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

*International Hypoglycaemia Study Group**

Diabetes Care 2017;40:155–157 | DOI: 10.2337/dc16-2215

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 hypoglycemia, be included in reports of clinical trials of glucose-lowering drugs evaluated for the treatment of diabetes mellitus.

The glycemic thresholds for symptoms of hypoglycemia and for glucose counterregulatory (including sympathoadrenal) responses to hypoglycemia, 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 glycemic control and at lower glucose concentrations in those with tight glycemic control (1–5). The shifts in glycemic threshold to lower glucose concentrations are largely the result of more frequent episodes of iatrogenic hypoglycemia during intensive glycemic therapy. Glycemic thresholds for responses to hypoglycemia vary, not only among individuals with diabetes but also in the same individual with diabetes as a function of their HbA_{1c} levels and hypoglycemic experience; it is therefore not appropriate to cite a specific glucose concentration that defines hypoglycemia in diabetes. As a consequence, the American Diabetes Association has defined hypoglycemia in diabetes nonnumerically 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 hypoglycemia 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 hypoglycemia, 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 minutes), or a laboratory measurement of plasma glucose. Both of these levels are distinctly low glucose concentrations that do not occur under physiological conditions in nondiabetic individuals (8). Thus, they are unequivocally hypoglycemic values. They approximate the upper and lower limits, respectively, of the nondiabetic glycemic threshold for symptoms of insulin-induced hypoglycemia (8–10). The generic nondiabetic glycemic threshold for impairment of cognitive

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This position statement was reviewed and approved by the American Diabetes Association Professional Practice Committee in September 2016 and ratified by the American Diabetes Association Board of Directors in October 2016.

**Members of the International Hypoglycaemia Study Group are listed in the APPENDIX.*

This article is being simultaneously published in Diabetes Care *and* Diabetologia *by the American Diabetes Association and the European Association for the Study of Diabetes.*

Table 1—Proposed glucose levels when reporting hypoglycemia 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 hypoglycemia
Level 3
Severe hypoglycemia, as defined by the ADA (6,7), denotes severe cognitive impairment requiring external assistance for recovery

function is <2.8 mmol/L (<50 mg/dL) (8–10), but higher glucose levels have been reported for some tests (11–14). Glucose concentrations of both <3.0 mmol/L (<54 mg/dL) and <2.8 mmol/L (<50 mg/dL) cause defective glucose counterregulation and impaired awareness of hypoglycemia, the core components of hypoglycemia-associated autonomic failure in diabetes (5). Avoiding these glucose levels could reverse impaired awareness of hypoglycemia (15–18), and some aspects of defective glucose counterregulation (15–17), in many affected patients. In type 1 diabetes, failure to recognize one's own hypoglycemia at a glucose concentration <3.0 mmol/L (54 mg/dL) increased the risk of severe hypoglycemia (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 (<50 mg/dL) 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 Outcome 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 (<54 mg/dL) 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 hypoglycemia. Possible terms used to describe this condition include "serious," "clinically important," "major," or "clinically significant." The group decided not to describe "severe hypoglycemia" in terms of glucose concentration since there is currently widespread agreement that severe hypoglycemia, 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 hypoglycemic risk (Table 1).

Funding. The International Hypoglycaemia Study Group (IHSG) is supported through an unrestricted educational grant from Novo Nordisk awarded to Six Degrees Academy (SDA) of Toronto, Ontario, Canada. Along with the IHSG chair, SDA has been solely responsible for membership recruitment/selection and content/outcomes for the meetings. The rationale for the formation of IHSG is that hypoglycemia is an under-recognized problem that deserves increased awareness and focus across the health care community. The group's ultimate goal is to improve the lives of patients with diabetes.

Duality of Interest. P.A. 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. B.C. has had research grant support from Halozyme and Lilly to the former MidAmerica Diabetes Associates. P.E.C. has served on scientific advisory boards for Novo Nordisk. B.E.d.G. has served on scientific advisory boards for Novo Nordisk and Sanofi and received research grant support from AstraZeneca. S.R.H. 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 U.K. Ltd. B.M.F. has served on scientific advisory boards and as a speaker for Boehringer Ingelheim, Janssen, Merck Sharp & Dohme, Novo Nordisk, and Lilly. L.G.-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. T.J. has served as a speaker for Novo Nordisk, Lilly, Medtronic, and Sanofi. K.K. 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. L.A.L. 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. R.J.M. has served on scientific advisory boards for Novo Nordisk and Sanofi. E.R.S. has undertaken consultancy for Sanofi, Novo Nordisk, Lilly, Locemia, and Medtronic and received grant support from Lilly. R.V. is an employee and owns stock in Medtronic Inc. S.Z. 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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