

European Association for the Study of Diabetes Conference Review

Making Education Easy

EASD 08, Rome, Italy

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Welcome

to our review of the 44th Annual Meeting of the European Association for the Study of Diabetes (EASD). The review begins with a truly significant long-term follow-up of the United Kingdom Prospective Diabetes Study (UKPDS), a study which has, above all others, determined the way type 2 diabetes is managed. The NEJM article of the follow-up was published synchronously with the EASD presentation.

The conference had over 17000 registrants, and multiple parallel sessions. The papers featured have been selected by Dr Brandon Orr-Walker an endocrinologist at Counties Manukau DHB who attended the conference.

I hope you find the Conference Review stimulating reading, and I look forward to receiving your feedback.

Kind Regards,

Dr Shaun Holt
Medical Advisor

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10-Year follow-up of intensive glucose control in type 2 diabetes

Authors: Holman RR et al

Summary: Results from the United Kingdom Prospective Diabetes Study (UKPDS) showed that intensive glucose therapy with a sulfonylurea or insulin (or metformin in overweight subjects) in patients with type 2 diabetes mellitus (T2DM) reduced the risk of microvascular complications compared with conventional dietary restriction. The current report presented 10-year follow-up data for 3277 participants (no attempt was made to maintain previously assigned therapies). Between-group differences in HbA1c levels seen at the end of UKPDS were no longer significant after 1 year of follow-up. In patients in the intensive glucose therapy group who received a sulfonylurea or insulin, relative risk reductions for any diabetes-related endpoint (9%, $p = 0.04$) and microvascular disease (24%, $p = 0.001$) were maintained for 10 years. Risk reductions for MI (15%, $p = 0.01$) and death from any cause (13%, $p = 0.007$) emerged in these patients during post-trial monitoring as more events occurred. In patients in the intensive glucose therapy who received metformin, significant reductions in relative risk persisted for any diabetes-related endpoint (21%, $p = 0.01$), MI (33%, $p = 0.005$), and death from any cause (27%, $p = 0.002$). In conclusion, there was a continued reduction in microvascular risk (and emergent risk reductions for MI and all cause mortality) during 10 years of follow-up after UKPDS, despite an early loss of between-group differences in glycaemic control.

Comment: The UKPDS remains the basis for proactive management in T2DM, and is the foundation for management guidelines worldwide. This latest follow-up shows persisting benefits for early aggressive glycaemic management from the time of diagnosis on microvascular endpoints, and emerging benefit on macrovascular endpoints. The original intensive treatment group have been "intensively treated" all of their 18-30 years duration of diabetes, the other group only half that time.

The separation of event rates of the two treatment arms, nearly a decade after the trial completion (and when separation of ongoing glycaemic control has been lost) has been termed a "legacy effect". Very high follow-up rates, and the achievement of long term glycaemic control (not a progressive worsening) are other notable features of this study.

Reference: *New Engl J Med* 2008; 359(15): 1577-1589

<http://dx.doi.org/10.1056/NEJMoa0806470>

Incidence trends for childhood type 1 diabetes in Europe during 1989-2003 and projection of numbers to 2025

Authors: Patterson CC et al on behalf of the EURODIAB Study Group

Summary: This study examined trends in the incidence of childhood type 1 diabetes mellitus (T1DM) in Europe and predicted future disease burden. 29,311 new cases of childhood T1DM were registered between 1989 and 2003 at 20 population-based EURODIAB registers in 17 countries. 18 out of 20 registers showed significant increases in the incidence of childhood T1DM over the 15-year period. The rates of increase were greatest among 0-4 year olds in Central and Eastern Europe. The number of new cases of childhood T1DM in Europe in 2005 was estimated to be 14,700 (23% of these were in children aged 0-4 years, 35% in children aged 5-9 years and 42% in children aged 10-14 years). It is predicted that there will be 29,000 new cases diagnosed in 2025, with percentage distribution across the age groups being more uniform. In conclusion, it is estimated that there will be a near doubling in the number of new cases of childhood T1DM in Europe in the next 2 decades if current trends continue.

Comment: While overshadowed by the dramatic numerical increase in T2DM, a substantial increase in T1DM incidence has been reported in Western countries (including NZ) for reasons that remain unclear. Large European registers suggest a near doubling of incidence likely in the next 20 years based on recent trends.

Reference: *Diabetologia* 2008; 51 (Suppl. 1): S49

Modern-day clinical course of type 1 diabetes mellitus. The DCCT/EDIC experience 1983-2008

Authors: Nathan DM et al

Summary: The US- and Canada-based DCCT/EDIC cohort of 730 patients with T1DM has been followed for up to 35 years. Patients started with conventional therapy (representing the standard of clinical care at the time) but in 1993 were offered intensive therapy. After 30 years' diabetes duration, the cumulative incidences of proliferative retinopathy, albumin excretion rate >300mg/24h and cardiovascular disease were found to be 49.7%, 25.1% and 14%, respectively, in patients receiving conventional therapy. These values were similar to those reported in the population-based Epidemiology of Diabetic Complications (EDC) study. However, patients treated with intensive therapy had substantially lower cumulative incidences (21.1%, 8.6% and 8.5%, respectively) after 30 years. In conclusion, these data of long-term outcomes in patients receiving current care should be used in models evaluating health outcomes and quality of life in patients with T1DM.

Comment: Long-term follow-up of significant "paradigm defining" clinical studies offer helpful assessment of long-term complications and benefits from intensive treatment strategies. With high follow-up rates, the findings are likely to be valid. The benefits of intensive treatment appear to include reduced microvascular and macrovascular events, which persist long term.

Reference: *Diabetologia* 2008; 51 (Suppl. 1): S50

Validating a coronary heart disease prediction model for type 1 diabetes

Authors: Zgibor JC et al

Summary: The objective of this study was to create and validate a CHD risk prediction model specific to T1DM. Data from 603 patients participating in the EDC study were used; CHD was defined as CHD death, fatal or non-fatal MI or Q-waves. Two risk equations were developed, one for males [$x = 1.8738 - 0.9452(\log \text{WBC}) - 1.0625(\text{presence of microalbuminuria}) + 1.4808(\log \text{HDL-c}) - 0.2286(\text{sqrt diabetes duration at baseline})$] and 1 for females [$x = 21.62 - 4.4331(\text{waist-hip ratio}) - 1.594(\log \text{non-HDL-c}) - 0.023(\text{SBP}) - 0.498(\text{use of BP-lowering medication}) - 0.705(\text{sqrt diabetes duration at baseline})$]. An equation for determining the probability of not having an event was also calculated. The model performed well when externally validated using the EURODIAB Prospective Complications Study (PCS) population although events were overpredicted in patients in the 10th decile. In conclusion, this clinically practical model can be used to improve patient and provider knowledge of CHD risk.

Comment: Cardiovascular risk assessment and management strategies in young people with diabetes (type 1 or type 2) remain controversial. Young age is protective against CVD events but young age of onset of diabetes exposes the individual to a longer duration of adverse risk factors. The creation of an externally validated T1DM risk model will help enhance risk assessment and management decisions in T1DM.

Reference: *Diabetologia* 2008; 51 (Suppl. 1): S50

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ROMEO (Rethink Organization to Improve Education and Outcomes). A 4-year multicentre randomised controlled trial of group care for the management of type 2 diabetes

Authors: Trento M on behalf of the ROMEO investigators

Summary: This study investigated the benefits of Group Care (40- to 50-min sessions every 3-4 months) in patients with T2DM in Italy. 815 patients were randomised to Group Care or traditional one-to-one care in 13 clinics. 592 patients from 11 clinics completed the 4-year follow-up. Patients receiving Group Care had lower HbA1c, fasting blood glucose, weight, BMI, SBP and DBP, triglycerides and total cholesterol levels than those receiving traditional care (all $p < 0.001$). They also had better QOL, knowledge and health behaviours (all $p < 0.001$). In conclusion, Group Care provides better outcomes than traditional one-to-one care but requires re-organisation of working practices.

Comment: A large study comparing group versus one-on-one care in T2DM. Improved clinical care outcomes were found. From a service delivery perspective this is likely to be more "scalable" and likely more cost effective. This is likely to be a model of care favoured with an increasing burden of type 2 diabetes.

Reference: *Diabetologia* 2008; 51 (Suppl. 1): S69

Clinical and patient reported outcomes in 5 European countries at 6 months following insulin initiation

Authors: Simpson A et al

Summary: This study (INSTIGATE) followed patients with T2DM after initiation of insulin during usual care in France, Germany, Greece, Spain and the UK. To date, data have been collected for 1153 patients at baseline and 1051 patients at 6 months. The following insulin regimens were initiated: basal only (46.6% of patients), mixtures (26.1%), short-acting (14.6%), basal bolus (10.7%) and other (1.9%). Mean HbA1c was lower after 6 months than at baseline in all countries but remained higher than the EASD/ADA target (except in Germany where more patients initiated intensive regimens). Fasting blood glucose levels also fell in the 6-month period. In conclusion, metabolic control and health-related QOL improved after insulin initiation in patients with T2DM.

Comment: Optimal control of diabetes requires self-management and adherence to lifestyle in addition to any pharmaceutical treatments. It is sometimes claimed that in achieving better control (for long-term gain) that quality of life may be sacrificed. This multicentre study across 5 European countries illustrates that efforts (and results) to improve diabetic control and improved quality of life may be congruent rather than conflicting.

Reference: *Diabetologia* 2008; 51 (Suppl. 1): S70-71

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Diabetes care practice variation among outpatient diabetes clinics: an urgent need for quality improvement initiatives

Authors: Nicolucci A et al

Summary: This study evaluated variability between 86 diabetes clinics in Italy. Variability was assessed using multi-level models adjusted for patient age and gender and clustering effect. A total of 114,249 patients with T2DM were evaluated at the clinics in 2004. There was wide inter-centre variability in the proportion of patients with at least 1 measurement of HbA1c (64.8–96.9% [10–90th percentile variation]), BP (18.4–98.1%), lipid profile (14.4–89.7%) or microalbuminuria (0.0–40.0%). There was also a high level of variability in the percentage of patients reaching specific targets, and in the rates of use of specific drug classes. In conclusion, intensive efforts to improve the consistency of care between diabetes clinics are warranted in an effort to reduce the clinical and economical burden of the disease.

Comment: Implementation of quality care remains the prime focus of evidence-based guidelines. This study shows the variability of process (e.g. prescribing) and outcomes (e.g. glycaemic control) in a large multicentre population between clinical centres after adjusting for some patient characteristics. Feedback of this information to the contributing centres can contribute to continuous quality improvement. There is a value in comparing centre results (as apposed to or additional to reporting centre results in isolation), to help drive quality. A similar sized audit in New Zealand might be possible.

Reference: *Diabetologia* 2008; 51 (Suppl. 1): S71

Mortality in a cohort of individuals with and without diabetes mellitus in a Swedish community during 30 years of follow up

Authors: Jansson SPO et al

Summary: This study investigated trends in the rate of all-cause mortality from 1972 through 2004 in a Swedish cohort with or without diabetes. Data were extracted from the Laxa primary healthcare centre's diabetes register, where all patients with diabetes have been registered since 1972. Each diabetic patient was matched for age and gender with 5 reference nondiabetic individuals. 473 diabetics and 2077 nondiabetics died during the follow-up period. The 10-year mortality rate in male diabetics decreased over time, from 40% in those diagnosed between 1972 and 1981, to 35.4% (diagnosed 1982-1991) and 29.7% (diagnosed 1992-2001). At the same time, 10-year mortality rates in matched referent males decreased from 45.6% to 35.1% and 19.8%. Corresponding rates were 30.1%, 26.6% and 20.9% in female diabetics and 34.8%, 26.3% and 13.7% in female referents. In conclusion, patients with diabetes showed only a small decline in mortality rates during follow-up compared with the referents.

Comment: This paper illustrates that mortality rates from CVD are only marginally improving from the 1970s to 1990s in diabetics despite much greater improvements in nondiabetics.

Reference: *Diabetologia* 2008; 51 (Suppl. 1): S175

About the Reviewer -

Dr Brandon Orr-Walker is an Endocrinologist based at Counties Manukau DHB, where he is the Clinical Head of the endocrine and diabetes services, and clinical director of "Let's Beat Diabetes".

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Perceived risk of type 2 diabetes in Australian women with a recent history of gestational diabetes mellitus

Authors: Morrison MK et al

Summary: This study investigated the self-perceived level of risk for T2DM in women with a recent history of gestational diabetes (GDM). 4098 women who had been diagnosed with GDM between 2003 and 2005 were sampled from the National Diabetes Services Scheme database; 1372 eligible women responded to the written postal survey. Up to 3 years after GDM, 57% of participants were overweight or obese. Self-perceived risk for T2DM was reported to be low or very low (32% of participants), moderate (42%), high (20%) or very high (6%). Factors associated with a high or very high level of perceived risk were BMI >25 kg/m², family history of diabetes, insulin use during pregnancy and being Australian born. In conclusion, there needs to be an increased awareness of GDM as an independent risk factor for T2DM because most of the women sampled did not perceive they were at high risk for T2DM despite having had GDM.

Comment: Gestational diabetes poses specific risks for a pregnancy but also offers a "window to the future" of later T2DM risk for the woman. Up to 50% of GDM mothers may develop T2DM and recent findings suggest good potential to reduce the risk of this progression. The majority of women with GDM do not rate their risk as high however. Further education of women offers the potential to reduce the risk of diabetes.

Reference: *Diabetologia* 2008; 51 (Suppl. 1): S98-99

Mechanism of improvement of glucose tolerance in obese subjects with type 2 diabetes following gastric bypass surgery

Authors: Anselmino M et al

Summary: This study investigated the mechanism by which gastric bypass surgery improves glucose tolerance in obese patients with T2DM. 12 patients with T2DM and 9 nondiabetic patients had glucose tolerance measured before and 45 days after undergoing Roux-en-Y gastric bypass surgery. BMI decreased similarly in each group in the 45 days after surgery. Insulin sensitivity improved significantly in all patients, as did glucose tolerance (especially in those with T2DM). β -cell glucose sensitivity improved in all patients after surgery, although it remained impaired in T2DM patients compared with nondiabetics. Improvements in β -cell glucose sensitivity after surgery were positively correlated with the corresponding changes in BMI. In conclusion, glucose tolerance improved after gastric bypass surgery in patients with T2DM as a result of increased insulin sensitivity and β -cell glucose sensitivity.

Comment: An interesting paper emphasising both β -cell function and insulin sensitivity improvements with gastric bypass surgery. Short-term improvements (45 days) are proportional to the degree of weight loss.

Reference: *Diabetologia* 2008; 51 (Suppl. 1): S317

Bariatric surgery for patients with type 2 diabetes and morbid obesity: improving psychological status?

Authors: Jackson S et al

Summary: This study used standardised questionnaires to assess the effects of bariatric surgery on psychological status in morbidly obese patients with or without T2DM. Two different groups of unmatched participants were used to determine psychological status before (group 1) and 6 months after (group 2) surgery. Mann-Whitney U tests showed that levels of anxiety and depression were significantly lower 6 months after surgery than they were before it. Quality of life was significantly higher after surgery for psychological, physical and environmental subscales of the WHO-QOL. Compared with relevant normative populations, the level of general anxiety and depression after surgery was still below the norm. Surgery did not improve social anxiety. In conclusion, these data suggest that bariatric surgery improves physiological and psychological status in morbidly obese patients with or without T2DM.

Comment: Bariatric surgery improves diabetic control and quality of life as well as reduces BMI.

Reference: *Poster presented at EASD 2008*

World six-month outcomes of patients initiating exenatide in a primary care electronic medical record database

Authors: Wintle M et al

Summary: This real-world study investigated the effects of exenatide on HbA1c and weight in patients with T2DM. Six-month follow-up data for 2086 adult patients were extracted from the General Electric electronic medical record (EMR) research database. When exenatide was initiated, patients were already receiving monotherapy with metformin (17.4%), a sulfonylurea (7.1%) or a thiazolidinedione (4.0%), or various combinations. At baseline, mean HbA1c was 8.4% and mean weight was 110.6kg. After 6 months' treatment with exenatide, HbA1c levels decreased significantly by a mean 0.7%; reductions ranged from 0.8% to 1.0% in patients previously taking monotherapy and from 0.5% to 0.8% in patients previously taking combination therapy. Mean weight loss was 2.8kg ($p < 0.0001$). Decreases in the need for concomitant therapy were also seen. In conclusion, exenatide reduced HbA1c and bodyweight over a 6-month period but these findings show how difficult it is to achieve HbA1c and bodyweight targets in the real world.

Reference: *Diabetologia* 2008; 51 (Suppl. 1): S352

Exenatide therapy in insulin treated patients with type 2 diabetes and obesity

Authors: Govindan JP et al

Summary: This study investigated the efficacy of exenatide when used in combination with insulin in obese patients with T2DM and poor glycaemic control. 27 patients received exenatide 5 mcg twice daily, increasing to 10 mcg twice daily after 4 weeks (insulin doses were halved at initiation and adjusted according to self blood glucose monitoring). Three patients withdrew because of intolerable GI effects so data were presented for the remaining 24 patients. After 3 months, mean bodyweight decreased by 8.7kg, and mean BMI fell from 43.0 kg/m² to 39.8 kg/m² ($p < 0.001$). No significant changes in HbA1c were observed. Insulin was stopped in 10 patients and reduced in the remaining 14. In conclusion, exenatide caused weight loss and a reduction in insulin dosage requirements but did not improve glycaemic control in patients with T2DM established on insulin therapy.

Reference: *Diabetologia* 2008; 51 (Suppl. 1): S352-353

The short term effects of exenatide therapy in insulin treated patients with type 2 diabetes mellitus – a new option to achieve weight loss

Authors: Samarasinghe YP et al

Summary: This study investigated the effects of exenatide on weight and diabetes control in insulin-treated patients with T2DM. 71 outpatients at a dedicated diabetes centre in a London teaching hospital were started on exenatide and had at least 1 follow-up visit. 23 of the 71 patients had been taking insulin (mean dose 69 units) prior to starting exenatide. Eight of these patients stopped their insulin (6 subsequently restarted), 9 had the dose decreased, 5 remained on the same dose and 1 had it increased when exenatide was initiated. After 3 months, mean bodyweight had decreased by 1.7kg but there was no change in mean HbA1c. In conclusion, exenatide caused weight loss in insulin-treated patients with T2DM without adversely affecting glycaemic control.

Reference: *Diabetologia* 2008; 51 (Suppl. 1): S353

In patients with type 2 diabetes, sitagliptin added to metformin effectively lowers HbA1c regardless of patient age, gender, body mass index, or baseline measure of beta cell function

Authors: Alba M et al

Summary: This pooled analysis of 2 randomised placebo-controlled phase III trials evaluated the consistency of sitagliptin therapy across various subgroups of patients with T2DM. Overall, 891 patients had sitagliptin 100mg once daily ($n = 560$) or placebo ($n = 331$) added to their current metformin regimen for up to 24 weeks. Compared with placebo, sitagliptin treatment reduced HbA1c irrespective of age, gender, BMI or baseline β -cell function. In conclusion, sitagliptin provided effective and consistent glycaemic control across all subgroups of patients with T2DM in this study.

Reference: *Diabetologia* 2008; 51 (Suppl. 1): S364-365

Safety and tolerability of sitagliptin, a selective DPP-4 inhibitor, in patients with type 2 diabetes: pooled analysis of 6139 patients in clinical trials for up to 2 years

Authors: Williams-Herman D et al

Summary: This study assessed the safety and tolerability of sitagliptin in 12 randomised, double-blind phase III studies involving 6139 patients with T2DM. Patients were given either sitagliptin 100 mg/day or placebo/active comparator (non-exposed group) for between 18 weeks and 2 years as monotherapy, initial combination therapy or add-on therapy. The incidences of overall adverse effects, serious adverse effects and adverse event-related discontinuations in sitagliptin recipients did not differ from those in the non-exposed group. The incidence of adverse GI events, ischaemia-related adverse events, immune-related adverse events or laboratory adverse events did not differ meaningfully between groups. In conclusion, sitagliptin 100mg/day for up to 2 years was well tolerated in clinical trials of patients with T2DM.

Reference: *Diabetologia* 2008; 51 (Suppl. 1): S365-6

Vildagliptin is as effective as TZDs in metformin failures: results of GALIANT – a primary care diabetes study

Authors: Braceras R

Summary: The GALIANT study tested the hypothesis that add-on therapy with vildagliptin would be non-inferior to a thiazolidinedione in patients with T2DM poorly controlled by metformin alone. 2478 patients were recruited from primary care sites and were randomised (2:1) to receive open-label vildagliptin 100mg once daily or a thiazolidinedione for 12 weeks. At study end, vildagliptin was found to be non-inferior to a thiazolidinedione for mean change in HbA1c in the overall population and for subgroups of race, age and BMI. The overall incidence of adverse events in each group was similar. Bodyweight decreased with vildagliptin and increased with thiazolidinediones. In conclusion, vildagliptin had similar efficacy to a thiazolidinedione when used as add-on therapy in patients with T2DM poorly controlled by metformin alone.

Reference: *Diabetologia* 2008; 51 (Suppl. 1): S366

Comment: Six interesting studies looking at glycaemic control with agents acting on the incretin pathway. These agents are new to NZ. They are attractive in being weight neutral or weight-losing whilst improving HbA1c. They appear to be additive to existing therapies, and are not associated with hypoglycaemia. Many patients with type 2 diabetes are not controlled on lifestyle management and existing treatments. While insulin therapy provides progressive response with

dose increments, patients or their health carers may be reluctant to commence insulin or increase treatment for amongst other reasons (eg occupational restriction) weight gain and risk of hypoglycaemia. The addition of treatments which enhance endogenous insulin release in a glucose-dependent manner are attractive, and appear effective up to two years. With mounting concern over the use of glitazones, there is a growing call for additional treatment strategies.