

ADA WATCH

SUMMARIES

2010 UPDATE FROM ORLANDO, USA

American Diabetes Association

25–29 June 2010

Contributors: J Aalbers, Dr F Mahomed, Prof WF Mollentze

CLINICAL TRIAL UPDATES

ACCORD retinopathy study shows intensive glycaemic control, and combination dyslipidaemia therapy with fenofibrate reduces retinopathy progression

A study group of the ACCORD study has shown that targeting glycaemic control at the 6% HbA_{1c} level and lipid therapy with fenofibrate instead of placebo significantly reduced the rate of progression of diabetic retinopathy.¹ Intensive blood pressure control did not reduce progression.

The ACCORD study was an independent study sponsored by the National Heart, Lung and Blood Institute and companies did not participate in the study design or conduct, data accrual or analysis, or manuscript preparation, providing only the study drugs.

The more than 10 000 ACCORD patients with type 2 diabetes and HbA_{1c} higher than 7.5% were randomly assigned to either the intensive glycaemic-control arm or standard control. Of these participants, 5 518 with dyslipidaemia were also randomly assigned in a two-by-two factorial design to receive simvastatin and fenofi-

brate or placebo. The remaining 4 733 participants were randomly assigned to either the intensive blood-pressure control (< 120 mmHg systolic blood pressure) or standard therapy (< 140 mmHg).

In this ACCORD eye study, participants with retinopathy at baseline were excluded; those included were comprehensively evaluated at baseline and at year four of the study. Progression of diabetic retinopathy was defined as at least three steps on the EDTRS severity scale or development of retinopathy requiring photocoagulation therapy or vitrectomy.

Results of the progression to retinopathy and moderate vision loss are summarised in Table 1.

The early stoppage of the intensive

glycaemic-control arm due to an increased rate of death from any cause after a mean of 3.5 years has influenced the retinopathy results in this arm, potentially underestimating the retinopathy benefits of good glycaemic control.

The beneficial effect of fenofibrate therapy on the progression of diabetic retinopathy at four years (6.3 vs 10.2% on placebo) provides further support to the findings of the FIELD study, which also showed visual benefits with fenofibrate.

1. The ACCORD study group and ACCORD Eye study group. Effects of medical therapies on retinopathy progression in type 2 diabetes. *N Engl J Med* 10.1056/NEJM oa1001288. Pub 29/6/2010.

Table 1. Progression to retinopathy and moderate vision loss

Treatment	Progression of retinopathy		Moderate vision loss	
	n	(%)	n	(%)
Glycaemic therapy				
Intensive	104/1429	(7.3)	266/1629	(16.3)
Standard	149/1427	(10.4)	273/1634	(16.7)
Dyslipidaemia				
With fenofibrate	52/806	(6.5)	145/908	(16)
With placebo	80/787	(10.2)	136/893	(15.2)
Antihypertensive				
Intensive	67/647	(10.4)	145/749	(19.4)
Standard	54/616	(8.8)	113/113	(15.8)

TABLE OF CONTENTS

CLINICAL TRIAL UPDATES	
ACCORD retinopathy study shows intensive glycaemic control, and combination dyslipidaemia therapy with fenofibrate reduces retinopathy progression.....1	Once-daily liraglutide lowers systolic blood pressure (SBP) in treated and untreated hypertensive patients.....3
Optimising glucose control in ICU patients reduces costs (TRIUMPH three-year results).....2	Dietary omega-3 polyunsaturated fatty acid (fish oil capsules) reduced atherosclerosis progression in type 2 diabetes.....3
VADT study: further analysis of results shows intensive glycaemic control offered some renal protection to patients with more advanced microvascular disease.....2	Costs of continuing sulphonylureas with insulin therapy in type 2 diabetes: more hypoglycaemia and weight gain but less insulin needed.....3
VADT trial: intensive glycaemic control did not prevent progression of calcified atherosclerosis in patients with long-standing type 2 diabetes.....2	REDUCING COMPLICATIONS OF DIABETES
Once-weekly exenatide injection improves blood sugar control more than daily oral sitagliptin or pioglitazone and induces more weight loss (DURATION-2 study).....2	Infliximab treatment improves visual acuity in diabetic macular oedema that does not respond to laser photocoagulation.....4
PATHOGENESIS OF TYPE 2 DIABETES	Point-of-care testing of diabetic keto-acidosis avoids unnecessary DKA work-ups in hyperglycaemic patients presenting at emergency departments.....4
Intramyocellular lipid accumulation does not occur in pre-diabetes, but only after manifestation of hyperglycaemia.....2	Rotating glucometer usage after achieving glucose control in the first patient improves HbA _{1c} levels in resource-constrained settings in Kenya.....4
Insulin resistance study (IRAS) shows problems for HbA _{1c} levels as diagnostic tool.....2	Poor glycaemic control slows wound healing.....4
New metabolic syndrome definition and value of waist circumference evaluated in type 2 diabetes.....3	Encouraging and educating physicians can result in earlier insulin prescription with enhanced HbA _{1c} control.....4
DIABETES THERAPY	Cardiovascular outcomes trial initiated for liraglutide.....4
Metformin protects against antidepressant diabetes risk?.....3	

Optimising glucose control in ICU patients reduces costs (TRIUMPH three-year results)

Targeting lower glucose levels (9.18 mg/dl, AACE guideline) in ICU patients has been shown to reduce length of stay (LOS) and ICU costs (\$8 000) in the extended three-year period of the TRIUMPH study involving more than 11 000 patients.

The use of intensive insulin therapy (IIT) also reduced complications and improved outcomes. The benefit of IIT was confirmed in this study, which compared intervention ICUs to control ICUs, which did not apply the intensive insulin therapy protocol.

Source: Presidents Poster, 0433-PP. Sadhu AR, Ang AC, Ingram-Drake LA, *et al.* Length of stay – cost-savings of intensive insulin therapy in ICU patients – 3-year results of the TaRgeted InsUlin therapy to iMProve Hospital outcomes (TRIUMPH) program.

VADT study: further analysis of results shows intensive glycaemic control offered some renal protection to patients with more advanced microvascular disease

The Veterans Affairs Diabetes Trial (VADT) in type 2 diabetes, although not able to show reduced cardiovascular events compared to average control in this further analysis of renal outcomes, provided data not yet published on the microvascular protection achieved by intensive control (INT).

In the VADT trial, the average age of patients was 60 years, duration of diabetes was 11 years, with HbA_{1c} levels of 9.4% at the outset of the study. With regard to renal function, patients were excluded if the serum creatinine was above 1.6 mg/dl. Renal progression was evaluated in terms of worsening urine albumin:creatinine ratio (ACR) and sustained worsening of estimated glomerular filtration rate (eGFR).

It was found that INT did not independently attenuate ACR or eGFR progression but did retard ACR progression by 72% in those who had photocoagulation, and by 95% in those requiring cataract surgery. The beneficial effect of INT was also more evident in patients with a BMI \geq 34 kg/m².

In conclusion, INT had no independent beneficial renal effect but afforded some protection in those with more advanced microvascular disease, lower baseline BP or higher baseline BMI.

Source: Presidents Poster 0412-PP. Agrawal L, Azad N, Emanuele N, *et al.* Renal outcomes in Veterans Affairs Diabetes Trial.

VADT trial: intensive glycaemic control did not prevent progression of calcified atherosclerosis in patients with long-standing type 2 diabetes

The VADT trial was able to show reduced cardiovascular events in participants with low levels of calcified coronary atherosclerosis at baseline. This newly presented study evaluated 197 patients with calcified atherosclerosis at baseline, as measured by CT scan and after 4.6 years in both the intensive glycaemic-control arm and the normal control group.

These scans showed no treatment benefit of intensive versus standard therapy with regard to either pre-existing coronary artery calcium (CAC) or abdominal aortic artery calcium (AAC).

Source: Presidents Poster 0405-PP. Saremi A, Anderson RJ, Duckworth WC, *et al.* Intensive glucose lowering therapy and progression of coronary (CAC) and abdominal aortic artery calcium (AAC) in the Veterans Affairs Diabetes Trial (VADT).

Once-weekly exenatide injection improves blood sugar control more than daily oral sitagliptin or pioglitazone and induces more weight loss (DURATION-2 study)

A convenient, once-weekly injection of exenatide in patients with type 2 diabetes was more effective at improving blood sugar control and inducing weight loss than were either daily oral sitagliptin or pioglitazone.

In this 26-week, randomised trial, the patients included all had type 2 diabetes and had been treated with metformin. The mean baseline glycosylated haemoglobin (HbA_{1c}) concentration in the cohort was 8.5%, the mean fasting plasma glucose was 9.1 mmol/l, and the mean body weight was 88.0 kg.

The study included patients from the USA, India and Mexico. Patients were randomly assigned to exenatide 2 mg injected once weekly plus daily oral placebo (170 patients); daily oral sitagliptin 100 mg plus placebo injected once weekly (172); or daily oral pioglitazone plus placebo injected once weekly (172). All patients continued their metformin treatment throughout the study.

Four hundred and ninety-one patients received at least one dose of the study drug and were included in the final analysis (160 exenatide, 166 sitagliptin, 165 pioglitazone). Treatment with exenatide reduced HbA_{1c} by 1.5%, compared with 0.9% in the

sitagliptin group and 1.2% in the pioglitazone group.

Patients in the exenatide group lost on average 2.3 kg, compared with a mean weight loss of 0.8 kg in the sitagliptin group and a mean weight gain of 2.8 kg in the pioglitazone group. No major episodes of hypoglycaemia (abnormally low blood sugar) occurred in any group.

The most frequent adverse events with exenatide and sitagliptin were nausea (24 and 10%, respectively) and diarrhoea (18 and 0%, respectively); while upper respiratory tract infection (10%) and peripheral oedema (fluid retention/swelling in the legs) (18%) were the most frequent events with pioglitazone.

Source: Oral presentation, ADA

PATHOGENESIS OF TYPE 2 DIABETES

Intramyocellular lipid accumulation does not occur in pre-diabetes, but only after manifestation of hyperglycaemia

Using prior gestational diabetes (GDM) as a model to study early changes in the development of type 2 diabetes, the researchers used magnetic resonance imaging (MRI) and MR spectroscopy to measure left ventricular function and myocardial lipid accumulation in the cardiac septum of women with prior GDM with normal glucose tolerance, in women with prior DGM and type 2 diabetes, and controls without GDM and with normal glucose tolerance.

There was no difference in left ventricular function between the groups except for stroke volume, which was decreased in women with type 2 diabetes. Also, these women showed increased intramyocellular lipid content compared to the women with GDM and normal glucose tolerance and decreased levels of high-density lipids, which were inversely related to the intramyocellular lipid content.

Source: Abstract ADA, 0014-OR. Winhofer Y, Krissak M, Anderwald C, *et al.* Cardiac function and lipid metabolism in women with prior gestational diabetes.

Insulin resistance study (IRAS) shows problems for HbA_{1c} levels as diagnostic tool

The IRAS study of some 417 patients at risk of developing diabetes has shown that the 6.5 and 5.7% HbA_{1c} thresholds have

a low sensitivity of detecting the onset of both diabetes and pre-diabetes, as defined by previous definitions of diabetes, using fasting glucose values (≥ 11.1 mmol/l), impaired glucose tolerance (IGT) (2-h glucose: 7.8–11.0 mmol/l) and impaired fasting glucose (IFG) (fasting glucose: 5.6–6.9 mmol/l).

The sensitivity and specificity of HbA_{1c} $\geq 6.5\%$ for detecting incident diabetes was 22 and 99.5%, respectively. The low sensitivity of these HbA_{1c} cut-off points could jeopardise the timely implementation of protective lifestyle and pharmacological interventions.

Source: Presidents Poster, 0424-PP. Haffer SM, Wagenknecht LE, Hanley AJ, *et al.* HbA_{1c} and fasting and 2-h glucose concentrations for detecting worsening of glucose tolerance status in individuals with normal glucose tolerance at baseline: the Insulin Resistance Atherosclerosis Study.

New metabolic syndrome definition and value of waist circumference evaluated in type 2 diabetes

The recent consensus definition of the metabolic syndrome allows for both the IDF and NCEP ATP III cut-off points for the diagnosis of a large waist in Caucasians. Its value in predicting type 2 diabetes has not yet been assessed.

This prospective study assessed and followed up for eight years, more than 500 non-diabetic Caucasians undergoing coronary angiography for evaluation of stable CAD. At baseline, 50% of the patients met the novel consensus metabolic syndrome definition but the predictability of this definition was enhanced when the NCEP ATP III waist circumference cut-off values of more than 102 cm for men and more than 88 cm in women were used.

The eight-year incidence of type 2 diabetes was 32% in patients defined according to these criteria, compared to 15% using the smaller waist circumference measure.

Source: Abstract 0381-OR. Saely CH, Vonbank A, Rein P, *et al.* Prediction of type 2 diabetes with the novel metabolic syndrome consensus definition: The importance of waist circumference.

DIABETES THERAPY

Metformin protects against antidepressant diabetes risk?

Continuous use of antidepressant medication increased the risk of developing

diabetes in the 10 years of the extended Diabetes Prevention Programme Outcomes Study (DPPOS) in those patients not receiving metformin. There was no association between antidepressant medication usage and diabetes risk in patients receiving metformin.

This ADA-sponsored research confirms the strong positive and statistically significant association between continuous antidepressant medication use and increased diabetes risk found in the three-year follow-up period of the DPP in those patients on the placebo and intensive lifestyle arm. The researchers noted that this association was still significant when controlled for depression symptom level.

While acknowledging that this finding does not allow the interpretation of a protective effect of metformin, it does alert clinicians to the higher diabetes risk facing patients who are being treated also for long-term depression.

Source: Presidents Poster. Abstract No 0479-PP. Rubin RR, Marrero DG, Yong MA, *et al.* Antidepressant medication use and risk of developing diabetes during the Diabetes Prevention Program and the Diabetes Prevention Programme Outcomes study.

Once-daily liraglutide lowers systolic blood pressure (SBP) in treated and untreated hypertensive patients

A meta-analysis of six randomised, controlled trials ($n = 3\ 967$) has shown that the reduction in SBP with liraglutide was independent of concomitant antihypertensive treatment (AH), and that this reduction was additive to concomitant antihypertensive therapy. The evaluation was done using an ANCOVA model, which included randomised treatment effect, use of AH therapy at 26 weeks and interaction with liraglutide/placebo at 26 weeks.

Source: Abstract 0296-OR. Fonseca V, Plutzky J, Montanya E, *et al.* Liraglutide, a once-daily human GLP-1 analog, lowers systolic blood pressure (SBP) independently or concomitant antihypertensive treatment.

Dietary omega-3 polyunsaturated fatty acid (fish oil capsules) reduced atherosclerosis progression in type 2 diabetes

This one-year study of 300 patients with type 2 diabetes showed that carotid intima-media thickness did not progress

in patients receiving fish oil capsules, compared to patients following the diet recommended by ESC/EASD.

The dosage of omega-3 was 1 g EPA, 1 g DHA and 0.1 g alpha-tocopherol acetate. Interestingly, total cholesterol, HDL cholesterol and triglyceride levels improved

Table 1. Change in SBP from baseline to week 26 (mmHg)

Patient group	Liraglutide		Difference between liraglutide and placebo
	1.8 mg	Placebo	
Overall	-2.55	0.19	-2.37
AH treat at week 26	-2.03	0.76	-2.79
No AH treat	-3.07	-1.13	-1.95

in those patients on the fish oil capsules.

Source: Abstract 0193-OR. Dragomir AD, Radulian G, Rosu E, *et al.* One-year administration of dietary omega-3 polyunsaturated fatty acid decreases oxidative stress and atherosclerosis progression in type 2 diabetes.

Costs of continuing sulphonylureas with insulin therapy in type 2 diabetes: more hypoglycaemia and weight gain but less insulin needed

There is no consensus on whether insulin secretagogues should be maintained when analogue insulin therapy is added to the type 2 diabetes regimen, while metformin is continued.

This multinational study of almost 1 000 insulin-naïve patients tracked diabetes control when basal insulin (glargine once daily or detemir twice daily) was added and sulphonylureas and glinides were retained/stopped.

Glucose control was not statistically significantly different but patients who continued with sulphonylureas had more hypoglycaemia (40 vs 24.5%) and gained significantly more weight (1.5 vs 0.4 kg). End-of study daily insulin doses were however significantly lower in patients continuing secretagogues than in those stopping these agents (0.6 vs 0.8 units/kg/day).

Source: Abstract 0037-OR. Swinnen SG, Dain MP, Mauricio D, *et al.* Continuation versus discontinuation of insulin secretagogues when initiating insulin in type 2 diabetes.

REDUCING COMPLICATIONS OF DIABETES

Infliximab treatment improves visual acuity in diabetic macular oedema that does not respond to laser photocoagulation

This small phase III study suggested that larger and long-term trials should be undertaken to assess the efficacy of the systemic or intravitreal anti-TNF monoclonal antibody, infliximab, to improve the vision of patients with diabetic macular oedema refractory to laser therapy.

This single-centre, double-blind, randomised, placebo-controlled, crossover study in 11 patients showed that intravenous infliximab (5 mg/kg) at weeks zero, two, six and 14, followed by placebo to 32 weeks, improved visual acuity by 24% compared to placebo-treated eyes.

Source: Presidents Poster 0416-PP. Tentolouris IV, Grigropoulos V, Emfietzoglou I, *et al.* Infliximab for diabetic macular edema refractory to laser photocoagulation.

Point-of-care testing of diabetic keto-acidosis avoids unnecessary DKA work-ups in hyperglycaemic patients presenting at emergency departments

The poor specificity of urine dipstick tests for diabetic ketones resulted in a high false-positive rate with increased hospital costs. This study used the point-of-care (POC) capillary beta-hydroxybutyrate test (the Precision Xtra meter, Abbott Laboratories) to obviate these additional costs.

Five hundred hyperglycaemic patients admitted to the emergency department were enrolled in the study and 53 met all ADA criteria for DKA. The urine dipstick had a sensitivity of 98%, but a specificity of 40%, whereas use of the Precision Xtra meter had an equal sensitivity but a specificity of 80%, thereby significantly reducing unnecessary DKA work-ups in hyperglycaemic patients.

Source: Presidents Poster 0386-PP. Arora S, Peters AL, Long T, *et al.* Utilising point-of-care testing to identify

diabetic ketoacidosis at emergency department triage: beta hydroxybutyrate vs urine dip.

Rotating glucometer usage after achieving glucose control in the first patient improves HbA_{1c} levels in resource-constrained settings in Kenya

A home glucose-monitoring programme for Kenyan patients with an HbA_{1c} above 10% and a cell phone has shown a mean drop in HbA_{1c} of 3% in a remotely managed cost-effective process of diabetes care.

Patients are given a glucometer and provided with glucose testing strips. They are called weekly by community workers, who record their results and relay the information to clinicians, who then adjust the insulin dose based on a standardised protocol.

Once a patient achieves good control, he/she returns the glucometer, which is then given to another patient. The researchers plan to extend this model to rural areas of Kenya.

Source: Presidents Poster, Abstract No 0432-PP. Ouma MN and Pastakia SK. A comprehensive collaborative enhanced diabetes care program in the rural resource constrained setting of Eldoret (western) Kenya.

Poor glycaemic control slows wound healing

This evaluation of raw data from several multi-centre, randomised, FDA-approved clinical trials among similar populations incorporated 411 diabetic patients with neuropathic foot ulcerations and evaluated the clinical and laboratory data during a 12-week period of wound healing.

The relationship between HbA_{1c} and successful wound healing over 12 weeks of standardised treatment was then evaluated. After adjusting for covariates (duration of diabetes, age, gender, race, etc), the evaluation showed that the odds of healing decreased by 15% for every 1% increase in HbA_{1c} during the preceding 12 weeks of wound care.

Source: Abstract 0189-OR. Cook EA, Cook JJ, Henao M, *et al.* The importance of sustained glycaemic control during wound healing.

Encouraging and educating physicians can result in earlier insulin prescription with enhanced HbA_{1c} control

Using the updated ADA/EASD consensus statement, which includes earlier use of insulin in patients not achieving HbA_{1c} goals on metformin and lifestyle, this certified diabetes educator (CDE) programme increased insulin use rates from 25 to 39%. Patient HbA_{1c} values improved with the proportion of diabetics with HbA_{1c} > 8.5% dropping from 36 to 24%.

The intervention was not too labour intensive, and was conducted over six months and included three main components: office-based education, print and monthly e-mail reminders.

Source: Abstract 0108-OR. Endsley S, Leal S, Choi J, Martinez AN. An office-based physician education program to enhance the earlier initiation of insulin: An evaluation of an academic detailing intervention in the US.

Cardiovascular outcomes trial initiated for liraglutide

Novo Nordisk announced at the ADA meeting details of the company's cardiovascular outcomes trial for liraglutide, which is set to start in the autumn of 2010.

The LEADER™ trial (Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results) aims to assess and confirm the cardiovascular safety of the company's new once-daily human GLP-1 analogue and potentially show its ability to improve cardiovascular outcomes. The trial also satisfies the new FDA guideline for type 2 diabetes treatments.

The protocol has been designed in close collaboration with an international expert steering committee as well as US and EU regulatory authorities, and with assistance from the Population Health Research Institute (PHRI) at McMaster University, Canada. Furthermore, an independent data-monitoring committee will monitor progress of the trial and ensure that it meets the highest standards of ethics and patient safety.

Kindly sponsored by

