UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

BERKELEY • DAVIS • IRVINE • LOS ANGELES • RIVERSIDE • SAN DIEGO • SAN FRANCISCO

SANTA BARBARA • SANTA CRUZ

SCHOOL OF MEDICINE

DEPARTMENT OF ANESTHESIA AND PERIOPERATIVE CARE

Please address reply to the undersigned at

Anesthesiology Service (129)
Veterans Affairs Medical Center
4150 Clement Street
San Francisco, California 94121

Date: November 11, 2007

The POISE trial results have been reported in abstract form by Dr. P.J. Devereaux at the American Heart Association Annual Scientific Session, Orlando , FL , November 2007. http://www.cardiosource.com/clinicaltrials/trial.asp?trialID=1629

The results are mixed.

The primary endpoint of CV death, MI or cardiac arrest was reduced in the metoprolol group compared with placebo (5.8% vs. 6.9%, hazard ratio [HR] 0.83, 95% CI 0.70-0.99, p = 0.04), driven by a reduction in non-fatal MI (3.6% vs. 5.1%, HR 0.70, p = 0.0007). There were also reductions with metoprolol in revascularization (0.3% vs. 0.6%, p = 0.01), atrial fibrillation (2.2% vs. 2.9%, p = 0.04). However, total mortality was increased in the metoprolol group (3.1% vs. 2.3%, HR 1.33, p = 0.03) as was stroke (1.0% vs. 0.5%, HR 2.17, p = 0.005). The metoprolol group also had increased rates of significant hypotension (15.0% vs. 9.7%, p < 0.0001) and significant bradycardia (6.6% vs. 2.4%, p < 0.0001).

Dr. Devereaux concludes: Among patients undergoing noncardiac surgery, treatment with the beta-blocker metoprolol was associated with a reduction in the primary endpoint of CV death, MI or stroke at 30 days compared with placebo, but total mortality was higher in the metoprolol group.

Dr. Devereaux concludes that routine prophylactic therapy does not appear to be a safe approach to reducing CV events in this population.

The POISE study is a very large prospective randomized clinical trial. The methods and results of the trial need to be very carefully reviewed and taken very seriously. There are major differences between the inclusion criteria and dosing of metoprolol used in the POISE trial and those used in the perioperative beta blocker protocol (PCRRT) developed at the San Francisco VA. The most obvious difference is the dose of metoprolol XL used in the POISE study. The POISE study used a starting dose of metoprolol XL 100 mg controlled release (or placebo) given 2 to 4 hours prior to surgery and again 0 to 6 hours after surgery. The daily doses of study drug (metoprolol XL 200 mg or placebo) were then taken for the next 30 days. The PCRRT protocol had a starting dose of Atenolol 25 mg QD and maximum dose of Atenolol 100 mg PO per day.

From the Physician's Desk Reference: For hypertension, the usual initial dosage of Metoprolol XL is 25 to 100 mg daily in a single dose. The dosage may be increased in weekly intervals. For angina, the dosage should be individualized but the usual initial dosage is 100 mg PO daily. The recommended dose in with NYHA Class II heart failure is 25 mg PO daily for two weeks, or 12.5 mg PO daily for patients with more severe heart failure.

The initial dose of metoprolol XL in the POISE trial is 2 to 8 times the recommended initial dosage from the physician's desk reference. The POISE starting dosage of Metoprolol XL is **8 times** the recommended dose in the PCRRT protocol. In the Poldermans study (NEJM 24:341 1999), the starting dose of bisoprolol was 5 mg PO QD. Bisoprolol 5 mg PO QD is similar to Atenolol 25 mg PO QD or Metoprolol XL 25 mg PO QD. The POISE starting dose was 8 times the initial dosage used in the Poldermans study.

The results of the POISE study need to be very carefully understood prior to making decisions about perioperative beta blockade. It is clear from the POISE study that perioperative beta blockers can have significant risk if used incorrectly. It is very important that protocols for perioperative beta blockade be extensively tested prior to implementation. The PCRRT protocol from the San Francisco VA was derived from the ISIS-1 protocol (Lancet 2:8498 p 56-55, 1986) for Acute Myocardial Infarctions. The PCRRT protocol was tested in a randomized controlled trial (NEJM 23:335 1713-20, 1996). It has been used at the San Francisco VA since 1998. The San Francisco PCRRT (beta blocker protocol) is distinctly different from the protocol used in the POISE trial. Some of the adverse events in the POISE study may be related to a starting dose of 8 times the starting dose in used in previous studies.

Sincerely

Arthur Wallace, M.D., Ph.D.
VAMC Anesthesiology (129)
4150 Clement St.
San Francisco, CA 94121

Phone: 415-750-2069
Pager: 415-210-6077
Fax: 415-750-6946
E-mail: awallace@cardiacengineering.com