ABCD Autumn meeting report, London

The Grand Hall at BMA House deserved its name and provided an excellent forum for the ABCD Autumn meeting, 9-10th November 2017

Session 1

This year's opening guest speaker, Professor Per-Henrik Groop, provided an excellent review of the pathogenesis and approaches to managing microvascular complications. Professor Groop, from Finland, who had previously worked in London, eloquently reviewed data on nephropathy-related mortality. He also explored what we can do to prevent the development and progression of disease, proposing we should be advocating intensive exercise in these patients.

Potential advantages of newer diabetes hypoglycaemic classes were reviewed; relevant data from sub-analyses of trials using empagliflozin and liraglutide were discussed. Of great interest were data presented reviewing the effects of SGLT2 and ACE inhibitor classes on glomerular function and tubular function.

A model of renal hypoxia was postulated which represents a paradigm shift in thinking.

A new 'Question Time' session panel which included experts Professor Clifford Bailey and Dr Rob Gregory debated questions relating to population versus individual HbA_{1c} targets and the use of newer glucose sensor methods.

Session 2

Session 2 included data-enriched clinical updates on retinopathy and lipid management.

Professor Mike Sampson discussed the benefits of a regional integrated pathway for severe hypoglycaemia for a large geographical area. Some variability in ambulance staff practice was highlighted in the Q&A which was of potential concern.

The oral abstract presentations included topics spanning a wide range of areas: a case highlighting major positive effects of hepatitis C treatment on type 2 diabetes prompted the audience to ask questions, improving inpatient hyponatraemia management with simple interventions; a common problem with simple solution; and use of the Endobarrier device in patients with sleep apnoea and risk scoring patients with SGLT-2 inhibition-related diabetic ketoacidosis.

The Niru Goenka lecture was not given this year due to speaker ill health. Instead, Professor Dev Singh provided a superb presentation on the concept of the 'glycation gap', highlighting variability in glycation of haemoglobin in individuals. He explained the relevance of this to the ACCORD trial. The concept of fructosamine-adjusted HbA_{1c} measurement was introduced and explained. A novel concept of intracellular deglycation was also presented in this thought-provoking lecture.

The endocrine update in adrenal disease was elegantly provided by Professor William Drake, which included novel methods of glucocorticoid replacement, a new trial investigating the utility of a functional scan for the spectrum of Conn's syndrome. Professor Hanna continued the theme by reviewing adrenal incidentaloma management and outlining a NIHR-funded study.

An excellent contemporary review by Professor Stephanie Amiel of the last 18 months in the field of type I diabetes was delivered. This included education, potential benefits of beta cell preservation with immune modulation and trials involving non-insulin classes of medication.

Closing the loop between glucose sensing and insulin delivery aptly closed the afternoon, and this was followed by the announcement of the joint ABCD Travel Research Grant winners.

Correspondence: Dr Dipesh Patel
E-mail: dpatel@doctors.org.uk
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ABCD Autumn Meeting Abstracts

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The ABCD meeting at BMA House, London in November 2017, saw another strong selection of research, service improvement work and clinical cases submitted for presentation. The top scoring abstracts are included here and the remaining can be found online at www.bjd-abcd.com

Modelling subcutaneous absorption of U100 and U300 insulin glargine in type 1 diabetes

Schiavon M,[1] Visentin R,[1] Dalla Man C,[1] Klabunde T,[2] Cobelli C[1]
[1] University of Padova, Department of Information Engineering, Padova, Italy
[2] Sanofi-Aventis Deutschland GmbH, Drug Design, Science and Medical Affairs, Frankfurt am Main, Germany

Background: Subcutaneous administration of long-acting insulin analogues is often employed in multiple daily injection (MDI) therapy of type 1 diabetes (T1D) to cover patients' basal insulin needs. Among these, U300 and U100 are formulations of insulin glargine indicated for once-daily subcutaneous administration of MDI therapy of T1D. U300 is a new formulation with different absorption kinetics from U100, resulting in less hypoglycaemia in clinical trials. Some models have already been proposed but were not assessed under controlled experimental conditions for both formulations. The objective is to develop a model of subcutaneous absorption of U100 and U300 glargine insulin formulations in T1D.
Methods: The database consists of 24 patients with T1D who

underwent a randomised, four-sequence, crossover, double-blind, dose-response euglycaemic clamp study, receiving single subcutaneous injections of 0.4, 0.6 and 0.9 U/kg U300 and 0.4 U/kg U100 (NCT01195454). Plasma insulin concentrations were measured for 36 hours using a validated radioimmunoassay. Model identification was performed on U100 and U300 data using a Bayesian maximum a posteriori technique.

Results: The model fits the data well and provides precise parameter estimates for both insulin formulations. It describes the gradual dissolution from the precipitate to soluble states and model parameters allow characterisation of the different rates of absorption between U100 and U300.

Conclusions: The model will be incorporated into the UVA/Padova T1D simulator together with the joint parameter distributions. This will open the door to perform in silico clinical trials for testing novel up-titration and insulin glargine switching rules.

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Lower glucose variability and risk for hypoglycaemia on insulin glargine 300 U/mL versus insulin glargine 100 U/mL evaluated by the Low Blood Glucose Index in randomised phase III clinical trials

Kovatchev BP,[1] Meng Z,[2] Breton MD,[3] Leroy B,[4] Cali A[4]

[1] Center for Diabetes Technology, University of Virginia, Charlottesville, Virginia, USA
[2] Sanofi, Bridgewater, New Jersey, USA
[3] Université de Sherbrooke, Sherbrooke, Canada
[4] Sanofi, Paris, France

Background: Glucose variability (GV) and GV-based metrics such as the Low Blood Glucose Index (LBGI) can detect hypoglycaemia risk in type 2 diabetes (T2D). Edition 2 (NCT01499095) and Edition 3 (NCT01676220) are 12-month studies comparing insulin glargine 300 U/mL (Gla-300) with insulin glargine 100 U/mL (Gla-100) in insulin-treated and insulin-naïve T2D patients, respectively.

Methods: GV and LBGI were computed using self-monitored blood glucose (BG) profiles recorded daily across the studies, and compared between Gla-300 and Gla-100. Total documented symptomatic hypoglycaemia (DSH) per patient, confirmed by BG readings <3 mmol/L, were stratified by LBGI.

Results: LBGI and night-time LBGI were significantly lower with Gla-300 compared with Gla-100 ($p<0.001$ for both in Edition 2; $p=0.036$ and $p=0.005$ in Edition 3). These differences in LBGI were more apparent during the titration phase (mean 0.327 [Gla-300] vs 0.452 [Gla-100] [titration], 0.409 vs 0.497 [maintenance], respectively [Edition 2]; 0.199 vs 0.250 [titration], 0.375 vs 0.409 [maintenance], respectively [Edition 3]). The largest differences were observed overnight (mean LBGI 0.693 [Gla-300] vs 1.118 [Gla-100] [titration], 0.985 vs 1.238 [maintenance], respectively [Edition 2]; 0.394 vs 0.476 [titration], 0.729 vs 0.922 [maintenance], respectively [Edition 3]). LBGI correlated with the observed number of hypoglycaemic episodes ($r=0.35$ and $r=0.26$, $p<0.001$ for both studies, respectively); patients who were at moderate risk (defined as LBGI ≥1.1) experienced six-fold more DSH than those at minimal risk (LBGI ≤1.1).

Conclusions: Use of Gla-300 versus Gla-100 showed significant reductions in GV as measured by LBGI, and LBGI predicted hypoglycaemia risk reductions with Gla-300 and Gla-100 consistently throughout both Edition studies.

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Achievement of HbA_{1c} targets in the Diabetes Unmet Need with Basal Insulin Evaluation (DUNE) real-world study

Meneghini L,[1,2] Mauricio D,[3] Orsi E,[4] Lalic N,[5] Cali A,[6] Westerbacka J,[6] Stella P,[6] Candelas C,[6] Pilorget V,[6] Perfetti R,[7] Khunti K[8]

[1] University of Texas Southwestern Medical Center, Dallas, Texas, USA
[2] Parkland Health & Hospital System, Dallas, Texas, USA
[3] Hospital Universitari Germans Trias i Pujol, Barcelona, Spain
[4] Endocrine and Metabolic Diseases Unit, Fondazione Ca' Granda IRCCS, Milan, Italy
[5] Faculty of Medicine University of Belgrade, Clinic for Endocrinology, Diabetes and Metabolic Diseases, Belgrade, Serbia
[6] Sanofi, Paris, France
[7] Sanofi, Bridgewater, New Jersey, USA
[8] Diabetes Research Centre, University of Leicester, Leicester, UK

Background: The association between achievement of individualised glycaemic targets and hypoglycaemia risk in the real-world setting is unknown. DUNE was a 12-week, prospective, observational, multinational, real-world study conducted from February 2015 to July 2016 in adults with T2D newly (at time of enrolment) or recently (<12 months) initiated on basal insulin (BI) therapy. The study aimed to assess individualised HbA_{1c} target achievement and its association with symptomatic hypoglycaemia (occurrence/frequency).

Methods: Of 3,139 evaluable participants from 28 countries, 99.7% were set individual HbA_{1c} targets by their physicians (57% set at 7.0–7.4%).

Results: At week 12, both insulin-naïve (N=1,716) and prior BI (N=1,423) participants showed a mean (SD) HbA_{1c} decrease from baseline (–1.4 (1.3)% and –0.8 (1.1)%, respectively), with limited up-titration of the mean (SD) daily insulin dose from baseline to week 12 (+0.10 (0.13) U/kg and +0.06 (0.10) U/kg, respectively); only 28% and 27% of participants, respectively, achieved individual HbA_{1c} targets, with an average insulin dose of 0.31 U/kg/day at week 12. Overall, symptomatic hypoglycaemia, defined as any event associated with typical hypoglycaemic symptoms regardless of blood glucose measurement, was reported by 16% of participants (insulin-naïve: 14%; prior BI: 18%). Univariate logistic regression analysis showed a positive association between HbA_{1c} target achievement and symptomatic hypoglycaemia occurrence (OR 0.697 (95% CI 0.568 to 0.854); $p<0.001$) and frequency of symptomatic hypoglycaemia ($p=0.004$).

Conclusions The results from this real-world study show that, while HbA_{1c} levels fell substantially, most participants did not achieve individual HbA_{1c} targets. Participants who reached target were more likely to experience symptomatic hypoglycaemia.

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Longer-acting basal insulin analogues: a therapeutic advance in selected patients

Koh WS, Shotliff K, Feher MD
Beta Cell Diabetes Centre, Chelsea and Westminster Hospital, London, UK

Background: Hypoglycaemia, weight gain or high volume dose are unwanted management issues of insulin. In clinical trials, longer-acting basal analogues insulin glargine U300 (Toujeo) and insulin degludec U100 (Tresiba), compared with glargine U100, reduced hypoglycaemic events and weight gain derived from formulation/pharmacokinetic/dynamic differences. Clinical utility of these insulins in selected patients requires evaluation.
Aim: To assess treatment effects of long-acting basal insulin analogues when used for selected clinical reasons in routine practice.
Methods: A non-randomised systematic audit of patients with type 1 (T1DM) or type 2 diabetes (T2DM) requiring treatment change to long-acting basal analogues was performed. Demographics, disease profiles and reasons for new insulin were obtained from electronic databases. Data on weight, BMI, HbA_{1c}, hypoglycaemic events and insulin dose were collected prospectively at 3–6 and 9–12 months.
Results: The study group, comprising 44 patients with T1DM and 15 with T2DM, were switched to Toujeo (n=21) or Tresiba (n=38) for the following clinical reasons: hypoglycaemia (62.7%), glycaemic control (14.7%), high basal insulin dose (12.0%), weight control (5.3%), injection site reaction (1.3%), injection frequency (2.7%), unspecified (1.3%). The following changes were seen after 6 months in T1DM patients: HbA_{1c} (–3.6%), weight (+0.5%), basal insulin dose (–9.3%); and in T2DM patients (Toujeo only): HbA_{1c} (+1.9%), weight (+0.9%), basal insulin dose (–6.8%). At follow-up, hypoglycaemic events decreased in patients with T1DM (–54%) and in those with T2DM (–36%).
Conclusions: In T1DM patients, switching to Toujeo or Tresiba may improve management of hypoglycaemia and insulin dose without compromising glycaemic control. However, in those with T2DM on Toujeo, an important reduction in hypoglycaemia was balanced by a small change in glycaemic control. In selected patients, longer-acting basal insulin analogues improve key therapeutic challenges of insulin therapy.

Clinical outcomes of patients with type 2 diabetes (T2D) who switched to insulin glargine 300 U/mL from insulin glargine 100 U/mL in real-world US treatment settings

Ye F,[1] Zhou FL,[1] Xie L,[2] Kariburyo F,[2] Meneghini L[3]
[1] Sanofi, Bridgewater, New Jersey, USA
[2] STATinMED Research, Ann Arbor, Michigan, USA
[3] University of Texas Southwestern Medical Center and Parkland Health & Hospital System, Dallas, Texas, USA

Aim: To compare insulin dose changes in a real-world setting for adults with type 2 diabetes on prior insulin glargine 100 U/mL (Gla-100) who either switched to insulin glargine 300 U/mL (Gla-300) or remained on Gla-100.
Methods: Retrospective patient data were extracted from the Optum Clinformatics database between 1 October 2014 and 31 March 2016. Data were assessed at baseline (≤6 months before inclusion) and follow-up (≤6 months after first Gla-300 claim or a randomly selected Gla-100 claim). Patients switching to Gla-300 were matched by propensity score matching. Endpoints included daily average consumption (DACON) of basal insulin and average percentage change of DACON per patient from baseline to follow-up. Patients were considered persistent if they remained on index basal insulin during follow-up.
Results: Matched patients for Gla-300 (n=443) and Gla-100 (n=1,241) had comparable DACON at baseline (56.0 vs 53.6 U/day, respectively; p=0.2109) and follow-up (58.8 vs 55.0 U/day, respectively; p=0.0975), corresponding to comparable changes in DACON (13.8 vs 12.6%, respectively; p=0.753). In persistent patients, DACON also increased from baseline to follow-up (Gla-300: 56.45 to 59.2 U/day, n=346; Gla-100: 54.7 to 55.0 U/day, n=1,090), with no statistical difference between cohorts (Gla-300: 9.7%; Gla-100: 7.3%, p=0.467). For the subset of patients with available HbA_{1c} measures, both cohorts showed comparable mean HbA_{1c} at baseline and follow-up.
Conclusions: Switching from Gla-100 to Gla-300 was not associated with a higher basal insulin dose compared with continuing on Gla-100. Similar changes in DACON and HbA_{1c} were observed. Despite the increase in DACON, mean HbA_{1c} remained elevated.
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Cost-effectiveness of insulin glargine 300 U/mL (Gla-300) versus insulin degludec 100 U/mL (IDeg) in type 2 diabetes

Murphy DR,[1] Yu X,[1] Fournier M,[2] Klein TM,[1] Fan T,[3] Perk S,[1] Preblick R,[3] Zhou FL[3]
[1] Medical Decision Modeling Inc, Indianapolis, Indiana, USA
[2] Sanofi, Chilly-Mazarin, France
[3] Sanofi, Bridgewater, New Jersey, USA

Background: This cost-effectiveness modelling analysis simulated a cohort of patients receiving Gla-300 (EDITION 2 and 3) or IDeg using the IMS Core Diabetes Model (lifetime [50 years]; n=1,000,000; age ≥62 years).
Methods: Efficiency parameters, HbA_{1c} reduction and hypoglycaemia event (HE) rates were estimated using a network meta-analysis: for Gla-300 vs IDeg, HbA_{1c} reduction over 24 weeks was 1.00 vs 0.98%; HE rates were estimated as 2.5 vs 4.0 (severe HEs (SHEs)) and 446 vs 555 (non-SHEs (NSHEs)) per 100 patient years, respectively. The cost/unit of Gla-300 was set to US$0.22 to maintain dose-adjusted price parity with insulin glargine using data from the EDITION trials; the cost/unit of IDeg was set to $0.296 from its US wholesale acquisition cost. Treatment costs were $1,561/SHE and $13.65/NSHE (2015 $). Utilities to estimate quality-adjusted life years (QALYs) for multiple comorbidities were applied using the minimum utility approach; a disutility of –0.0118 was applied for SHEs and a method of diminishing marginal disutility was applied for NSHEs.
Results: Compared with IDeg, Gla-300 provided a total cost reduction per patient of $8,998 ($162,288 vs $171,286) and a QALYs gain of 0.035 (7.677 vs 7.642) for lifetime in base-case analysis. One-way sensitivity analysis showed that 10% change in HbA_{1c}, SHE/NSHE rates and treatment costs did not change the incremental cost-effectiveness ratio dominance for Gla-300. Probabilistic sensitivity analysis found that Gla-300 was less costly in 95.4% of cases and more effective in 60.1% of cases vs IDeg. Real-world data are needed to confirm this finding.
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Audit: Assessment of appropriate dosing of diabetic medications in people with type 2 diabetes and renal impairment

Zaman S, Corallo C, Martineau M
West Middlesex Hospital, Chelsea and Westminster Hospitals NHS Foundation Trust, London, UK

Background: Chronic kidney disease (CKD) can be found in up to 23% of people with diabetes.[1] However, treatment options for people with type 2 diabetes and CKD are limited as the reduced glomerular filtration rate results in accumulation of certain drugs and/or their metabolites. Therefore, it is extremely important to review diabetic medications in people with renal disease.
Objectives: To audit the optimal and safe dosing of diabetic medications in patients with type 2 diabetes and CKD.
Methods: Data were collected retrospectively through paper and electronic medical records of patients with type 2 diabetes and CKD stage 3 or below (eGFR <60) who attended diabetes clinics from 1 January 2015 to 31 July 2016. The data were recorded and analysed on MS Excel.
Results: The total number of patients was 162. Of these, 69% had safe and optimal dosing, 30% had non-optimal dosing and 0.6% of patients' records were unavailable. Non-optimal dosing was further divided into two groups: patients on doses of oral diabetic medications that were not appropriately adjusted according to their renal function (33%) and patients at risk of hypoglycaemia with HbA_{1c} <53 mmol/mol (67%).
Recommendations: To ensure there is a plan to optimise medication dosing for patients approaching CKD3 and 4 in the clinic letters. Hypoglycaemic episodes should be actively addressed and doses need to be optimised in patients with tight diabetes control even if they do not report hypoglycaemia.

Reference
1 Cavanaugh KL. Diabetes management issues for patients with chronic kidney disease. *Clin Diabetes* 2007;**25**:90–7. http://dx.doi.org/10.2337/diaclin.25.3.90

World travel with type 1 diabetes: a review (and experience of a couple with type 1 diabetes)

Charlton AR, Charlton JR
University Hospitals of Leicester NHS Trust, Camp Charnwood, Leicester, UK.

Background: Living with type 1 diabetes and using insulin pump therapy (IPT), the authors travelled together for four months through 11 countries. Travelling with type 1 diabetes presents various added challenges. These are reviewed along with the personal experience of the authors.
Air travel: Flying at altitude causes increased insulin resistance, a condition that is compounded by prolonged periods of inactivity during air travel. Another consideration is that unintended insulin delivery from IPT occurs during ascent, and bubbles can form or increase in size within the insulin chamber. Insulin must not be subjected to low temperatures and therefore must be carried in hand luggage, and the risk of hold luggage becoming lost or delayed meant that all the paraphernalia for IPT and glucose monitoring had to be carried with them.
Crossing time zones: Using IPT allows insulin to be infused in correlation with the circadian rhythm, matching insulin infusion to insulin resistance through a 24-hour period. This is an important consideration when crossing time zones.
Airport security: Damage to insulin pumps can be caused from exposure to x-ray or full body scanner technology while negotiating airport security. This, combined with increasingly stringent security and a lack of knowledge among security staff, results in a negative experience for IPT users.
Altitude: Physiological changes at altitude lead to increased insulin resistance and risk of diabetic ketoacidosis, and altitude sickness can mask symptoms of hypoglycaemia, making altitude potentially hazardous for people with type 1 diabetes.
Climate: Tropical climates increase insulin sensitivity, risk of fever and cause temperature-related insulin failure.