CARDia trial (Coronary Artery Revascularisation in Diabetes)

The CARDia trial with 510 patients is the largest randomised trial specifically comparing coronary artery bypass surgery (CABG) and percutaneous coronary intervention (PCI) in patients with diabetes and multivessel disease to date. The BARI trial (which recruited patients from 1987 to 1991) had a subset of 353 patients with diabetes and suggested that CABG patients had improved survival compared to angioplasty, a finding which has guided practice since then.

Preliminary results of the CARDia trial at one year show no apparent difference between CABG and PCI in terms of the composite endpoints of death, non fatal MI and non fatal stroke (10.2% vs. 11.6%, p=0.63). Comparison of the individual endpoints of CABG vs. PCI were as follows: death (3.3% vs. 3.2%, p=0.83), non fatal MI (5.7% vs. 8.4%, p=0.25) and non fatal stroke (2.5% vs. 0.4%, p=0.09). Repeat revascularisation was higher in the PCI group as expected with a rate of 9.9% vs. 2.0% for CABG. Comparing CABG and a subgroup of 179 PCI patients who received drug eluting Cypher stents rather than bare metal stents, the composite endpoint of death, non fatal MI and non fatal stroke was 10.2% vs. 10.1% (p=0.98) again showing no difference in this composite endpoint.

CARDia shows that at 1 year, there is no apparent difference between CABG and PCI in terms of death or the composite of death, non fatal MI and non fatal stroke and suggests that PCI is a safe alternative to CABG in selected patients with diabetes and multi-vessel coronary artery disease. “We are very excited about these results. For the first time we have evidence from a randomised trial using modern treatments that PCI may offer safe coronary revascularisation in diabetic patients compared to surgery.” said Akhil Kapur, Study Director and presenter at the ESC Congress in Munich on September 1st 2008.

Background

During the United Kingdom Prospective Diabetes Study (UKPDS), patients with type 2 diabetes mellitus who received intensive glucose therapy had a lower risk of microvascular complications than did those receiving conventional dietary therapy. A post-trial monitoring was conducted to determine whether this improved glucose control persisted and whether such therapy had a long-term effect on macrovascular outcomes.

Methods

Of 5102 patients with newly diagnosed type 2 diabetes, 4209 were randomly assigned to receive either conventional therapy (dietary restriction) or intensive therapy (either sulphonylurea or insulin or, in overweight patients, metformin) for glucose control. In post-trial monitoring, 3277 patients were asked to attend annual UKPDS clinics for 5 years, but no attempts were made to maintain their previously assigned therapies. Annual questionnaires were used to follow patients who were unable to attend the clinics, and all patients in years 6 to 10 were assessed through questionnaires. We examined seven pre-specified aggregate clinical outcomes from the UKPDS on an intention-to-treat basis, according to previous randomisation categories.

Results

Between-group differences in glycated haemoglobin levels were lost after the first year. In the sulphonylurea–insulin group, relative reductions in risk persisted at 10 years for any diabetes-related end point (9%, P=0.04) microvascular disease (24%,
Background Post-trial monitoring of patients in the United Kingdom Prospective Diabetes Study (UKPDS) examined whether risk reductions for microvascular and macrovascular disease, achieved with the use of improved blood-pressure control during the trial, would be sustained.

Methods Among 5102 UKPDS patients with newly diagnosed type 2 diabetes mellitus, over a 4-year period beginning in 1987, 1148 patients with hypertension were randomly assigned to tight or less-tight blood-pressure control regimens. The 884 patients who underwent post-trial monitoring were asked to attend annual UKPDS clinics for the first 5 years, but no attempt was made to maintain their previously assigned therapies. Annual questionnaires completed by patients and general practitioners were used to follow patients who were unable to attend the clinic in years 1 through 5, and questionnaires were used for all patients in years 6 to 10. Seven prespecified aggregate clinical end points were examined on an intention-to-treat basis, according to the previous randomisation categories.

Results Differences in blood pressure between the two groups during the trial disappeared within 2 years after termination of the trial. Significant relative risk reductions found during the trial for any diabetes-related end point, diabetes-related death, microvascular disease, and stroke in the group receiving tight, as compared with less tight, blood-pressure control were not sustained during the post-trial follow-up. No risk reductions were seen during or after the trial for myocardial infarction or death from any cause, but a risk reduction for peripheral vascular disease associated with tight blood-pressure control became significant (P=0.02).

Conclusions The benefits of previously improved blood-pressure control were not sustained when between-group differences in blood pressure were lost. Early improvement in blood-pressure control in patients with both type 2 diabetes and hypertension was associated with a reduced risk of complications, but it appears that good blood-pressure control must be continued if the benefits are to be maintained. (UKPDS 81; Current Controlled Trials number, ISRCTN75451837 [controlled-trials.com]).

---

EASD 2008: Coronary versus Carotid Atherosclerosis

Coronary atherosclerosis is characterised by a higher prevalence of abnormal glucose tolerance and insulin resistance, compared with carotid atherosclerosis, researchers have reported. Specialists from the Scientific Institute San Raffaele, in Milan, Italy, studied 66 patients with asymptomatic ischaemic cardiopathy (and no atherosclerotic carotid lesions) and 88 patients with carotid vasculopathy (and no atherosclerotic coronary lesions).

The patients with coronary atherosclerosis had significantly higher levels of fasting plasma glucose, HOMA index, NOx, IL-6, and TNF-alpha levels, compared with those with carotid atherosclerosis. After an oral glucose load, only 26.5% of the patients with coronary atherosclerosis were shown to have normal glucose tolerance, compared with 44.5% of the patients with carotid atherosclerosis. Impaired glucose tolerance was seen in 40.5% and 35% respectively, while type 2 diabetes was seen in 33% and 20% respectively.

The researchers concluded: “Patients affected by coronary atherosclerosis seem to be characterised by a higher degree of glucose intolerance, insulin resistance, reduced anti-lipolytic insulin activity, and a more severe endothelial dysfunction.” They said the preliminary data suggest that two different pathogenetic pathways determine atherosclerotic lesions in coronary and carotid districts, although more evidence is needed to confirm the findings.

Source: European Association for the Study of Diabetes' 44th Annual Scientific Meeting, Rome, Italy, 7-11 September 2008, presentation number 1322.

---

“...coronary atherosclerosis seem to be characterised by a higher degree of glucose intolerance, insulin resistance, reduced anti-lipolytic insulin activity, and a more severe endothelial dysfunction”
Reducing HbA1c in patients with type 2 diabetes to ever lower target levels is not warranted, researchers have concluded. Their data suggest that below a certain level there are no further significant reductions in all-cause mortality. For the study, researchers from centres in The Netherlands, analysed data on a group of 1,143 patients with type 2 diabetes who were enrolled in 1998 and followed up for an average of 5.8 years.

The study group comprised 653 women and 490 men, with a median baseline HbA1c of 7.3%. Almost one-third of the patients (31%) died during the follow-up period, with 48% of these dying from cardiovascular disease. The analyses and models took into account potentially confounding variables such as age, sex, smoking, duration of diabetes, body mass index, blood pressure, cholesterol/HDL, macrovascular complications, statin use, insulin use, and albuminuria.

Overall, the standardised mortality ratios for all-cause mortality and for cardiovascular mortality were 1.86 (95% confidence interval [CI] 1.66-2.06) and 2.24 (95% CI 1.91-2.61) respectively. Calculating the hazard ratio for all-cause mortality for HbA1c as a continuous variable, the researchers found that for each 1% increase in HbA1c there was a 21% increase in the risk of all-cause mortality. This finding of increased mortality associated with poorer glycaemic control is in line with the findings of the landmark UKPDS study.

In analyses of HbA1c as a grouped variable, the hazard ratios for all-cause mortality were 0.92 (95% CI 0.55-1.55) for HbA1c 6-7%, 1.06 (95% CI 0.63-1.79) for HbA1c 7-8%, 1.43 (95% CI 0.84-2.46) for HbA1c 8-9%, and 1.80 (95% CI 1.02-3.17), compared to the reference group of patients with HbA1c below 6%.

Discussing their findings, the researchers noted that a recent trial of intensive therapy to reduce HbA1c to below 6% found an association with increased mortality. They concluded that, in this study, “HbA1c was a significant predictor for mortality and this effect seems largely attributable to patients in very poor glycaemic control.” They added: “The absence of differences in mortality between the lower HbA1c cohorts in our study suggested that there is no basis for an ever-decreasing target level of HbA1c in type 2 diabetes mellitus.”

Source: European Association for the Study of Diabetes’ 44th annual scientific meeting, Rome, Italy, 7-11 September 2008, presentation number 434.

Protocol Endorsed for Diabetic Foot Care by U.S. Diabetes Organisations

A simple protocol can assess the diabetic foot for the presence of predisposing factors for ulcerations and amputation, and can be used to guide treatment, according to recommendations developed by an ADA task force. The protocol consists of a history, general examination, and an assessment of dermatologic, musculoskeletal, neurologic, and vascular factors. Details of the protocol were issued by the ADA, with the endorsement of the AACE, in a report in the August issue of Diabetes Care by Andrew J. M. Boulton et al in a task force of the ADA’s Foot Care Group.

The history should explore previous foot ulceration or amputation, neuropathic or peripheral vascular symptoms, impaired vision, renal replacement therapy, and tobacco use.

Key components of the diabetic foot exam include dermatologic inspection for skin status, sweating, infection, ulceration, and calluses, as well as musculoskeletal inspection for deformity (claw toes, prominent metatarsal heads, Charcot’s joint) or muscle wasting.

Neurologic assessment for loss of protective sensation (LOPS) should include the use of a 10-g monofilament test, with the device placed at specific points on the bottom of the foot while the patient’s eyes are closed, as well as one of these additional tests:

⇒ Vibration using a 128-Hz tuning fork.
⇒ Pinprick sensation.
⇒ Ankle reflexes.
⇒ Vibration perception threshold testing.

Vascular assessment using ankle brachial pressure index testing should be performed to determine the presence of peripheral arterial disease (PAD) in two groups of patients: those who are symptomatic (claudication, rest pain, or non-healing ulcer) and those who have absent posterior tibial or dorsalis pedis pulses (Diabetes Care 2008; 31:1679-85).

Patients assessed using the protocol should be assigned to a foot risk category from 0 to 3, with 0 being no LOPS, no PAD, and no deformity, 1 being LOPS with or without deformity, 2 being PAD with or without LOPS, and 3 being a history of ulcer or amputation.

Subsequent therapy and follow-up care should be provided according to the category assigned: Primary care monitoring is appropriate for risk categories 0 and 1. Specialist care is indicated for risk categories 2 and 3.
Evidence from large-scale, randomised studies shows that statin therapy reduces the incidence of heart attacks, strokes, and revascularization procedures by about 20% for each reduction of 1 mmol per litre in the low-density lipoprotein (LDL) cholesterol level. In rare cases, statins can cause muscle pain or weakness in association with elevated CPK levels (i.e., myopathy), and occasionally, this leads to muscle breakdown and myoglobin release (i.e., rhabdomyolysis), with a risk of renal failure and death. The mechanisms by which statins cause myopathy remain unknown but appear to be related to statin concentrations in the blood. The incidence of myopathy is typically only about 1 per 10,000 patients/year with standard doses of statins (e.g., 20 to 40 mg of simvastatin daily), but it increases with higher doses (e.g., 80 mg daily) and with concomitant use of certain drugs (e.g., cyclosporine, which can inhibit statin metabolism). Although higher doses of statins may well result in larger reductions in the risk of vascular events, large, long-term, randomised studies comparing different doses are needed to make a reliable assessment of the balance between efficacy and safety.

The ongoing Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH), a randomised trial involving 12,064 participants with prior myocardial infarction, aims to determine whether a daily dose of 80 mg of simvastatin (Zocor, Merck) safely produces greater benefits than does a daily dose of 20 mg of simvastatin. During an average follow-up of about 6 years among the 6031 participants who were assigned to receive 80 mg of simvastatin, there were 98 definite or incipient cases of myopathy; more than half occurred in the first year, and all of the patients had a full recovery. Interim analyses revealed a strong, previously unrecognised, association of myopathy with 80 mg of simvastatin daily and the concomitant use of amiodarone (relative risk of nearly 10). Consequently, participants who were taking amiodarone were given 20 mg of simvastatin daily (irrespective of their original assignment), and treatment with amiodarone is now contraindicated with higher doses of simvastatin. We hypothesised that similarly strong associations might exist between myopathy with high-dose statin regimens and genetic variants, especially those affecting blood statin levels.

Previous studies have considered the relevance to myopathy of various candidate genes, such as CYP3A4, which is involved in the metabolism of certain statins, genes encoding organic anion–transporting polypeptides, some of which are associated with statin elimination, and genes involved in ubiquinone (coenzyme Q10) deficiency. Genetic associations with statin-induced myopathy, myalgia, or intolerance have been reported, but none were statistically convincing, owing to the large numbers of candidate genes and single-nucleotide polymorphisms (SNPs) assessed. Moreover, the apparent differences in the risk of myopathy in those studies may have been confounded by differences in statin regimens and concomitant use of other drugs. The comparatively large number of cases of myopathy among patients who were taking a high dose of simvastatin in SEARCH and the inclusion of well-matched controls from the same population allowed the conduct of a genomewide association study with good power to detect genetic variants that have plausibly large effects.

Conclusions from genomewide association study using approximately 300,000 markers (and additional fine-mapping) in 85 subjects with definite or incipient myopathy and 90 controls: Common variants in SLCO1B1 that are strongly associated with an increased risk of statin-induced myopathy have been identified. Genotyping these variants may help to achieve the benefits of statin therapy more safely and effectively. (Current Controlled Trials number, ISRCTN74348595 [controlled-trials.com]).

SOURCE Published at www.nejm.org July 23, 2008 (10.1056/NEJMoA0801936)

Citing new information on obesity, poor diet, and lack of exercise, the American Academy of Paediatrics has called for more aggressive screening in children for dyslipidaemia. AAP now recommends that children aged 2-10 years should be screened if they have a family history of dyslipidaemia or premature CVD. Screening also is advised in children with an unknown family history and in those who exhibit other risk factors for cardiovascular disease including overweight / obesity, hypertension, or diabetes mellitus.

Children whose results are within the normal reference range should be retested in 3-5 years, according to the AAP.