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POSITION STATEMENT

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 Europian Association for the Study of Diabetes

The International Hypoglycaemia Study Group

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The International Hypoglycaemia Study Group recommends that the frequency of detection of a glucose concentration <3.0 mmol/l (<54 mg/dl), which it considers to be clinically significant biochemical hypoglycaemia, be included in reports of clinical trials of glucose-lowering drugs evaluated for the treatment of diabetes mellitus.

The glycaemic thresholds for symptoms of hypoglycaemia and for glucose counterregulatory (including sympathoadrenal) responses to hypoglycaemia, as plasma glucose concentrations fall, are not fixed in patients with insulin-, sulfonylurea- or meglitinide- (glinide)-treated diabetes. They are at higher glucose concentrations in those with poor glycaemic control and at lower glucose concentrations in those with tight glycaemic control [1–5]. The shifts in glycaemic threshold to lower glucose concentrations are largely the result of more frequent episodes of iatrogenic hypoglycaemia during intensive glycaemic therapy. Glycaemic thresholds for responses to hypoglycaemia vary, not only among individuals with diabetes but also in the same individual with diabetes as a function of their HbA_{1c} levels and hypoglycaemic experience; it is therefore not appropriate to cite a specific glucose concentration that defines hypoglycaemia in diabetes. As a consequence, the American Diabetes Association has defined hypoglycaemia in diabetes non-numerically as 'all episodes of an abnormally low plasma glucose concentration that expose the individual to potential harm' [6, 7].

Nonetheless, the International Hypoglycaemia Study Group believes that it is important to identify and record a level of hypoglycaemia that needs to be avoided because of its immediate and long-term danger to the individual. A single glucose level should be agreed to that has serious clinical and health-economic consequences. This would enable the diabetes and regulatory communities to compare the effectiveness of interventions in reducing hypoglycaemia, be they pharmacological, technological or educational. It would also permit the use of meta-analysis as a statistical tool to increase power when comparing interventions.

In its discussion, the International Hypoglycaemia Study Group considered glucose concentration levels of <3.0 mmol/l (<54 mg/dl) and <2.8 mmol/l (<50 mg/dl) detected by self-monitoring of plasma glucose, continuous glucose monitoring (for at least 20 min) or a laboratory measurement of plasma glucose. Both of these levels are distinctly low glucose concentrations that do not occur under physiological conditions in non-diabetic individuals [8]. Thus, they are unequivocally hypoglycaemic values. They approximate the upper and lower limits, respectively, of the non-diabetic

Members of the International Hypoglycaemia Study Group are listed in the Appendix.

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glycaemic threshold for symptoms of insulin-induced hypoglycaemia [8–10]. The generic non-diabetic glycaemic threshold for impairment of cognitive function is <2.8 mmol/l [8–10], but higher glucose levels have been reported for some tests [11–14]. Glucose concentrations of both <3.0 mmol/l and <2.8 mmol/l cause defective glucose counterregulation and impaired awareness of hypoglycaemia, the core components of hypoglycaemia-associated autonomic failure in diabetes [5]. Avoiding these glucose levels could reverse impaired awareness of hypoglycaemia [15–18] and some aspects of defective glucose counterregulation [15–17] in many affected patients. In type 1 diabetes, failure to recognise one's own hypoglycaemia at a glucose concentration <3.0 mmol/l increased the risk of severe hypoglycaemia (defined as needing the help of another person for recovery) fourfold [17]. In type 2 diabetes, both glucose concentrations were associated with cardiac arrhythmias [19, 20]. Finally, a glucose concentration <2.8 mmol/l was associated with mortality in patients with type 2 diabetes in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial (NCT00000620) [21], and possibly in the Outcomes Reduction with an Initial Glargine Intervention (ORIGIN) trial (NCT00069784) [22] and among patients treated in intensive care units in the Normoglycemia in Intensive Care Evaluation—Survival Using Glucose Algorithm Regulation (NICE-SUGAR) trial (NCT00220987) [23]. A glucose concentration <3.0 mmol/l was associated with mortality in the NICE-SUGAR trial [23] and, possibly, in the ORIGIN trial [22].

Ultimately, the International Hypoglycaemia Study Group members agreed that a glucose concentration <3.0 mmol/l (<54 mg/dl) is sufficiently low to indicate serious, clinically important hypoglycaemia. Possible terms used to describe this condition include 'serious', 'clinically important', 'major' or 'clinically significant'. The group decided not to describe 'severe hypoglycaemia' in terms of glucose concentration since there is currently widespread agreement that severe hypoglycaemia, as defined by the American Diabetes Association [6, 7], denotes severe cognitive impairment requiring external assistance for recovery. The group also proposed that the frequency of detection of the glucose alert value of 3.9 mmol/l (70 mg/dl) or less [24] need not be reported routinely in clinical trials.

In conclusion we propose that the following glucose levels be adopted by the diabetes community to address the issue of hypoglycaemic risk (text box).

Proposed glucose levels when reporting hypoglycaemia in clinical trials

Level 1

A glucose alert value of 3.9 mmol/l (70 mg/dl) or less. This need not be reported routinely in clinical studies, although this would depend on the purpose of the study

Level 2

A glucose level of <3.0 mmol/l (<54 mg/dl) is sufficiently low to indicate serious, clinically important hypoglycaemia

Level 3

Severe hypoglycaemia, as defined by the ADA [6,7], denotes severe cognitive impairment requiring external assistance for recovery

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Duality of Interest PA has served on scientific advisory boards and/or as a lecturer for AstraZeneca, Boehringer Ingelheim/Lilly, Bristol-Myers Squibb, GlaxoSmithKline, Janssen, Merck Sharp & Dohme, Novartis and Sanofi. BC has had research grant support from Halozyme and Lilly to the former MidAmerica Diabetes Associates. PEC has served on scientific advisory boards for Novo Nordisk. BEdG has served on scientific advisory boards for Novo Nordisk and Sanofi and received research grant support from AstraZeneca. SRH has served on scientific advisory boards and provided consultancy for which his institution has received remuneration from Lilly, Novo Nordisk, Takeda, Merck Sharp & Dohme and Becton Dickinson, has served as a speaker for which he received remuneration from AstraZeneca, Lilly, Novo Nordisk, Boehringer Ingelheim and Takeda and has received research support from Medtronic UK Ltd. BMF has served on scientific advisory boards and as a speaker for Boehringer Ingelheim, Janssen, Merck Sharp & Dohme, Novo Nordisk and Lilly. LG-F has served as a consultant or speaker and/or has received research grant support from Abbott Diabetes Care, AstraZeneca, Dexcom, Johnson & Johnson and Merck Sharp & Dohme. TJ has served as a speaker for Novo Nordisk, Lilly, Medtronic and Sanofi. KK has

served as a consultant or speaker for AstraZeneca, Boehringer Ingelheim, Janssen, Lilly, Merck Sharp & Dohme, Novartis, Novo Nordisk and Sanofi and has received research grant support from AstraZeneca, Boehringer Ingelheim, Lilly, Novartis, Novo Nordisk, Roche and Sanofi. LAL has served as a consultant or speaker for Abbott, AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Lilly, GlaxoSmithKline, Janssen, Merck Sharp & Dohme, Novo Nordisk, Sanofi, Servier and Takeda. RJM has served on scientific advisory boards for Novo Nordisk and Sanofi. ERS has undertaken consultancy for Sanofi, Novo Nordisk, Lilly, Locemia and Medtronic and received grant support from Lilly. RV is an employee and owns stock in Medtronic Inc. SZ has served on scientific advisory boards for Amgen, Bristol-Myers Squibb, AstraZeneca, Janssen, Merck Sharp & Dohme, Novo Nordisk, Sanofi and Takeda, has served as a speaker for Bristol-Myers Squibb, AstraZeneca, Janssen, Merck Sharp & Dohme, Servier and Takeda, and has received research grant support from Bristol-Myers Squibb and AstraZeneca. No other potential conflicts of interest relevant to this article were reported.

Author Contributions The issues discussed here were developed at meetings of the International Hypoglycaemia Study Group with a final meeting taking place on 9 June 2016.

Appendix

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References

1. Amiel SA, Sherwin RS, Simonson DC, Tamborlane WV (1988) Effect of intensive insulin therapy on glycemic thresholds for counterregulatory hormone release. Diabetes 37:901–907
2. Boyle PJ, Schwartz NS, Shah SD, Clutter WE, Cryer PE (1988) Plasma glucose concentrations at the onset of hypoglycemic symptoms in patients with poorly controlled diabetes and in non-diabetics. N Engl J Med 318:1487–1492
3. Heller SR, Cryer PE (1991) Reduced neuroendocrine and symptomatic responses to subsequent hypoglycemia after 1 episode of hypoglycemia in nondiabetic humans. Diabetes 40:223–226
4. Dagogo-Jack S, Craft S, Cryer PE (1993) Hypoglycemia-associated autonomic failure in insulin-dependent diabetes mellitus: recent

antecedent hypoglycemia reduces autonomic responses to, symptoms of, and defense against subsequent hypoglycemia. J Clin Invest 91:819–828
5. Cryer PE (2013) Mechanisms of hypoglycemia-associated autonomic failure in diabetes. N Engl J Med 369:362–372
6. Workgroup on Hypoglycemia, American Diabetes Association (2005) Defining and reporting hypoglycemia in diabetes: a report from the American Diabetes Association Workgroup on Hypoglycemia. Diabetes Care 28:1245–1249
7. Seaquist ER, Anderson J, Childs B et al (2013) Hypoglycemia and diabetes: a report of a workgroup of the American Diabetes Association and the Endocrine Society. Diabetes Care 36:1384–1395
8. Cryer PE (2001) The prevention and correction of hypoglycemia. In: Jefferson LS, Cherrington AD (eds) Handbook of physiology, section 7, volume II, The Endocrine Pancreas and Regulation of Metabolism. Oxford University Press, New York, pp 1057–1092
9. Cryer PE (2016) Hypoglycemia in diabetes, 3rd edition. American Diabetes Association, Alexandria, p 33
10. Frier BM, Heller SR, McCrimmon RJ (eds) (2014) Hypoglycaemia in clinical diabetes, 3rd edn. John Wiley & Sons, Chichester, p 49
11. Heller SR, Macdonald IA (1996) The measurement of cognitive function during acute hypoglycaemia: experimental limitations and their effect on the study of hypoglycaemia unawareness. Diabet Med 13:607–615
12. Choudhary P, Lonnen K, Emery CJ et al (2009) Comparing hormonal and symptomatic responses to experimental hypoglycaemia in insulin- and sulphonylurea-treated type 2 diabetes. Diabet Med 26:665–672
13. Matyka K, Evans M, Lomas J, Cranston L, Macdonald I, Amiel SA (1997) Altered hierarchy of protective responses against severe hypoglycemia in normal aging in healthy men. Diabetes Care 20:135–141
14. Gonder-Frederick LA, Zrebiec JF, Bauchowitz AU et al (2009) Cognitive function is disrupted by both hypo- and hyperglycemia in school-aged children with type 1 diabetes: a field study. Diabetes Care 32:1001–1006
15. Fanelli CG, Epifano L, Rambotti AM et al (1993) Meticulous prevention of hypoglycemia normalizes the glycemic thresholds and magnitude of most neuroendocrine responses to, symptoms of, and cognitive function during hypoglycemia in intensively treated patients with short-term IDDM. Diabetes 42:1683–1689
16. Fanelli C, Pampanelli S, Epifano L et al (1994) Long-term recovery from unawareness, deficient counterregulation and lack of cognitive dysfunction during hypoglycaemia following institution of rational, intensive insulin therapy in IDDM. Diabetologia 37:1265–1276
17. Cranston I, Lomas J, Maran A, Macdonald I, Amiel SA (1994) Restoration of hypoglycemia awareness in patients with long-duration insulin-dependent diabetes. Lancet 344:283–287
18. Dagogo-Jack S, Rattarasarn C, Cryer PE (1994) Reversal of hypoglycemia unawareness, but not defective glucose counterregulation, in IDDM. Diabetes 43:1426–1434
19. Chow E, Bernjak A, Williams S et al (2014) Risk of cardiac arrhythmias during hypoglycemia in patients with type 2 diabetes and cardiovascular risk. Diabetes 63:1738–1747
20. Pistrosch F, Ganfacz X, Bornstein SR, Birkenfeld AL, Henkel E, Hanefeld M (2015) Risk of and risk factors for hypoglycemia and associated arrhythmias in patients with type 2 diabetes and cardiovascular disease; a cohort study under real world conditions. Acta Diabetol 52:889–895
21. Bonds DE, Miller ME, Bergenstal RM et al (2010) The association between symptomatic, severe hypoglycaemia and mortality in type 2 diabetes: retrospective epidemiological analysis of the ACCORD study. BMJ 340:b4909
22. Outcomes Reduction with an Initial Glargine Intervention (ORIGIN) Investigators (2013) Does hypoglycemia increase the risk of cardiovascular events? A report from the ORIGIN trial. Eur Heart J 34:3137–3144
23. Normoglycemia in Intensive Care Evaluation—Survival Using Glucose Algorithm Regulation (NICE-SUGAR) Investigators (2012) Hypoglycemia and risk of death in critically ill patients. N Engl J Med 367:1108–1118
24. International Hypoglycemia Study Group (2015) Minimizing hypoglycemia in diabetes. Diabetes Care 38:1583–1591