



# Latest Trend for Standards of Medical Care in Diabetes

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## Abstract

American Diabetes Association (ADA) presents “the Standards of Medical Care in Diabetes-2022” on Jan 1, 2022. Metformin has been for long years strongly recommended as a first-line agent for type 2 diabetes mellitus (T2DM). In latest edition, metformin becomes not necessarily first-line, for atherosclerotic cardiovascular disease (ASCVD), heart failure or chronic kidney disease (CKD). For initial combination therapy, glucagon-like peptide 1 receptor agonists (GLP-1RAs) and sodium–glucose cotransporter 2 inhibitors (SGLT2i) can be applied. If eGFR is  $25 \text{ mL/min/1.73m}^2 <$  or urinary albumin is  $300 \text{ mg/gCr} <$ , SGLT2i is required to prevent CKD progression and to suppress cardiovascular risk.

**Keywords:** Standards of Medical Care in Diabetes-2022; American Diabetes Association (ADA); Atherosclerotic cardiovascular disease (ASCVD); Chronic kidney disease (CKD); Glucagon-like peptide 1 receptor agonists (GLP-1RAs); Sodium–glucose cotransporter 2 inhibitors (SGLT2i)

## Commentary Article

American Diabetes Association (ADA) presents “the Standards of Medical Care in Diabetes-2022” on Jan 1, 2022 [1]. The official comments were announced on the internet site in late December, 2021. This significant document has been positioned as a standard clinical practice guideline for diabetes in the United States (US) and revised annually for incorporating several new evidence.

When observing the current situation concerning diabetes, the prevalence of diabetes mellitus (DM) has been increased across the world for long period [2]. International Diabetes Federation (IDF) has contributed medical progress of diabetes and estimated that about one in two adult from 20 to 79 years population with diabetes are unaware of having diabetes status [3]. Then, adequate management for diabetes was recommended according to the previous standard guideline from several points of view [4].

For current ADA guideline-2022, some characteristic comments were found concerning the pharmacological treatment recommendation. One of the most popular oral hypoglycemic agents (OHAs) is metformin. It is finally stepped down from the only first-line medicine for T2DM [5]. Its reason includes the presence of the complication of atherosclerotic cardiovascular

disease (ASCVD). Until the guideline-2021, metformin has been strongly recommended as a first-line agent for T2DM as long as it is not contraindicated and tolerated [6]. On the other hand, latest 2022 edition states that i) first-line treatments basically include metformin and comprehensive lifestyle-related improvements, ii) it is changed to the recommendation of judgement for the situation due to actual diabetic complications, patient-centered medical factors, and current therapeutics [5].

What kind of medical situation can be found in the case that metformin is not the first-line agent? There are several recommended medical states when the patient has diabetic complications, such as present history of ASCVD, high-risk condition, heart failure or chronic kidney disease (CKD). In this regard, other medications can be appropriate for initial treatment for T2DM including glucagon-like peptide 1 receptor agonists (GLP-1RAs) and sodium–glucose cotransporter 2 inhibitors (SGLT2i), which are with/without metformin based on glycemic needs. This comment was estimated as level A evidence.

When the differences of ADA guidelines for 2021 and 2022 are investigated, some chapters were actually changed. Edition in 2021 revealed a chapter including diabetic microangiopathy and

**Received date:** 25 December 2021; **Accepted date:** 28 December 2021; **Published date:** 31 December 2021

**Citation:** Bando H (2021). Latest Trend for Standards of Medical Care in Diabetes. SunText Rev Endocrine Care 1(1): 106.

**DOI:** <https://doi.org/10.51737/endocrine.2021.006>

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foot care. In contrast, 2022 edition summarized for different chapters of "CKD and risk management" and "retinopathy, neuropathy, foot care". This indicates more important clinical significance of CKD and/or diabetic kidney disease (DKD) in recent diabetic practice and research. Latest guideline edition has introduction, 1-17 chapters and others [7]. Among them, 9<sup>th</sup>, 10<sup>th</sup> and 11<sup>th</sup> chapters have described Pharmacologic Approaches to Glycemic Treatment, Cardiovascular Disease and Risk Management, and Chronic Kidney Disease and Risk Management, respectively.

Recommended difference was observed for specific agent selection algorithms between 2021 and 2022. In 2021, metformin is the preferred initial pharmacologic agent for T2DM. In 2022, first-line therapy depends on some comorbidities. They include patient-centered factors, required management, metformin administration and comprehensive lifestyle modification [5]. In 9<sup>th</sup> chapter for pharmacologic approaches, impressive description is found. For beneficial clinical efficacy of metformin, Food and Drug Administration (FDA) in US revised the label for metformin to reflect its safety in patients who has their eGFR > 30 mL/min/1.73m<sup>2</sup> [8]. From a randomized trial report, metformin use may bring vitamin B<sub>12</sub> deficiency and exacerbation of neuropathy [9]. For combination therapy of metformin, longer durability was found for glycemic efficacy [10]. According to VERIFY (Vildagliptin Efficacy in combination with metformin for early treatment of type 2 diabetes) trial, initial combination treatment showed superiority to sequential medication addition for extending primary/secondary failure [11].

In recent practice for diabetes, some new class of non-insulin agents are observed. They include GLP-1RAs, SGLT2i, and dipeptidyl peptidase-4 inhibitors (DPP-4i). From meta-analysis for comparative effectiveness, these agents in addition to metformin as initial therapy could generally decrease HbA<sub>1c</sub> value about 0.7 to 1.0% successfully [12]. In addition to metformin-based background treatment, a systemic review and network meta-analysis research was conducted. As a result, greatest HbA<sub>1c</sub> decreases were observed with specific GLP-1RAs and insulin regimens [13]. There is recent remarkable pharmacologic progress concerning GLP-1 RA. As most GLP-1 RAs have been provided by injection, oral administration became possible in the case of semaglutide [14]. It is already commercially available with evidence of clinical efficacy by a series of PIONEER studies [15,16].

In order to obtain the reduction in risk of diabetes-related complications, comprehensive approach method is indispensable [17]. It is like constructing a robust building. As a concrete foundation plate, lifestyle modification and diabetes education are set in the ground. As a framework of four steel frames, 4 pillars of glycemic management, blood pressure management, lipid management and agents with cardiovascular and kidney benefit

are set upright. After that, broad roof can be put on 4 pillars, which indicates the reduction in diabetes complications. From these construction and maintenance, global risk reduction in diabetes will be expected [18].

As regards to CKD or DKD, some changes in recommendation were observed [19]. In the previous edition, considering SGLT2i was recommended for eGFR 30 mL/min/1.73 m<sup>2</sup> or higher and urinary albumin 300 mg/gCr or higher for T2DM with DKD. In contrast, latest edition describes as follow: if eGFR is 25 mL/min/1.73m<sup>2</sup> or more and urinary albumin is 300 mg/gCr or more, SGLT2i is required to prevent CKD progression and to suppress cardiovascular risk. Furthermore, a novel mineral corticoid receptor antagonist (MRA) as finerenone was described [20]. It can be given to the patients with high cardiovascular risk or risk of CKD progression who cannot tolerate SGLT2i, associated with the evidence level A [21].

In summary, latest information and news concerning ADA guideline-2022 was introduced. This article becomes hopefully a useful reference for diabetic practice.

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