CLINICAL GUIDELINE

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Medicines for Treatment Intensification in Type 2 Diabetes and Type of Insulin in Type 1 and Type 2 Diabetes in Low-Resource Settings: Synopsis of the World Health Organization Guidelines on Second- and Third-Line Medicines and Type of Insulin for the Control of Blood Glucose Levels in Nonpregnant Adults With Diabetes Mellitus

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Description: The World Health Organization developed these guidelines to provide guidance on selection of medicines for treatment intensification in type 2 diabetes and on use of insulin (human or analogue) in type 1 and 2 diabetes. The target audience includes clinicians, policymakers, national diabetes program managers, and medicine procurement officers. The target population is adults with type 1 or 2 diabetes in low-resource settings in low- or high-income countries. The guidelines also apply to disadvantaged populations in high-income countries.

Methods: The recommendations were formulated by a 12-member guideline development group and are based on high-quality systematic reviews identified via a search of several bibliographic databases from 1 January 2007 to 1 March 2017. The GRADE (Grading of Recommendations Assessment, Development and Evaluation) system was used to assess the quality of the evidence and the strength of the recommendations. The guideline was peer-reviewed by 6 external reviewers.

Recommendation 1: *Give a sulfonylurea to patients with type 2 diabetes who do not achieve glycemic control with metformin alone or who have contraindications to metformin (strong recommendation, moderate-quality evidence).*

Recommendation 2: *Introduce human insulin treatment to patients with type 2 diabetes who do not achieve glycemic control with metformin and/or a sulfonylurea (strong recommendation, very-low-quality evidence).*

Recommendation 3: *If insulin is unsuitable, a dipeptidyl peptidase-4 (DPP-4) inhibitor, a sodium–glucose cotransporter-2 (SGLT-2) inhibitor, or a thiazolidinedione (TZD) may be added (weak recommendation, very-low-quality evidence).*

Recommendation 4: *Use human insulin to manage blood glucose in adults with type 1 diabetes and in adults with type 2 diabetes for whom insulin is indicated (strong recommendation, low-quality evidence).*

Recommendation 5: *Consider long-acting insulin analogues to manage blood glucose in adults with type 1 or type 2 diabetes who have frequent severe hypoglycemia with human insulin (weak recommendation, moderate-quality evidence for severe hypoglycemia).*

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Globally, more than 400 million adults are living with diabetes (1), and the disease directly caused 1.6 million deaths in 2015. Blood glucose management has an important role in preventing the development and progression of complications in both type 1 and type 2 diabetes. Economically disadvantaged populations experience greater adverse consequences of diabetes and have much higher chances of incurring catastrophic personal medical expenses than persons without diabetes, particularly in places where the health system requires user fees or is based on private insurance. Diabetes also imposes a large economic burden on health care systems and national economies.

Recent years have brought a better understanding of the pathophysiologic mechanisms of type 2 diabetes, and new medicines for glycemic control have been developed. The 2013 World Health Organization (WHO) guidelines for low-resource settings recommended metformin for first-line treatment of type 2 diabetes, sulfonylureas for second-line treatment, and human insulin for third-line treatment (2). New oral medicines and insulins are currently being intensively marketed globally and are recommended for treatment intensification in guidelines from high-income countries.

One of WHO's core functions is to provide technical guidance for a broad range of public health problems that is intended for a global audience but focuses on low- and middle-income countries, where technical expertise and financial resources are often lacking. The public health approach in WHO guidelines addresses the health needs of a population rather than focusing primarily on individual patients. In the context of diabetes management, this approach aims to ensure the widest possible access to services and medicines at the population level and to strike a balance between implementing the best-established standard of care and what is feasible on a large scale in resource-limited settings.

The guidelines had 2 objectives. The first was to consider the use of dipeptidyl peptidase-4 (DPP-4) inhibitors, sodium–glucose cotransporter-2 (SGLT-2) inhibitors, thiazolidinediones (TZDs), and insulin as

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second- and third-line treatment for control of hyperglycemia in nonpregnant adults with type 2 diabetes after failure of metformin and sulfonylureas. Glucagon-like peptide-1 analogues were not considered because they are infrequently available in low-income countries. The second objective was to provide guidance on use of insulin analogues for type 1 and 2 diabetes. Only insulin analogues for which trial comparisons with human insulin were available were considered. These guidelines (3) update earlier WHO recommendations on second- and third-line treatment by reviewing newer medicines that are most frequently marketed in low- and middle-income countries (2). The target audience includes anyone implementing a public health approach to diabetes care in low-resource settings, including clinicians, policymakers, national diabetes program managers, and medicine procurement officers. The target patient population is nonpregnant adults with type 1 or 2 diabetes in low-resource settings.

Guideline Development and Review Process

WHO has standard methods and a quality assurance process to ensure that all of its guidelines meet the highest international standards. The topic was selected on the basis of specific requests from policymakers and diabetes program managers from several low- and middle-income countries. The work was coordinated by an internal WHO steering group, and the scope, key questions, outcomes, and recommendations were formulated by an ad hoc panel of 12 experts who were selected to encompass a broad range of expertise and experiences, to consider the patient's perspective, and to provide global representation. The recommendations are based on evidence from systematic reviews of randomized controlled trials (4–8) judged to be of high quality using AMSTAR (A Measurement Tool to Assess Systematic Reviews) (9) and identified through searches of PubMed, Embase, the Cochrane Library, PROSPERO, and the National Guideline Clearinghouse from 1 January 2007 to 1 March 2017. The GRADE (Grading of Recommendations Assessment, Development and Evaluation) system was used to assess the quality (certainty) of the evidence (10). An explicit evidence-to-decision framework was used to formulate the recommendations on the basis of the balance of benefits and harms and other considerations, including feasibility, acceptability, resource use, and the potential effect of the intervention on equity across populations. The guideline was peer-reviewed by 6 reviewers, predominantly from low- and middle-income countries. The WHO process for identification and management of potential conflicts of interest was followed (11).

Recommendation Relating to Second-Line Treatment of Type 2 Diabetes

Recommendation 1: Give a sulfonylurea to patients with type 2 diabetes who do not achieve glycemic control with metformin alone or who have contraindications to metformin (strong recommendation, moderate-quality evidence).

When added to metformin, the evaluated hypoglycemic agents produced similar and statistically significant improvements in hemoglobin A_{1c} (HbA_{1c}) level. The mean increase in HbA_{1c} level with placebo ranged from 0.58% to 0.85% compared with active agents (moderate-quality evidence). The agents had a similar effect on HbA_{1c} level when compared with each other, except DPP-4 inhibitors, which increased HbA_{1c} level by a mean of 0.12% (95% credible interval [CrI], 0.01% to 0.24%) compared with sulfonylureas and 0.19% (CrI, 0.05% to 0.33%) compared with TZDs. Risk for severe hypoglycemia was lower with DPP-4 inhibitors (odds ratio [OR], 0.14 [CrI, 0.07 to 0.26]) and SGLT-2 inhibitors (OR, 0.09 [CrI, 0.02 to 0.44]) than with sulfonylureas (moderate-quality evidence). Both DPP-4 inhibitors and SGLT-2 inhibitors were associated with modest weight loss, whereas TZDs and basal insulin were associated with weight gain. Evidence on other critical outcomes, such as quality of life and late complications, was either not available or of very low quality. In a separate analysis of a subgroup of patients at high risk for cardiovascular disease (CVD), there was no significant difference in CVD mortality (very-low-quality evidence).

The evaluated medications generally performed similarly for blood glucose lowering. Both DPP-4 inhibitors and SGLT-2 inhibitors conferred lower risk for severe hypoglycemia than sulfonylureas and promoted weight loss. However, data on absolute risk for severe hypoglycemia with sulfonylureas were sparse, and there were too few data on long-term patient-important outcomes in persons with diabetes who are not at high risk for CVD. Moreover, the price of these new oral agents is currently several times higher than that of human insulin in most markets. Therefore, the expert panel decided that recommending these new agents for universal use as second- or third-line treatment in resource-limited settings would be premature.

Recommendations Relating to Third-Line Treatment of Type 2 Diabetes

Recommendation 2: Introduce human insulin treatment to patients with type 2 diabetes who do not achieve glycemic control with metformin and/or a sulfonylurea (strong recommendation, very-low-quality evidence).

Recommendation 3: If insulin is unsuitable, a DPP-4 inhibitor, an SGLT-2 inhibitor, or a TZD may be added (weak recommendation, very-low-quality evidence).*

** Insulin could be unsuitable when circumstances make its use difficult (for example, in persons who live alone and depend on others to administer the injection).*

When added to metformin and a sulfonylurea, only insulin and TZDs statistically significantly decreased HbA_{1c} level compared with placebo (very-low-quality evidence). Both DPP-4 inhibitors (mean difference, −0.23 kg [95% CI, −0.46 to 0.00 kg]) and SGLT-2 inhib-

itors (mean difference, −0.33 kg [CI, −0.59 to −0.07 kg]) were associated with weight loss compared with TZDs (moderate-quality evidence). Data were insufficient for all other critical and important outcomes.

In persons with type 2 diabetes, there was no significant difference in HbA_{1c} level between glargine or detemir compared with neutral protamine Hagedorn (NPH) insulin (low-quality evidence). However, moderate-quality evidence showed fewer severe hypoglycemic events in persons treated with glargine (OR, 0.65 [CI, 0.49 to 0.88]) or detemir (OR, 0.37 [CI, 0.16 to 0.92]). Body weight was lower with detemir than with NPH insulin (mean difference, −1.26 kg [CI, −1.78 to −0.73 kg]) (high-quality evidence). Data on other critical and important outcomes were not available.

Recommendations Relating to Type of Insulin for Type 1 and 2 Diabetes

Recommendation 4: Use human insulin to manage blood glucose in adults with type 1 diabetes and in adults with type 2 diabetes for whom insulin is indicated (strong recommendation, low-quality evidence).*

Recommendation 5: Consider long-acting insulin analogues to manage blood glucose in adults with type 1 or type 2 diabetes who have frequent severe hypoglycemia with human insulin (weak recommendation, moderate-quality evidence for severe hypoglycemia).

** Recommendation 4 covers both short-acting (regular human insulin) and intermediate-acting (NPH insulin) human insulin.*

For persons with type 1 diabetes, the mean difference in HbA_{1c} level between short-acting insulin analogues and regular human insulin was −0.15% (CI, −0.20% to −0.10%) (low-quality evidence). Long-acting insulin analogues and human NPH insulin had similar effects on HbA_{1c} level (moderate-quality evidence). Both detemir and glargine reduced risk for severe hypoglycemia, but only the reduction with detemir was statistically significant (moderate-quality evidence). Data on other critical and important outcomes were not available.

The lower mean HbA_{1c} level in patients with type 1 diabetes treated with short-acting insulin analogues compared with those treated with regular human insulin was not considered clinically meaningful by the guidelines development group. Although there was moderate-quality evidence of reduced risk for severe hypoglycemia with long-acting detemir and glargine insulin analogues in both type 1 and type 2 diabetes and small weight loss with detemir in type 2 diabetes, the expert panel concluded that the relatively modest overall benefit from insulin analogues was outweighed by the large price difference between human insulin and insulin analogues. Thus, universal use of long-acting detemir and glargine insulin analogues is not recommended, although it can be justified in some circumstances, such as unexplained and frequent severe hypoglycemic events.

Discussion

Type 2 diabetes is highly prevalent in most settings, and the increase in prevalence has been greatest in low- and middle-income countries in the past few decades. These guidelines are intended for settings with limited health system resources where the health care budget can be quickly exhausted with widespread use of expensive brand-name medications. In such settings, patients frequently have to pay out of pocket for treatment. The guidelines also apply to high-income countries where patients with limited resources need evidence-based care that takes into account costs and value.

From World Health Organization, Geneva, Switzerland (G.R., S.L.N.).

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