Clinical Trial Highlights

ACTIVE-W Discontinued-Oral Anticoagulants Remain Treatment of Choice in Atrial Fibrillation

ACTIVE-W—one study under the larger umbrella of the ACTIVE (Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events) Trial—was discontinued in September 2005 after an excess risk of vascular events was observed in participants receiving clopidogrel plus aspirin compared with those receiving warfarin.

An increased risk of 1.7% (47% relative increase) of stroke and MI was noted in the clopidogrel/ASA arm versus the warfarin arm.

The ACTIVE trial, with 600 sites in 30 countries and more than 6,500 participants, is the largest randomized study program ever conducted to evaluate therapeutic strategies in atrial fibrillation (AF). ACTIVE has three study components, ACTIVE-A, ACTIVE-I, and ACTIVE-W. Both ACTIVE-A and ACTIVE-I are ongoing.

In announcing the halt of ACTIVE-W, Stuart Connolly, MD, director of the Division of Cardiology at McMaster University, Hamilton, Ontario, Canada, and principal investigator of ACTIVE, said that "the Data and Safety Monitoring Board alerted the ACTIVE Steering Committee to the difference in efficacy, clearly in favor of oral anticoagulants compared with the clopidogrel/aspirin arm in ACTIVE-W."

Oral anticoagulation (OAC) remains the standard of care in preventing stroke in AF, but clinicians must also confront management concerns including frequent INR monitoring and a narrow therapeutic window. And patients at higher risk for bleeding cannot take warfarin—but the alternative, aspirin, offers limited protection against embolic events.

ACTIVE-A will assess clopidogrel + aspirin compared with aspirin alone in patients with a contraindication to OACs or who are unwilling to take an OAC. ACTIVE-I will evaluate irbesartan versus placebo (along with antihypertensive therapy) in preventing vascular events in patients with atrial fibrillation. The ongoing ACTIVE trials will offer new information and alternatives in managing the significant risk of stroke and other vascular events associated with AF.

OmniHeart: Shifting Carb, Protein, and Fat Balance Lowers Heart Disease Risk

Substituting protein or monounsaturated fats for carbohydrates in a healthy diet will reduce heart disease risk, according to the OmniHeart Collaborative Research Group.

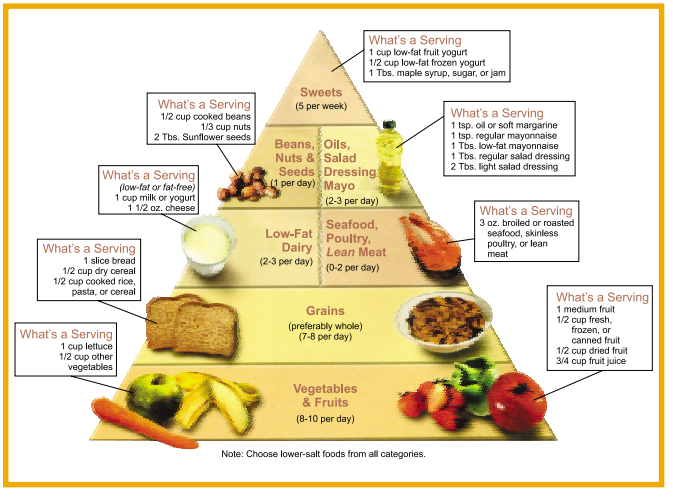
OmniHeart compared the effects of three healthy diets on blood pressure and cholesterol levels in 164 adults with elevated blood pressure – systolic of 120-159 mm/Hg or diastolic at 80-99 mm/Hg.

"While we know that lowering dietary saturated fat reduces cardiovascular risk, there is less certainty about which macronutrient balance offers optimum risk reduction," said Dr. Lawrence J. Appel, a principal investigator of OmniHeart and professor of medicine at Johns Hopkins University.

"OmniHeart offers evidence that substituting carbohydrates with protein or with unsaturated fat can lower blood pressure, improve cholesterol levels, and reduce heart disease risk."

All diets were low in saturated fat and healthier than the average diet prior to start of the study. One diet was rich in carbohydrates and is essentially similar to the Dietary Approaches to Stop Hypertension (DASH) diet which emphasizes fruits, vegetables, and low-fat or fat-free dairy products.

The second diet shifted 10 percent of its calories to protein,



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compared to the carbohydrate diet. The third shifted 10 percent of its calories to unsaturated fat, predominantly monounsaturated fat (found in peanuts, olives, and oils such as canola oil). Study participants were randomized to one of the three diets for six weeks at a time.

"In comparison to baseline levels (obtained when participants were eating their own food), all three diets lowered systolic blood pressure by 8.2-9.5 mm/Hg and LDL-C by 11.6-14.2 mg/dL," Appel said.

When compared to the carbohydrate diet, the protein diet reduced systolic blood pressure, lowered LDL, and reduced triglycerides by nearly 16mg/dL. (However, HDL decreased by 1.4 mg/dL.) The unsaturated fat diet reduced systolic blood pressure and while it had no significant effect on LDL, it raised HDL levels and lowered triglyceride levels.

The OmniHeart study demonstrated that protein and unsaturated fat diets offer the lowest CHD risk. There was a 16 percent risk reduction in the carbohydrate diet, but nearly 20 percent risk reduction in the unsaturated fat and protein diets.

"OmniHeart provides convincing evidence that the amount of carbohydrates, protein and fat people eat influence risk," said Appel. OmniHeart data can help policy makers in making public health recommendations, as well as assist clinicians in advising patients. Further information is available at www.omniheart.org.

PROactive: In Prior MI Patients Pioglitazone Lowers Risks

PROactive, a prospective, multicenter, randomized, double-blind placebo-controlled parallel-group trial, compared up to 45 mg/day of pioglitazone (PGZ) on top of other medication (optimal treatment of diabetes, dyslipidemia and hypertension) to placebo in 5,238 patients with type 2 diabetes and macrovascular disease. The PROactive study objective was to see if the glucose-lowering agent, already known to have beneficial effects on cardiovascular disease risk factors such as HDL cholesterol, triglycerides, LDL particle size and inflammatory mediators, would reduce total mortality and macrovascular morbidity in these high-risk patients.

No prior prospective studies have demonstrated that oral diabetes agents prevent major cardiovascular events in patients with type 2 diabetes, noted lead investigator professor Erland Erdmann, MD, Universitat zu Koeln, Denmark. Previously reported PROactive results showed a nonsignificant (p=0.095) 10% relative reduction in the primary endpoint of combined all-cause mortality, non-fatal MI (excluding silent MI) and stroke. This substudy analysis, among 2,445 patients (mean age 61.8 years, 8 years since diabetes diagnosis) with MI prior to randomization, included pre-specified measures of time to fatal or non-fatal MI, time to CV death or non-fatal MI, and time to CV death, non-fatal MI or stroke.

Figure: Results for Pioglitazone (n=1230) versus placebo (n=1215)

	Hazard Ratio
Fatal/non-fatal MI	0.72
CV death or non-fatal MI	0.84
CV death, non-fatal MI, stroke	0.84

For fatal/non-fatal MI, there was a significant advantage for pioglitzone versus placebo (95% CI 0.52, 0.99, p=0.045), and favorable trends for CV death or non-fatal MI (p=0.164) and CV death, non-fatal MI, stroke (p=0.123). In addition, non-prespecified "exploratory" analyses showed significant pioglitazone advantages for ACS (HR 0.63, p=0.035) and time to composite cardiac endpoint (cardiac death, non-fatal MI, coronary revascularization or ACS) (HR 0.81, p=0.034).

While serious adverse events were reduced in the pioglitazone group (47.2% versus 51.0%), heart failure leading to hospitalization was higher (7.5% versus 5.2%). Misdiagnosis of edema as heart failure, Erdmann speculated, may account for that increase. He concluded that in this population of patients with type 2 diabetes and prior MI, "Pioglitazone significantly reduced the risk of a second MI and of ACS."

Erdmann said finally, "Adding pioglitazone to the medication of 1,000 type 2 diabetes patients who have already had an MI (myocardial infarction) will prevent 22 recurrent MI and 23 ACS (acute coronary syndrome) events over 3 years."