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RAPID RECOMMENDATIONS

Cardiovascular, kidney related, and weight loss effects of therapeutics for type 2 diabetes: a living clinical practice guideline

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ABSTRACT

CLINICAL QUESTION

What are the benefits and harms of medications for adults with type 2 diabetes at varied risks of cardiovascular and kidney related complications?

CONTEXT

Emerging clinical trials of novel medications have demonstrated benefits on cardiovascular, kidney, and weight related outcomes in people with type 2 diabetes. Dynamically updated practice guidelines adhering to standards of trustworthiness are necessary in response to a rapidly evolving evidence base and the availability of multiple medication alternatives. This living practice guideline incorporates the latest available medications and evidence and provides recommendations stratified by risks of cardiovascular and kidney complications to inform diabetes management.

RECOMMENDATIONS

The panel issued risk-stratified recommendations regarding four prioritised medications for adults with type 2 diabetes (SGLT-2 inhibitors, GLP-1 receptor agonists, finerenone and tirzepatide):

- Lower risk (three or fewer cardiovascular risk factors without established cardiovascular disease (CVD) or chronic kidney disease (CKD)): weak recommendation against SGLT-2 inhibitors or GLP-1 receptor agonists.
- Moderate risk (more than three cardiovascular risk factors without established CVD or CKD; or established CVD and/or CKD at lower risk of complications): weak recommendation in favour of SGLT-2 inhibitors or GLP-1 receptor agonists; and a weak recommendation against finerenone in adults with CKD.
- Higher risk (established CVD and/or CKD at higher risk of complications, or established heart failure): strong recommendation in favour of SGLT-2 inhibitors or GLP-1 receptor agonists; and a weak recommendation in favour of finerenone in adults with CKD.
- Across risk strata: weak recommendation in favour of tirzepatide in adults with obesity.

ABOUT THIS GUIDELINE AND HOW IT WAS CREATED

An international panel including two patient partners, clinicians, and methodologists produced these recommendations. The panel followed standards for trustworthy guidelines and used the GRADE approach, explicitly considering the balance of benefits, harms and burdens of treatment from an individual patient perspective. Recommendations were informed by a linked living systematic review and network meta-analysis evaluating relative benefits and harms updated to 31 July 2024; and by linked systematic reviews addressing risk prediction models and values and preferences of adults with type 2 diabetes. Candidate therapeutics are prioritised based on availability of sufficient randomised trial data, relevance to a global audience and likelihood of changing practice.

This is the first version of the living guideline. The guideline is part of the *BMJ Rapid Recommendations* series. MAGICapp displays the most recent version of the guideline and full content including evidence summaries and decision aids; major updates will be published in *The BMJ*. We encourage re-use, adaptation and translation of these living guidelines, and recognise that the lack of availability or high costs of some medications may be prohibitive and will impact on how these recommendations are implemented across different health care systems.

Why is the guideline needed?

Type 2 diabetes affects half a billion people worldwide. It is the ninth leading cause of death internationally, and is associated with multi-organ morbidity.[1,2] Preventing macrovascular and microvascular sequalae including cardiovascular and kidney complications is central to diabetes management. Randomised trials of emerging medications including SGLT-2 inhibitors, GLP-1 receptor agonists and finerenone (a non-steroidal selective mineralocorticoid receptor antagonist with more potent anti-inflammatory and anti-fibrotic effects and less risk of causing hyperkalaemia than steroidal alternatives like spironolactone) have demonstrated cardiovascular and kidney protective benefits.[3-5] These medications have contributed to a shift in diabetes management from a long-standing focus on glycaemic control to a focus on reducing the risk of cardiovascular and kidney complications. Trials have also demonstrated substantial weight loss effects with some new medications including GLP-1 receptor agonists and tirzepatide, a dual glucose-dependent insulinotropic polypeptide (GIP)/GLP-1 receptor agonist.[6]

More evidence is anticipated to address existing and emerging drug classes and their impact on patient-important outcomes. Clinical decision-makers require up-to-date and trustworthy guidance

regarding effects of these treatments and how they compare to each other. To accomplish this, practice guidelines should leverage dynamically updated systematic reviews responsive to latest evidence. Moreover, guidelines should incorporate variable prognoses of adults with type 2 diabetes through a risk-stratified approach to recommendations, and explicitly and systematically address patient values and preferences.

In 2021, a previous *BMJ Rapid Recommendation* on SGLT-2 inhibitors and GLP-1 receptor agonists for adults with type 2 diabetes provided risk-stratified recommendations across five risk groups for cardiovascular and kidney outcomes.[3] Several limitations in the previously adopted risk stratification approach (summarised in MAGICapp), combined with a rapid evolution in evidence and available medications, has underscored the need for the current living practice guideline.

This living guideline complies with standards for trustworthy guidelines (box 1)[11] and commits to a living model, where updated evidence will inform updates to existing recommendations and the development of new recommendations.[12] Given its international scope, the guideline takes an individual patient perspective (see "How this living guideline was created" below). We welcome re-use, adaptation and translation of our living guidelines to promote increased efficiency and reduced duplication. With the current likely prohibitive costs for some medications, health care systems may need to incorporate considerations on cost-effectiveness in adapting these recommendations.

Box 1: Linked resources in this *BMJ* Rapid Recommendations package

The living guideline is available in two formats:

- MAGICapp – interactive, user-friendly platform providing recommendations, associated evidence summaries with risk-stratified benefits and harms for each candidate medication, and more detailed explanations regarding guideline methods and judgements: https://app.magicapp.org/#/guideline/noaRMj.
- *The BMJ* – featuring major updates to guideline recommendations in journal publication format (current publication).

An interactive decision support tool allows further visualization of the comparative benefits and harms across therapeutics to support shared decision-making (https://matchit.magicevidence.org/250709dist-diabetes/#!/). The infographic accompanying this publication includes evidence summaries, recommendations and an overview of other decisional factors and practical considerations.

Guideline recommendations, evidence summaries, risk stratification and judgments regarding underlying patient values and preferences are informed by:

- A systematic review and network meta-analysis evaluating benefits and harms of medications for type 2 diabetes, planned for iterative updates to incorporate new evidence and medications over time: Nong K, Jeppesen BT, Shi Q, et al. Medications for adults with type 2 diabetes: a living systematic review and network meta-analysis. *BMJ* 2025;390:e083039. doi:10.1136/bmj-2024-083039[7]
- A systematic review of prognostic models for estimating the likelihood of cardiovascular and kidney complications for adults with type 2 diabetes: Rayner D, Shah D, Dai S, et al. Prognostic models for cardiovascular and renal outcomes in patients with type 2 diabetes: a living systematic review and meta-analysis of observational studies. *BMJ Med* 2025;4:e001369[8]
- A systematic review of values and preferences of patients with type 2 diabetes: González-Cruz DC, Moreno-Peña PJ, Garcia-Campa M, et al. Values, preferences, and treatment burden for initiation of GLP-1 receptor agonists, SGLT-2 inhibitors, tirzepatide and finerenone in adult patients with type 2 diabetes: a systematic review. [Pending submission to *BMJ*][9]

This living guideline contributes to the *BMJ Rapid Recommendations* series, which provides clinicians with trustworthy recommendations guided by potentially practice-changing evidence. *BMJ Rapid Recommendations* represent a collaborative effort between MAGIC and *The BMJ*. The guideline is produced by a team of clinicians, patient partners and methodologists using an established approach,[25] described in the "How this guideline was made" section. This guideline exists alongside a *BMJ Rapid Recommendation* addressing the use of SGLT-2 inhibitors for people with chronic kidney disease (CKD)[10] and a prior *Rapid Recommendation* addressing the use of SGLT-2 inhibitors and GLP-1 receptor agonists for adults with type 2 diabetes.[3]

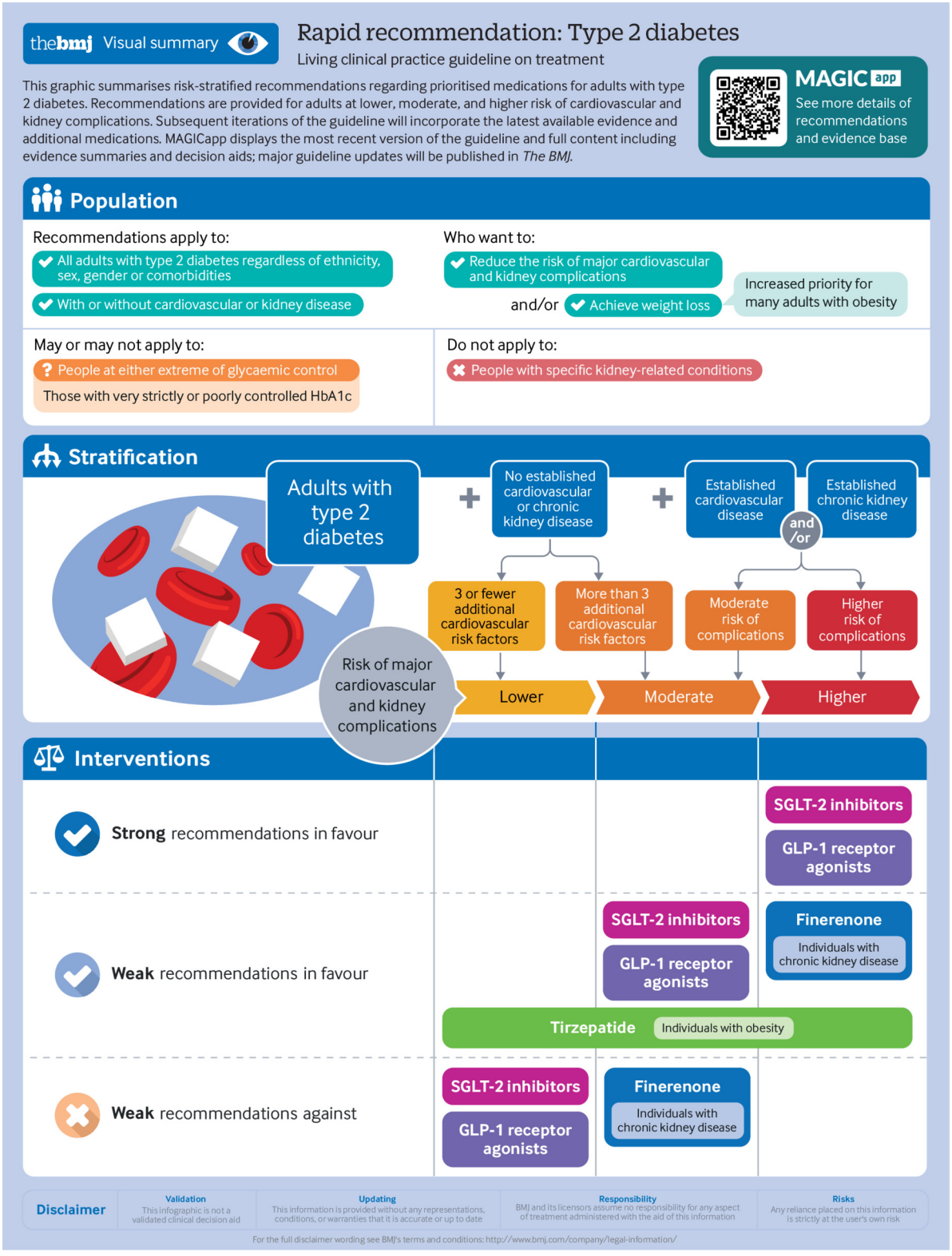
All updates to the guideline will be made available via MAGICapp. Major updates will be published via *The BMJ*.

The guideline provides recommendations that are stratified by adults' risk of cardiovascular and kidney complications to allow clinicians to tailor care and optimise use of resources. The guideline also highlights uncertainties with respect to what evidence is needed to improve recommendations, patient care and resource use in the future.

The guideline makes recommendations for or against medications for adults with type 2 diabetes. These recommendations may be strong or weak in terms of strength, and in favour or against medications in terms of direction. The panel provided strong recommendations in favour of medications with the highest certainty of large net benefits; weak recommendations in favour for those with either smaller net benefits or lower certainty evidence; and recommendations against medications where net effects were not positive, evidence was too uncertain or risk of harms was substantial. Strong recommendations indicate that the guideline panel believed all or almost all adults would be inclined to receive therapy, whereas weak recommendations indicate there is likely to be important variability, emphasising the need for shared decision making with the patient.

Our guideline in the context of current practice

At the inception of this living guideline in 2024, numerous professional societies in cardiology, nephrology, and endocrinology had incorporated cardiovascular and kidney related risk considerations and outcomes into their guidelines (supplement 1). Many professional societies, including the National Institute of Health and Care Excellence (NICE), American Diabetes Association, European Society of Cardiology, American Association of Clinical Endocrinologists, American College of Endocrinology, American College of Cardiology, Canadian Cardiovascular Society, Chinese Diabetes Society, Chinese Society of Endocrinology, and Kidney Disease Improving Global Outcomes (KDIGO), recommended the use of SGLT-2 inhibitors and GLP-1 receptor agonists. Some societies made recommendations pertaining to finerenone. Guidelines incorporated varied risk stratification approaches and prognostic models for adults without established cardiovascular or kidney disease. Most guidelines incorporated recommendations for adults with established cardiovascular or kidney disease, but many did not consider the gradient of risk that exists within each disease category or the overlap in risks of complications between the disease categories. Many guidelines also provided recommendations pertaining to obesity, but few explicitly considered the comparative effectiveness of medications for weight loss. Furthermore, few guidelines reported risk-stratified, absolute treatment effects for outcomes of benefit and harm; explicitly incorporated the values and preferences of adults living with type 2 diabetes; and adopted living models for summarising evidence regarding treatment effects and prognostic models to inform recommendations.



This living guideline prioritises the impact of medications on cardiovascular and kidney complications above effects on HbA1c and other markers of glyacemic control, given that complications are of considerable importance to patients and the growing evidence that intensive lowering of blood glucose does not correlate with large reductions in these complications.[13 14] We do, however, acknowledge that glycaemic control may remain an important consideration in treatment decision-making for many patients (box 2).

Box 2: Glycaemic control as a determinant for clinical decision-making

Clinical decision-making in type 2 diabetes has long centered around optimising glycaemic control and reducing HbA1c measurements. This practice guideline prioritises consideration of cardiovascular and kidney risk rather than HbA1c and other markers of glycaemic control when making recommendations, while acknowledging that these markers may be considerations for decision making for some individuals.

Although several medications addressed in this review have glucose lowering effects (such as SGLT-2 inhibitors, GLP-1 receptor agonists, tirzepatide), others have not demonstrated such effects (finerenone). Among included medications with glucose lowering effects, the impact on cardiovascular and kidney outcomes has been demonstrated to be independent of their glucose lowering effects.[15 -17]

We acknowledge that there may be other indications to initiate or discontinue treatments based on glycaemic control. For instance, an adult with very poor glycaemic control may be more inclined to add on a candidate medication irrespective of their risk category and anticipated cardiovascular and kidney effects of therapy. Our guideline does not currently account for specific glycaemic indications for medication-related decisions.

Of note, most of the randomised trials that inform our guideline include adults with baseline HbA1c readings between 48 mmol/mol (6.5%) and 64 mmol/mol (8.0%); our recommendations may therefore be less applicable at either extreme of glycaemic control. Effects of candidate medications on HbA1c are summarised in the linked systematic review and network meta-analysis and are accessible via the linked interactive MATCH-IT tool (see box 1).

This guideline adopts a relatively narrow focus in the wide array of management options for patients with type 2 diabetes. Recommendations therefore serve to complement rather than replace other local, national, or international practice guidelines. Clinicians and patients may use these recommendations in combination with other resources to help inform their decision making.

What triggered this guideline and what is coming next

- This living guideline was triggered by:
  - Emerging evidence regarding the cardiovascular, kidney, and body weight effects of existing medications for type 2 diabetes, including SGLT-2 inhibitors and GLP-1 receptor agonists, as well as evidence regarding harms
  - Publication of landmark trials evaluating new candidate medications for adults with type 2 diabetes, including finerenone for patients with chronic kidney disease and tirzepatide for adults with obesity
  - Limited pre-existing risk-stratified practice guidance adequately accounting for varied prognoses for adults with type 2 diabetes
  - Limited pre-existing trustworthy guidance committed to a living model whereby dynamically updated evidence informs updates to existing recommendations and development of new recommendations.
- The focus of subsequent iterations of the living guideline will be guided by emerging evidence and are likely to include one or several of:
  - De-prescription of medications without comparable cardiovascular and kidney benefits relative to alternatives and/or with increased risk of serious adverse events
  - Combinations of candidate medications
  - New emerging candidate medications, informed by the linked living network meta-analysis
  - Other existing commonly used medications
  - Refined baseline risk estimates, particularly for moderate and higher risk adults with diabetes and for outcomes for which risk-stratified baseline risk estimates are unavailable
  - Refined risk stratification approach and presentation to represent best available evidence and increase interpretability.

Context for recommendations

These recommendations apply to all adults with type 2 diabetes, regardless of ethnicity, sex, gender or comorbidities; and to adults with or without concomitant cardiovascular risk factors, cardiovascular disease (CVD) and/or chronic kidney disease (CKD). These guidelines do not apply to individuals receiving kidney replacement therapy or having received a kidney transplant, those with polycystic kidney disease, those with rare kidney diseases, and those with an estimated glomerular filtration rate (eGFR) below the threshold for safe use of a candidate medication (medication-specific but typically <20 mL/min per 1.73 m^2) and not receiving kidney replacement therapy. The recommendations focus exclusively on available medications for diabetes management; non-pharmacological interventions are outside the scope of the guideline.

Assessing a patient's risk

Benefits and harms of medications are likely to vary considerably according to an individual's baseline risk of cardiovascular and kidney complications without additional treatment. In general, the higher the baseline risk for a given cardiovascular or kidney complication, the greater the benefit of treatment with a disease-modifying agent. Recommendations provided are therefore stratified by the risk of such complications, classifying individuals as being at either lower, moderate or higher risk based on the presence of cardiovascular risk factors or of established CVD or CKD. In the absence of credible baseline risk estimates for other prioritised outcomes, risk stratification is currently limited to five patient-important outcomes (all-cause death, non-fatal myocardial infarction, non-fatal stroke, hospitalisation for heart failure, and kidney failure). The three defined risk strata represent a simple and pragmatic representation of the gradient of risk encompassed across patients with type 2 diabetes, and facilitate risk-stratified recommendations. They are designed to be practically helpful for clinical decision makers. However, the quality of evidence to support the defined risk categories and associated baseline risks across prioritised outcomes is variable (see methods and Summary of Findings tables in MAGICapp for full details).

When considering which risk group is appropriate for an individual patient, users of the guideline should first consider whether they have established CVD or CKD.

Adults without established CVD or CKD are classified based on presence of cardiovascular risk factors. Those with three or fewer risk factors (excluding diabetes) are classified as being at lower risk for cardiovascular and kidney complications, and those with more than three are classified as being at moderate risk. These cardiovascular risk factors include (but are not limited to) poor glycaemic control, hypertension, dyslipidaemia, smoking or tobacco use, harmful alcohol use or other substance use, sedentary lifestyle, family history of premature CVD or CKD, and obesity. The Risk Equations for Complications of Type 2 Diabetes (RECODe) and SCORE2-Diabetes models may further inform individual-level

judgments regarding risks of cardiovascular and kidney complications.[18 19]

Adults with established CVD or CKD are classified as being at either moderate risk or higher risk of complications. Adults with CKD may be classified based on eGFR and degree of albuminuria based on the KDIGO classification (supplement 2).[20]

For patients with established CVD, clinicians should rely on gestalt or one of several publicly available prognostic models (supplement 3) to assess a patient's risk of cardiovascular and kidney complications. While we identified no single prognostic model that facilitated risk stratification across all major outcomes of interest for the guideline, the summarised models were selected based on predictive performance and representativeness of adults with type 2 diabetes and established CVD. Decision makers should additionally consider the presence (or absence) of factors such as: history of myocardial infarction, coronary intervention, ischaemic heart disease, heart failure, cerebrovascular disease, peripheral vascular disease, or atrial fibrillation; older age; male sex; cardiovascular risk factors (summarised above); and kidney function. For instance, an adult with a prior myocardial infarction with mild troponin elevation, no impairment in left ventricular function, no angina, and optimally controlled risk factors may be deemed to be at moderate risk, whereas another adult with a prior ischaemic stroke, peripheral vascular disease, and poorly controlled risk factors may be at higher risk for subsequent cardiovascular and kidney complications.

The proposed three risk groups facilitate overarching risk-stratified decision making. Beyond this, clinicians may consider a specific patient's risk of cardiovascular and kidney complications for more individualised decision making. The panel acknowledged that classifying patients based on presence or absence of cardiovascular risk factors or established CVD or CKD alone (without considering other factors) may underestimate or overestimate risk in some patients. For instance, the risk of complications may be higher in a patient with two cardiovascular comorbidities that are poorly controlled compared with a patient with four cardiovascular comorbidities that are well controlled.

We provide a summary of baseline risks for key risk-stratified cardiovascular and kidney outcomes across the proposed risk groups in table 1. These baseline risks directly informed absolute effect estimates for medications and informed recommendations across the three risk strata.

Table 1 | Summary of baseline risks for key cardiovascular and kidney outcomes across risk strata

	Five-year risk (per 1000 adults)		
	Lower risk	Moderate risk	Higher risk
All-cause death	20	60	240
Non-fatal myocardial infarction	30	70	110
Non-fatal stroke	30	40	90
Hospitalisation for heart failure	5	20	60-300*
Kidney failure	2	10	100

* Baseline risk was 60/1000 for adults with CKD and 300/1000 for adults with CVD.

Applicability to adults with diabetes and obesity

Approximately 90% of adults with type 2 diabetes are overweight or have obesity, emphasising the strong association between excess weight and diabetes.[20] Growing evidence supports the weight loss effects of candidate medications for diabetes, including GLP-1 receptor agonists and tirzepatide. The panel judged that weight loss is an important goal for many adults with diabetes and obesity. Recommendations therefore take into account the increased importance of this outcome for this subset of patients.

When providing class-related recommendations (such as across GLP-1 receptor agonists), anticipated weight reduction may depend on the specific medication and the degree of obesity of the individual (with adults with higher body weights expected to benefit to a proportionally greater extent). In the absence of clear estimates of treatment effects on weight loss across varied body weights, a baseline weight of 90 kg was used to inform recommendations. When applying this evidence and related recommendations to an individual, users should consider the proportional effect on weight anticipated and apply this to the individual's body weight.

Choosing between treatment alternatives

Users should generally prioritise medications for which a strong recommendation in favour of use is provided for the relevant risk stratum, followed by medications for which a weak or conditional recommendation in favour is provided.

When faced with multiple recommended alternatives, choice of medications should be contextual, tailored to the individual and informed by shared decision making. For instance, adults with obesity have multiple medication alternatives for weight lowering (including GLP-1 receptor agonists and tirzepatide); decision making is anticipated to vary based on anticipated benefits and harms, certainty of evidence, underlying values and preferences, and the extent to which the individual is at risk of cardiovascular and kidney complications (an adult in the higher risk group may select a GLP-1 receptor agonist with comparatively higher certainty of evidence for cardiovascular and kidney benefits, whereas an adult in the lower risk group may select tirzepatide for larger weight loss benefits). Similarly, adults with established CVD or CKD have multiple treatment alternatives (including SGLT-2 inhibitors and GLP-1 receptor agonists); decision making is anticipated to vary based on the extent to which specific cardiovascular and kidney outcomes are prioritised (adults with higher risk kidney disease or with established heart failure may prioritise SGLT-2 inhibitors, whereas adults with prior stroke and at higher risk of recurrent events may prioritise GLP-1 receptor agonists), and the extent to which weight loss is prioritised (favouring GLP-1 receptor agonists).

Choices will also depend on the availability of medications, preferences regarding route of administration (some are only available as subcutaneous formulations), co-administered medications, and comorbidities (for instance, SGLT-2 inhibitors may be less preferred for adults with a history of frequent genital

mycotic infections). Evidence-informed shared decision making can be facilitated using the interactive MATCH-IT tool (see box 1).

Combining medications

Most medications for which recommendations are provided can be used in combination (except for GLP-1 receptor agonists and tirzepatide, which have similar mechanisms of action). Clinicians and patients may choose to avoid combining candidate medications in certain contexts, including where the additive burden of administration or additive harms of treatment are substantial, or where additive benefits are not anticipated to be substantial. For example, adults taking multiple medications may choose to avoid adding another oral or subcutaneous treatment if the incremental benefit is small. Adults already taking medications with gastrointestinal side effects (such as metformin) may choose to avoid adding in other drugs with similar side effects (such as GLP-1 receptor agonists) if the cumulative risk of gastrointestinal events exceeds anticipated benefits or is perceived as being too large a harm overall. Here, treatment decisions are expected to vary across patients depending on the anticipated benefits a patient may derive from combined therapy, their risk of cumulative harms, and how they value the balance of these effects. Of note, recent evidence supports the additive effects of drugs with strong recommendations in favour of use (SGLT-2 inhibitors and GLP-1 receptor agonists in moderate and higher risk adults).[21 22]

Recommendations

Below we summarise risk-stratified recommendations, evidence regarding benefits and harms and their associated certainties, and rationales for judgments made by the panel.

To utilise these recommendations, users will first need to assess an individual's risk based on the risk stratification approach summarised above. Patients should ideally be involved in shared decision making. Critical remarks accompanying recommendations, applicability issues, and practical considerations for each medication are further detailed in MAGICapp (see box 1).

Adults at lower risk of cardiovascular and kidney complications

Adults with type 2 diabetes at lower risk are defined as those with three or fewer cardiovascular risk factors (not including diabetes) and without established CVD or CKD.

Recommendation 1: For adults at lower risk of cardiovascular and kidney complications, we suggest against using SGLT-2 inhibitors or GLP-1 receptor agonists (weak recommendation against)

Evidence—110 trials (86 803 participants) for SGLT-2 inhibitors and 109 trials (102 687 participants) for GLP-1 receptor agonists informed treatment effect estimates.

Understanding the recommendation—Given little or no benefit (high certainty evidence), risk of harms (genital mycotic infections for SGLT-2 inhibitors and severe gastrointestinal events for GLP-1 receptor agonists, both informed by moderate certainty evidence), and treatment burdens, the majority of adults were anticipated to be disinclined to accept SGLT-2 inhibitors or GLP-1 receptor agonists. A reasonable proportion of adults, however, were anticipated to be inclined to receive treatment in light of marginal cardiovascular and kidney benefits and the reversible nature of harms. The panel also considered possible longer term preventive benefits of initiating SGLT-2 inhibitors and GLP-1 receptor agonists early (for instance, to prevent progression to moderate or higher risk disease) balanced against concerns regarding potential harms, overtreatment, and pill burden from the patient perspective when formulating the recommendation. They judged that for most individuals at lower risk, both treatments were anticipated to yield marginal benefits over a five year time frame; and a large proportion of these individuals were unlikely to develop cardiovascular or kidney disease in the long term with or without treatment. Variability in anticipated decision making justified a weak recommendation against both medication classes and emphasised the need for shared decision making.

Adults with obesity and type 2 diabetes may be more inclined to receive GLP-1 receptor agonists in light of the associated reduction in body weight (moderate certainty evidence for several medications within the class).

Adults at moderate risk of cardiovascular and kidney complications

Adults with type 2 diabetes at moderate risk are defined as having either more than three cardiovascular risk factors (not including diabetes) without established CVD or CKD; or having established CVD or CKD at lower risk of complications.

Recommendation 2: For adults at moderate risk of cardiovascular and kidney complications, we suggest in favour of using SGLT-2 inhibitors or GLP-1 receptor agonists (weak recommendation in favour)

Evidence—110 trials (86 803 participants) for SGLT-2 inhibitors and 109 trials (102 687 participants) for GLP-1 receptor agonists informed treatment effect estimates

Understanding the recommendation—The cumulative cardiovascular and kidney benefits across outcomes (moderate to high certainty evidence) likely outweigh the risk of harms (genital mycotic infections for SGLT-2 inhibitors and severe gastrointestinal events for GLP-1 receptor agonists, both informed by moderate certainty evidence). A considerable majority of adults at moderate risk were anticipated to benefit and to be inclined to accept treatment, though a reasonable proportion were anticipated to be disinclined. Anticipated variability in decision making, particularly between adults with the lowest baseline risks (who may be most disinclined) and highest risks (who may be most inclined) for complications within the group, justified a weak recommendation in favour and underscores the need for shared decision making.

The choice between SGLT-2 inhibitors or GLP-1 receptor agonists is contextual and is likely to vary based on individual attributes, context, and values. When choosing between alternatives, patients should consider the relative impact of specific cardiovascular and kidney benefits and reduction in body weight offered by both medications. Adults with obesity are anticipated to place greater value on weight reduction and may be more inclined to consider GLP-1 receptor agonist initiation before considering SGLT-2 inhibitors. Recent evidence has demonstrated that the independent beneficial effects of each of the two medications is preserved regardless of background use of the other, supporting their use in combination where appropriate.[21 22]

Practical issues—See MAGICapp for details.

Recommendation 3: For adults with CKD at moderate risk of cardiovascular and kidney complications, we suggest against using finerenone (weak recommendation against)

Evidence—Two trials (13 026 participants) informed treatment effect estimates.

Understanding the recommendation—Given little or no benefit (moderate to high certainty evidence), risk of harms (particularly

severe hyperkalaemia, informed by moderate certainty evidence), comparatively limited clinical experience, resource considerations (including cost and access to therapy), and treatment burdens, the majority of adults were anticipated to be disinclined to accept therapy. A reasonable proportion, however, were anticipated to accept treatment in light of the possibility of marginal cardiovascular and kidney benefits. Variability in anticipated decision-making justified a weak recommendation against finerenone in this risk group and emphasised the need for shared decision making.

Adults at higher risk of cardiovascular and kidney complications

Adults with type 2 diabetes at higher risk are defined as having established CVD or CKD at higher risk of complications; or having established heart failure.

Recommendation 4: For adults at higher risk of cardiovascular and kidney complications, we recommend in favour of using SGLT-2 inhibitors or GLP-1 receptor agonists (strong recommendation in favour)

Evidence—110 trials (86 803 participants) for SGLT-2 inhibitors and 109 trials (102 687 participants) for GLP-1 receptor agonists informed treatment effect estimates.

Understanding the recommendation—Given the benefit on overall survival (high certainty evidence), important benefits on cardiovascular and kidney outcomes (moderate to high certainty evidence), and taking into account risk of harms (moderate certainty evidence) and treatment burdens, all or almost all higher risk patients with established disease were anticipated to be inclined to accept treatment; this justified a strong recommendation in favour. The panel also considered high certainty evidence of important benefits associated with SGLT-2 inhibitors for patients with established heart failure irrespective of diabetes status and agreed a strong recommendation in favour was in keeping with these established benefits.[23 24]

As summarised in Recommendation 2 and the "Choosing between medication alternatives" section above, the choice between SGLT-2 inhibitors or GLP-1 receptor agonists is contextual and is likely to vary based on individual attributes, context, and values. Adults with established heart failure may favour SGLT-2 inhibitors over alternatives. SGLT-2 inhibitors and GLP-1 receptor agonists can be combined.[21 22]

Practical issues—See MAGICapp for details.

Recommendation 5: For adults with CKD at higher risk of cardiovascular and kidney complications, we suggest in favour of using finerenone (weak recommendation in favour)

Evidence—Two trials (13 026 participants) informed treatment effect estimates.

Understanding the recommendation—The survival and kidney benefits (moderate certainty evidence) offered by finerenone likely outweigh the risk of harms (particularly hyperkalaemia requiring hospital admission, informed by moderate certainty evidence), uncertainties related to relatively limited clinical experience, resource considerations (including cost and access to therapy), and treatment burdens. Patients and clinicians are also likely to consider the availability of other medications with higher certainty evidence for cardiovascular and kidney benefits and safety (SGLT-2 inhibitors and GLP-1 receptor agonists). Taken together, a considerable majority of patients at higher risk were anticipated to accept therapy, though a reasonable proportion were anticipated to decline. Anticipated variability in decision making justified a weak recommendation in favour and underscores the need for shared decision-making.

Practical issues—See MAGICapp for details.

Adults across all risk groups, irrespective of likelihood of cardiovascular and kidney complications

Recommendation 6: For adults with obesity, we suggest in favour of using tirzepatide (weak recommendation in favour)

- Tirzepatide should not be given in combination with GLP-1 receptor agonists, but can be combined with SGLT-2 inhibitors and finerenone.
- When choosing between GLP-1 receptor agonists and tirzepatide, decision makers should weigh the higher certainty of cardiovascular and kidney benefits (offered by GLP-1 receptor agonists) against larger weight loss benefits (offered by tirzepatide).
- An interactive decision aid (MATCH-IT) facilitates visualisation of benefits and harms across multiple treatments to help facilitate shared decision making (box 1).
- In adults at higher risk of cardiovascular and kidney complications, tirzepatide should generally not replace medications effective in reducing the risk of these complications. If replacing a GLP-1 receptor agonist with tirzepatide, initiation or continuation of an SGLT-2 inhibitor is indicated.

Evidence—Six trials (2252 participants) informed treatment effect estimates.

Understanding the recommendation—For adults with diabetes and obesity, the large reduction in body weight (relative to 90 kg baseline weight, mean of 8.63 kg weight loss; moderate certainty evidence) need to be balanced against key uncertainties regarding effects on cardiovascular, kidney, and other outcomes (generally low or very low certainty evidence), risk of harms including severe gastrointestinal events (moderate certainty evidence), resource considerations (subcutaneous administration, access to therapy, and cost), and treatment burdens. The extent of weight reduction with tirzepatide is anticipated to vary across individuals, with those with higher baseline body weights likely to benefit from the largest reduction in absolute terms.

A large proportion of adults with obesity are likely to be classified as lower risk, with few or no other cardiovascular risk factors. Most of these individuals were anticipated to accept treatment with tirzepatide, given larger weight loss benefits relative to alternatives, though a reasonable proportion may not do so, warranting shared decision making and justifying a weak recommendation for the lower risk stratum. For patients with obesity at lower risk of cardiovascular or kidney complications, most adults were anticipated to choose tirzepatide over a GLP-1 receptor agonist, given superior weight loss effects.

For adults with obesity at moderate or higher risk of cardiovascular and kidney complications, decision making requires more nuance. A weak recommendation in favour is in place for SGLT-2 inhibitors or GLP-1 receptor agonists for all adults at moderate risk, irrespective of obesity status. A strong recommendation in favour is in place for both medications for higher risk individuals, given high certainty of benefit on key cardiovascular and kidney related outcomes. This leaves the residual question of how tirzepatide, with superior weight loss effects but currently uncertain cardiovascular and kidney benefits, should be positioned in the treatment of obese adults in either risk strata. For adults prioritising initiation of tirzepatide over

GLP-1 receptor agonist therapy due to larger weight loss effects, initiation or continuation of an SGLT-2 inhibitor is indicated.

The panel acknowledged that recommendations for tirzepatide may require updating in future iterations of the living guideline as more evidence accumulates regarding its effects on cardiovascular and kidney related complications.

Practical issues—See MAGICapp for details.

How this living guideline was created

Standards, methods, and processes for trustworthy guidance

This living *BMJ* Rapid Recommendation was developed in accordance with standards for trustworthy guidance from the Institute of Medicine,[11] and strives to meet criteria for methodological rigour.[25,26]

Who was involved?

We recruited an international guideline panel including patient partners living with diabetes (with and without established CVD or CKD), general practitioners, internists, endocrinologists, nephrologists, cardiologists, and methodologists. Panel members were diverse in geography, sex, and expertise. The panel collectively determined the scope of this guideline and formulated recommendations. Methods and clinical co-chairs were selected by the MAGIC Evidence Ecosystem Foundation to lead panel deliberations.

No panel member reported financial conflicts of interest. Intellectual conflicts of interest were minimised and managed.

What research did the guideline panel request and review?

The panel defined the clinical question and related population, intervention, outcomes, and subgroups of interest to be addressed by the guideline. To fully address the specified question, an independent team of epidemiologists, clinical experts, and biostatisticians updated a published systematic review and network meta-analysis examining benefits and harms of medications for type 2 diabetes.[7] Team members had expertise in GRADE methods.[27]

Two independent teams of researchers conducted systematic reviews of the literature to identify prognostic models for cardiovascular and kidney outcomes (summarised below and in box 1 above) and values and preferences of adults with diabetes pertaining to the four candidate medications in this first iteration.

What outcomes did the guideline panel request and review?

The panel initially identified six key patient-important outcomes to be addressed: all-cause death, non-fatal stroke, non-fatal myocardial infarction, hospitalisation for heart failure, kidney failure, and body weight change (weight loss). To comprehensively address treatment effects including harms and other diabetes-related complications, the panel additionally prioritised 13 other patient-important outcomes.

Panel members completed a survey to prioritise selected outcomes from the perspective of an average adult living with diabetes. The panel deemed the following outcomes as being of critical importance (rated 7 to 9 on a 9-point ordinal scale): all-cause death, non-fatal stroke, kidney failure, health-related quality of life, amputation, non-fatal myocardial infarction, hospitalisation for heart failure, blindness (data available for retinopathy), and dementia (data primarily available for major cognitive impairment).

The panel also deemed the following outcomes as being of importance (rated as 4 to 6 on a 9-point ordinal scale): diabetic ketoacidosis, severe hypoglycaemia, severe gastrointestinal events, body weight change, genital infections, urinary tract infections, hyperkalaemia requiring hospitalisation, neuropathy, fractures, and falls.

For adults with diabetes and obesity, the panel judged that weight reduction is likely to be critically important.

How did the panel formulate recommendations?

Pre-established standards, methods, and processes for the *BMJ* Rapid Recommendations for developing trustworthy guidelines were adopted.[25] The GRADE approach provided the framework for evaluating certainty of available evidence and determining the strength and direction of recommendations. With GRADE, recommendations can be strong or weak, and for or against a treatment or course of action.[27] Given the international scope of this guideline, the panel took a patient centred perspective. The panel assessed the balance between benefits, harms, and burdens of medication alternatives—including certainty of evidence—in light of assumed values and preferences of adults living with diabetes. This means that healthcare systems interested in adapting these recommendations need to consider resource use, applicability, feasibility, and equity considerations. For example, currently prohibitive costs of some medications means that they will not necessarily be cost-effective, suggesting a need for robust economic analyses and health technology assessments to inform reimbursement decisions.

In addition to outcome prioritisation, a second survey of panel members was conducted asking for preliminary judgments regarding the proportion of adults who, when presented with absolute treatment effects for risk-stratified outcomes informed by the linked systematic review,[7] were anticipated to choose to receive a candidate medication.

Panel meetings were subsequently facilitated by methods and clinical co-chairs, and were conducted on 5 April 2023, 29 May 2023, 1 June 2023, 5 December 2023, 22 January 2024, and 16 February 2024 via web conference. The panel reviewed survey results regarding outcome prioritisation and preliminary judgments regarding likelihood of accepting therapy. They reached agreement regarding an approach to risk stratification, patient values and preferences, and implicit thresholds for judging absolute effects as being either patient-important or unimportant (that is, trivial or having little or no effect). They subsequently reviewed Summary of Findings tables, providing absolute treatment effect estimates across prioritised outcomes and their respective certainty ratings. A consensus based approach was adopted to move from evidence to recommendations, with informal voting used to anchor discussions and facilitate consensus. When the panel was unable to reach a consensus by discussion, a priori voting rules were established; voting was limited to panel members with clinical expertise and to patient partners.

In addition to consideration of absolute benefits and harms for prioritised patient-important outcomes and associated certainty of the evidence, recommendations were informed by judgements regarding patient values and preferences, feasibility, and acceptability.[28] Issues related to equity were discussed but did not weigh heavily on deliberations when making recommendations. The panel also provided input regarding practicalities of administering candidate medications, and issues related to applicability of recommendations to specific groups, including individuals with obesity.

The linked systematic review and network meta-analysis[7] was updated as of July 2024 to include newly available evidence, with plans in place for regular updates moving forward. The parallel systematic review on patient values and preferences was updated to January 2025. Evidence was reviewed by the core methods team, who judged that no significant changes in the evidence base warranted re-evaluation of recommendations from the panel.

Guidance was drafted by the methods co-chair with direct input and contributions from clinical co-chairs, and was circulated for review to the panel. All feedback was incorporated, and the panel approved the final version of the guidance prior to submission.

What is the approach to prognosis and risk prediction for cardiovascular and kidney outcomes?

A detailed description of methods regarding prognosis, risk stratification, and establishment of baseline risks across prioritised outcomes is available in MAGICapp (see box 1).

How were values and preferences of patients incorporated?

In addition to direct input from patient partners, recommendations were informed by a systematic review of patient values, preferences, and treatment burdens associated with candidate medications. Results indicated that patients generally preferred SGLT-2 inhibitors, GLP-1 receptor agonists, and dipeptidyl peptidase 4 inhibitors over other therapies; that they did not have a clear preference between SGLT-2 inhibitors and GLP-1 receptor agonists; and that they preferred oral once daily or weekly injectable regimens, and to avoid complicated injection devices.

The panel accordingly made judgments regarding the values and preferences of typical well-informed patients with diabetes:

- Most adults are inclined to accept therapy when faced with moderate or high certainty of important benefits, and moderate or high certainty of little or no increased risk of harms
- Most adults are inclined to accept therapy when faced with moderate or high certainty of important benefits, and moderate or high certainty of potential harm where harmful outcomes are less patient-important
- The larger the potential benefits relative to potential risks, the more adults are inclined to accept therapy
- Most adults would be disinclined to accept therapy when faced with moderate or high certainty of little or no benefit, regardless of harms
- Most adults would be disinclined to accept therapy when faced with moderate or high certainty of potential harm for outcomes of critical patient importance
- The larger the potential harms relative to potential benefits, the more adults would be disinclined to accept therapy.

Given higher value placed on body weight change, adults with obesity were anticipated to be more inclined to accept medications with little or no cardiovascular and kidney benefit (or with low or very low certainty of any such benefits) but substantial weight loss effects.

When will the guideline be updated?

The guideline is planned for updates on an annual basis at minimum, and ideally every six months pending acquisition of adequate funding and resources. MAGICapp will display the most recent version of the guideline and full content including evidence summaries and decision aids; major updates will be published in *The BMJ*.

How patients were involved in the creation of this article

The panel included two patient partners with diabetes. Despite intensive efforts to recruit more patient partners with international representation, we encountered difficulty recruiting adults with lived experience of diabetes prior to guideline proceedings. The perspectives and contributions of the two patient partners involved were actively solicited and encouraged throughout the guideline process and were crucial in informing the values and preferences underlying recommendations. Future iterations of the guideline will prioritise increased patient partner representation.

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Main infographic: Summary of recommendations and evidence

Supplement 1: Summary of existing practice guidelines

Supplement 2: Approach to risk stratification of adults with established chronic kidney disease

Supplement 3: Selected prognostic models for risk stratification of adults with established cardiovascular disease