Drug Monitor

A Gender Paradox in Fibrinolysis

Women are almost twice as likely as men to suffer moderate or severe bleeding when treated with fibrinolysis for ST-segment elevation myocardial infarction (STEMI), according to researchers from the Duke Clinical Research Institute, Durham, North Carolina; the University Hospital, Leuven, Belgium; New York University, New York, New York; the Auckland City Hospital, Auckland, New Zealand; and the Scripps Clinic, San Diego, California. On the other hand, women have a lower risk of death due to bleeding. Such data highlight the importance of understanding factors associated with gender-related differences in bleeding, say the researchers. They note that the correlation of excess bleeding in women with subsequent outcomes has not been previously studied.

The researchers analyzed data from subjects enrolled in 6 large, randomized, clinical trials: Global Utilization of Strategies to Open Occluded Arteries (GUSTO) I and III; Assessment of the Safety and Efficacy of a New Thrombolytic (ASSENT) 2 and 3; HERO-2; and patients with STEMI treated with fibrinolysis from GUSTO-IIb. The researchers compared the differences between men and women, with and without bleeding, in clinical features, angiographic characteristics, and outcomes.

Of 73,994 men, 5,279 (7%) developed bleeding; as did 3,377 (13%) of 25,385 women. Women had nearly twice the incidence of moderate bleeding (11% vs 6% in men) and intracranial hemorrhage (1.04% vs 0.59% in men). The most common bleeding sites were coronary artery bypass graft (29%), gastrointestinal (15%), and genitourinary (7%), although bleeding at the site of cardiac catheterization was reported in 35% of GUSTO III participants.

Medical treatments were similar in patients with and without bleeding. Patients with bleeding were more likely to have left main or 2-vessel coronary artery disease; and women were more likely to be older and nonsmokers, have hypertension, diabetes, obesity, and previous congestive heart failure.

One-year mortality was similar in men and women without bleeding, but when bleeding was entered in the mortality model, women had a lower risk of death, even though bleeding remained associated with an increased risk of death.

The researchers say they can't provide any "mechanistic insight" into the paradox of women's greater risk of bleeding but lower risk of death. They note, however, that women had a higher prevalence of lower baseline readings of hemoglobin and creatinine clearance, 2 factors associated with an increased risk of bleeding. They point out that lower creatinine clearance levels have been shown to be involved in dosing errors for antiplatelet and antithrombotic medications, which can raise bleeding risk.

Equally, researchers are somewhat at a loss to explain the lower mortality rate in women. Apart from unmeasured confounding factors and "simply chance," they say that because women are more tolerant to bleeding; have more procoagulant activity in general; and have faster, more effective, and firmer clot formation, they may be more likely to attain rapid hemostasis after bleeding; thus, the lower mortality rate. Age and comorbidity could play a part as well: age, because most women in the study were postmenopausal. Lack of estrogen has been associated with an increased propensity for vasoconstriction and higher levels of fibrinogen and anticoagulation factors; comorbidity, because that could mean a lower threshold for early aggressive treatment of bleeding.

Regardless of the underlying reasons, the researchers conclude, just knowing that there are gender differences in bleeding represents an opportunity to improve outcomes in both women and men with STEMI with, for instance, dose adjustment for weight and renal function.

Source: Mehta RH, Stebbins AS, Lopes RD, et al. *Am J Cardiol.* 2012;109(3):320-326. doi:10.1016/j.amcard.2011.09.012.

PPIs and Hip Fracture: Evaluating the Risk

More women are using proton pump inhibitors (PPIs) than ever before. In 2000, about 7% of women enrolled in the Nurses' Health Study regularly used a PPI, and by 2008, that number had risen to 19%, according to researchers from the Massachusetts General Hospital, the Brigham and Women's Hospital, and Harvard Medical School, all in Boston, Massachusetts. In low doses and for short periods, PPIs are safe, they say, but the risk of fracture triples with long-term use.

In their prospective study of 79,899 postmenopausal women, the researchers documented 893 hip fractures. The absolute risk of hip fracture among regular users of PPIs was 2.02 events per 1,000 person years compared with 1.51 events per 1,000 person years among nonusers.

Women who used PPIs regularly for more than 2 years had a 35% higher risk of hip fracture. The risk estimates were unchanged after adjusting for factors associated with fracture risk (eg, body mass index, use of postmenopausal hormones, calcium intake, and physical activity)—except for smoking, which raised the risk by more than 50%. Smoking inhibits calcium absorption and may have a synergistic effect with PPIs, which are also suspected of inhibiting bone growth by a variety of means. Although the risk persisted for women who stopped using PPIs within 2 years, eventually their risk dropped to that of women who had never used a PPI.

In May 2010, the FDA issued a warning about PPIs and fracture risk. After reviewing the available safety data, the FDA concluded that fracture risk with short-term, low-dose PPIs is unlikely. However, the FDA advises health care professionals to be aware of the risk for fracture with using over-the-counter PPIs at higher doses or for longer periods of time than recommended.

Source: Khalili H, Huang ES, Jacobson BC, Camargo CA Jr, Feskanich D, Chan AT. *BMJ.* 2012;344:e372. doi: 10.1136/bmj.e372.

How Long Do the Effects of Tyrosine Kinase Inhibitors Last?

Second-generation tyrosine kinase inhibitors (2G-TKIs) induce complete cytogenetic responses (CCyRs) in about 50% of patients with chronic myeloid leukemia (CML) who are still in the chronic phase. But how long do those responses last? Durability is an important issue, say researchers from the Hammersmith Hospital, London, England. Patients for whom imatinib fails to work are more likely to acquire resistance or transformed clones that may be responsible for early relapse. Moreover, patients who eventually respond may be forced to stop the first-choice 2G-TKI because of toxicity and require alternative treatment.

In the study, 119 patients with CML in the chronic phase who were resistant to imatinib were treated with dasatinib (70 mg/12 h or 100 mg/qd), nilotinib (400 mg/12 h), or bosutinib (500 mg/qd). Doses were adjusted according to tolerance. Eleven patients received an allogeneic stem-cell transplantation after a second- or third-line TKI failed to work. The patients were followed for 6 to 73 months (median, 36.3 months); one-third were followed for more than 48 months.

In an intention-to-treat analysis, the 4-year probability of survival was 82%; the event-free survival probability was 35%. The researchers used a concept of "current CCyR-survival" (c-CCyRS) to determine the durability of the cytogenetic response. The c-CCyRS at 4 years was 54%, which the researchers say over time shows remarkable stability.

However, 62 patients (52%) discontinued the first-choice 2G-TKI because of primary resistance, acquired resistance, or intolerance. Those patients required dose reduction or dose interruption during the first 3 months of second-line therapy and had a harder time compared with the 54 patients who received the full dose. These patients had a significantly lower cumulative incidence of CCyR and event-free survival at 4 years (29% vs 76% and 30% vs 44%, respectively). The deleterious effect of a low-dose intensity during the beginning of the second-line therapy was mainly limited to patients with hematologic toxicity. Patients with nonhematologic adverse effects responded well to an alternative TKI and had a 4-year c-CCyRS comparable with that of patients who received the full-dose intensity during the first 3 months of therapy.

Patients destined to fare poorly can be identified early, the researchers say. BCR-ABL1 transcript levels after 3 months on the first-choice 2G-TKI strongly predicted the most relevant clinical outcomes. A high 3-month transcript level identified patients with intrinsic resistance to TKI therapy. The 77 patients who, after 3 months of second-line therapy, had a BCR-ABL1/ABL2 ratio of ≤ 10% had a significantly superior overall survival (91% vs 72%, $P = .02$), as well as superior event-free survival (49% vs 13%, $P < .001$) than did the 30 patients with values > 10%. Those patients gained only a "very modest" reduction in transcript levels during follow-up. Changing to an alternative TKI appeared to offer limited benefit; the 4-year CCyRS for this cohort was only 11% compared with 67% for the other patients, $P = .0001$.

Patients with adverse effects may need to be treated with more than one 2G-TKI (after imatinib) in order to achieve an optimal outcome, the researchers say. Interestingly, they add, patients who discontinued second-line therapy because of adverse effects often fared well on third-line therapy.

Source: Milojkovic D, Apperley JF, Gerrard G, et al. *Blood.* 2012:119(4):1838-1843. doi: 10.1182/blood-2011-10-383000.