diabetic patients at this point in the research process, however "pioglitazone may be part of a novel strategy to reduce residual CV risk in patients with type 2 diabetes" concluded Dr. Theodore Mazzone, University of Illinois, Chicago. The results of the CHICAGO trial were published online on November 13, 2006 in JAMA (www.jama-ama-assn.org; Mazzone et al. *JAMA* 2006; 296; DOI 10.1001/jama.296.21.joc60158).

Etoricoxib Similar to Diclofenac in Rates of Cardiovascular Events: Results of the MEDAL Trial

Christopher P. Cannon, MD, Brigham and Women's Hospital, Boston presented the results of the cardiovascular outcomes Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) program. The MEDAL program consisted of pooled data from three trials conducted at 1,380 sites in 46 countries: the EDGE trial (osteoarthritis, 7,111 patients), the EDGE II trial (rheumatoid arthritis, 4,086 patients), and the MEDAL trial (osteoarthritis and rheumatoid arthritis, 23,504 patients). The goal of this program was to determine whether cardiovascular event rates were similar in patients treated daily with a COX-2 inhibitor (etoricoxib) compared with those treated with a widely used traditional NSAID (diclofenac). Patients over 50 years of age with a diagnosis of either rheumatoid arthritis (RA) or osteoarthritis (OA) of the hand, hip, knee, or spine were eligible for participation. Patients meeting all eligibility criteria were randomized either to etoricoxib (60 or 90 mg/day for OA or 90 mg/day for RA) or diclofenac (150mg/day).

A total of 34,701 patients were enrolled in the program, 17,412 in the etoricoxib group and 17,289 in the diclofenac group. The mean (SD) duration of therapy was 18.2 months (11.7) for etoricoxib and 17.7 (11.9) months for diclofenac. The demographic characteristics were similar between the two treatment groups. "Over the three year period that the patients were followed, there was no difference over time in the risk of [cardiac] events with these two different agents" said Dr. Cannon. The primary outcome measure of thrombotic cardiovascular event rates had a hazard ratio (HR) of 0.95 [95% CI, 0.81-1.11].

	Etoracoxib n=16,819	Diclofenac n=16,483	HR (95% CI)
Total thrombotic events	1.24	1.30	0.95 (0.81-1.11)
Cerebrovascular events	0.34	0.32	1.08 (0.80-1.46)
Cardiac events	0.71	0.78	0.96 (0.63-1.46)

Subgroup analyses were also performed and revealed no differences between treatments when factors such as age, gender, diabetes, established atherosclerotic cardiovascular disease (ASCVD), established ASCVD or ≥ 2 risk factors, low-dose aspirin usage, type of arthritis, or etoricoxib dose were examined. Rates of upper gastrointestinal tract events were significantly lower with etoricoxib (HR=0.69; [95% CI, 0.57-0.83]).

"Observational studies may lead us astray" in making therapeutic decisions, said Dr. Cannon, emphasizing the importance of controlled, randomized trials such as those in the MEDAL program. Other questions regarding cardiovascular events and the use of these medications remain unanswered, as this study had only one comparator and many others agents are routinely utilized. The choice of diclofenac as the comparator has also been criticized. "The investigators are justified in saying diclofenac is the most widely used traditional NSAID on the market worldwide and therefore it's a worthy competitor in a head-to-head comparison", said Robert M. Califf MD of

Duke University in his discussion of the trial data. He noted, however, that "this leaves open whether naproxen is actually cardio protective and would have come out significantly better than the COX-2 specific drug. It also leaves open the 10-20 other potential comparisons one can make." For now, clinicians must continue to tailor arthritis pain pharmacotherapy after considering the needs, history, and risks of each individual patient. The results of this study were published online in *The Lancet* on November 13, 2006 (Cannon et al, www.thelancet.com; DOI: 10.1016/S0140-6736(06)69666-9).

VLTS-394 Ineffective in the Treatment of Intermittent Claudication

Patients with peripheral artery disease (PAD) often experience difficulty walking and painful cramps because of the narrowing of arteries in the legs. This painful condition, known as intermittent claudication (IC), can range in severity from being mildly irritating to extremely debilitating. The efficacy and safety of VLTS-934 (Valentis, Inc.), a compound believed to increase microvascular blood flow, was evaluated in a Phase 2b randomized, double-blind, placebo-controlled multicenter trial of patients with IC conducted in the United States. VLTS-934 is a non-ionic, block co-polymer known as a poloxamer. *In vitro* studies have shown that VLTS-934 binds to damaged cell membranes, which subsequently leads to a decrease in cytokine (IL8, IL6 and MCP1) release and inflammation. This cellular repair is hypothesized to result in better functioning of the surrounding microvasculature.

One hundred and fifty seven participants diagnosed with severe IC secondary to PAD and were randomized in a 1:1 ratio to receive either VLTS-934 (79) or a saline placebo (78). The treatments were administered as 21 intramuscular (IM) injections (2 mL each) into each leg. The injections were administered in a specified pattern under local anesthesia: three rings x 4 injections per ring above the knee in the superior aspect of the patella, two rings x 4 injections below the knee in the tibialis arterior muscle, and one injection in the superior aspect of the popliteal fossa. The primary outcome measure was the change in peak walking time (PWT) from the baseline evaluation to 90 days post-injection.

Results of the trial were disappointing. At day 90, both groups showed improvement, but there was no statistically significant difference between the two treatment groups in PWT as measured on an escalating treadmill. No treatment effect was observed in the secondary outcome measures of PWT at day 30, ankle-brachial index at day 30 and day 90, total work capacity at day 30 and day 90, or quality of life at day 90. According to statements made by the manufacturer, there are no plans to further pursue development of the drug. "While disappointing, the uniformity of the data between the groups suggests that these results are a very accurate picture of the placebo effect in subjects with peripheral arterial disease and may be considered in the design of future claudication trials", said principal investigator P. Michael Grossman, MD.

The National Heart, Lung, and Blood Institute of the National Institutes of Health has formed a partnership with the PAD Coalition to promote awareness of PAD. For guidelines, helpful information, and free educational items for clinicians, please visit http://www.padcoalition.org/wp/.