News from the Scientific Sessions 2006 of the American Heart Association

We report the highlights from this year's American Heart Association (AHA) meeting held in Chicago, Ohio, US, from November 11th-16th, 2006. These included studies showing regression of atherosclerosis, a study showing the effect of statins in renal disease, and a study showing the cost-effectiveness of BNP testing in diagnosing heart failure.

CHICAGO: pioglitazone slows atherosclerosis *vs.* glimepiride

In a comparison of two diabetes drugs, pioglitazone reduced the progression of carotid intima-media thickness more than glimepiride in patients with type 2 diabetes.

Presenting the results of the Carotid Intima-media Thickness in Atherosclerosis using pioglitazone (CHICAGO) study, Dr Theodore Mazzone (University of Illinois College of Medicine, Chicago, US) explained that both pioglitazone, a thiazoldinedione, and glimepiride, a sulphonylurea, are antidiabetic agents and about equally efficacious in reducing blood glucose, but work through different mechanisms. He also noted that pioglitazone has other effects including reductions in markers of systemic inflammation and lipid levels that might be expected to translate into potential reduction of cardiovascular risk. Thiazoldinediones have also been shown to reduce atherosclerotic plaque in animals independently of glucose or lipid levels, he added.

The CHICAGO study randomised 462 patients with type 2 diabetes to receive 72 weeks of treatment with either pioglitazone or glimepiride, titrated to the HbA_{1C} target. Results showed that carotid intima media thickness was less with pioglitazone compared with glimepiride at all time points – weeks 24, 48 and 72.

There was a highly significant increase in high-density lipoprotein (HDL) cholesterol and a significant decrease in triglycerides in the pioglitazone group. Adverse events occurred in approximately 89% of patients in both groups; with serious adverse events occurring in 10.9% of pioglitazone patients and 13.2% of those taking glimepiride.

The study was not powered to look at clinical outcomes but there appeared to be more clinical events in the glimepiride group (10) than in the pioglitazone group (4). These were mostly coronary revascularisation. One patient in the pioglitazone group developed heart failure. Peripheral oedema and weight gain were also more common with pioglitazone as was previously observed, he added.

Designated discussant of the trial, Dr Peter Wilson (Emory University, Atlanta, US) said he felt that CHICAGO had fairly answered the question it set out to address but he would like to see further research with thiazoldinedione agents in the prevention of atherosclerotic progression, including more trials with clinical end points and focusing on other vascular territories.

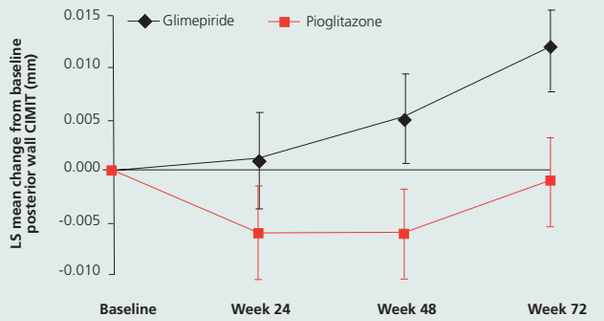
CHICAGO: implications for cardiovascular and stroke prevention

Thiazolidinediones (TZDs) affect the expression of multiple genes in a variety of different tissues. Most of the early interest in TZDs focused on their metabolic profile due to changes in the expression of genes that influence glucose and lipid metabolism in muscle, liver and fat, but more recently it has become clear that TZDs regulate a host of genes involved in vascular structure and function.[1] In particular, experimental studies in established animal and cellular models have shown that TZDs have favourable disease-modifying and disease-stabilising effects on atherosclerosis, in part by attenuating the inflammatory, thrombotic and metalloproteinase pathways which lead to vascular remodelling, arterial stenosis and plaque rupture in major coronary and cerebral vessels.[2]

Against this background, the recently published CHICAGO study is timely and highly relevant.[3] Thickening of the intima-media layer of the carotid artery, measured by high-resolution B-mode ultrasound, is a well-established marker of atherosclerotic disease progression which correlates well with the incidence of major clinical events, including stroke, myocardial infarction and cardiovascular death.[4]

CHICAGO was a prospective, randomised, double-blind trial to compare the effects of pioglitazone and glimepiride (a sulphonylurea) on carotid intima-media thickness

Figure 1. Change from baseline to week 72 in mean posterior carotid intima-media thickness of the common carotid artery, comparing pioglitazone and glimepiride treatment groups. Study treatments were double-blind. A single ultrasonographer performed all of the scans, which were analysed by a single blinded reader using automated edge-detection technology[3]



Key: LS = least square; CIMT = carotid intima-media thickness
Adapted from Mazzone T *et al*. JAMA[3]

(CIMT) in 462 newly diagnosed patients with type 2 diabetes. Longitudinal scans of the right and left common carotid arteries were undertaken at baseline and after 18-months treatment by a single ultrasonographer. The primary end point was absolute change from baseline to final visit in mean posterior wall CIMT.

Arterial disease progression, as reflected by serial measurements of CIMT, was significantly attenuated in the pioglitazone-treated group (Figure), yet both treatment groups had similar levels of glycaemic, BP and lipid control. Furthermore, the beneficial effect of pioglitazone was consistent across all the prespecified subgroups based on, for example, age, HbA_{1C}, duration of diabetes and body mass index.[3]

Modern treatments for the syndrome of type 2 diabetes should go well beyond glucose reduction. Preventing cardiovascular death and disability is the real end point by which therapeutic strategies are assessed. The CHICAGO study adds further information to that obtained in previous outcome trials, e.g the PROactive study, showing that pioglitazone has clinically relevant disease-modifying effects on vascular structure and function.

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New ASTEROID findings show lumen enlargement

New findings from the ASTEROID trial of rosuvastatin show that regression of coronary atherosclerosis is associated with arterial lumen enlargement.

ASTEROID investigator, Dr Neal Uren (Royal Infirmary of Edinburgh) commented: "The ASTEROID study was the first study to demonstrate that statins can reverse plaque build up. These new data from ASTEROID are important as not only can we reverse atheroma in the majority of patients but we are also able to increase the lumen size in those who have the greatest atheroma regression, perhaps with the potential to improve coronary blood flow in the long term."

Main results showed that: in the overall study population, there was a 6.8% reduction in total atheroma volume; in the group showing substantial regression of atheroma, there was a 3.5% increase in lumen volume; in the overall atheroma regression group there was no change in lumen volumes, and in the group where plaque progression occurred it was accompanied by a 9.1% reduction in lumen volume.

Ezetimibe/simvastatin combination shows influence on CHD risk markers in type 2 diabetes

An ezetimibe/simvastatin combination (Inegy®) more favourably influenced risk factors of coronary heart disease (CHD) than atorvastatin in type 2 diabetes patients according to the results of two analyses presented at the meeting.

Results showed that significantly more patients with type 2 diabetes treated with the combination reached optional recommended levels of low-density lipoprotein (LDL) cholesterol and achieved predefined values for apolipoprotein B (ApoB), non-high-density lipoprotein cholesterol (non-HDL-C), or C-reactive protein (hs-CRP) compared to those treated with atorvastatin.

In addition, the ezetimibe/simvastatin combination also produced significantly greater reductions in a variety of lipoprotein and apolipoprotein ratios.

Atorvastatin reduces cardiovascular events in patients with renal disease

Results of a new subgroup analysis of the Treating to New Targets (TNT) trial have shown that patients with both heart disease and chronic kidney disease who took atorvastatin 80 mg reduced their relative risk of major cardiovascular events by 40% compared with patients taking a 10 mg dose of atorvastatin.

The TNT renal analysis studied 2,656 patients with moderate to severe chronic kidney disease enrolled in the TNT trial. The primary end point of the TNT study was the time to first major cardiovascular event, including death from heart disease, non-fatal myocardial infarction, resuscitated cardiac arrest, and fatal or non-fatal stroke, as defined using a standard measure of kidney function. The absolute risk reduction was 5.6%, yielding a number needed to treat of 18 to prevent one major cardiovascular event over 4.9 years.

"These findings show that more aggressive treatment with atorvastatin in patients with kidney disease can help reduce the risk of heart attack and stroke," said TNT investigator, Professor James Shepherd (University of Glasgow Medical School).

MEDAL: similar cardiovascular risks for etoricoxib and diclofenac

Merck's new COX-2 inhibitor, etoricoxib, showed the same rate of thrombotic cardiovascular events as the traditional non-steroidal anti-inflammatory drug (NSAID), diclofenac, in the MEDAL (Multinational Etoricoxib and Diclofenac Arthritis Long-term) trial, which involved more than 34,000 patients with arthritis. Chief investigator, Dr Christopher Cannon (Brigham & Women's Hospital, Boston) said the results suggested that increasing COX-2 selectivity does not necessarily increase cardiac events.

But rates of other side-effects differed between the two agents, with etoricoxib showing small increases in congestive heart failure and discontinuations due to oedema or hypertension, while diclofenac was associated with higher rates of uncomplicated upper gastrointestinal (GI) events and discontinuations due to GI and hepatic adverse events. There was no difference in complicated upper GI events, and the two drugs showed similar rates of effectiveness against arthritis symptoms. The MEDAL trial was published online in *The Lancet* to coincide with its presentation at the AHA meeting.

The use of diclofenac as the comparator drug in this trial has been questioned, however, as it has some COX-2 selectivity itself and showed a high rate of adverse cardiovascular outcomes in a recent meta-analysis of NSAID studies published in *JAMA*. In an editorial accompanying *The Lancet* publication, Drs Luis Alberto García Rodríguez (Centro Español de Investigación Farmacoepidemiológica, Madrid, Spain) and Paola Patrignani (G d'Annunzio University, School of Medicine, Chieti, Italy) say it would have been preferable to have used a less COX-2 selective NSAID as the comparator, such as naproxen or ibuprofen. The editorialists say that both naproxen and ibuprofen are commonly used in the general population, where they are associated with a more favourable cardiovascular profile than that of diclofenac, and for this reason the application of the MEDAL results to general practice is limited.

Discussant of the trial at the AHA's late breaking clinical trial session, Dr Robert Califf (Duke University, Durham, US) said the trial provided "a relatively definitive result for the direct comparison done". But he added that the single comparison in this trial leaves open the issue of whether naproxen or a different NSAID would have shown a better result.

At an AHA press conference, Dr Cannon explained that diclofenac was chosen as the comparator drug as it was the most widely prescribed NSAID in the world and, unlike ibuprofen and naproxen, it does not interfere with the antiplatelet effects of low-dose aspirin. He pointed out that the *JAMA* meta-analysis suggesting diclofenac to have an increased risk of cardiovascular events compared with other NSAIDs was based on observational data, which were well known to be unreliable, and noted that randomised data suggest that all COX-2 selective drugs and NSAIDs are similar in terms of cardiovascular risk, apart from high dose naproxen which has an anti-platelet effect.

AHA statement

The American Heart Association issued a statement after the MEDAL presentation reminding that COX-2 inhibitors have important cardiovascular side effects, which are likely to be greatest in patients with a prior history of, or at high risk for, heart disease. In these patients, use of COX-2 inhibitors for pain relief should be limited to patients for whom there are no appropriate alternatives, and then only in the lowest dose and for the shortest duration necessary, the statement said. Conventional NSAIDs, including those available over the counter, may also not be completely safe for cardiovascular patients, it adds.

New vasopressin antagonist looks good in hyponatraemia

A new oral vasopressin V2-receptor antagonist, tolvaptan (in development by Otsuka), effectively increased serum sodium concentrations without affecting renal function, heart rate, or blood pressure in patients with hyponatraemia associated with heart failure and other conditions, in two studies.

The trials, known as SALT 1 and 2 (Sodium Assessment with increasing Levels of Tolvaptan in hyponatraemia), were identical trials carried out in the US and Europe, respectively, which compared tolvaptan with placebo in a total of around 450 patients with heart failure, cirrhosis, or the syndrome of inappropriate antidiuretic hormone secretion (SIADH), all conditions where hyponatraemia is common.

Lead investigator, Dr Mihai Gheorghiade (Northwestern University Feinberg School of Medicine, Chicago, US), explained that low sodium levels are associated with increased morbidity and mortality in patients with heart, liver and neurologic disease, and even mild chronic hyponatraemia has been associated with neurological defects, including impairment of balance. Diuretics, which are traditionally used to reduce congestion, tend also to produce electrolyte abnormalities and may adversely affect renal function, whereas tolvaptan induces the excretion of electrolyte-free water, without changing the total level of electrolyte secretion, he added.

Results showed that serum sodium concentrations increased significantly more with tolvaptan than placebo both at four days and at 30 days, and in both patients with mild and severe hyponatraemia, and sodium levels fell to levels similar to the placebo group within seven days after withdrawal of tolvaptan. Patient self-assessment data also suggested significant improvement from baseline to day 30 in the tolvaptan group on mental components of a general health survey.

No changes were seen in serum creatinine levels or in electrolyte levels including potassium and magnesium. The most common adverse events were thirst, dry mouth, and increased urination. Serious adverse events occurred in eight patients on tolvaptan, including hypotension, dizziness and syncope.

A larger trial (EVEREST) of the drug in patients hospitalised for worsening heart failure is now ongoing.

New test can stratify low ejection fraction patients for defibrillators

A non-invasive test can help target implantable cardioverter defibrillator (ICD) devices to patients with a low ejection fraction that are most likely to need them for prevention of sudden death, according to the results of a new study.

The microvolt T-wave alternans test resembles a stress ECG test but uses a built in algorithm to detect small variations in T-wave voltage, which are a marker of increased risk of sudden death. In the ABCD (Alternans Before Cardioverter Defibrillator) trial, the microvolt T-wave alternans test showed positive and negative predictive values for sudden death that were about the same as those of electrophysiological testing, a much more invasive method of assessing risk. But the combination of the two tests together produced the best results.

Reporting the study, Dr Ottorino Costantini (Case Western Reserve University, Cleveland, US) said the T-wave alternans test can improve the therapeutic efficacy of ICDs – measured as the number of devices implanted per lives saved – with minimal risk to patients. But he added that using the T-wave alternans test together with electrophysiological testing gave the best estimate of patient risk of sudden death, with the risk highest in those with two abnormal tests, extremely low in patients with two normal tests, and intermediate in patients with one positive and one negative test.

Ablation better than pacing for treating AF in heart failure

Pulmonary vein isolation with ablation was superior to biventricular pacing for the treatment of atrial fibrillation in chronic heart failure patients in a small pilot trial. The PABA-CHF (Pulmonary Vein Antrum Isolation versus AV Node Ablation with Biventricular Pacing for the Treatment of Atrial Fibrillation in Patients with Congestive Heart Failure) study showed that ablation eliminated the arrhythmia and improved ejection fraction, quality of life, and six-minute walk distances.

Lead investigator, Dr Andrea Natale (Cleveland Clinic, Cleveland, US) noted that atrial fibrillation is extremely prevalent in patients with heart failure and as so many of these patients do not respond to drug treatment, new options – such as pulmonary vein ablation – are needed.

Designated discussant of the study, Dr Alan Kadish (Northwestern University

Medical School, Chicago. US) said the results supported the use of rhythm control using state-of-the-art ablation therapy for this patient group. Comparing PABA-CHF with AFFIRM, which showed a benefit for rate control, Dr Kadish said the different patient population, as well as the improvement in techniques for maintaining sinus rhythm, were probably responsible for the different findings. "Despite the small number of patients (77), the data from PABA-CHF are compelling enough to change practice at experienced centres with atrial fibrillation ablation in drug-resistant patients with heart failure," he noted, adding that difficulty of the ablation technique could limit the widespread applicability of the results.

BNP testing proves cost-effective in diagnosing heart failure in Canadian study

Using BNP (brain natriuretic peptide) testing to help diagnose heart failure in patients coming to the emergency department with shortness of breath is cost-effective, saving around $1,000 per patient, a Canadian study has shown.

The study, presented by Dr Gordon Moe (St Michael's Hospital, Toronto, Canada), randomised 501 patients presenting with shortness of breath to seven emergency departments across Canada to usual care or BNP testing. The emergency department doctor's diagnoses were then compared with diagnoses by cardiologists blinded to the BNP results both in the emergency department and again at 72 hours in those who were hospitalised.

Results showed that the group who received BNP tests stayed in the emergency department for a shorter time than those in the usual care group (5.6 hours versus 6.3 hours). While there was no difference in admission to intensive care or stay, or initial hospitalisation, there was a reduction in rehospitalisation within 60 days in the BNP group (33 patients versus 51). Total costs were reduced by $961 per patient ($4,631 for BNP patients versus $5,592 for those in the usual care group). "In a healthcare system that mandates judicious use of resources, the use of the BNP test will improve the overall management of these patients and should be part of the routine management," Dr Moe concluded.

Late angioplasty no better than medical therapy for occluded infarct arteries

Performing late angioplasty on a persistent total occlusion after myocardial infarction (MI) does not reduce major cardiac events, according to the results of OAT (the Occluded Artery Trial).

In the trial, 2,166 stable patients with total occlusions of their infarct-related arteries were randomised - three to 28 days after their MI - to either routine angioplasty plus stenting and optimal medical therapy, or optimal medical therapy alone. After four years of follow-up, the primary end point - a composite of death, reinfarction, or heart failure - was no different in the late angioplasty group than in the medical group, but when looking at the individual components of the end point, there was a significant increase in non-fatal reinfarction in the angioplasty group (table 1).

Presenting the results, Dr Judith Hochman (New York University, US) said the results supported routine use of aggressive secondary prevention without revascularisation as the preferred strategy for stable MI survivors who do not receive angioplasty within the first 12 hours. Designated discussant, Dr Robert Califf (Duke University, Durham, US) agreed, saying: "There is no compelling reason to intervene on asymptomatic patients more than 24 hours after infarction with total occlusion of the infarct artery".

Table 1. OAT: four-year event rates

Outcome	Late angioplasty	Medical ratio	Hazard	P value
Death, MI, HF	17.2%	15.6(%)	1.16	0.20
Non-fatal MI	6.9%	5.0%	1.44	0.08

Key: MI = myocardial infarction; HF = heart failure

Angioplasty still reasonable

Fewer patients had angina among the angioplasty-treated patients at four months and one year but, over time, the occurrence of angina declined in the overall study population and the differences between the two groups disappeared. Commenting on this observation, Dr Hochman said that angioplasty was still a reasonable strategy to treat persistent angina, but not to prevent angina.