction, external cephalic version with cephalic vaginal delivery, or cesarean section. Exclusion criteria included monoamniotic twins, fetal reduction at $\geq$13 weeks' gestational age, and contraindication to labor or vaginal delivery. Mothers and neonates were followed to 28 days after delivery. The primary outcome was a composite of fetal or neonatal death and serious neonatal morbidity.

Cesarean deliveries were performed in 90.7% of the planned cesarean group. In the planned vaginal delivery group, 39% had cesarean delivery for both twins and 4.2% had cesarean for the second twin only. The rates of the composite primary outcome were 1.9% with planned vaginal delivery vs 2.2% with planned cesarean (not significant) (level 1 [likely reliable] evidence). Fetal or neonatal death occurred in 0.6% with planned vaginal delivery and 0.9% with cesarean, and serious neonatal morbidity occurred in 1.3% of each group. No significant differences in rates

of maternal death or serious morbidity were seen between groups. This trial suggests one way to safely reduce the current high rates of cesarean section.

PEDIATRICS

Steroids Reduce Time to Discharge From Observation Unit in Infants With Acute Bronchiolitis and Suspected Asthma

Bronchiolitis commonly affects young children and is the most frequent cause of hospitalization among infants during the winter months. A recent Cochrane review [*Cochrane Database Syst Rev* 2013 Jun 4;(6):CD004878] found that systemic and inhaled corticosteroids do not reduce rates of hospital admissions or readmissions in children with acute bronchiolitis, and current guidelines do not recommend routine use of steroids in this patient population [*Pediatrics* 2006 Oct;118(4):1774-1793]. However, some infants initially presenting with bronchiolitis are subsequently diagnosed with asthma, and corticosteroids are used for long-term symptom control. Data evaluating the efficacy of steroids in infants with bronchiolitis who are at high risk for asthma have been limited thus far. A recent randomized trial compared oral dexamethasone vs placebo in 200 such infants [*Pediatrics* 2013 Oct;132(4):e810].

Infants (median age 3.5 months) presenting for emergency care with acute bronchiolitis were randomized to dexamethasone (1 mg/kg orally on day 1 followed by 0.6 mg/kg orally once daily for 4 more days) vs placebo. All infants were at high risk for asthma based on either the presence of eczema or history of asthma in a first-degree relative. All infants received nebulized salbutamol 2.5 mg 4 times during the first 2 hours and every 2 hours until discharge, and infants could receive nebulized epinephrine or other treatments at the discretion of the treating physician. Infants were evaluated for readiness for discharge from an observation unit at least every 6 hours and were followed for 1 week after discharge.

A modified intention-to-treat analysis was used to assess the efficacy of dexamethasone after excluding 10 infants for admission to intensive care unit, failure to meet inclusion criteria, or withdrawal after randomization. The mean time to readiness for discharge was 18.6 hours with dexamethasone vs 27.1 hours with placebo (P=0.015), and the dexamethasone group had a lower rate of nebulized epinephrine use (19% vs 34.4%, P=0.03, NNT 7). However, the frequency of return visits within 1 week of discharge was 22% for dexamethasone vs 21% for placebo (not significant). No hospitalizations or adverse events occurred in either group (level 1 [likely reliable] evidence).

Collectively, these results suggest that oral dexamethasone may be useful for treatment of bronchiolitis in the emergency department in this subpopulation by substantially decreasing the amount of time infants spend under observation. The increased turnaround associated with short-term dexamethasone treatment may be particularly beneficial during the winter months when cases of bronchiolitis in the emergency department are at their maximum frequency. However, these data do not support continued treatment for 5 days because no reduction in return visits in the week following discharge was seen.

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Level 1 [likely reliable] Evidence: research results addressing clinical outcomes and meeting an extensive set of quality criteria that minimize bias.

Level 2 [mid-level] Evidence: research results addressing clinical outcomes and using some method of scientific investigation, but not meeting the quality criteria to achieve level 1 evidence labeling.

Level 3 [lacking direct] Evidence: reports that are not based on scientific analysis of clinical outcomes. Examples include case series, case reports, expert opinion, and conclusions extrapolated indirectly from scientific studies.