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SPECIAL RESEARCH REPORT

A consensus statement from the Japan Diabetes Society: A proposed algorithm for pharmacotherapy in people with type 2 diabetes – 2nd edition (English version)

Ryotaro Bouchi[1]*†, Tatsuya Kondo[2†], Yasuharu Ohta[3†], Atsushi Goto[4], Daisuke Tanaka[5], Hiroaki Satoh[6], Daisuke Yabe[7], Rimei Nishimura[8], Norio Harada[5†], Hideki Kamiya[9†], Ryo Suzuki[10†], Toshimasa Yamauchi[11‡], JDS Committee on Consensus Statement Development

[1]Diabetes and Metabolism Information Center, Diabetes Research Center, National Center for Global Health and Medicine, Tokyo, Japan, [2]Department of Diabetes, Metabolism and Endocrinology, Kumamoto University Hospital, Kumamoto, Japan, [3]Division of Endocrinology, Metabolism, Hematological Sciences and Therapeutics, Yamaguchi University Graduate School of Medicine, Yamaguchi, Japan, [4]Department of Health Data Science, Graduate School of Data Science, Yokohama City University, Yokohama, Japan, [5]Department of Diabetes, Endocrinology and Nutrition, Graduate School of Medicine, Kyoto University, Kyoto, Japan, [6]Department of Diabetes and Endocrinology, Juntendo University Urayasu Hospital, Chiba, Japan, [7]Department of Diabetes, Endocrinology and Metabolism and Department of Rheumatology and Clinical Immunology, Gifu University Graduate School of Medicine, Gifu, Japan, [8]Division of Diabetes, Metabolism and Endocrinology, Jikei University School of Medicine, Tokyo, Japan, [9]Division of Diabetes, Department of Internal Medicine, Aichi Medical University, Nagakute, Japan, [10]Department of Diabetes, Metabolism and Endocrinology, Tokyo Medical University, Tokyo, Japan, and [11]Department of Diabetes and Metabolic Diseases, University of Tokyo Graduate School of Medicine, Tokyo, Japan

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***Correspondence**
Ryotaro Bouchi
Tel.: +81-3-3202-7181
Fax: +81-3-6228-0593
E-mail address:
rybouchi@hosp.ncgm.go.jp

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PREFACE

The Japan Diabetes Society (JDS) adopted a sweeping decision to release consensus statements on relevant issues in diabetes management that require updating from time to time and launched a 'JDS Committee on Consensus Statement Development'. In March 2020, the committee's first consensus statement on 'Medical Nutrition Therapy and Dietary Counseling for People with Diabetes' was published. In September 2022, a second consensus, 'algorithm for pharmacotherapy in people with type 2 diabetes', was proposed. In developing an algorithm for diabetes pharmacotherapy in people with type 2 diabetes, the working concept was that priority should be given to selecting such medications as would appropriately address the diabetes pathology in each patient while simultaneously weighing the available evidence for these medications and the prescribing patterns in clinical practice in Japan. These consensus statements are intended to present the committee's take on diabetes management in Japan, based on the evidence currently available for each of the issues addressed. It is thus hoped that practicing diabetologists will not fail to consult

†Committee member.
‡Chairperson.
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these statements to provide the best available practice in their respective clinical settings. Given that the persistent dual gastric inhibitor polypeptide (GIP)/glucagon-like peptide-1 (GLP-1) receptor agonist, tirzepatide, was approved in April 2023, these consensus statements have been revised[1].

In this revision, specifically, tirzepatide was added to the end of [likely involving insulin resistance] 'Obese patients' in Step 1: 'Select medications to address the diabetes pathology involved' in Figure 2. While the sentence, 'Insulin insufficiency and resistance can be assessed by referring to the various indices listed in the JDS "Guide to Diabetes Management"' was mentioned in the previous edition as well, 'While insulin resistance is analogized based on BMI, abdominal obesity, and visceral fat accumulation, an assessment of indicators (e.g., Homeostatic Model Assessment-Insulin Resistance) is desirable' was added as information to more accurately recognize the pathology. Regarding Step 2: 'Give due consideration to safety', 'For renal excretion' was added to the 'Rule of thumb 2: Avoid glinides in patients with renal impairment'. The order of the medications in 'rule of thumb 3: Avoid thiazolidinediones and biguanides in patients with heart failure (in whom they are contraindicated)' was changed to thiazolidinediones then biguanides. In the description of the lowest part of Figure 2, for each patient failing to achieve his/her glycated hemoglobin (HbA1c) control goal, 'while reverting to step 1' was changed to 'while reverting to the opening' and 'including reassessment if the patient is indicated for insulin therapy' was added. In the separate table, the column for tirzepatides was added, while the two items, 'Characteristic side effects' and 'Persistence of effect' were added to the area of interest.

The revision also carried additional descriptions of the figure and table, such as tirzepatides and 'Characteristic side effects' in the statement, and although not mentioned in the proposed algorithm figure, nonalcoholic fatty liver disease (NAFLD) is covered in this revision for patients with comorbidities calling for medical attention. Furthermore, detailed information was added to the relative/absolute indication for insulin therapy, the Kumamoto Declaration 2013 for glycemic targets and glycemic targets for older people with diabetes.

Again, in this revision, it is hoped that the algorithm presented here will not only contribute to improved diabetes management in Japan, but will continue to evolve into a better algorithm over time, reflecting new evidence as it becomes available.

CHARACTERISTICS OF TYPE 2 DIABETES IN THE JAPANESE AND ASIAN POPULATIONS

Type 2 diabetes is a metabolic disease in which insulin insufficiency or decreased insulin sensitivity (insulin resistance), combined with relatively decreased insulin action to varying degrees, accounts for such a lack of insulin action, which causes chronic hyperglycemia[2]. Again, multiple genetic factors responsible for insulin insufficiency or insulin resistance and environmental factors (e.g., overeating or lack of physical activity and resultant obesity) combine to lead to such lack of insulin action as to cause type 2 diabetes.

A comparison of insulin secretory capacity and insulin resistance between Western individuals and Japanese individuals stratified by glucose tolerance shows that Japanese individuals have less insulin secretory capacity than Westerners, even though their glucose tolerance is normal, and that although Western individuals show acutely increased insulin resistance as they move from normal glucose tolerance to diabetes, Japanese individuals tend to show lower insulin secretory capacity than that usually associated with increased insulin resistance[3,4]. Again, a study comparing insulin sensitivity and initial insulin response between East Asian, white and black individuals showed that these races vary in terms of the balance between their insulin-secretory capacity and insulin resistance, and that East Asian and black individuals are more susceptible to diabetes than white people[5]. The pathology of type 2 diabetes in the Japanese population is also shown to be characterized by decreased initial insulin response, regardless of the presence of obesity[6]. In contrast, a recent study in Hisayama-cho investigated the correlation between pancreatic β-cell failure (i.e., low insulinogenic index/Homeostatic Model Assessment-Insulin Resistance) or insulin resistance and the onset of type 2 diabetes, and found that although pancreatic β-cell failure and insulin resistance are both associated with the risk of type 2 diabetes, they are associated with a markedly increased risk of type 2 diabetes when they are found together in obese individuals[7].

In addition, histological studies of the pancreas have shown that, among non-diabetic Western individuals, obese individuals have a significantly greater islet mass than non-obese individuals, and that, among Western individuals with type 2 diabetes, both obese and non-obese individuals have an islet mass approximately 50% lower than that in non-diabetic individuals, and that no increase in pancreatic β-cell mass is noted, even in obese Japanese individuals[8,9]. Studies have also shown that among individuals with type 2 diabetes, amyloid deposition is noted in >80% of Western individuals, but in only 30% of Japanese individuals[10,11]. Thus, it is suggested that histological findings on the pancreas differ greatly between different races, suggesting that these differences might contribute to the differences in the pathogenesis of diabetes.

Additionally, advances in the genetic analysis of type 2 diabetes have led to the identification of numerous type 2 diabetes susceptibility loci, including KCNQ1[12–14]. A meta-analysis of genome-wide association studies in type 2 diabetes patients has recently shown that many Japanese individuals, but very few Western individuals, have the R131Q mutation in the GLP-1 receptor gene, which is known to be involved in inducing a twofold increase in insulin secretion. Furthermore, a cross-racial molecular biological pathway analysis showed that the pathways involved in the onset of maturity-onset diabetes of the young are the most strongly associated with type 2 diabetes in both races evaluated, and that the pathways involved in the

regulation of insulin secretion are significantly associated with type 2 diabetes only in Japanese individuals[15].

Taken together, the pathology of type 2 diabetes clearly differs between Japanese and Western individuals, not only functionally, but also histologically and genetically, with decreased insulin secretory capacity having a greater role in the onset of type 2 diabetes in Japanese individuals than in Western individuals.

DIFFERENCES IN TREATMENT STRATEGIES FOR JAPANESE AND WESTERN PEOPLE WITH TYPE 2 DIABETES

As detailed above, type 2 diabetes can be primarily characterized as having an underlying core pathology in most Japanese individuals, insulin resistance and insulin insufficiency, the respective contributions of which vary from individual to individual. In contrast to that, in Western individuals, core pathologies can be characterized as having obesity and insulin resistance. Owing to its ability to reduce the risk of microangiopathy, macroangiopathy and death, as well as its beneficial impact on bodyweight, low hypoglycemia risk and low cost[16,17], metformin has long been recommended as the first-line therapy in Western countries[18,19]. However, the Standards of Medical Care in Diabetes by the American Diabetes Association were extensively revised in 2022 to address compelling issues in diabetes management, such as diabetic comorbidities (e.g., atherosclerotic cardiovascular disease), patient-related factors in diabetes treatment and the therapeutic needs of affected individuals[20]. In contrast, the treatment strategy for type 2 diabetes in Japan is to allow for the choice of medications from all classes to address the diabetes pathology in each affected individual, while taking into account the extent of their metabolic derangement, their age, the extent of their obesity, the status of their insulin secretion/insulin resistance, the severity of their chronic complications and the status of their liver/renal function[21]. The rationale for this approach has indeed been provided through the accumulation of relevant evidence, including that from the Kumamoto study[22] and the Japan Diabetes Outcome Interventional Trial 3 (J-DOIT3)[23], which corroborated the importance of multifactorial intervention, including glycemic control, in reducing complications in Japanese people with diabetes.

INITIAL ANTIDIABETIC MEDICATION PRESCRIBING PATTERNS FOR PEOPLE WITH DIABETES JAPAN

It is not difficult to imagine how significantly such differences in treatment strategies for type 2 diabetes might impact the choice of medications or their prescription patterns. In this regard, although there are studies on antidiabetic medication prescribing patterns in Japan[24,25], they each suffered from a small sample size and lack of data from older people with diabetes, so a nationwide survey is needed to provide a full picture of the prescribing patterns in clinical practice. Thus, the JDS carried out a nationwide survey to clarify prescription patterns in clinical practice as a step in developing an algorithm for diabetes pharmacotherapy[26]. The survey showed that, among the more than 1 million people with type 2 diabetes registered with the National Database of Health Insurance Claims and Specific Health Check-ups from the latter half of the fiscal year 2014 to the fiscal year 2017, the most frequently prescribed antidiabetic medications were, unlike those in Western countries[27], dipeptidyl peptidase-4 (DPP-4) inhibitors, followed by biguanides and sodium–glucose cotransporter 2 (SGLT2) inhibitors, with age shown to be the factor most strongly influencing this prescribing pattern. Furthermore, the older the patients were, the more likely they were to have been prescribed DPP-4 inhibitors, and the markedly less likely they were to have been prescribed biguanides and SGLT2 inhibitors. An analysis of the initial prescription pattern by prefecture also showed that the biguanide and DPP-4 inhibitor prescriptions varied from prefecture to prefecture, while an analysis of the initial prescription pattern by facility (JDS-certified vs non-JDS-certified) showed that no patients receiving initial medication therapy had been initially prescribed biguanides at 38.2% of non-JDS-certified facilities, and that the DPP-4 inhibitor prescription pattern varied greatly between JDS-certified and non-JDS-certified facilities (i.e., there were considerable non-JDS-certified facilities where almost 100% of patients had been initially prescribed DPP-4 inhibitors alone). Thus, although survey results suggested that antidiabetic medications were being chosen to address the characteristics of diabetes in each individual patient, and that the JDS recommendations on the use of metformin and SGLT2 inhibitors[28,29] were widely adhered to by primary care physicians, there was a disparity in DPP-4 inhibitor and biguanide prescribing patterns between regions and facilities. In contrast, it is pointed out that there is a need to renew awareness of the JDS-proposed principle of medication choice for each patient based not only on the extent of their metabolic derangement, but also on their age, the extent of their obesity, the severity of their chronic complications, the status of their liver/renal function and the status of their insulin secretion/insulin resistance, Therefore, an algorithm needs to be developed as a tool to promote the appropriate use of antidiabetic medications.

WORKING CONCEPT OF AN ALGORITHM FOR PHARMACOTHERAPY IN PEOPLE WITH TYPE 2 DIABETES

Given that type 2 diabetes differs in pathology between Asian people, including Japanese and Western people, JDS has advanced a different treatment strategy for Japanese people from that for Western people. The survey results clearly show that the initial diabetes medication prescribing patterns differ greatly between Japan and Western countries[26], suggesting that the JDS-proposed treatment strategy for diabetes has become widespread among diabetologists and general practitioners. It is also likely that the initial diabetes medication prescription patterns reflected the informed use of antidiabetic medications, except imeglimin and tirzepatide, on the part of many

physicians, based on their glucose-lowering efficacy and safety profiles that became known after a certain amount of time after their approval. Furthermore, it became clear that the disparity in the prescribing patterns of DPP-4 inhibitors and biguanides between facilities and regions must be resolved to ensure the proper use of these medications. Given that evidence has recently been accumulated, mostly overseas, showing the efficacy of GLP-1 receptor agonists and SGLT2 inhibitors against diabetic comorbidities (i.e., atherosclerotic cardiovascular disease, heart failure [HF] and chronic kidney disease [CKD]), it has been suggested that these additional benefits (i.e., cardio-/renoprotective and mortality-reducing effects) are worth considering in medication selection for people with type 2 diabetes. Thus, overall, based on the basic concept (medications can be selected to address the diabetes pathology in Japanese and Asian people; the medication selection should reflect the prescribing patterns in clinical practice in Japan; and medications can be selected for their additional benefits in patients with comorbidities that call for medical attention), an algorithm for diabetes pharmacotherapy was developed to allow for such a choice of medications to address each patient's pathology/condition, with the priority in medication selection determined, with consideration given to current prescribing patterns and other relevant factors (Figure 1).

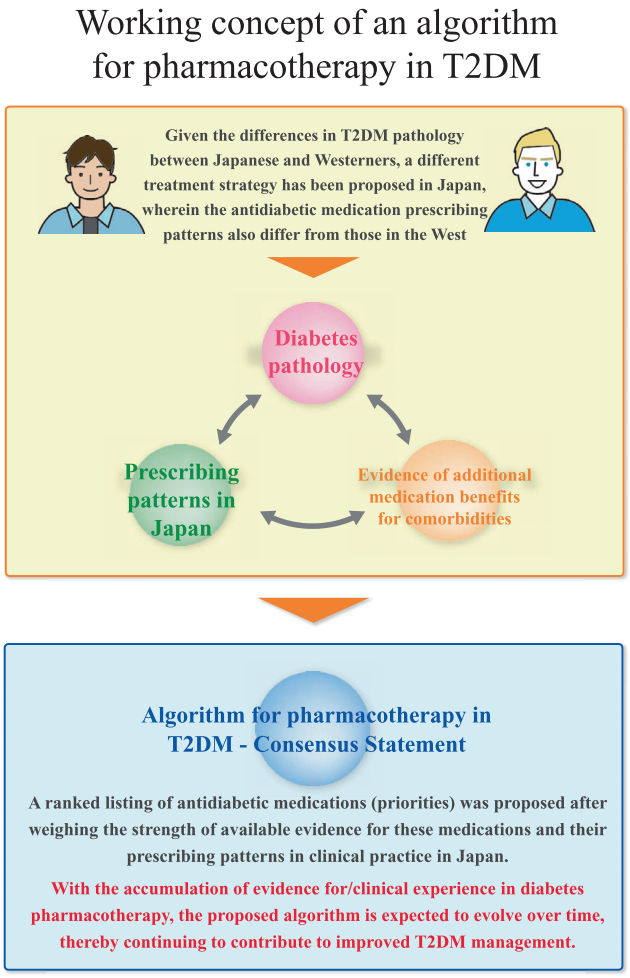

Figure 1 | Working concept of an algorithm for pharmacotherapy in type 2 diabetes (T2DM).

PROPOSED ALGORITHM ANNOTATED

Assessing the indications for insulin and determining the HbA1c control target

The overriding premise of diabetes pharmacotherapy is that it must be safe. Thus, medication selection was first assumed to involve assessing whether there were any absolute or relative indications for insulin therapy for each patient (Figure 2). Among the absolute/relative indications for insulin therapy, the absolute indications include: (1) an insulin-dependent state; (2) hyperglycemic coma (diabetic ketoacidosis, hyperosmolar hyperglycemic state); (3) patients complicated by severe hepatic disorder or renal impairment, severe infection or injury and moderate-to-severe surgery (such as under general anesthesia); (4) pregnant women with diabetes mellitus (including gestational diabetes, even when favorable glycemic control cannot be achieved by medical nutrition therapy); and (5) glycemic control during parenteral nutrition. Many of these pathologies require hospitalization; therefore, it is desirable to refer patients to diabetologists. Likewise, the relative indications include: (1) significant hyperglycemia (i.e., fasting blood glucose ≥250 mg/dL and casual blood glucose ≥350 mg/dL) is observed in non-insulin-dependent patients; (2) favorable glycemic control cannot be achieved by oral medication therapy alone; (3) nutritional status is compromised in lean patients; (4) severe hyperglycemia is recognized during steroid treatment; and (5) glucotoxicity is actively eliminated. As individuals aged ≥65 years account for more than half of all people with diabetes in Japan, the HbA1c control goal was determined based on those proposed in the Kumamoto Declaration 2013 and the JDS-proposed 'Glycemic targets (HbA1c values) for older people with diabetes'[21,30]. Based on the evidence in the Kumamoto Declaration 2013 in Japan, the Kumamoto Declaration 2013 proposed that although an HbA1c control goal of <7% was determined to prevent complications in people with diabetes and <6% for patients in whom a far greater goal is likely to be reached, a less strict control goal of <8% was determined for patients in whom strict control was arduous (i.e., patients with a high risk of hypoglycemia). 'Glycemic targets for older people with diabetes' recommend that glycemic targets (HbA1c values) for older people with diabetes be determined individually by activities of daily living, cognitive function, the presence or absence of comorbidities and use of medications associated with a high risk of severe hypoglycemia (insulin, sulfonylureas [SUs] and rapid-acting insulin secretagogues [glinides]). Detailed information on comorbidities, activities of daily living, cognitive function and medications used represents an important part of safe glycemic control, so consideration should be given to determining glycemic targets (HbA1c values).

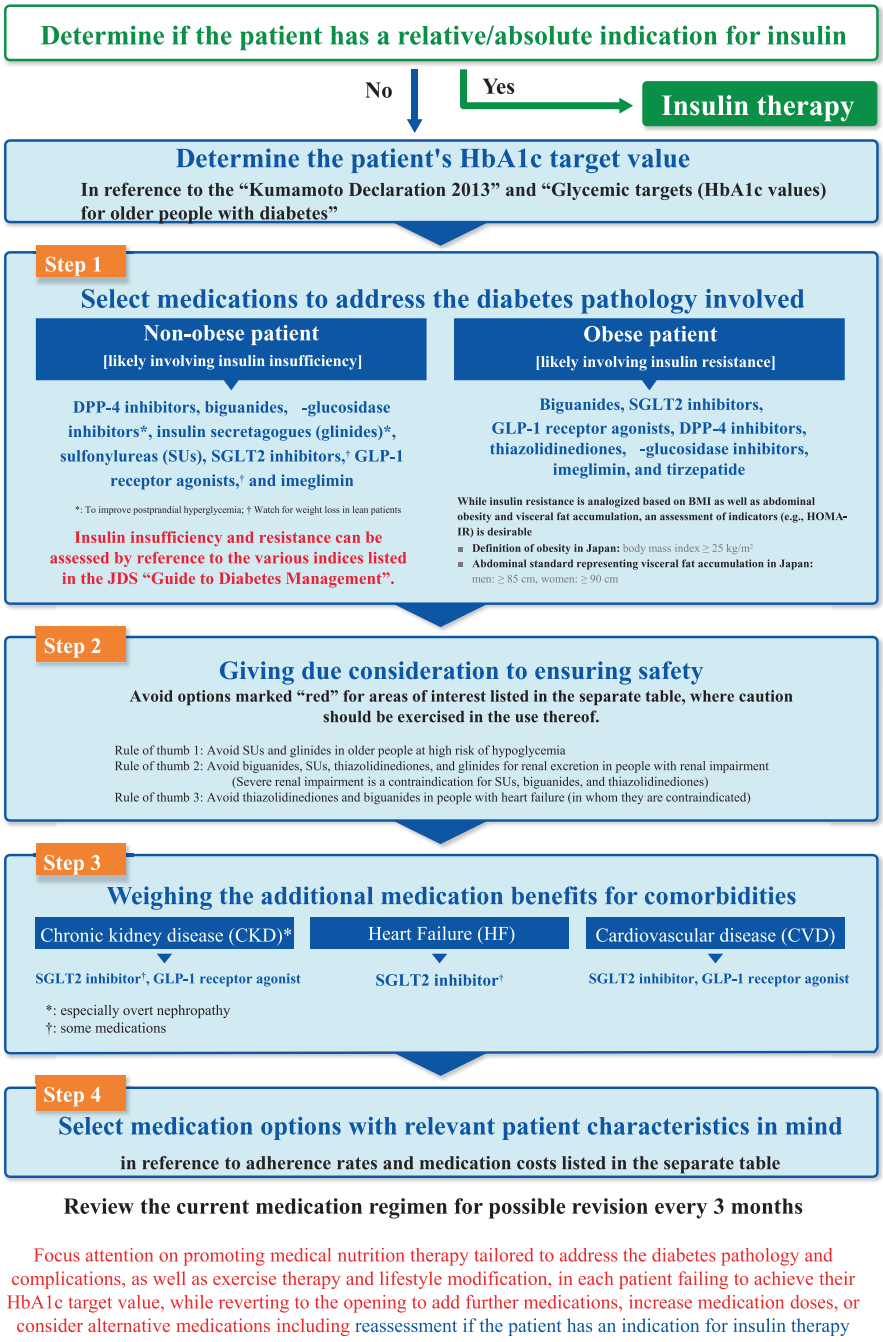

Figure 2 | Proposed algorithm for pharmacotherapy in type 2 diabetes. DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; HbA1c, glycated hemoglobin; HOMA-IR, Homeostatic Model Assessment-Insulin Resistance; JDS, Japan Diabetes Society; SGLT2, sodium–glucose cotransporter 2; SUs, sulfonylureas.

Assessing people with type 2 diabetes for the presence of obesity as a relevant measure (step 1)

The insulinogenic index or C-peptide index remains useful as a measure of insulin secretory capacity, and Homeostatic Model Assessment-Insulin Resistance remains useful as a measure of insulin resistance in people with diabetes. However, the sheer number of patients attending the hospital for type 2 diabetes makes it difficult in practical clinical practice to assess all patients using these indicators. Given that one of the important aims of the proposed algorithm is to guide the proper use of antidiabetic medications among non-experts, the presence or absence of obesity was adopted as the most convenient and

valid indicator that can reflect the core pathophysiology of diabetes to some extent. Thus, it is recommended that patients be assessed for obesity using the definition of obesity in Japan, body mass index (BMI) ≥25 kg/m^2 [31] when selecting medications for type 2 diabetes. Given that the extent of obesity (BMI) and insulin resistance are positively correlated[32], insulin resistance is assumed to have a greater contribution to type 2 diabetes in highly obese patients, prompting the choice of medications to address the pathology in question. It is important to note that the accumulation of visceral fat is often observed in Japanese and Asian people, including Japanese people, even if their BMI is much lower than that of obese Western people; therefore, insulin resistance might be associated with visceral fat accumulation in some of these patients, although they are usually categorized by BMI as non-obese[5,33,34]. It is assumed that patients can be accurately assessed for excessive visceral fat accumulation by assessing their BMI and waist circumference at the same time, and it is important to note that excessive visceral fat accumulation might be suspected in men with a waist circumference ≥85 cm, as well as in women with a waist circumference of ≥90 cm[31]. Candidate medications for patients with obesity include non-insulin secretagogues, such as biguanides, SGLT2 inhibitors and thiazolidinediones, as well as insulin secretagogues, such as GLP-1 receptor agonists with potential for weight-reducing effects, and imeglimin, for which obesity/insulin resistance is a good indication, given its insulin-sensitizing properties. The persistent dual GIP/GLP-1 receptor agonist, tirzepatide, approved in April 2023, has been shown to be extremely effective in Japanese patients for glycemic improvement, as well as highly potent dose-dependent weight reduction[35,36], suggesting a good indication in patients with obesity- and insulin resistance-based diabetes for glucose metabolism, as well as lipid metabolism, given its weight-reducing properties.

In most non-obese individuals with type 2 diabetes in whom insulin insufficiency is assumed to constitute the core pathology, insulin secretagogues should be selected as the mainstay of treatment. Of these, DPP-4 inhibitors remain the most frequently prescribed for people with type 2 diabetes in Japan, particularly older patients, probably reflecting the high expectations for their safety, even in the older patients[26]. DPP-4 inhibitors have been shown to exert a far greater glucose-lowering efficacy in Asian people than in other races[37,38], suggesting that non-obese people with type 2 diabetes are likely to be a good indication for this medication class in terms of safety and efficacy. Although numerous studies have been carried out in the hopes of reducing cardiovascular risk with DPP-4 inhibitors[39–41], some of them were reported to be associated with an increased risk of HF, thus calling for their judicious use in patients at a high risk of HF[42]. Of the insulin secretagogues, SUs are also of interest, because they are non-glucose-dependent insulin secretagogues and are associated with a high risk of hypoglycemia[43]. In contrast, glinides and α-glucosidase inhibitors are good medication candidates for patients showing marked postprandial hyperglycemia. Metformin has been shown to exert comparable HbA1c-lowering efficacy in both non-obese and obese Japanese people with type 2 diabetes, and thus represents an option for non-obese people with type 2 diabetes[44,45]. Non-obese patients might include older, emaciated patients (BMI <18.5 kg/m^2). Therefore, caution should be exercised when using antidiabetic agents with weight-loss properties; that is, GLP-1 receptor agonists and SGLT2 inhibitors, in lean patients, as they might increase the risk of geriatric syndromes, such as sarcopenia and frailty[17]. As aforementioned, in clinical trials of tirzepatide in Japanese people with type 2 diabetes, it has been clearly shown to be highly effective in weight reduction[35,36], although there is a paucity of data in patients with a BMI of <23 kg/m^2 or older patients; thus, tirzepatide was refrained from being named as a candidate medication in non-obese patients.

Giving due consideration to ensuring safety (step 2)

Note that the most desirable attribute required for antidiabetic medications is their ability to 'lower blood glucose safely'. Thus, the proposed algorithm has included a summary of their glucose-lowering potency relative to their efficacy, safety and risk of hypoglycemia, as well as precautions (particularly contraindications) for their use in patients with organ derangement (e.g., renal impairment, hepatic disorder [particularly cirrhosis], cardiovascular disorder and HF) and newly added characteristic side-effects in Table 1, with a running commentary on areas in which caution should be exercised in their use: (1) use in older patients taking SUs and glinides, both of which are associated with a high risk of hypoglycemia; (2) safety precautions in medication selection in patients with renal impairment, a highly common comorbidity in people with type 2 diabetes; and (3) medications contraindicated in patients with HF.

According to a network meta-analysis of the HbA1c-lowering efficacy of antidiabetic medications, GLP-1 receptor agonists are the most potent medications in lowering HbA1c, followed by metformin, pioglitazone and SUs[46]. It was also shown that metformin dose-dependently lowered glucose and exerted highly potent glucose-lowering effects at high doses, and that thiazolidinedione lowered glucose through its insulin-sensitizing effects on adipose tissue and skeletal muscle, indicating that it is more effective in obese patients. Tirzepatide is deemed to be a favorable choice in patients expecting to achieve normoglycemia, given that tirzepatide produces a greater reduction in HbA1c in Japanese people with type 2 diabetes than the GLP-1 receptor agonist, dulaglutide, with a high achievement rate of HbA1c <5.7%[35,36].

Safety against hypoglycemia remains the most important requirement for antidiabetic medications. As single agents, antidiabetic medications other than non-glucose-dependent SUs and glinides are generally associated with a low risk of hypoglycemia, whereas SUs are among the agents associated with a high risk of hypoglycemia. Indeed, according to a report from the JDS Committee on a Survey of Severe Hypoglycemia

Table 1 | Summary of the characteristics of antidiabetic medications for safe glycemic control: A comparison of glucose-lowering potency, hypoglycemia risk, contraindications, adherence rates and medication costs (A ranked listing of medications initially prescribed in Japan by frequency)

Areas of interest	DPP-4 inhibitors	Biguanides	SGLT2 inhibitors	Sulfonylureas	α-glucosidase inhibitors	Thiazolidinediones	Insulin secretagogues (glinides)	GLP-1 receptor agonists	Imeglimin	Tirzepatide
Glucose-lowering effect	Mid	High (dose-dependent)	Mid	High	Improvement in postprandial hyperglycemia	Mid (highly effective in obese patients)	Improvement in postprandial hyperglycemia	High	Mid	High
Risk of hypoglycemia (as single agents)	Low	Low	Low	High	Low	Low	Mid	Low	Low	Low
Impact on body weight	Neutral	Neutral to decrease	Decrease	Increase	Neutral	Increase	Increase	Decrease	Neutral	Decrease
Renal function	Dose reduction required for some renal excretion agents	Dose reduction required in patients with renal impairment Contraindicated in patients with severe renal impairment	No effect expected in patients with severe renal impairment	Caution required (hypoglycemia) Contraindicated in patients with severe renal impairment		Contraindicated in patients with severe renal impairment	Caution required (hypoglycemia) Nateglinide is contraindicated in patients with severe renal impairment	Exenatide is contraindicated in patients with severe renal impairment	Not recommended in patients with eGFR <45 mL/min/1.73 m^2	
Liver function	Vildagliptin is contraindicated in patients with severe hepatic disorder	Contraindicated in patients with severe hepatic disorder		Contraindicated in patients with severe hepatic disorder		Contraindicated in patients with severe hepatic disorder	Caution required (hypoglycemia)		No clinical trial in patients with severe hepatic disorder	
Cardiovascular disorder		Contraindicated in patients with hemodynamically unstable diseases, such as myocardial infarction		Contraindicated in patients with hemodynamically unstable diseases, such as myocardial infarction						
Heart failure	Some agents may increase the risk of HF	Contraindication				Contraindication				
Characteristic side-effects	Bullous pemphigoid Interstitial pneumonia	Digestive symptoms Lactic acidosis Vitamin B_{12} deficiency (for long-term use)	Urinary tract, genital infection Euglycemic diabetic ketoacidosis	Cytopenia Aplastic anemia	Hepatic disorder Digestive symptoms (especially abdominal distension)	Edema Lower bone density Risk of bladder cancer (for long-term use)	Hepatic disorder	Digestive symptoms Acute pancreatitis Gallstone Cholecystitis/cholangitis	Digestive symptoms	Digestive symptoms Acute pancreatitis Gallstone Cholecystitis/cholangitis
Adherence rate	High (particularly with once weekly dosing)	Mid (digestive symptoms etc.)	Mid (micturition, genital infection etc.)	Mid (weight gain, hypoglycemia etc.)	Low (route of administration, digestive symptoms etc.)	Mid (edema, hypoglycemia etc.)	Low (route of administration, hypoglycemia etc.)	Mid (injections, route of administration, digestive symptoms etc.)	Mid (digestive symptoms)	Mid (digestive symptoms)
Cost	Mid	Low	Mid to high	Low	Mid	Low	Mid	High	Mid	High
Persistence of effect (durability)	Low to mid	Mid	High	Low	Low	High		High		

BMI, body mass index; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; SGLT2, sodium–glucose cotransporter 2. *Note:* Blue letters and color formatting mean favorable effects such as high efficacy, high safety, high weight loss, and high adherence rates, while red letters and formatting mean the opposite for each.

Associated with Diabetes Treatment, patients treated with SUs accounted for approximately 30% of all patients treated with any antidiabetic medication who required emergency transportation for severe hypoglycemia (or ~85% of all patients treated with medications other than insulin therapy)[43]. A finding of particular interest from this survey is that older patients accounted for a large proportion of those transported for severe hypoglycemia, suggesting that caution should be exercised when using SUs in older patients.

The impact of antidiabetic medications on bodyweight is also particularly relevant to the correction of obesity and prevention of geriatric syndrome. SGLT2 inhibitors have been shown to be associated with a weight reduction of 2 kg compared with a placebo[17], suggesting their suitability for use in obese people with type 2 diabetes. GLP-1 receptor agonists are also shown to have weight-reducing effects, and are thus deemed suitable for use in obese people with type 2 diabetes. The reduction in bodyweight is reported to be 2 kg on average in patients treated with these medications compared with those treated with a placebo[17]. Of these, semaglutide was evaluated for its efficacy in Japanese people with type 2 diabetes in a recent study that showed that the medication was associated with a significant reduction in bodyweight (ranging 2–3 kg) at high doses[47,48]. The reduction in bodyweight by GLP-1 receptor agonists varies from agent to agent; therefore, patients requiring weight loss are likely to be more likely to use medications that are more effective in reducing weight (i.e., semaglutide). Miglitol, one of the α-glucosidase inhibitors, has been shown to be associated with weight reduction in obese Japanese people with type 2 diabetes[49]. Conversely, many studies reported a weight gain of approximately 2 kg in patients treated with SUs compared with patients treated with a placebo, whereas pioglitazone was shown to be associated with a weight gain of 1–4 kg[50], as well as edema. In Japanese people with type 2 diabetes and a BMI of ≥23 kg/m^2, 5, 10 and 15 mg tirzepatide produces a significant reduction in bodyweight compared with 0.75 mg of the GLP-1 receptor agonist, dulaglutide[35], whereas 5, 10 and 15 mg tirzepatide in the SURPASS-2 trials carried out overseas produced a significant reduction in bodyweight compared with the GLP-1 receptor agonist, semaglutide 1.0 mg[51]; Thus, tirzepatide is deemed the most effective medication in bodyweight reduction among existing antidiabetic medications. Its medication is a good indication in highly obese patients with type 2 diabetes. However, consideration needs to be given to the indication in non-obese patients (particularly lean patients) at the time of this review, as very few results were shown in Japanese patients with a BMI of <23 kg/m^2.

Caution should be exercised in the use of multiple antidiabetic medications in people with diabetes complicated by renal impairment. Given that most non-glucose-dependent insulin secretagogues (e.g., SUs and glinides) are renally excreted, their use is thought to be associated with an increased risk of hypoglycemia; therefore, SUs and nateglinide are both contraindicated for use in patients with renal impairment[43], whereas, as a glinide with biliary excretion, repaglinide is shown to be relatively safer for use in patients with renal impairment than other glinides. Mitiglinide has also been shown to be relatively safer for use in patients with renal impairment, as there is no glucose-lowering efficacy with metabolites. Metformin has been shown to be associated with an increased risk of lactic acidosis in patients with renal dysfunction, and is thus contraindicated in patients with estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2, but is acceptable for use at a daily maximum dose of 750 and 1,500 mg in those with eGFR of ≥30 mL/min/1.73 m^2 and <45 mL/min/1.73 m^2, and of ≥45 mL/min/1.73 m^2 and <60 mL/min/1.73 m^2, respectively[29]. Pioglitazone is available for use overseas, even in renally impaired patients, but is contraindicated for use in severely renally impaired patients in Japan. As their glucose-lowering efficacy is diminished in patients with renal impairment, SGLT2 inhibitors raise concerns over their failure to achieve adequate glucose lowering in severely renally impaired patients.

A severe hepatic disorder is a contraindication for biguanides, SUs and thiazolidinediones (despite being a relative indication for insulin therapy). Among all patients with cardiovascular disease (CVD), metformin is contraindicated for those with hemodynamic instability or HF, but not in Western countries (although still contraindicated in patients with hemodynamic instability or acute HF), based on the reports of reductions in the need for hospitalization due to HF and mortality risk with metformin[52–54]. According to a recent meta-analysis of observational studies investigating the association between metformin use and all-cause mortality in type 2 diabetes patients with congestive HF, as well as hospitalization for HF, a significant reduction was shown in mortality risk with metformin and hospitalization risk due to HF[55], suggesting significant prognostic findings for the use of metformin in people with type 2 diabetes complicated by HF with and without a reduced left ventricular ejection fraction[56,57]. Accumulation of safety evidence is awaited for the use of metformin in patients with compensated HF in Japan. Although thiazolidinediones are deemed a contraindication for patients with stage C or higher symptomatic HF, but not those with stage A and B, consideration should be given to their dose adjustment, salt restriction and concomitant use of diuretics for associated fluid retention.

The characteristic side-effects of each antidiabetic medication have been added to Table 1 as a further consideration for safety in the revision of the algorithm. This report outlines several characteristic adverse effects. Among autoimmune bullous diseases, bullous pemphigoid might occur after the initiation of DPP-4 inhibitors, although it occurs less frequently. Note here that bullous pemphigoid is likely to be a factor in septicemia and disseminated intravascular coagulation due to bacterial infection after systemic blisters and erosions[58]. Severe side-effects due to biguanides include lactic acidosis, reported mostly in patients complicated by severe renal dysfunction. Whereas, some cases of lactic acidosis were reported in non-older

patients with normal renal function, suggesting that caution should be exercised, especially in patients with dehydration or who drink alcohol heavily. In Japanese patients with long-term use, thiazolidinediones reduced bone density and increased the risk of bone fractures in women[59], and consideration should be given to its use in older women after menopause. Given that long-term use of thiazolidinediones might also be associated with an increased risk of bladder cancer (however, the incidence is remarkably low and increased risk is also small)[60–62], the use of thiazolidinediones should be avoided in patients with bladder cancer. The risk of bladder cancer should be explained at the initiation of thiazolidinediones, and periodic urinalysis should be carried out. Diseases at increased risk of developing with GLP-1 receptor agonists include gallstones, cholecystitis, cholangitis and cholestatic jaundice. Consideration should be given to its indication in patients with gallstones or a history of acute biliary tract infection. A meta-analysis of large-scale clinical trials did not show any increased risk of pancreatic cancer and pancreatitis[63]. It is important that patients receiving SGLT2 inhibitors be closely monitored for euglycemic diabetic ketoacidosis. SGLT2 inhibitors are expected to increase urinary glucose excretion, and lower blood glucose and insulin levels, leading to an increased glucagon/insulin ratio and hepatic glycogenesis/lipolysis in adipose tissue, thus resulting in increased use of lipids for energy metabolism. Therefore, SGLT2 inhibitors are associated with a risk of ketoacidosis due to an acute increase in ketone bodies, even in normoglycemic patients with underlying insulin insufficiency or during sick days. Also of interest are urinary tract and genital infections, among the characteristic side-effects of SGLT2 inhibitors, suggesting that consideration should be given to the high risk thereof[64]. Despite the paucity of data from Japan on the use of tirzepatide, its pharmacological properties are assumed to be associated with the risk of gallstones and acute biliary tract infection, as is the case with GLP-1 receptor agonists. Although the occurrence is low (<1%), a summary of side-effects, such as gallstones, acute biliary tract infection and acute pancreatitis, have been reported from abroad[65], and the risks need to be considered.

Weighing the additional medication benefits for comorbidities (step 3)

Given that numerous large-scale clinical trials carried out overseas have shown the efficacy of SGLT2 inhibitors and GLP-1 receptor agonists against CKD (particularly overt nephropathy), CVD and HF, the proposed algorithm included CVD, HF and CKD (particularly overt nephropathy) as target diseases for which antidiabetic medications might provide additional benefits. However, it should be noted that the algorithm draws mainly on the evidence available from overseas due to the paucity of data from Japan on this issue. These comorbidities appear to be a valid indication for the use of SGLT2 inhibitors and GLP-1 receptor agonists, with the caveat that the reduction seen in cardiovascular events in these trials might be accounted for in part by that in HbA1c[66]. Further studies are required to elucidate the mechanisms involved. According to a meta-analysis of recently approved tirzepatide, which assessed the safety of cardiovascular outcomes, tirzepatide did not increase the risk of major cardiovascular disease, all-cause mortality and cardiovascular death[67]. Although tirzepatide binds to GLP-1 and GIP receptors with strong affinity, *in vitro* studies have shown that the binding affinity of GIP receptors is similar to that of intrinsic GIP, whereas the binding affinity of the GLP-1 receptor is fivefold lower than that of intrinsic GLP-1. Thus, GIP is deemed to have a different pharmacological property from GLP-1 receptor agonists *in vivo*. Therefore, further studies are needed to elucidate whether tirzepatide could reduce cardiorenal events.

Weighing the additional benefit of antidiabetic medications for CVD

Large-scale clinical trials of SGLT2 inhibitors (i.e., EMPA-REG, CANVAS and DECLARE TIMI)[59] have been carried out in people with type 2 diabetes and CVD, or those with type 2 diabetes at a high risk of CVD with major adverse cardiovascular events (a composite of cardiovascular death, non-fatal myocardial infarction and non-fatal ischemic stroke) as the primary endpoint. They showed a significant reduction in major adverse cardiovascular events using these agents[68–70], with this finding also confirmed by independent meta-analyses of these trials[71,72]. Likewise, clinical trials of GLP-1 receptor agonists have been carried out (i.e., LEADER, SUSTAIN6 and Harmony), which show significant reductions in major adverse cardiovascular events[73–75]. The outcome was also confirmed by a meta-analysis[70]. Thus, while it should be noted that there is a paucity of data from trials in Japanese patients, and that Japanese people with diabetes are at lower risk of CVD than their Western counterparts, the evidence based on overseas trials is so numerous and of such high quality that SGLT2 inhibitors and GLP-1 receptor agonists were highly recommended in the order listed for their additional benefit against CVD.

Weighing the additional benefit of antidiabetic medications for HF

Assessing and treating HF is of vital importance, given that even asymptomatic people with type 2 diabetes are deemed to be in a state called 'pre-HF'; that is, at high risk of HF. In this regard, SGLT2 inhibitors (i.e., such as empagliflozin, canagliflozin and dapagliflozin) have been shown to be useful in the prevention of HF in clinical trials examining cardiovascular efficacy[68–70], with a similar finding shown in a subset analysis of Asian individuals[76]. In addition, a study that compared real-world evidence for SGLT2 inhibitors versus DPP-4 inhibitors in global populations, including Japanese and Korean populations, also confirmed the usefulness of SGLT2 inhibitors in preventing HF[77]. Furthermore, SGLT2 inhibitors have been shown in a clinical trial of HF people with or without type 2 diabetes showing heart failure with reduced ejection fraction to produce a significant reduction in HF aggravation and cardiovascular death[78,79], an outcome that was confirmed by a

meta-analysis[80]. SGLT2 inhibitors are also shown to produce a significant reduction in HF aggravation and cardiovascular death in people with or without type 2 diabetes showing heart failure with preserved EF[81,82]. SGLT2 inhibitors were included as first-choice medications in people with type 2 diabetes and HF.

In contrast, GLP-1 receptor agonists are not consistently shown to be useful in preventing HF in clinical studies evaluating their cardiovascular safety, but are nevertheless shown to be useful as a class in preventing HF in a meta-analysis[83]. However, their usefulness in the Japanese population remains unclear at the time of this review. The FIGHT trial evaluated the effect of liraglutide in patients with acute HF showing decreased left ventricular ejection fraction, and showed that, contrary to expectations, treatment with liraglutide increased the risk of HF in people with type 2 diabetes[84], suggesting the need to further investigate the usefulness of GLP-1 receptor agonists for various HF pathology or stage, as well as their respective mechanisms of action.

Weighing the additional benefit of antidiabetic medications for CKD (particularly overt nephropathy)

In subanalyses of data from people with type 2 diabetes and CVD or those at a high risk of CVD participating in cardiovascular safety trials, SGLT2 inhibitors (i.e., empagliflozin, canagliflozin and dapagliflozin) have been shown to be useful in reducing composite renal events[68–70]. Of note, reanalysis of the canagliflozin trial data using a rigorous composite endpoint (doubling of serum creatinine, end-stage renal failure and renal death) showed a significant reduction in the composite renal endpoint, as well as in renal dysfunction and albuminuria, with the medication[85]. In addition, findings from large-scale clinical trials have evaluated the usefulness of SGLT2 inhibitors (i.e., DAPA-CKD, CREDENCE and EMPA-kidney)[86–88]. Although the DAPA-CKD, CREDENCE and EMPA-Kidney trials involved different patient populations (CKD patients with or without type 2 diabetes, of whom those without type 2 diabetes accounted for 32.5% [eGFR 25–75 mL/min/1.73 m^2; urinary albumin/creatinine ratio (ACR) 200–5,000 mg/g], type 2 diabetes patients with CKD showing overt albuminuria [eGFR ≥30/<90 mL/min/1.73 m^2; urinary ACR 300–5,000 mg/g] and EMPA-Kidney patients [non-diabetic individuals 54.0%; eGFR ≥20/<45 mL/min/1.73 m^2 or eGFR ≥45/<90 mL/min/1.73 m^2 and urinary ACR, ≥200 mg/g], respectively), all studies showed a significant reduction in the composite renal endpoint. Interestingly, dapagliflozin was examined for its renoprotective effect by the primary cause of CKD in an exploratory analysis of the DAPA-CKD study data, which showed that despite there being no interaction between its renoprotective effect and any primary cause of CKD, the medication offered renoprotection to people with diabetic nephropathy[89]. Given that most patients in the DAPA-CKD and CREDENCE trials were shown to have overt albuminuria (urinary ACR ≥300 mg/g), it appears that the evidence of renoprotection with SGLT2 inhibitors remains nearly limited to people with type 2 diabetes having overt nephropathy. In light thereof, this algorithm noted that SGLT2 inhibitors should be considered as medications of first choice for patients with albuminuria (particularly overt nephropathy), regardless of their glucose-lowering effects, while not only SGLT2 inhibitors, but GLP-1 receptor agonists, should be considered for patients without albuminuria. It should also be noted that the renoprotective effect of SGLT2 inhibitors remains unclear in highly renally impaired patients (eGFR <20 mL/min/1.73 m^2).

Of the GLP-1 receptor agonists currently available, liraglutide has been shown to inhibit the onset of persistent overt albuminuria, thereby reducing the occurrence of a composite renal endpoint in a subset analysis of people with type 2 diabetes at a high risk of CVD treated with this medication[90]. Semaglutide has been shown to reduce the composite renal endpoint in people with type 2 diabetes at high risk of CVD[74], and dulaglutide inhibits the deterioration of eGFR, thereby significantly reducing albuminuria in people with type 2 diabetes showing eGFR ≥30/<60 mL/min/1.73 m^2[91]. GLP-1 receptor agonists have also been reported to reduce the composite cardiovascular endpoint (cardiovascular death, non-fatal myocardial infarction and non-fatal cerebral infarction) in people with type 2 diabetes with renal dysfunction (eGFR <60 mL/min/1.73 m^2)[92]. GLP-1 receptor agonists were recommended as medications of second choice in people with type 2 diabetes having albuminuria. Hence, in this algorithm, SGLT2 inhibitors and GLP-1 receptor agonists are worth considering for people with type 2 diabetes without albuminuria.

Weighing the additional benefit of antidiabetic medications for NAFLD

Although not mentioned in the proposed algorithm, NAFLD is covered by this revision as a comorbidity that requires medical attention. Given that NAFLD often occurs in people with type 2 diabetes, consideration should be given to selecting medications that are expected to be effective in improving NAFLD. According to the Evidence-based Clinical Guidelines for Nonalcoholic Fatty Liver Disease/Nonalcoholic Steatohepatitis 2020 (2nd Edition) from the Japanese Society of Gastroenterology, thiazolidinediones are recommended, as are SGLT2 inhibitors and GLP-1 receptor agonists[93]. Evidence in Japanese patients has been provided through some reports, suggesting a correlation between the blood concentration of pioglitazone or its metabolites and improvement of active NAFLD in hepatic tissue[94], and that SGLT2 inhibitors might improve histology of NAFLD[95–97]. Maturation of adipocytes, normalized adipokine and normalized energy influx[98,99] are deemed to contribute to NAFLD improvement by pioglitazone. Likewise, SGLT2 inhibitors are expected to reduce the hepatic glycogen content after reduced insulin concentration in the blood, promote oxidation of fatty acids and increase lipolysis of adipose tissue[100]. Overseas studies have also reported that of the GLP-1 receptor agonists with significant weight-reducing effects, semaglutide has

been shown to be effective in non-alcoholic steatohepatitis patients with histological improvement of non-alcoholic steatohepatitis without hepatic fibrosis aggravation[101]. The mechanisms include central nervous system-mediated reduction of food intake and bodyweight, suppression of hepatic lipid synthesis through decreased expression of fatty acid synthesis genes and inflammatory genes, and suppression of inflammatory cell infiltration.[102]. It has been shown that tirzepatide, a dual GLP-1/GIP receptor agonist, exerts highly potent weight-reducing dose-dependent effects in Japanese people with type 2 diabetes[35,36]. The weight-reducing rate of ≥7% is likely to be achieved with the potential for reduction in liver steatosis, inflammatory cells and ballooning of adipocytes at high doses. It is hoped that further clinical trials in Japanese people with type 2 diabetes will show the beneficial effects of GLP-1 receptor agonists and GLP-1/GIP receptor agonists on NAFLD.

Patient background to consider (step 4)

In this algorithm, the patient background that should be taken into account is the medication compliance rate and medical cost (Figure 2, Table 1). Given that medication adherence in people with type 2 diabetes has been shown not only to impact their glycemic control, but also to be associated with CVD morbidity, mortality and hospitalization risk, paying attention to maintaining medication adherence represents an extremely important part of diabetes clinical practice. The medical cost burden should be weighed for each patient, as it includes not only the medication costs, but also the associated healthcare costs.

Individuals with chronic diseases, such as diabetes mellitus, must recognize that they need to be on long-term pharmacotherapy while adhering to the dosage and usage of prescribed medications. Indeed, a decline in adherence to these medications not only diminishes their antidiabetic efficacy, but also increases the risk of hypoglycemia through inappropriate intensification of therapy and contributes to polypharmacy. Unfortunately, adherence rates for patients prescribed antidiabetic medications have been reported to be only 68.6% for new prescriptions, and 78.1% for all prescriptions[103]. According to a meta-analysis of eight observational studies in people with type 2 diabetes, the relative risks for all-cause mortality and hospitalization were shown to be 0.72 (95% confidence interval 0.62–0.82) and 0.90 (95% confidence interval 0.87–0.94) among those in the high adherence (≥80%) group compared with the low adherence (<80%) group. It is also reported that low adherence is associated with increased CVD risk[104]. Overseas studies have also reported that there is a significant correlation between medication adherence and changes in HbA1c among people with type 2 diabetes; that is, a 10% increase in adherence translates into a 0.15% decrease in HbA1c[105,106]. Similar results have been shown in a questionnaire survey carried out among 1,022 people with type 2 diabetes in Japan. There was a significant difference in adherence between those receiving and those not receiving their medications as one package[107]. Notably, a systematic review and meta-analysis of medication adherence in people with type 2 diabetes has become available[108]. In that review, a comparison of adherence to metformin, SUs and thiazolidinediones showed that medication adherence was significantly higher with SUs and thiazolidinediones than with metformin; higher with thiazolidinediones than with SUs; and higher with DPP-4 inhibitors than with thiazolidinediones or SUs. In a retrospective study to evaluate the need for intensification of therapy after treatment with biguanides or DPP-4 inhibitors in medication-naïve Japanese people with type 2 diabetes, DPP-4 inhibitors were superior to biguanides[109]. Although glinides and α-glucosidase inhibitors, which need to be taken before meals, are assumed to be associated with lower adherence rates than SUs, biguanides or thiazolidinediones[110], this might be remedied by implementing appropriate measures, such as ensuring that all other medications are also taken before meals[107]. Thus, based on the evidence summarized above, this algorithm includes a summary of adherence rates for available antidiabetic medications in a separate table. In an increasingly aging society, such as Japan, it is important to focus on minimizing dosing frequency, as well as on maintaining or improving medication adherence through appropriate measures; for example, provision of medications in one package or use of mixture medications.

Medical expenditures are increasing with the aging of the population[111]. A survey on medical expenditure for non-communicable diseases in 2019 by the National Federation of Health Insurance Societies showed that of the 10 non-communicable diseases, including cerebrovascular disease, ischemic heart disease and end stage kidney disease (dialysis), diabetes mellitus imposes a huge economic burden on affected individuals, accounting for the third largest share in hospitalization costs, the largest share in non-hospitalization costs and the second largest share next to dialysis in terms of daily healthcare costs[112]. As high medical expenditures are associated with a decline in adherence to medications[113], it is also likely to be associated with a decline in their efficacy. Thus, consideration needs to be given to the choice of antidiabetic medication(s), as they vary widely in their prices in Japan, and expensive choices impose an increased burden on patients. Furthermore, the financial burden on patients is not limited by medication costs. Of note, here is a survey carried out using the National Database of Health Insurance Claims and Specific Health Check-ups to investigate total medical expenditures incurred by Japanese people with type 2 diabetes in the 1 year after their initial antidiabetic prescription (adjusted for age, sex, comorbidities, healthcare institutional attributes and other relevant factors), which showed that, of all antidiabetic medications, biguanides represented the lowest 1-year expenditure, followed by thiazolidinediones and α-glucosidase inhibitors, whereas GLP-1 receptor agonists represented the highest[26]. An estimation of the economic burden associated with the use of antidiabetic medications is provided in a separate table in terms of their prices and the associated total medical expenditure.

Therefore, to help reduce the economic burden placed on each patient, consideration should be given to using generics, switching to biguanides or switching from multiple single agents to mixture medications.

Although not mentioned in the proposed algorithm, the durability of the effects was added to Table 1 in this revision as a factor that needs to be considered. According to the ADOPT trial, which examined the durability of glycemic improvement effects of three medications (rosiglitazone in the thiazolidinedione class, metformin and glyburide in the SUs class), greater durability of effects was shown in thiazolidinedione than metformin and SUs[114]. A comparison of pioglitazone and gliclazide also showed that pioglitazone represents a better medication, given the durability of its glycemic improvement effects[115]. The GRADE trial in people with type 2 diabetes receiving metformin therapy has recently reported that sitagliptin, glimepiride, liraglutide or glargine were added to the regimens of those patients receiving metformin to conduct a follow-up survey of the period to reach HbA1c ≥7%, and found that liraglutide and glargine were superior to other medications in terms of the durability of the effects[116]. The durability of the glucose-lowering effects of thiazolidinediones and SGLT2 inhibitors was shown to be higher than that of SUs, metformin and DPP-4 inhibitors[117]. It has also been reported that the persistence of HbA1c reduction after the initiation of α-glucosidase inhibitors is approximately 3 years[118]. Thus, based on the aforementioned reports, thiazolidinediones, SGLT2 inhibitors and GLP-1 receptor agonists represent medications with high durability, whereas SUs and α-glucosidase inhibitors represent medications with low durability.

Periodic assessment of treatment efficacy and the need for adjustments in pharmacotherapy

It is proposed in the present algorithm that each medication regimen be reviewed for possible revision every 3 months after its initiation to avoid delays when target HbA1c cannot be achieved in addressing patients requiring intensification of therapy. Attention should be focused on promoting medical nutrition therapy tailored to address their diabetes pathology and comorbidities, including nephropathy, exercise therapy and lifestyle modification, in each patient. It is important to revert to the opening of the algorithm, as required, to add further medications, increase their medication doses or consider alternative medications, including the reassessment for insulin therapy.

It should be noted that if left untreated, hyperglycemia increases the subsequent risk of diabetic microangiopathy, macroangiopathy or death in people with diabetes[119,120], and that inappropriate glycemic control results, at least in part, from delays in initiation or intensification of therapy (i.e., clinical inertia)[121]. Indeed, it has been reported in a USA study that antidiabetic therapy was not appropriately initiated, and intensified within 6 months of consultation in 37% and 18% of people with diabetes requiring initiation and intensification of therapy, respectively[122]; furthermore, it has also been reported that antidiabetic therapy was not intensified within 6 months of consultation in 44% of people with type 2 diabetes having HbA1c ≥9%[123]. Given the clinical inertia that often occurs in clinical practice, pharmacotherapy needs to be immediately adjusted in patients who fail to achieve their respective HbA1c control goals. Although it is recommended by the American Diabetes Association that any medication regimen be reviewed for efficacy, as well as for revision, every 3–6 months[20], the revision of medication regimen in a 3-month cycle is recommended in Japan. Basically, it is reflecting the usual frequency of hospital visits by people with diabetes in Japan.

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