Pioglitazone Exhibits a Beneficial Effect on CIMT in Patients with Type 2 Diabetes

Patients with type 2 diabetes are at greater risk for cardiovascular (CV) events, and thiazolidinediones, approved for the management of type 2 diabetes, have demonstrated an atheroprotective effect in animal models of atherosclerosis. The CHICAGO study sought to further elucidate the potential protective effect of the thiazolidinedione pioglitazone in patients with type 2 diabetes. This study was conducted at multiple centers in the city of Chicago and enrolled an ethnically and racially diverse population that had adequate control of their cardiac risk factors. Patients were treated for 72 weeks with either pioglitazone (15 to 45 mg daily) or another diabetes medication, glimepiride (1 to 4 mg daily). The primary endpoint was the change in mean posterior wall carotid intima-media thickness (CIMT) from baseline to the final evaluation. The CIMT is a validated surrogate marker of CV risk, as thickening of the CIMT correlates with a higher risk of CV events. The CIMT measurements in the CHICAGO study, taken at baseline, 24, 48 and 72 weeks, were performed at a single center with a single reader in order to minimize the variability of study results.

A total of 462 patients were randomized in the trial, 232 to pioglitazone and 230 to glimepiride. There were no statistically significant differences in the baseline demographic characteristics of the participants. The mean change in the posterior wall CIMT was 0.771 mm for pioglitazone, compared to 0.779 mm for glimepiride ($p=0.017$), indicating that the CIMT thickened more in the glimepiride group. The magnitude of the effect was somewhat smaller than that observed in prior trials and with inherent variability in CIMT measurements might not be clinically significant, although it was shown to be statistically significant. The mean change in maximal CIMT (a secondary measure) was also significantly better in the pioglitazone group ($p\leq0.01$). The observed treatment difference increased over time. Patients in the pioglitazone group also had better HbA1c ($p\leq0.05$), HDL cholesterol ($p<0.0001$) and triglycerides ($p<0.001$) when compared to glimepiride at Week 72. The change is CIMT was not adjusted for effects on HbA1c or HDL levels. No significant changes were observed in LDL cholesterol or systolic blood pressure. Protocol subgroup analyses did not reveal any differences when factors such as age, gender, presence of hypertension, number of years with diabetes, obesity, glucose control, or cholesterol lowering agent use were considered.

There were four adjudicated first CV events in the pioglitazone group, versus 10 in the glimepiride group. The most common adverse events associated with pioglitazone were edema and weight gain, with one case of congestive heart failure in the pioglitazone group. The data do not warrant treating pre-

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