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LETTER

Comment on: Nathan DM, Buse JB, Davidson MB et al (2006) Management of hyperglycaemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy. A consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. Diabetologia 49:1711–1721

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To the Editor:

The consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes, published in both *Diabetologia* [1] and *Diabetes Care* [2], included the following statement concerning the incidence of hypoglycaemia in insulin-treated type 2 diabetes: 'In clinical trials aimed at normoglycaemia and achieving a mean HbA_{1c} of ~7%, severe hypoglycaemic episodes (defined as requiring help from another person to treat) occurred at a rate of between 1 and 3 per 100 patient-years ....' This is not a balanced description of the published literature.

The authors cited five publications to support the statement quoted [3–7]. However, two of these do not include event rates for severe hypoglycaemia as defined in the statement [5, 6] and one was a review with no original data [7]. Notably, the latter review cited studies reporting event rates for severe hypoglycaemia in insulin-treated type 2 diabetic patients of 28 and 35 per 100 patient-years [7], which are well in excess of 'between 1 and 3 per 100 patient-years' [1, 2]. Thus, only two [3, 4] of the five publications cited, involving 127 patients with insulin-treated type 2 diabetes, support the authors' statement (Table 1).

The authors did not cite original publications reporting severe hypoglycaemia event rates of 10 [8], 28 [9], 35 [10], 44 [11] and 73 [12] per 100 patient-years, involving 907 patients with insulin-treated type 2 diabetes (Table 1). (Admittedly, one [11] was published at about the same time as the consensus statement.) These five reports included a prospective study of a population-based random sample of patients with insulin-treated type 2 diabetes that found a severe hypoglycaemia event rate of 35 per 100 patient-years [10]. These severe hypoglycaemia event rates, ranging from 10–73 per 100 patient-years, in insulin-treated type 2 diabetes [8–12] approach those in type 1 diabetes, which range from 62–170 per 100 patient-years [10, 12–14] (Table 1).

Furthermore, the authors did not cite additional population-based data in which the event rates for severe hypoglycaemia requiring emergency medical treatment in insulin-treated type 2 diabetes ranged from 40–100% [15, 16] of those in type 1 diabetes.

The barrier of hypoglycaemia precludes maintenance of euglycaemia over a lifetime of diabetes and thus full realisation of the now well-established vascular benefits of glycaemic control [17]. In contrast to type 1 diabetes, hypoglycaemia is relatively infrequent early in the course of type 2 diabetes when glucose counter-regulatory defences against falling plasma glucose concentrations are intact [17, 18]. However, as discussed here and summarised in Table 1, there is a body of evidence—including prospective, population-based data—indicating that hypoglycaemia becomes progressively more frequent, approaching the incidence rate seen in type 1 diabetes, as patients approach the insulin-deficient end of the spectrum of type 2 diabetes, where physiological and behavioural defences against falling glucose levels become compromised [17, 18].

I quite agree with the authors of the consensus statement that insulin is the most effective of diabetes medications in

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Table 1 Event rates for severe hypoglycaemia (that requiring the assistance of another person) in insulin-treated type 2 diabetes and in type 1 diabetes

Citation	*n*	HbA_{1c} (%) (mean±SD)	Event rate per 100 patient-years	Comment
Type 2 diabetes				
Ohkubo Y et al. 1995 [3]	52	7.1±1.1	0	Clinical trial, intensive insulin group
Abraira C et al. 1995 [4]	75	<7.3	3	Clinical trial, intensive insulin group
Saudek CD et al. 1996 [8]	62	7.5±0.8	10	Clinical trial, multiple insulin injection group
Henderson JN et al. 2003 [9]	215	8.6±1.5	28	Retrospective clinic survey
Donnelly LA et al. 2005 [10]	173	8.9±1.4	35	Prospective study of a population-based random sample
Akram K et al. 2006 [11]	401	8.3	44	Retrospective clinic survey
MacLeod KM et al. 1993 [12]	56	NR	73	Retrospective clinic survey
Type 1 diabetes				
DCCT Research Group 1993 [13]	711	~7.1	62	Clinical trial, intensive insulin group
Reichard P and Pihl M 1994 [14]	48	7.1±0.7	110	Clinical trial, intensive insulin group
Donnelly LA et al. 2005 [10]	94	8.5±1.6	115	Prospective study of a population-based random sample
MacLeod KM et al. 1993 [12]	544	NR	170	Retrospective clinic survey

NR, not reported

lowering glycaemia [1, 2]. In my opinion, insulin should be introduced earlier, rather than later, in inadequately controlled type 2 diabetes. However, our associations should provide a balanced view of the downside of this effective therapy, hypoglycaemia.

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Duality of interest The author has served on advisory boards for Novo Nordisk, Takeda Pharmaceuticals North America, MannKind Corporation, and Merck & Co. in recent years.

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