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REDUCTION OF LOW-DENSITY LIPOPROTEIN CHOLESTEROL IN PATIENTS WITH CORONARY HEART DISEASE AND METABOLIC SYNDROME: ANALYSIS OF THE TNT STUDY.

Despite the prognostic value of metabolic syndrome for predicting cardiovascular events, few trials have investigated the effects of statin therapy on cardiovascular morbidity and mortality in patients with the metabolic syndrome. This post hoc analysis of the Treating to New Targets (TNT) study assessed whether intensive lowering of low-density lipoprotein cholesterol with high-dose atorvastatin therapy results in cardiovascular benefits for patients with both coronary heart disease and the metabolic syndrome.

The TNT study was a prospective, double blind, parallel-group trial done at 256 sites in 14 countries between April 1998 and August 2004 with a median follow-up of 4.9 years. 10,001 patients were enrolled aged 35-75 years with clinically evident coronary heart disease. Analysis included 5584 patients with metabolic syndrome based on the 2005 NCEP ATP III criteria. Patients were randomly assigned to receive either atorvastatin 10 mg per day (n=2820) or 80 mg per day (n=2764). The primary outcome measure was time to first major cardiovascular event, defined as death from coronary heart disease, non-fatal non-procedure related myocardial infarction, resuscitated cardiac arrest, or fatal or non-fatal stroke.

In patients with coronary heart disease and metabolic syndrome, mean on-treatment low-density lipoprotein cholesterol concentrations at 3 months were 2.6 mmol/L (99.3 mg/dL) with atorvastatin 10 mg, and 1.9 mmol/L (72.6 mg/dL) with atorvastatin 80 mg. At a median follow-up of 4.9 years, major cardiovascular

events occurred in 367 (13%) patients receiving atorvastatin 10 mg, compared with 262 (9.5%) receiving atorvastatin 80 mg. Irrespective of treatment assignment, significantly more patients with metabolic syndrome (11.3%) had a major cardiovascular event at a median of 4.9 years than those without metabolic syndrome. This increased risk was significantly reduced by intensive therapy with atorvastatin 80 mg beyond that achieved with atorvastatin 10 mg. These data indicate that patients with coronary heart disease and metabolic syndrome derive incremental benefit from high-dose atorvastatin therapy, irrespective of the presence of diabetes.

Deedwania P, Barter P, Carmena R, Fruchart JC, Grundy SM, Haffner S, Kastelein JJ. Reduction of low-density lipoprotein cholesterol in patients with coronary heart disease and metabolic syndrome: analysis of the Treating to New Targets study. Lancet. 2006 Sep 9;368(9539):919-28.

Comment:

This study is the first to evaluate patients with metabolic syndrome and coronary artery disease who are treated with a statin. Briefly, the metabolic syndrome is: *Hyperinsulinemia (defined as the upper quartile of a measure of insulin resistance in the nondiabetic population) or a fasting plasma glucose (FPG) 110 mg/dL (6.1 mmol/L) or a plasma glucose two hours after an oral glucose tolerance test 200 mg/dL (11.1 mmol/L). Plus at least two of the following: Abdominal obesity, defined as a waist-to-hip ratio >0.90, a body mass index (BMI) 30 kg/m², or a waist girth 94 cm (37 in). Dyslipidemia, defined as serum triglyceride 150 mg/dL (1.7 mmol/L) or high-density lipoprotein HDL cholesterol <35 mg/dL (0.9 mmol/L) Blood pressure 140/90 mmHg or the administration of antihypertensive drugs.* It is well established that the metabolic syndrome is an independent and very potent risk factor for

atherosclerosis. Most of these patients, however, do not have significant elevations of their LDL cholesterols.

In this patient population, aggressive treatment with atorvastatin had a marked effect in terms of decreasing virtually all forms of cardiovascular morbidity and mortality. This further broadens the population of patients who would receive benefit not just from treatment, but from very aggressive treatment.

—**M. Nicholas Burke, MD**, Senior Consulting Cardiologist, Minneapolis Heart Institute.

ANGIOTENSIN-CONVERTING-ENZYME INHIBITORS IN STABLE VASCULAR DISEASE WITHOUT LEFT VENTRICULAR SYSTOLIC DYSFUNCTION OR HEART FAILURE: A COMBINED ANALYSIS OF THREE TRIALS.

Angiotensin-converting-enzyme (ACE) inhibitors reduce cardiovascular mortality and morbidity in patients with heart failure or left ventricular systolic dysfunction (LVSD). Three large trials have assessed the effect of ACE inhibitors in stable patients without these conditions but with atherosclerosis. This study undertook a systematic review of the Heart Outcomes Prevention Evaluation (HOPE), the European trial on Reduction Of cardiac events with Perindopril among patients with stable coronary Artery disease (EUROPA), and the Prevention of Events with ACE inhibition (PEACE) studies to determine the consistency with which ACE inhibitors reduce total mortality and fatal and non-fatal cardiovascular events.

The study computed cardiovascular outcomes and total mortality in the 29,805 patients of these three trials, randomly assigned an ACE inhibitor or placebo and followed up for a mean of about 4.5 years. The results were also analyzed within the context of five large trials of ACE inhibitors in patients with heart failure or LVSD.

When the findings of the HOPE, EUROPA, and PEACE trials were combined, ACE inhibitors significantly reduced all-cause

mortality (7.8 vs 8.9%, $p=0.0004$), cardiovascular mortality (4.3 vs 5.2%, $p=0.0002$), non-fatal myocardial infarction (5.3 vs 6.4%, $p=0.0001$), all stroke (2.2 vs 2.8%, $p=0.0004$), heart failure (2.1 vs 2.7%, $p=0.0007$), coronary-artery bypass surgery (6.0 vs 6.9%, $p=0.0036$) but not percutaneous coronary intervention (7.4 vs 7.6%, $p=0.481$). The composite outcomes of cardiovascular mortality, non-fatal myocardial infarction, or stroke occurred in 1599 (10.7%) of the patients allocated ACE inhibitor and in 1910 (12.8%) of those allocated placebo (odds ratio, 0.82; 95% CIs 0.76-0.88; $p<0.0001$). Except for stroke and revascularisation, these results were similar to those of the five trials in patients with heart failure or LVSD. ACE inhibitors reduce serious vascular events in patients with atherosclerosis without known evidence of LVSD or heart failure. Results showing these benefits in intermediate-risk patients complement existing evidence of similar benefit in higher-risk patients with LVSD or heart failure. Therefore, use of ACE inhibitors should be considered in all patients with atherosclerosis.

Dagenais GR, Pogue J, Fox K, Simoons ML, Yusuf S. Angiotensin-converting-enzyme inhibitors in stable vascular disease without left ventricular systolic dysfunction or heart failure: a combined analysis of three trials. Lancet. 2006 Aug 12;368(9535):581-8.

Comment:

This combined analysis of three very large studies evaluated the effects of ACE-inhibition in patients with documented atherosclerosis without heart failure or decreased LV function. Not surprisingly, there was a definite benefit to treatment with an ACE-I in these patients. At this point it appears that anyone with documented atherosclerotic vascular disease should be treated with an ACE-inhibitor, aspirin, and an aggressive dose of a statin regardless of the absence of any other comorbidities (HTN, DM, CHF, or hyperlipidemia).

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