Conference over coffee: New medicines, goals of triple therapy, AI prescribing, hypoglycaemia and lipids

The 17th Scottish Conference of the Primary Care Diabetes Society took place in Glasgow on 29 October 2024. In this short report, Jane Diggle highlights key messages from the main sessions to take back to our practice. Slides and a resource pack will be made available soon: click here to access.

New medicines: The present and the future

Hannah Beba, Consultant Pharmacist for Diabetes, Leeds Health and Care Partnership

- Diabetes care has moved away from a glucocentric approach to one that considers the whole person (and is "person-centric"). We need to know the people we care for – not just the drugs – and use this knowledge and understanding to develop shared and personalised management plans.
- Upstream interventions addressing prevention offer cost-effective strategies.
- We are entering an era of co-ownership of therapies with our weight management, cardiology, renal and hepatology colleagues. There are exciting new drugs for the future and opportunities to manage comorbidities together.
- The evidence base for use of CGM in people with type 2 diabetes is expanding – improvements in glycaemic control, time in range and glycaemic variability have been shown, but there remains a lack of outcomes data on severe hypoglycaemia, microvascular and macrovascular complications.
- Once-weekly insulins (insulin icodec, insulin efsitora alfa) are in phase 3 trials – results suggest comparable glucose-lowering effects but higher rates of level 1 hypoglycaemia (<3.9 mmol/L but ≥3.0 mmol/L).
- Screening to identify and treat pre-symptomatic type 1 diabetes and delay progression, including a 14-day regimen of IV teplizumab (human monoclonal antibody to CD3 on T-cells), has the potential to delay the development of stage 3 type 1 diabetes and improve beta-cell function.
- New obesity drugs are in development, including glucagon/amylin receptor agonists and tri-incretins – see *Box 1*.
- Indications for established drugs are set to expand; for example, finerenone in heart failure and semaglutide in chronic kidney disease.

Debate: Triple therapy – do you treat to HbA_{1c} or secondary outcomes?

Kashif Ali, GP and primary care lead, NHS Greater Glasgow & Clyde

Naresh Kanumilli, GPwSI Diabetes and Cardiology, Manchester

- A lively debate was held over which approach to type 2 diabetes management should be promoted: a holistic cardiorenal metabolic approach versus one that primarily focuses on glycaemic control?
- At the start the votes were in favour of the more holistic multifactorial approach; however, by the end, a good proportion of the audience supported a focus on glucose control:
  - ➤ There is a weight of evidence to support this in reducing diabetes-related complications (see our recent *Diabetes Distilled*; Brown, 2024).
  - ➤ In particular, the benefit of more aggressive control early on has been demonstrated.
  - ➤ By definition, diabetes is a condition of hyperglycaemia.
- Ultimately, however, a consensus was reached that, whatever the approach, the person with diabetes should be at the centre of their care, as illustrated in the ADA/EASD consensus report (Buse et al, 2022).

Box 1. Obesity drugs in development.

GLP-1 receptor agonists (higher doses)
- Semaglutide 2.4 mg once weekly

GLP-1/GIP receptor agonists
- Tirzepatide
- MariTide (maridebart cafraglutide) – monthly administration; phase 2 completed in 2024

GLP-1/Amylin receptor agonists
- Cagrisema (cagrilintide + semaglutide) – phase 3 to complete in 2027
- Amycretin

GLP-1/Glucagon receptor agonists
- Survodutide
- Cotadutide
- Efinopegdutide

Tri-incretin (GLP-1/GIP/Glucagon) receptor agonists
- Retatrutide (phase 3 to complete in 2026)

Melanocortin 4 receptor (MC4R) agonist (for severe obesity caused by genetic disorders)
- Setmelanotide

AI prescribing: Clinician versus machine

Chris Sainsbury, Consultant Physician, NHS Greater Glasgow & Clyde

- In primary care settings, 75% of family doctor contacts involve medication decisions.
- There is a higher risk of adverse events in primary care due to complex decision making involving multiple factors: patient demographics, comorbidities, other medications and so on.
- Some of this decision making could be undertaken using artificial intelligence (AI).
- How can we use AI/machine learning to assist prescribing?
  - ➤ Enhancing the use of evidence already generated and extracting new information from current evidence and datasets.
- Raises many issues:
  - ➤ Can a machine replicate compassionate care?
  - ➤ It is based on logic and could reduce risk of human error, but at what price?
  - ➤ If AI systems make an error, who is accountable?

Outstanding Contribution Award: 100 years of hypoglycaemia

Brian M Frier, Honorary Professor of Diabetes, University of Edinburgh

Professor Brain Frier was awarded the first PCDS Scotland Outstanding Contribution Award and gave a fascinating account of 100 years of hypoglycaemia research.

- Hypoglycaemia in humans was recognised as a biochemical anomaly in the early 20th century but was not considered to have any clinical significance.
- Hypoglycaemia became established as a clinical entity after the introduction of insulin to treat people with diabetes in 1922.
- Initial attempts to use pancreatic extracts in animals often produced acute toxic reactions, many of which were probably caused by profound hypoglycaemia.
- When insulin was first used, batches differed in potency and recurrent hypoglycaemia was common.
- Accurate and rapid measurement of blood glucose was very difficult and did not improve until the 1940s with the development of the autoanalyser.
- Studies in the 1970s and 1980s investigated the counter-regulatory responses that occur in hypoglycaemia and, later, the discovery that these responses became deficient in insulin-treated diabetes and exacerbated by strict glycaemic control and antecedent hypoglycaemia.
- The human brain uses 50–80% of glucose in the resting state (fasting). Function depends on continuous supply of glucose for energy needs, and profound hypoglycaemia causes coma.
- Cognitive function deteriorates at blood glucose levels <3 mmol/L.
- Attention-demanding and more complex tasks are impaired – accuracy is impaired at the expense of speed and recovery delayed after blood glucose returns to normal. Effects on everyday life are widespread and may be dangerous (for example, driving).
- The ADA and EASD have adopted the classifications of hypoglycaemia in *Table 1*, as recommended by the International Hypoglycaemia Study Group (2017).
- Professor Frier provided a recap of the hypoglycaemia symptoms (*Table 2*), impaired hypo awareness (more common after prolonged or repeated hypoglycaemia) and the physiological

Table 1. International Hypoglycaemia Study Group (2017) hypoglycaemia definitions.

Level	Plasma glucose concentration	Description
Level 1	≤3.9 mmol/L	**Hypoglycaemia alert value** Not true hypoglycaemia, but action is required to prevent a further decline of glucose; does not need to be reported in clinical studies
Level 2	<3.0 mmol/L	**Clinically significant hypoglycaemia** Sufficiently low to indicate serious, clinically important hypoglycaemia
Level 3	No glucose threshold specified	**Severe hypoglycaemia** Hypoglycaemia associated with severe cognitive impairment requiring external assistance for recovery

Table 2. Symptoms of hypoglycaemia (Deary et al, 1993).

Autonomic	Neuroglycopenic	General malaise
Shaking	Confusion	Nausea
Palpitations	Odd behaviour	Headache
Sweating	Drowsiness	
Hunger	Difficulty with speech	
	Incoordination	

and pathophysiological consequences of hypoglycaemia (effects can last up to a week and include inflammation, endothelial dysfunction and haemodynamic changes).

- He finished with reference to harm – sometimes intentional – brought about by medication-induced hypoglycaemia with a quote from Elliot Joslin: *"Insulin is a potent preparation, alike for evil and for good."*

Lipids: How low should we go?

Naveed Sattar Professor of Cardiometabolic Medicine, University of Glasgow

- Cardiovascular risks are higher for people with diabetes.
- In primary prevention, for those with type 2 diabetes, risk scores should be used from age 25 years onwards. A different approach is advocated in people with type 1 diabetes, based on diabetes duration and other cardiovascular risk factors.
- Aim for LDL cholesterol <2.5 mmol/L for primary prevention and lower for secondary prevention, although European guidelines advocate an LDL <1.8 mmol/L and possibly a lower target in the future.
- Statins remain the mainstay of therapy, but ezetimibe should be considered more often, as it has a good evidence base especially in those with diabetes.
- Where there is perceived intolerance, it is worth pausing the statin (recommending a "statin holiday"), as >90% of intolerance is not genuine. Consider retrying with a lower dose to gain confidence and then increase.
- Additional lipid-lowering therapies beyond these, such as injectable PCSK9 inhibitors for secondary prevention and bempedoic acid in combination with ezetimibe, especially in those who are truly statin-intolerant. ■

Brown P (2024) Diabetes Distilled: Optimising glycaemic control is still important, especially early in type 2 diabetes. *Diabetes & Primary Care* **26**: 185–7

Deary IJ, Hepburn DA, MacLeod KM, Frier BM (1993) Partitioning the symptoms of hypoglycaemia using multi-sample confirmatory factor analysis. *Diabetologia* **36**: 771–7

International Hypoglycaemia Study Group (2017) Glucose concentrations of less than 3.0 mmol/L (54 mg/dL) should be reported in clinical trials: A joint position statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* **40**: 155–7