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St. Michael's Hospital Research Ethics Board Guidance Document for Reviewing Clinical Trials in Diabetes

1.0 Introduction

This document provides guidance for members of the Research Ethics Board (REB) at St. Michael's Hospital who are reviewing clinical trials in diabetes. This guidance is intended to ensure a consistent approach in the REB review of such trials, and should be used by investigators when they are preparing their REB submissions.

Each section is organized into three parts:

1) Summary of the clinical trial evidence supporting the 2013 Canadian Diabetes Association (CDA) Clinical Practice Guideline statement
2) CDA guideline statement
3) Guidance for the REB.

Trials that meet the guidelines will generally be considered acceptable by the REB. Trials that do not meet these guidelines will require compelling rationale to gain REB approval.

The 2013 CDA Guidelines includes the following statements with respect to research:

"Canada continues to be a world leader in diabetes research. This research is essential for continued improvement in the lives of people with diabetes. Regulatory agencies should not apply these guidelines in a rigid way with regard to clinical research in diabetes. It is suggested that study protocols may include guideline recommendations, but individual decisions belong in the domain of the patient physician relationship. The merits of each research study must be assessed individually so as to not block or restrict the pursuit of new information. The Canadian Diabetes Association welcomes the opportunity to work with regulatory agencies to enhance research in Canada and, ultimately, to improve the care of people with diabetes." [Reference 4: Canadian Diabetes Association 2013 Clinical Practice Guidelines]

2.0 Blood glucose levels above currently recommended targets during a clinical trial:

2.1 *Background*: "There is compelling evidence from randomized controlled studies that improved glycemic control reduces the risk of microvascular complications but has no significant effect on macrovascular outcomes in recently diagnosed type 1 and type 2 diabetes, as well as more long-standing type 2 diabetes)." [Reference 4: Canadian Diabetes Association 2013 Clinical Practice Guidelines]

Microvascular complications of diabetes are retinopathy, nephropathy and neuropathy. Macrovascular complications are CAD (coronary artery disease), PAD (peripheral artery disease) and CVD (cerebrovascular disease).

"Contrasting results from recent studies should not discourage physicians from controlling blood glucose levels. Intensive glucose control, lowering A1C values to ≤7% in both type 1 and type 2 diabetes, provides strong benefits for microvascular complications and, if achieved early in the disease, might also provide a significant macrovascular benefit, especially as part of a multifactorial treatment approach. More intensive glucose control, A1C ≤6.5%, may be sought in patients with a shorter duration of diabetes, no evidence of significant CVD and longer life expectancy, provided this does not result in a significant increase in hypoglycemia. An A1C target <8.5% may be more appropriate in type 1 and type 2 patients with limited life expectancy, higher level of functional dependency, a history of severe hypoglycemia, advanced comorbidities, and a failure to attain established glucose targets despite treatment intensification." [Reference 4: Canadian Diabetes Association 2013 Clinical Practice Guidelines]

2.2 CDA Guidelines:

RECOMMENDATIONS

"1. Glycemic targets should be individualized based on age, duration of diabetes, risk of severe hypoglycemia, presence or absence of cardiovascular disease, and life expectancy [Grade D, Consensus].

2. Therapy in most individuals with type 1 or type 2 diabetes should be targeted to achieve an A1C ≤7.0% in order to reduce the risk of microvascular [Grade A, Level 1A] and, if implemented early in the course of disease, macrovascular complications [Grade B, Level 3].

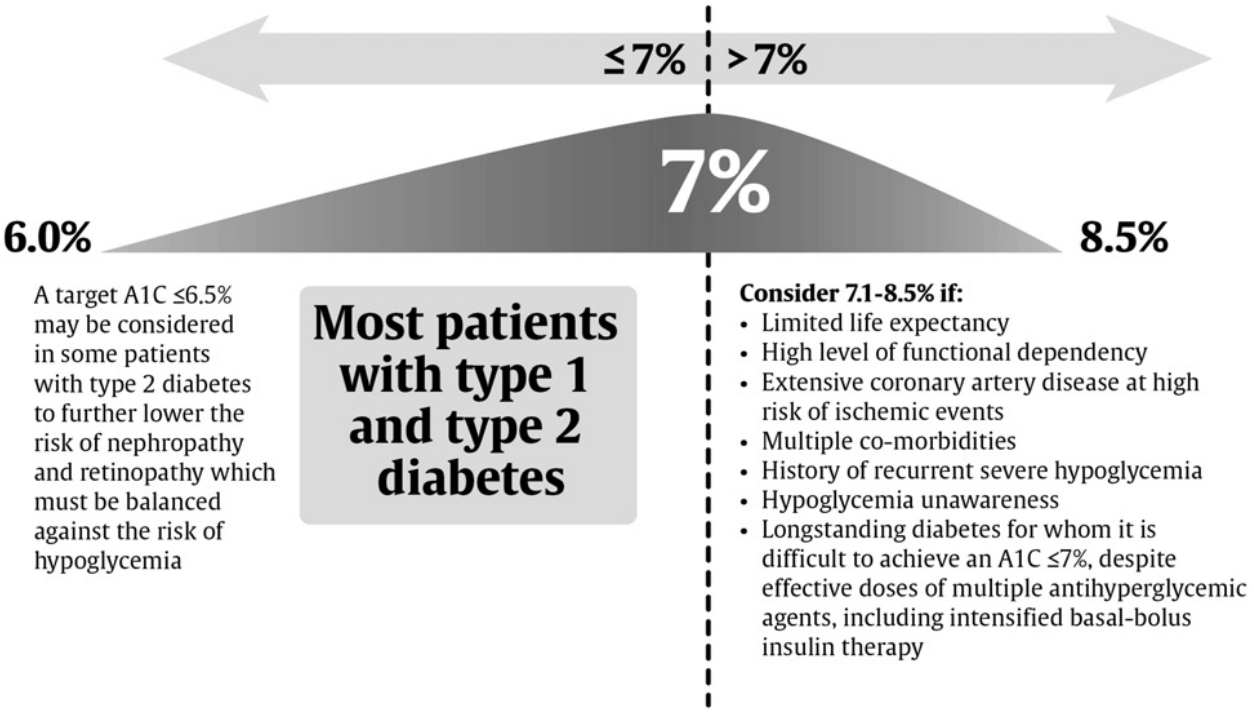
3. An A1C ≤6.5% may be targeted in some patients with type 2 diabetes to further lower the risk of nephropathy [Grade A, Level 1] and retinopathy [Grade A, Level 1, but this must be balanced against the risk of hypoglycemia [Grade A, Level 1].

4. Less stringent A1C targets (7.1%-8.5% in most cases) may be appropriate in patients with type 1 or type 2 diabetes with any of the following [Grade D,
Consensus]:
a) Limited life expectancy
b) High level of functional dependency
c) Extensive coronary artery disease at high risk of ischemic events
d) Multiple comorbidities
e) History of recurrent severe hypoglycemia
f) Hypoglycemia unawareness
g) Longstanding diabetes for whom it is difficult to achieve an A1C ≤7.0% despite effective doses of multiple antihyperglycemic agents, including intensified basal-bolus insulin therapy

5. In order to achieve an A1C ≤7.0%, people with diabetes should aim for:

FPG or preprandial PG target of 4.0-7.0 mmol/L and a 2-hour PPG target of 5.0-10.0 mmol/L [Grade B, Level 2 for type 1; Grade B, Level 2 for type 2 diabetes].

If an A1C target ≤7.0% cannot be achieved with a PPG target of 5.0-10.0 mmol/L, further PPG lowering to 5.0-8.0 mmol/L should be achieved [Grade D, Consensus, for type 1 diabetes; Grade D, Level 4 for type 2 diabetes]." [Reference 4: Canadian Diabetes Association 2013 Clinical Practice Guidelines]



[Reference 4: Canadian Diabetes Association 2013 Clinical Practice Guidelines. Chapter 8]

3.0 Participants not receiving metformin as first line therapy in the management of hyperglycemia in Type 2 Diabetes during a clinical trial:

*3.1 Background: "*The recommendation to use metformin as the initial agent in most patients is based on its effectiveness in lowering blood glucose, its relatively mild side effect profile, its long-term safety track record, its negligible risk of hypoglycemia and its lack of causing weight gain. The demonstrated cardiovascular benefit in overweight patients is also cited as a reason to select metformin as first-line treatment but more recent evidence has been equivocal on this matter.

3.2 CDA Guidelines:

1. In people with type 2 diabetes, if glycemic targets are not achieved using lifestyle management within 2 to 3 months, antihyperglycemic agent therapy should be initiated [Grade A, Level 1A]. Metformin may be used at the time of diagnosis, in conjunction with lifestyle management (Grade D, Consensus).

    i. If A1C ≥ 8.5%, antihyperglycemic agents should be initiatedconcomitantly with lifestyle management, and consideration should be given to initiating combination therapy with 2 agents,one of which may be insulin (Grade D, Consensus).

    ii. Individuals with symptomatic hyperglycemia and metabolic decompensation should receive an initial antihyperglycemic regimen containing insulin [Grade D, Consensus].

2. Metformin should be the initial drug used [Grade A, Level 1A for overweight patients; Grade D, Consensus for nonoverweight patients].

3. Other classes of antihyperglycemic agents, including insulin, should be added to metformin, or used in combination with each other, if glycemic targets are not met, taking into account the information in Figure 1 and Table 1 [Grade D, Consensus], and these adjustments to and/or additions of antihyperglycemic agents should be made in order to attain target A1C within 3 to 6 months [Grade D, Consensus].

4. Choice of pharmacological treatment agents should be individualized, taking into consideration [Grade D, Consensus]:

- Patient characteristics:
    - Degree of hyperglycemia
    - Presence of comorbidities
    - Patient preference and ability to access treatments

- Properties of the treatment:
    - Effectiveness and durability of lowering BG
    - Risk of hypoglycemia
    - Effectiveness in reducing diabetes complications
    - Effect on body weight
    - Side effects
    - Contraindications"

[Reference 4: Canadian Diabetes Association 2013 Clinical Practice Guidelines]

3.3 *Guidance:* Participants entering a trial where metformin is not used as initial therapy for the treatment of hyperglycemia should be informed of its recommended place in therapy and the reasons for this in the consent form. In addition, clinicians should be given the option of prescribing metformin to those participants they feel would benefit.

3.3.1. *Example of consent form wording:* "Current guidelines from the Canadian Diabetes Association recommend that metformin should generally be the initial medication used to lower blood sugar levels in most persons with Type 2 diabetes because of long experience with it and its excellent safety record with minimal risk for hypoglycemia (low blood sugar) or weight gain. If you are not already on metformin, you should feel free to ask your doctor about metformin (although there are appropriate reasons why some persons with diabetes are not on metformin)."

References

1. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med. 1993;329:977-986.

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3. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet. 1998;352:837-853.

4. Canadian Diabetes Association Clinical Practice Guidelines Expert Committee. Canadian Diabetes Association 2013 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada. Can J Diabetes 2013;37(suppl 1):S1-S212. http://guidelines.diabetes.ca/

5. Guidance for Industry: Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention- Draft Guidance by the U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research, February 2008.

6. Health Canada Standards for Clinical Trials in Type 2 Diabetes in Canada Guidance Document, November 2007.

7. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). The Lancet.1998;352:854-865.

8. Boussageon R, Supper I, Bejan-Angoulvant T, et al. Reappraisal of metformin efficacy in the treatment of type 2 diabetes: a meta-analysis of randomized controlled trials. PLoS Med 2012;9:e1001204.