Chapter 3
Guidelines for the Treatment of Type 2 Diabetes Mellitus

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3.1 Introduction

Evidence-based clinical practice guidelines are systematically developed statements intended to assist practitioners and patients about making and understanding care decisions for specific clinical circumstances. The evidence base should be obtained using an unbiased and transparent process of systematically reviewing and appraising published clinical research, which is then synthesized into recommendations for clinical practice. There is a hierarchy of evidence involved, from meta-analysis or systematic reviews of randomized controlled trials (RCTs), to case-controlled or cohort studies, to expert opinion. Evidence-based guidelines have largely replaced consensus statements, which typically involves a group of experts meeting and producing a series of recommendations based on the consensus of the group at that time. However, these can be prone to bias depending on the opinions of those involved in the process, and often would be based on a limited literature review which might miss key publications, especially if the results are negative.

Guidelines for the management of type 2 diabetes exist at local, national, and international levels and some examples of these are given in Table 3.1 [1–13]. These usually

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Table 3.1 A selection of major treatment guidelines for the management of type 2 diabetes

Region	Guideline
International	International Diabetes Federation (IDF): Global Guideline for Type 2 Diabetes (2012) [1]
	American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD): Management of Hyperglycemia in Type 2 Diabetes: A Patient-Centered Approach (2012; 2015) [2, 3]
National	
Canada	Canadian Diabetes Association (CDA): Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada (2013) [4]
England, Wales, and Northern Ireland	National Institute for Health and Care Excellence (NICE): Type 2 Diabetes in Adults: Management (2015) [5]
Scotland	Scottish Intercollegiate Guidelines Network (SIGN): Management of Diabetes (2011) [6]
USA	American College of Physicians (ACP): Oral Pharmacological Treatment of Type 2 Diabetes (2012) [7]; American Association of Clinical Endocrinology (AACE)/American College of Endocrinology (ACE) (2015) [8]
Spain	Working Group for Consensus Documents and Clinical Guidelines of the Spanish Diabetes Society: Recommendations for the Pharmacologic Treatment of Hyperglycemia in Type 2 Diabetes. Consensus Document (2011) [9]
Germany	German National Disease Management Guideline on the Treatment of Type 2 Diabetes (2013) [10]
Japan	Japan Diabetes Society: Evidence-based Practice Guidelines for the Treatment of Diabetes in Japan (2013) [11]

Table 3.1 (continued)

Region	Guideline
India	Indian Council of Medical Research: Guidelines for Management of Type 2 Diabetes. Pharmacological Treatment of Diabetes (2005) [12]
Brazil	Brazilian Diabetes Society: Algorithm for the Treatment of Type 2 Diabetes. Position Statement (2010) [13]

include glycemic targets for HbA1c and recommendations on the therapeutic options that can be used to reach these targets. Pharmacological monotherapy is started after a period of lifestyle adjustment, including changes to the diet and increases in physical activity. Most guidelines recommend first-line therapy with metformin based on the results of the United Kingdom Prospective Diabetes Study (UKPDS) plus the slight reduction in weight that is obtained with metformin [14]. Thereafter, if targets are not met then the choice of second-line therapy varies from guideline to guideline.

3.2 International Diabetes Federation Guidelines

The 2012 International Diabetes Federation (IDF) global guideline for type 2 diabetes focuses particularly on cost, availability, and side effects of drugs [1]. The IDF guidelines recommend that metformin should be used as first-line therapy, with sulfonylureas as second-line and insulin third. More recent drug classes such as dipeptidyl peptidase-4 (DPP-4) inhibitors or glucagon-like peptide-1 (GLP-1) receptor agonists are mentioned as second-line alternatives, based on the fact that the cost of these drugs is greater than

metformin and sulfonylureas because there are no generic formulations and they are not available for clinical use in every country. Sodium glucose cotransporter 2 (SGLT2) inhibitors are not included in the IDF guidelines, as no drugs in this class had been approved when the guideline was developed.

3.3 Joint American Diabetes Association and European Association for the Study of Diabetes Position Statement

In 2012, the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) published a joint position statement on the management of hyperglycemia in patients with type 2 diabetes [2]. This was published in response to the increasing number of antidiabetic drugs being developed and was intended to be more evidence-based than previous joint statements, which had primarily been consensus reports. An important emphasis was placed on taking a patient-centered approach to making clinical decisions and aiming to provide care that is respectful of and responsive to individual patient preferences, needs, and values. Less stringent glycemic targets were suggested, depending on factors such as risks of hypoglycemia, disease duration, life expectancy, important comorbidities, and established vascular complications. Patient attitude, expected treatment efforts, resources, and support system are also to be taken into consideration (Fig. 3.1).

Considerations for the choice of glucose-lowering agent include age, weight, gender, racial, and genetic differences, as well as serious comorbidities such as coronary artery disease, heart failure, chronic kidney disease, and liver dysfunction. Again, as no SGLT2 inhibitors had been approved, they were not included as a treatment option in the 2012 ADA/EASD position statement.

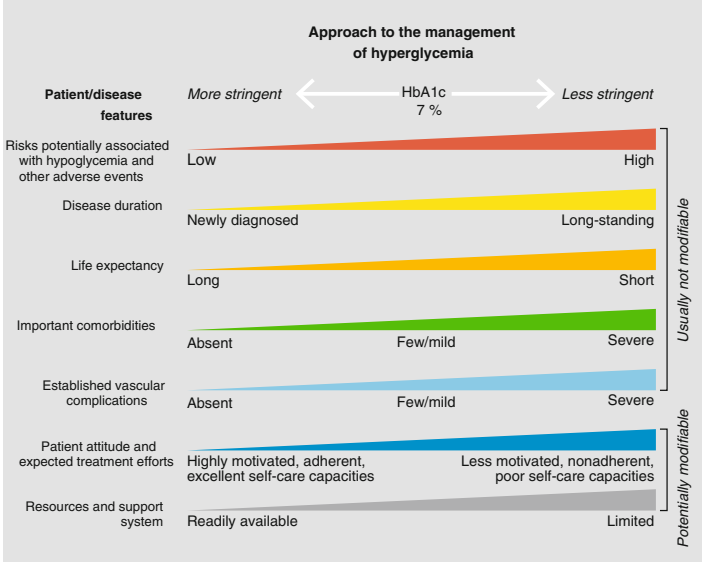

FIGURE 3.1 Depiction of the elements affecting choice of appropriate treatment to achieve glycemic targets (Reproduced with permission from Inzucchi et al. [3]; based on a figure by Ismail-Beigi et al. [15] ©American Diabetes Association)

3.3.1 Update to the Joint ADA/EASD Position Statement

The position statement was updated in 2015 to reflect new data from recent clinical trials and intended as an addendum to the 2012 full version [3]. In the update, SGLT2 inhibitors were described as a major change in antidiabetic treatment and that because the mode of action was independent of insulin action, could be used at any stage of type 2 diabetes, including when insulin secretion had waned significantly. Potential advantages of using SGLT2 inhibitors were noted and included lower risk of hypoglycemia, potential weight loss, and lowering of systolic and diastolic blood pressure, as well as potential disadvantages such as genitourinary infections, volume depletion, an increase

in low density lipoprotein (LDL) cholesterol, and a transient increase in creatinine. The cost of SGLT2 therapy was described as "high" (Table 3.2).

The ADA/EASD treatment algorithm for patients with type 2 diabetes was also updated and SGLT2 inhibitors were added as possible part of dual or triple therapy combination with metformin and either a sulfonylurea, thiazolidinedione, DPP-4 inhibitor, or insulin (Fig. 3.2). The 2015 update urges that optimal treatment must take into account comorbidities that are frequently encountered in patients with diabetes, particularly as they age. Consideration of renal status when taking an SGLT2 inhibitors is also addressed.

3.4 Country Case Study: Developing Guidelines in the UK

To illustrate the use of country-specific guidelines, the process in the United Kingdom is a particularly interesting case study. The National Institute for Health and Care Excellence (NICE), a special advisory body used to standardize and develop public health guidance, recently updated a clinical practice guideline on type 2 diabetes for use in the National Health Service (NHS) in England, Wales, and Northern Ireland [5]. This has been a controversial process, as the guideline seems to be dominated by a need to recommend generic drugs such as sulfonylureas, repaglinide, and pioglitazone, rather than considering more modern alternatives. This strong emphasis on drugs that promote weight gain, hypoglycemia, or both, is somewhat contrary to the ethos of the guideline, which is intended to promote patient-centered care.

The approach to including SGLT2 inhibitors has also been idiosyncratic. In the first draft of the guideline (published for consultation in January 2015), there was a single mention that combinations of medicines including SGLT2 inhibitors may be appropriate for some people, without defining who these people might be [16]. A reference was then made to separate health technology appraisals (HTAs) for two SGLT2 inhibitors, dapagliflozin and canagliflozin. Following critical feedback on

Table 3.2 Properties of SGLT2 inhibitors according to 2015 American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) position statement

Class	Compounds	Cellular mechanisms	Primary physiological actions	Advantages	Disadvantages/ adverse effects	Cost
SGLT2 inhibitors	Canagliflozin Dapagliflozin Empagliflozin	Inhibits SGLT2 in the proximal nephron	Blocks glucose reabsorption by the kidney, increasing glycosuria	No hypoglycemia Weight loss Reduces blood pressure Effective at all stages of type 2 diabetes	Genitourinary infections Polyuria Volume depletion/ hypotension/ dizziness Increases LDL cholesterol Increases creatinine (transient)	"High"

Adapted from ADA/EASD [3] © American Diabetes Association
LDL low density lipoprotein cholesterol, *SGLT2* sodium glucose cotransporter-2

FIGURE 3.2 Antihyperglycemic therapy in type 2 diabetes: general recommendations. Metformin monotherapy is added at, or soon after, diagnosis, unless there are contraindications. If the HbA1c target is not achieved after 3 months, consider one of the six treatment options combined with metformin: a sulfonylurea, TZD, DPP-4 inhibitor, SGLT2 inhibitor, GLP-1 receptor agonist, or basal insulin. DPP-4i, dipeptidyl peptidase 4 inhibitors; GI, gastrointerstinal; GLP-1 RA, glucagon- like peptide 1 receptor agonist; GU, genitourinary; SGLT-2i, sodium- glucose cotransporter 2 inhibitors; SU, sulphonylureas; TZD, thiazolidinediones. *See ADA supplementary data for description of efficacy categorization. †Consider initial therapy at this stage when HbA1c is ≥9% (≥75 mmol/mol). **Consider initial therapy at this stage when blood glucose is ≥300–350 mg/dL (≥16.7–19.4 mmol/L) and/or HbA1c ≥10–12% (≥86–108 mmol/mol), especially if patient is symptomatic or if catabolic features (weight loss, ketosis) are present, in which case basal insulin + mealtime insulin is the preferred initial regimen. ***Order not meant to denote any specific preference - choice dependent on variety of patient and disease-specific factors. §Usually a basal insulin (eg, NPH, glargine, detemir, degludec). (Reproduced with permission from Inzucchi et al. [3] ©American Diabetes Association)

multiple aspects of the guideline, a further draft was produced in July 2015 [17–19]. In this version, there was again a single mention of SGLT2 inhibitors in the text, with an added reference to the HTA for empagliflozin [19]. Following further consultation, the guideline was published at the end of 2015. It includes a complex algorithm for blood glucose-lowering therapy in adults with type 2 diabetes and SGLT2 inhibitors are now included (Fig. 3.3) [5]. Unfortunately, the intended effect of the revised guidelines may be to limit the use of SGLT2 inhibitors and GLP-1 receptor agonists, despite improving patient-based outcomes by reducing weight.

Guidelines in Scotland are developed by the Scottish Intercollegiate Guidelines Network (SIGN). The most recent SIGN guideline on diabetes, SIGN 116, was produced in 2010, with a minor revision in 2011 to reflect the removal of the license for rosiglitazone in Europe [6]. Like the IDF guidelines, there was no mention of SGLT2 inhibitors and these guidelines are now in need of an update.

3.5 Conclusion

Many guidelines for the treatment of type 2 diabetes either fail to mention SGLT2 inhibitors or do not give clear guidance as to when they should be used. Even the joint ADA/EASD position statement, which includes SGLT2 inhibitors as a clear therapeutic option, may require further updating to reflect the fact that empagliflozin may have preferred role in patients with coronary heart disease or heart failure (see Chap. 4). International, national, and local guidelines need revision and updating to specifically include the SGLT2 inhibitor class of drugs, which patients might benefit most, and which patients may need special consideration (e.g., patients with reduced kidney function).

Key Points

- Evidence-based clinical practice guidelines on the management of type 2 diabetes are systematically developed statements to assist practitioners and patients about health care for people with type 2 diabetes.

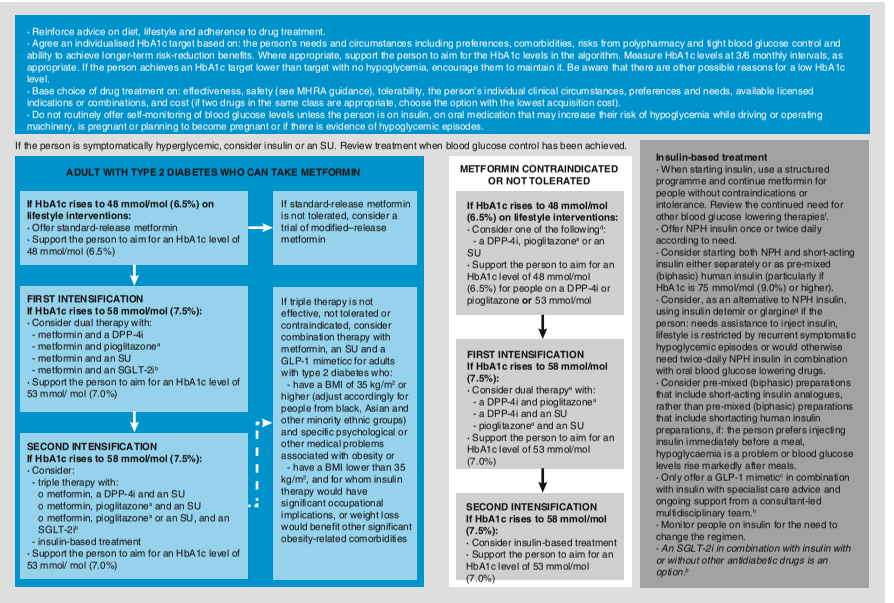

FIGURE 3.3 National Institute for Health and Care Excellence (NICE) algorithm for blood glucose-lowering therapy in adults with type 2 diabetes (UK). (**a**) When prescribing pioglitazone, exercise particular caution if the person is at high risk of the adverse effects of the drug. Pioglitazone is associated with an increased risk of heart failure, bladder cancer and bone fracture. Known risk factors for these

conditions, including increased age, should be carefully evaluated before treatment: see the manufacturers' summaries of product characteristics for details. Medicines and Healthcare products Regulatory Agency (MHRA) guidance (2011) advises that 'prescribers should review the safety and efficacy of pioglitazone in individuals after 3–6 months of treatment to ensure that only patients who are deriving benefit continue to be treated'. (**b**) Treatment with combinations of drugs including sodium–glucose cotransporter 2 inhibitors may be appropriate for some people at first and second intensification; see NICE technology appraisal guidance 288, 315 and 336 on dapagliflozin, canagliflozin and empagliflozin respectively. All three SGLT-2 inhibitors are recommended as options in dual therapy regimens with metformin under certain conditions. All three are also recommended as options in combination with insulin. At the time of publication, only canaglifozin and empagliflozin are recommended as options in triple therapy regimens. The role of dapagliflozin in triple therapy will be reassessed by NICE in a partial update of TA288. Serious and life-threatening cases of diabetic ketoacidosis have been reported in people taking SGLT-2 inhibitors (canagliflozin, dapagliflozin or empagliflozin) or shortly after stopping the SGLT-2 inhibitor. MHRA guidance (2015) advises testing for raised ketones in people with symptoms of diabetic ketoacidosis, even if plasma glucose levels are near normal. (**c**) Only continue GLP-1 mimetic therapy if the person has a beneficial metabolic response (a reduction of HbA1c by at least 11 mmol/mol [1.0%] and a weight loss of at least 3% of initial body weight in 6 months). (**d**) Be aware that, if metformin is contraindicated or not tolerated, repaglinide is both clinically effective and cost effective in adults with type 2 diabetes. However, discuss with any person for whom repaglinide is being considered, that there is no licensed non-metformin-based combination containing repaglinide that can be offered at first intensification. (**e**) Be aware that the drugs in dual therapy should be introduced in a stepwise manner, checking for tolerability and effectiveness of each drug. (**f**) MHRA guidance (2011) notes that cases of cardiac failure have been reported when pioglitazone was used in combination with insulin, especially in patients with risk factors for the development of cardiac failure. It advises that if the combination is used, people should be observed for signs and symptoms of heart failure, weight gain, and oedema. Pioglitazone should be discontinued if any deterioration in cardiac status occurs. (**g**) The recommendations in this guideline also apply to any current and future biosimilar product(s) of insulin glargine that have an appropriate Marketing Authorisation that allows the use of the biosimilar(s) in the same indication. (**h**) A consultant-led multidisciplinary team may include a wide range of staff based in primary, secondary and community care. DPP-4i, dipeptidyl peptidase-4 inhibitor. GLP-1, glucagon-like peptide-1; SGLT2, sodium-glucose cotransporter 2; SU, sulfonylurea. (Reproduced with permission from NICE [5] ©National Institute for Health and Care Excellence)

- Guidelines developed before 2012 do not include mention of SGLT2 inhibitors, as this class of antidiabetic drugs was not available for clinical use until dapagliflozin was launched in late 2012.
- The American Diabetes Association and the European Association for the Study of Diabetes position statement on the management of hyperglycemia in type 2 diabetes was recently updated to include SGLT2 inhibitors as a major change in treatment options since 2012.
- Additional potential advantages of modest weight loss and lowering of systolic and diastolic blood pressure are noted in the position statement, and SGLT2 inhibitors are included as possible dual and triple therapy combinations.
- Many guidelines are in need of updating based on the results of new efficacy and safety studies with SGLT2 inhibitors.

References

1. International Diabetes Federation (IDF). Glucose control therapy. In: Global guidelines for type 2 diabetes. Brussels: International Diabetes Federation; 2012. p. 55–64.
2. Inzucchi SE, Bergenstal RM, Buse JB, Dimant M, Ferrannini E, Nauck M, et al. Management of hyperglycemia in type 2 diabetes: a patient-centered approach. Position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care. 2012;35:1364–79.
3. Inzucchi SE, Bergenstal RM, Buse JB, Dimant M, Ferrannini E, Nauck M, et al. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care. 2015;38:140–9.
4. Harper W, Clement M, Goldenberg R, Hanna A, Main A, Retnakaran R, et al. Pharmacologic management of type 2 diabetes. Can J Diabetes. 2013;37 Suppl 1:S61–8.
5. National Institute for Health and Care Excellence (NICE). Type 2 diabetes in adults: management. Last updated December 2015. www.nice.org.uk/guidance/ng28. Accessed 5 Sept 2016.

6. Scottish Intercollegiate Guidelines Network (SIGN). Pharmacological management of glycaemic control in people with type 2 diabetes. In: SIGN 116 management of diabetes. Edinburgh: Scottish Intercollegiate Guidelines Network; 2011. p. 39–55.
7. Qaseem A, Humphrey LL, Sweet DE, et al. Oral pharmacological treatment of type 2 diabetes: a clinical guideline from the American College of Physicians. Ann Intern Med. 2012;15693: 218–31.
8. Garber AJ, Abrahamson MJ, Barzilay JI, et al. AACE/ACE comprehensive diabetes management algorithm 2015. Endocr Pract. 2015;21:438–47.
9. Menéndez Torre E, Lafita Tejedor J, Artola Menéndez S, Milán Núñez-Cortés J, Alonso García A, Puig Domingo M, et al. Nefrologia. 2011;31:17–26.
10. Bundesärztekammer (BÄK) Kassenärztliche Bundesvereinigung (KBV), Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF) Nationale VersorgungsLeitlinie Therapie des Typ-2-Diabetes-Langfassung, 1st edition, Version 2. Last updated on September 2013. www.versorgungsleitlinien.de/themen/diabetes2/dm2_Therapie. Accessed 5 Sept 2016.
11. Japan Diabetes Society. Evidence-based practice guideline for the treatment for diabetes in Japan 2013. www.jds.or.jp/modules/en/index.php?content_id=44. Accessed 5 Sept 2016.
12. Indian Council of Medical Research. Pharmacological treatment for diabetes. http://icmr.nic.in/guidelines_diabetes/section7.pdf. Accessed 5 Sept 2016.
13. Lerario AC, Chacra AR, Pimazoni-Netto A, Malerbi D, Gross JL, Oliveira JEP, et al. Algorithm for the treatment of type 2 diabetes: a position statement of Brazilian Diabetes Society. Diabetol Metab Syndr. 2010;2:35. http://dmsjournal.biomedcentral.com/articles/10.1186/1758-5996-2-35. Accessed 5 Sept 2016.
14. 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). Lancet. 1998;352:854–65.
15. Ismail-Beigi F, Moghissi E, Tiktin M, Hirsch IB, Inzucchi S, Gunuth S. Individualizing glycemic targets in type 2 diabetes mellitus: implications of recent clinical trials. Ann Intern Med. 2011;154:554–9.

16. National Institute for Health and Care Excellence (NICE). Type 2 diabetes in adults: diagnosis and management of type 2 diabetes in adults. Draft for consultation, January 2015. www.nice.org.uk/guidance/gid-cgwave0612/resources/type-2-diabetes-draft-nice-guideline2. Accessed 5 Sept 2016.
17. O'Hare JP, Miller-Jones D, Hanif W, et al. The new NICE guidelines for type 2 diabetes – a critical analysis. Br J Diabetes. 2015;15:3–7.
18. Barnett AH. NICE draft type 2 diabetes guidelines: a cause for concern. Lancet Diabetes Endocrinol. 2015;3:403–5.
19. National Institute for Health and Care Excellence (NICE). Type 2 diabetes in adults: diagnosis and management of type 2 diabetes in adults. Draft for consultation, June 2015.