American Diabetes Association 74th Scientific Sessions Conference Review™

June 13-17 2014, San Francisco, California, USA

In this review:

Abbreviations used in this review:

GTT = glucose tolerance test
SGLT2 = sodium glucose cotransporter 2
T1DM = type 1 diabetes mellitus
T2DM = type 2 diabetes mellitus

Welcome to this review of the American Diabetes Association 74th Scientific Sessions.

This review has been created to allow those unable to attend, but with a keen professional interest, to access a summary of some of the presentations. Selection and review of the research has been carried out independently by Associate Professor Neale Cohen, a physician specialising in Diabetes and Endocrinology, and the General Manager of Diabetes Services at the Baker IDI Heart and Diabetes Institute who attended the meeting.

Highlights of this review include results of the OpT2mise study of insulin pump therapy in patients with type 2 diabetes and a detailed analysis of hypoglycaemic events in the ORIGIN trial which, amongst other findings, suggested that sulphonylureas may be a particular concern in people with underlying cardiovascular disease.

We report growing evidence that patients with severe hypoglycaemic events who require ambulance transport should be subject to frequent review and perhaps more conservative use of hypoglycaemic agents such as insulin. Also featured are an interesting 4-year real world follow-up of patients with type 2 diabetes initiated on insulin which showed little difference in outcomes between regimes and highlighted the challenges and limitations of insulin therapy, and an encouraging study of salsalate in healthy subjects which raises the hope that this and similar agents may provide the basis for another new class of oral therapeutics with a novel mechanism of action.

We hope you enjoy these selections, and as always, look forward to hearing your comments and feedback.

Kind Regards,

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Abstracts from the meeting are available here.
http://tinyurl.com/ps7mawe

Efficacy and safety of insulin pump therapy in type 2 diabetes: the OpT2mise study

Authors: Reznik Y et al.

Summary: This large multicentre, randomised, controlled trial compared continuous subcutaneous insulin infusion (CSII) vs multiple daily injections (MDI) in 495 subjects with T2DM with poor glycaemic control on MDI (basal-bolus with insulin analogs). Following insulin dose optimisation (≥0.7 and ≤1.8 U/kg/d) those with ongoing hyperglycaemia (HbA_{1c} ≥8% and ≤12%, n=331) were randomised to continued MDI or CSII for 6 months. CSII was associated with a 20.4% reduction in total daily insulin dose, significantly greater reductions in HbA_{1c} vs MDI (-1.1 ± 1.2 vs -0.4 ± 1.1%, p<0.001) and a significantly greater proportion of subjects who achieved HbA_{1c} <8.0% (57 vs 27%, OR 1.9, 95% CI 1.47-2.46, p<0.001). Severe hypoglycaemia was reported in 0 and 1 participant in the CSII and MDI groups respectively.

Comment: This is likely to be the definitive type 2 insulin pump trial. While the result was positive in favour of CSII compared with MDI, the HbA_{1c} difference was only 0.7% with only 57% reaching HbA_{1c} less than 8% with CSII. While CSII was shown to improve glycaemic control, this type of modest HbA_{1c} reduction has been seen with much lower cost, simpler interventions. Examples would include addition of other agents (DPP-4 inhibitors, GLP-1 agonists, SGLT2 inhibitors). The treatment algorithm in the CSII group was fairly conservative, and I suspect with a more aggressive approach the outcome may have been more impressive. As it stands, it would seem difficult to recommend CSII as an important therapeutic option for type 2 diabetes.

Reference: 102-LB — 2014: Late Breaking Posters

Different clinical predictors of nonsevere and severe hypoglycemia during treatment with glargine or standard care in the ORIGIN trial

Authors: Riddle MC et al.

Summary: The goal of this analysis of data from the ORIGIN trial was to determine baseline and on-treatment factors associated with symptomatic hypoglycaemia (glucose ≤3 mmol/L) or severe hypoglycaemia. Subjects were 12,537 individuals with impaired glucose tolerance, impaired fasting glucose or T2DM and high cardiovascular risk who received treatment with insulin glargine or usual care during a median follow-up of 6.2 years. Factors independently associated with increased risk of hypoglycaemia were sulfonylurea use (HR 2.07 for non-severe, 1.35 for severe) and glargine treatment (HR 4.53 for non-severe, 3.57 for severe). Non-severe events were increased with diabetes (HR 1.52), and higher baseline HbA_{1c} (HR 1.24) but were reduced with older age (HR 0.98) and higher BMI (HR 0.97). Severe events increased with older age (HR 1.04), hypertension (HR 1.51) and higher serum creatinine (HR 1.01), were reduced with higher MMSE score (HR 0.96) and were unaltered by baseline HbA_{1c}. Those receiving insulin glargine had the highest risk of severe and non-severe hypoglycaemic events with lower on-treatment HbA_{1c}, whereas severe events were increased at higher HbA_{1c} in subjects receiving standard care.

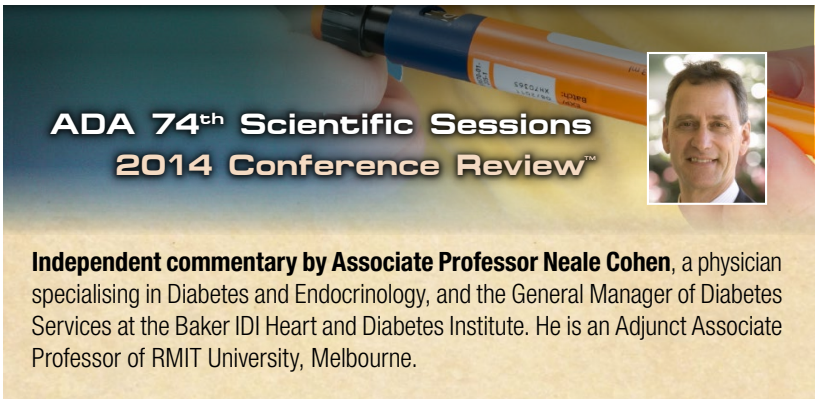
Comment: This study looked in detail at hypoglycaemic events in the ORIGIN trial, a trial looking at the effects and safety of glargine insulin in patients with early type 2 diabetes or pre-diabetes. While hypoglycaemia rates were low, the large patient numbers allowed for analysis of risk factors particularly for the relatively rare severe hypoglycaemic events. Use of insulin and sulphonylureas were not surprisingly key risk factors for both severe and non-severe hypos. In further analyses, severe hypos were associated with mortality and cardiovascular mortality with a strong signal from the non-glargine group. Like other recent studies, this is suggestive that sulphonylureas may be a concern in people with underlying cardiovascular disease.

Reference: 2-LB — 2014: Late Breaking Posters

Both patients with type 1 and type 2 diabetes who require ambulance assistance for severe hypoglycaemia have more than twice the mortality rate of the general diabetes clinic

Summary: The authors of this retrospective review used data from the Yorkshire Ambulance Service to examine mortality rates in patients with T1DM and T2DM utilising ambulance assistance for severe hypoglycaemic events compared with a population attending the general diabetes clinic. 22.9% of individuals with ambulance-assisted hypoglycaemic events died during 4.4 year follow-up compared to 10.7% of clinic attendees ($p<0.00001$). Patients with T2DM and ambulance-assisted hypoglycaemic events were older and were more likely to live alone, to receive transport to hospital, and to die compared to those with T1DM (all $p<0.05$). Of those who died, 54.4% of those with T2DM and 17.6% of those with T1DM died within 12 months of the initial hypoglycaemic event ($p=0.003$).

Comment: This study looked at severe hypoglycaemia in type 1 and type 2 diabetes based on ambulance assistance, and follow up mortality. Worryingly, the mortality of patients with severe hypoglycaemia was more than double over the following 4 years compared with other patients attending the general diabetes clinic. Although we cannot conclude that hypoglycaemia was related to the cause of death, it seems that severe hypoglycaemia, at the least, signals a more frail patient with high mortality risk. There is growing evidence that these patients should be subject to frequent review and perhaps more conservative use of hypoglycaemic agents such as insulin.



Independent commentary by Associate Professor Neale Cohen, a physician specialising in Diabetes and Endocrinology, and the General Manager of Diabetes Services at the Baker IDI Heart and Diabetes Institute. He is an Adjunct Associate Professor of RMIT University, Melbourne.

Credit study-France: four-year evaluation of insulin prescriptions, glycemic control, hypoglycemia, and body weight after starting insulin therapy in type 2 diabetes

Authors: Balkau B et al.

Summary: The authors describe 4-year results from the French arm of the multinational CREDIT study which aimed to determine patterns of insulin use in subjects with T2DM beginning insulin therapy. 394 participants were enrolled and 253 (64%) completed the study. Baseline insulin therapies were basal insulin alone (83%), meal-time plus basal (4.3%), premix (9.6%), meal-time only (1.0%), and other (2.3%). At 4 year follow-up insulin regime was unchanged in 55% of participants. Usage was basal alone (49%), meal-time plus basal (21%), premix (15%), meal-time only (0%), other (9.1%), and no insulin (5.9%). Total insulin dose increased from 0.3 ± 0.2 to 0.5 ± 0.2 U/kg, use of oral treatment declined from 85% to 79% and HbA_{1c} decreased to 7.5 ± 0.8%.

Comment: This is an interesting 4 year real world follow-up of patients with type 2 diabetes initiated on insulin. The most popular regime was basal insulin which progressed to mixed or basal plus insulin in a significant number. Notably the mean starting HbA_{1c} was 9.3% and, despite a good HbA_{1c} drop, only 28% reached target HbA_{1c}. As with other clinical trials, there was little difference in outcomes between the regimes. This study highlights the challenges and limitations of insulin therapy. The relatively high initial HbA_{1c}, very low level of severe hypoglycaemia and low percentage of patients achieving target suggest clinical inertia and poor acceptance of therapy and/or intensification of therapy by patients.

Reference: 922-P — 2014: General Poster Sessions

Effect of salsalate on insulin action, secretion, and clearance in non-diabetic, insulin-resistant individuals: a randomized, placebo-controlled study

Authors: Kim SH et al.

Summary: The aim of this 4-week randomised, single-blind, placebo-controlled clinical trial was to investigate the effect of salsalate (3.5 g/day) on insulin action, secretion, and clearance rate in non-diabetic subjects with insulin resistance. Patients in the salsalate group (n=27) had improvements in fasting blood glucose (mean change -7%, 95% CI -10 to -14) in comparison to placebo-treated subjects ([n=14] 1%, -3 to 5, p=0.005). Fasting triglycerides were lowered with salsalate (-25%, -34 to -15) vs placebo (-6%, -26 to 14), p=0.04) and insulin clearance rate was decreased (-23%, -30 to -16) compared with placebo (3%, -10 to 15, p<0.001). Salsalate did not affect postprandial or steady-state plasma glucose concentrations or insulin secretion rate. Dose reduction was required in 4 individuals receiving salsalate but the drug was otherwise well tolerated.

Comment: The use of salsalate in type 2 diabetes is under investigation with studies showing a blood glucose lowering effect. The mechanism of action is unclear and initially thought to be associated with anti-inflammatory actions and possible reduction in insulin resistance. This study demonstrates no change in insulin resistance but, surprisingly, a decrease in insulin clearance associated with salsalate use over 4 weeks in non-diabetics. This may provide the basis for another new class of oral agents potentially with a novel mechanism of action that may complement other hypoglycaemic agents.

http://care.diabetesjournals.org/content/37/7/1944.abstract

TTP399, a liver-selective glucose kinase activator, lowers glucose and does NOT increase lipids in subjects with type 2 diabetes mellitus

Summary: This multi-centre, randomised, placebo-controlled, double-blind trial evaluated the safety, tolerability, and pharmacodynamics of TTP399, a liver-selective glucose kinase activator (GKA). Participants with T2DM on stable metformin were randomised to TTP399 400 mg BID (n=29), 800 mg QD (n=31), 800 mg BID (n=30) or placebo (n=30) for 6 weeks. There were no between-group differences in hypoglycaemia incidence or severity, fasting triglycerides, cholesterol, lactate, insulin, or C-peptide. Regardless of dose, TTP399 was associated with a decreased mean daily glucose profile. Normalised glycaemia (HbA_{1c} <6.5%) was achieved in 85 and 40% of subjects well controlled on metformin who received 800 mg BID or any dose of TTP399 respectively compared to 0% of placebo-treated subjects.

Comment: Glucokinase (GK) is effectively an intracellular glucose sensor present in beta cells, liver cells and the brain. Genetic GK abnormalities can lead to monogenic diabetes, and GK has therefore been of interest as a therapeutic target for type 2 diabetes. GKAs have been under investigation for some time, however adverse effects including hypoglycaemia, lipid effects and potential liver toxicity have limited their progression to large phase 3 trials. This study in patients with well controlled type 2 diabetes looked at a hepatoselective GKA, and showed impressive improvement in glycaemic control without hypoglycaemia or lipid abnormalities. This looks promising although long term effects, particularly liver function, will need close assessment.

Less nocturnal hypoglycemia and weight gain with new insulin glargine 300 U/mL compared with 100 U/mL: 1-year results in people with T2DM using basal insulin with OADs (EDITION 2)

Authors: Yki-Järvinen H et al.

Summary: The authors reported 12-month data from the EDITION 2 trial following completion of the 6-month open-label extension phase. Participants (n=811) with T2DM and inadequate glycaemic control with basal insulin and oral anti-diabetic drugs received once daily insulin glargine 300 U/mL (Gla-300) or 100 U/mL (Gla-100). Glycaemic control was comparable between groups at 12 months. Per-participant annualised hypoglycaemic event rates were lower with Gla-300 vs Gla-100 (1.74 vs 2.77, RR 0.63; 95% CI 0.42-0.96) and fewer Gla-300-treated subjects had ≥1 hypoglycaemic event (RR 0.84; 95% CI 0.71-0.99). Severe nocturnal hypoglycaemia was also reduced with Gla-300 (RR 0.84; 95% CI 0.71-0.99). Adverse event rates were comparable between groups, but bodyweight gain was less with Gla-300 (mean 0.42 vs 1.14 kg, p=0.0091).

Comment: New improved basal insulins are topical and were prominent at this year's ADA meeting. Sanofi initially set out to produce a U300 glargine higher concentration insulin designed for patients requiring high dose insulin. Fortuitously however, U300 has been shown to have altered pharmacokinetics resulting in a more prolonged action and a "flatter" profile. This study demonstrates a similar HbA_{1c} reduction compared with standard glargine U100 insulin in patients with type 2 diabetes, associated with a 37% reduction in nocturnal hypoglycaemia. Overall the gains seem small although this is likely to be a valuable product in patients not achieving goals, particularly those requiring high dose insulin.

Reference: 93-LB — 2014: Late Breaking Posters

Basal insulin peglispro demonstrates preferential hepatic vs. peripheral action relative to insulin glargine in healthy subjects

Authors: Henry RR et al.

Summary: This single-centre, randomised, open-label, crossover study examined the effects of the novel, pegylated insulin analogue basal insulin peglispro (BIL) compared with insulin glargine on suppression of endogenous glucose production (EGP) and stimulation of glucose disposal rate (GDR) in 8 healthy subjects. Increasing concentrations of both insulins suppressed EGP and stimulated GDR. At insulin concentrations where EGP was significantly suppressed, insulin glargine increased GDR whereas BIL had little impact.

Comment: PEGylation is the process of attachment of polyethylene glycol polymer chains to molecules, and is sometimes used to alter pharmacokinetics of drugs. A pegylated version of lispro insulin has been developed as a new long acting basal insulin. Initial studies suggest weight loss and a possible hepatoselective action of this new insulin. This study in non-diabetic subjects has demonstrated the differential effects of glargine compared with Peglispro and confirmed the predominantly hepatic effects of Peglispro. Although the reason for hepatoselectivity is not clear it may relate to release of the large pegylated insulin preferentially into hepatic sinusoids as compared with standard capillary beds. This novel compound may result in more physiological insulin delivery compared with standard therapy.

Reference: 886-P — 2014: General Poster Sessions

Imeglimin normalizes glucose tolerance and insulin sensitivity in improving mitochondrial function in a high-fat high-sucrose diet mice model

Authors: Hallakou-Bozec S et al.

Summary: The authors aimed to further elucidate the mechanism of action of imeglimin, the first of a new class of oral glucose-lowering agents in 16-week high-fat, high-sucrose diet mice (HFHSD) with insulin resistance, glucose intolerance, liver steatosis and mitochondrial dysfunction. Treatment with imeglimin resulted in restoration of normal glucose tolerance (AUC glucose 7.9 ± 0.7 vs 25.2 ± 1.8 g/dL x min for HFHSD, p<0.001) and increased insulin secretion (+98% vs HFHSD, p=0.01) during intraperitoneal GTT. Insulin sensitivity was normalised with imeglimin, liver steatosis was decreased and mitochondrial function was improved. The authors concluded that, "…*imeglimin normalizes glucose tolerance and insulin sensitivity in preserving mitochondrial function from oxidative stress and favoring lipid oxidation in a HFHS diet model.*"

Comment: Imeglimin is a novel agent that has been shown to target hepatic gluconeogenesis, muscle glucose uptake and insulin resistance, and acts on liver, muscle and beta cells. The mechanism of action is not clear but recent studies suggest a mitochondrial action. This animal study confirms improvement in mitochondrial function by protection against reactive oxygen species. Imeglimin is currently undergoing phase II trials and appears to be an effective hypoglycaemic agent. It has the potential to improve the key metabolic defects involved in the pathogenesis of type 2 diabetes.

http://care.diabetesjournals.org/content/37/7/1944.abstract

Sodium glucose cotransporter 2 inhibition with empagliflozin reduces microalbuminuria in patients with type 2 diabetes

Authors: Cherney D et al.

Summary: This analysis used pooled data from 4 phase III randomised controlled trials to examine the effects of empagliflozin plus standard care (including stable doses of renin angiotensin system inhibitors) on microalbuminuria (MA) in patients with T2DM and pre-existing MA (urine albumin to creatinine ratio [UACR] 30-300 mg/g). UACR was significantly reduced at week 24 with empagliflozin 10 and 25 mg/daily; 30 and 25% respectively vs placebo (p<0.01). These results were clinically significant.

Comment: The SGLT2 inhibitors act on renal reabsorption of glucose and are effective hypoglycaemic agents associated with weight loss. Blood pressure lowering effects are well documented, however effects on renal function are not clear. This study looks at pooled data from 4 clinical trials with empagliflozin, looking at UACR in patients with pre-existing microalbuminuria. There was a significant decrease in UACR after 6 months which is reassuring and may suggest a nephroprotective effect. Prospective trials are needed (and underway) looking at longer term benefits of empagliflozin and other SGLT2 inhibitors.

Reference: 1125-P — 2014: General Poster Sessions

