Letters

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Insulin avoidance and treatment outcomes among patients with a professional driving licence starting glucagon-like peptide 1 (GLP-1) agonists in the Association of British Clinical Diabetologists (ABCD) nationwide exenatide and liraglutide audits

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Mainly as a result of the concerns regarding hypoglycaemia and the risk to public safety, most persons with insulin-treated diabetes are ineligible to obtain a Group 2 vehicle licence. As defined by the Driver and Vehicle Licensing Agency (DVLA), Group 2 vehicles include large goods vehicles (such as lorries) and passenger carrying vehicles (such as buses). They do not include taxis or emergency vehicles (such as police vehicles or ambulance), although it has been recommended that similar medical standards be applied (see also Supporting Information, Appendix S1) [1,2].

Treatment for Type 2 diabetes with the glucagon-like peptide (GLP-1) agonists exenatide and liraglutide is associated with weight loss and a low hypoglycaemia risk [3,4]. The Driver and Vehicle Licensing Agency raises no specific caution to the use of GLP-1 agonists unless used concurrently with a sulphonylurea [1]. Guidelines by the National Institute for Health and Clinical Excellence (NICE) list GLP-1 agonists as alternatives to insulin when a patient's occupation is significantly affected by insulin use. This was beyond the usual treatment indication in patients with suboptimal control and a BMI ≥ 35 kg/m^2 [5,6].

The Association of British Clinical Diabetologists (ABCD) conducted two nationwide audits on the use of exenatide, and liraglutide, based in clinical practice. The exenatide audit received data on 6717 patients from 126 centres. The liraglutide audit is ongoing and so far includes 3010 patients from 65 centres. Information on possessing a professional driving licence (driving Group 2 vehicles, taxis or emergency vehicles) was collected in both audits. The audits provided a unique opportunity to evaluate characteristics and treatment outcomes of these patients. The nature of the audits, however, precluded a comparison with a strategy of starting insulin instead.

Out of 9727 patients, 282 (2.9%) reported being professional drivers (178 on exenatide and 104 on liraglutide). In contrast to other audit patients, they were predominantly male (93.6 vs. 53.2%, $P < 0.001$), more poorly controlled [mean baseline HbA_{1c} 84 mmol/mol (9.81%) vs. 79 mmol/mol (9.40%), $P < 0.001$] and were younger (53.4 vs. 55.1 years, $P = 0.001$). In accordance with the provisions made by the NICE guidelines, more had a BMI of < 35 kg/m^2 (46.2 vs. 29.1%, $P < 0.001$). To compare outcomes, we matched professional drivers with other audit patients with similar baseline characteristics and duration of follow-up (Table 1).

When compared with other matched patients, professional drivers were less likely to be on insulin at baseline (14.6 vs. 34.8%, $P < 0.001$), while those on insulin were much more likely to stop insulin after GLP-1 agonist treatment (50.0 vs. 28.6%, $P = 0.004$). In contrast, they were more likely to be on three oral hypoglycaemic agents (34.0 v 17.8%, $P < 0.001$), including more frequent sulphonylurea use (72.0 vs. 47.9%, $P < 0.001$). The Driver and Vehicle Licensing Agency identifies treatment with sulphonylurea as a hypoglycaemia risk, but not a reason to disallow a Group 2 licence.

At 6 months, professional drivers achieved similar treatment responses when compared with matched counterparts. Mean (± SE) HbA_{1c} reductions were −10 mmol/mol (± 2) [−0.91% (± 0.16)] vs. −10 mmol/mol (± 0) [−0.88% (± 0.04)] (difference, $P = 0.862$). Weight reductions were −4.7 kg (± 0.4) vs. −4.3 kg (± 0.1) (difference, $P = 0.259$). At median follow-ups of 40 and 37 weeks, hypoglycaemia (defined by individual centres) was reported in 6.7 and 4.0% in each group, respectively ($P = 0.027$). No cases of hypoglycaemia requiring third-party assistance were reported among professional drivers. In the same time period, rates of GLP-1 agonist discontinuation were similar; 15.2 vs. 17.4% ($P = 0.349$).

The audits demonstrated clear benefits of GLP-1 agonist treatment on glycaemia and weight among patients with a driving occupation affected by insulin use. Hypoglycaemia was infrequent, although slightly more common among professional drivers, possibly because of a higher rate of sulphonylurea use. Not surprisingly, our results suggest a general avoidance of insulin; proportionally fewer were on insulin at baseline and more stopped insulin after starting GLP-1 agonists. Nevertheless, they achieved a similar HbA_{1c} reduction compared with other matched patients. This contrasts with our previous report showing poorer glycaemic outcomes among patients stopping insulin at exenatide initiation [7]. We hypothesize that these patients have resisted insulin treatment despite poor diabetes control, but were motivated to try GLP-1 agonists as an alternative.

Despite significant glycaemic reduction among professional drivers, the mean HbA_{1c} level was still suboptimal. We are concerned that some of these patients do not progress to insulin treatment when insufficient glycaemic response has been achieved with GLP-1 agonists. It may be that treatment with GLP-1 agonists delays the requirements for insulin in some

Table 1 Baseline characteristics comparing patients with a professional driving licence and matched patients in the Association of British Clinical Diabetologists (ABCD) nationwide exenatide and liraglutide audits

	Patients with a professional driving licence (n = 282)	Matched audit patients (n = 3388)*	P-value
Duration of follow-up (weeks)	40 (20–57)	37 (23–53)	0.702
Exenatide/liraglutide (n,%)	178/104 (63.1)	2287/1101 (67.5)	0.132
Gender (men/women, % men)	263/18 (93.6)	3055/240 (92.7)	0.585
Caucasian (%)	94.2	92.4	0.318
Age (years)	53.4 (8.4)	53.6 (9.3)	0.685
Diabetes duration (years)	8 (5-12)	9 (5-12)	0.274
HbA_{1c} (mmol/mol)	84 (20)	83 (17)	0.633
HbA_{1c} (%)	9.81 (1.79)	9.76 (1.55)	0.633
Weight (kg)	111.4 (22.2)	112.2 (17.2)	0.587
BMI (kg/m^2)	36.5 (7.0)	36.8 (4.7)	0.483

Results for age, HbA_{1c}, weight and BMI expressed as mean (SD) and duration of follow-up and diabetes duration as median (interquartile range).
*From a total of 9445 patients without a professional driving licence.

patients, but they should not be a substitute when insulin therapy is clearly required.

In conclusion, patients with a professional driving licence treated with exenatide and liraglutide in real-life practice achieved similar glycaemic outcomes to other patients in the audits, despite a significant proportion avoiding insulin. These findings from the ABCD nationwide audits support the special provisions made by NICE guidelines in allowing the use of GLP-1 agonists in such patients. However, patients should still be encouraged to start insulin if their diabetes control remains poor.

Competing interests

KYT is employed as an Association of British Clinical Diabetologists (ABCD) research fellow and MLC as a data administrator in the Nationwide ABCD audit programme (which include audits of exenatide and liraglutide) by the Sandwell and West Birmingham Hospitals National Health Service (NHS) Trust. These posts are funded by the ABCD from grants provided by Eli Lilly and Novo Nordisk. KYT has received educational sponsorship from Eli Lilly, Novo Nordisk, Sanofi-Aventis and Takeda. REJR has received speaker fees from Eli Lilly, consultancy fees from Novo Nordisk and educational sponsorship from Sanofi-Aventis, Takeda and GlaxoSmithKline. CW has received educational sponsorship from Boehringer-Ingelheim, Eli-Lilly, Novo Nordisk and Takeda. This audit was independently initiated and performed by the ABCD and the authors remained independent in the analysis and the writing of this report.

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K. Y. Thong[1], R. E. J. Ryder[1], M. L. Cull[1] and C. Walton[2]
on behalf of the ABCD nationwide exenatide and liraglutide audit contributors
(for list of contributors, see Supporting Information, Appendix S2)
[1]Diabetes, City Hospital, Birmingham and
[2]Diabetes, Hull Royal Infirmary, Hull, UK

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Licence groups.

Appendix S2. List of contributors in the ABCD nationwide exenatide audit.

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Effective treatment of diabetes caused by activating *ABCC8*/SUR1 mutation with glimepiride

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Diabetes mellitus caused by gain-of-function mutations in the *KCNJ11* and *ABCC8* genes encoding the ATP-sensitive potassium (K_{ATP}) channel subunits Kir6.2 and sulphonylurea receptor 1 (SUR1) is characterized by the clinical phenotypes of transient or permanent neonatal diabetes and permanent adult-onset diabetes [1,2]. Enhanced stimulatory action of such a mutant receptor attenuates insulin release, leading to functional insulin deficiency and hyperglycaemia. Patients with mutant K_{ATP} channels have been shown to be responsive to various high-dose sulphonylurea compounds acting by an ATP-independent mechanism to close these channels [1,2], but the preferred treatment in affected patients is still unclear. Here, we report successful therapy with glimepiride, a long-acting sulphonylurea with reduced potential for hypoglycaemia.

Diabetes was diagnosed in a 3-week-old infant, blood glucose > 11.1 mmol/l, without ketonaemia. C-peptide was 0.41 nmol/l. Auto-antibodies against glutamate decarboxylase 65, tyrosine phosphatase IA-2, islet cells and insulin were negative. Without specific treatment, blood glucose normalized at the age of 3 months, confirming transient neonatal diabetes. HbA_{1c} was 40 mmol/mol (5.8%) at the age of 9 months. The infant's 36-year-old mother (Fig. 1a) had insulin-treated diabetes since her first pregnancy at the age of 19 years. At presentation, she was treated with multiple daily injections of regular insulin and once-daily insulin glargine, associated with poor glycaemic control [HbA_{1c} 92 mmol/mol (10.6%)] and repeated episodes of severe hypoglycaemia.

The 17-year-old sister of the infant had transient neonatal diabetes and was diagnosed with diabetes at the age of 17 years. Her laboratory tests were: fasting plasma glucose 6.4 mmol/l; 2-h plasma glucose after 75-g oral glucose 8.6 mmol/l; homeostasis model assessment of insulin resistance (HOMA-IR) 6.0; HbA_{1c} 48 mmol/mol (6.5%). Her BMI was 28.9 kg/m^2. Six months after nutritional intervention and increased physical activity, BMI decreased to 27.1 kg/m^2, fasting plasma glucose was 5.6 mmol/l, 2-h plasma glucose after 75-g oral glucose was 5.8 mmol/l, HOMA-IR 4.6 and HbA_{1c} 42 mmol/mol (6.0%). Two healthy 9- and 1-year-old sisters had normal blood glucose and HbA_{1c}. The 71-year-old maternal grandmother with insulin-treated diabetes had a C-peptide of 1.6 nmol/l and HbA_{1c} of 44 mmol/mol (6.2%).

Sequence analysis of the *ABCC8* gene showed a heterozygous mutation, R1380C (c.4138C>T; p.Arg1380Cys), in the neonate, her mother and the 17-year-old sister (Fig. 1a). The amino acid exchange within the nucleotide-binding domain (NBD) 2 of

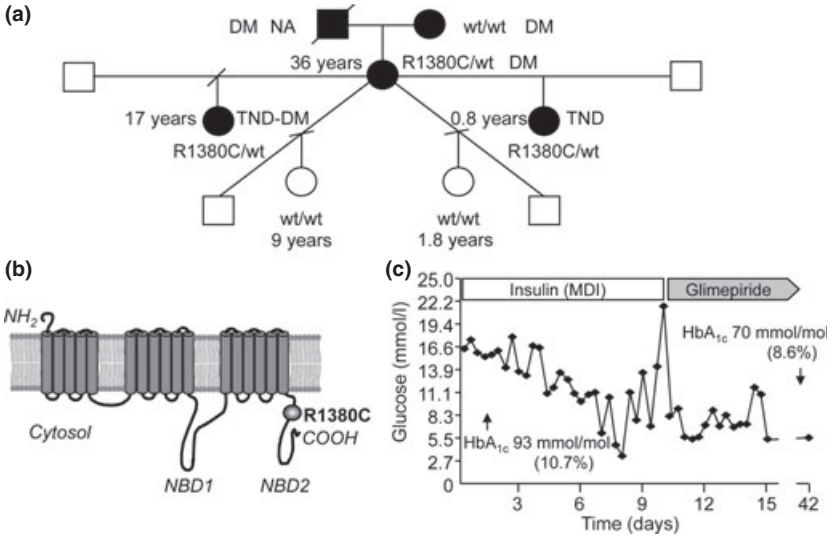

FIGURE 1 (a) Family with activating *ABCC8* R1380C mutation. Diabetes (closed symbols); no diabetes (open symbols). DM, adult-onset diabetes mellitus; NA, not analysed; TND, transient neonatal diabetes; wt, wild type. (b) Localization of R1380C mutation within the nucleotide binding domain (NBD) 2 of the sulphonylurea receptor (SUR) subunit of the β-cell K_{ATP} channel (grey circle). (c) Blood glucose profile during multiple daily insulin injection (MDI) and glimepiride therapy in the 36-year-old patient. HbA_{1c} decreased from 93 mmol/mol (10.7%) to 70 mmol/mol (8.6%) after 6 weeks.