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Recommendations for the pharmacological treatment of hyperglycaemia in type 2 diabetes. Consensus document

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INTRODUCTION

Type 2 diabetes is a disease characterised by chronic hyperglycaemia secondary to a dual pathogenic mechanism: resistance to the action of insulin combined with a progressive decline in pancreatic insulin secretion. Insulin resistance usually remains throughout the evolution of the disease, but may improve with lifestyle changes (nutritional therapy and exercise), some drugs, and by achieving more favourable anthropometric characteristics. The progressive decline in pancreatic insulin secretion means that taking early and active action is advisable, increasing the dosis and the number of drugs to meet control targets.

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Some scientific societies[1-6] have drawn up consensus documents with recommendations regarding control targets, the staging of different drugs, and how to adapt both to patient characteristics. There is both agreement and discrepancies between these documents, caused by the lack of extensive randomized clinical trials which directly compare the different treatment guidelines. For this reason, the board of directors of the Spanish diabetes society (SED) decided to commission our Working Group to produce a document adapted as far as possible to the available evidence and the different recommendations to the situation in Spain, bearing in mind that the final treatment decision will always depend on the doctor, who must personalise treatment in accordance with patient characteristics. The Working Group considered that the document should be dynamic and must be updated regularly in accordance with any new evidence that emerges and the suggestions of members of the SED.

Components of the working group for consensus documents and clinical guidelines of the Spanish diabetes society:
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CONTROL TARGETS

Achieving good metabolic control can avoid or delay the onset of microvascular and macrovascular complications, as several long-term follow-up studies have shown both in patients with type 1 (DCCT/EDIC[7]) and type 2 diabetes (UKPDS[8]). However, strict glucose control of patients with late-stage diabetes with advanced complications or severe associated pathologies, does not improve cardiovascular prevention (ADVANCE[9] and VADT[10]), and may even increase mortality (ACCORD).[11] For that reason, a very strict control is recommended in the early stages of diabetes treatment (glycosylated haemoglobin [HbA_{1c}]<6.5%) provided that the patient is under 70 years old, has no advanced microvascular or macrovascular complications at the time of diagnosis or is suffering from an associated pathology that needs to avoid hypoglycaemia. In these cases, a control target of HbA_{1c} <7.5% is recommended, or the lowest possible level, giving priority to safe treatment, adapted to the patient's situation and compatible with the drugs combined. Generally, after a 10 year course of the disease, monotherapy is usually inadequate and most patients will need combined treatment, often insulin. In these situations, it may be advisable to raise the control target to HbA_{1c}<7.5%, unless the classic target of 7% is feasible, patient safety always coming first.

We must not forget that hyperglycaemia is another risk factor in patients with diabetes and that there are other associated risk factors such as dyslipidaemia, high blood pressure, obesity or tobacco smoking. These will determine, to a great extent, the possible onset of complications and patient survival. For this reason, although not within the scope of this document, we explicitly recommend that these risk factors are kept under control as it is an approach which has proven to be very effective (STENO-2[12]).

THERAPEUTIC INERTIA

After the onset of treatment, or if changes are introduced, it is necessary to assess a series of aspects: metabolic control by the determination of HbA_{1c} and with capillary glucose profiles (when indicated); tolerance to modifications; and the progress of the complications and associated pathologies.

This will all take place approximately every 3 months after the acute phase of the treatment modification, and at least until symptoms have stabilized. After that, when the targets have been reached, all patients will have a check-up at least twice a year. If the modifications have not been effective at achieving control targets in the first 3-month period, with no intercurrent diseases or drug use to justify it, it will be necessary to intensify treatment and do not delay decision-making. It is extremely important to maintain good metabolic control, above all in patients with diabetes of short evolution who may be asymptomatic despite not having met control targets. The main barrier for intensifying the treatment is that the change of therapy requires additional diabetic education, for example, with the introduction of insulin secretagogues or insulin, situations which we must have accounted for to avoid unnecessary delays.

If it is important to establish action guidelines for doctors and nursing staff and for pharmacotherapeutic monitoring by pharmacists when increasing doses. It is just as important as planning the necessary treatment modifications when faced with acute intercurrent conditions that can cause dehydration or food intake problems (fever, vomiting, diarrhoea, etc.) These conditions can make the patient's usual treatment unsafe and make it necessary to modify it urgently.[13]

TREATMENT STAGING

Nowadays we have a series of drugs for treating diabetes, such as metformin, sulphonylureas, glinides, thiazolidinediones, disaccharidase inhibitors, dipeptidyl peptidase 4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists. Together with insulin, these can be used in monotherapy or in combination. These drugs must be used after studying their respective data sheets. Some combinations have been proven to be safe, others are not recommended, and the long-term safety of others in not known. The choice of treatment will depend on: the potential to reduce HbA_{1c}; the risk of causing hypoglycaemia and the previous degree of control; its influence on body weight and dyslipidaemia; its preferential impact on basal or prandial blood glucose; the complications or associated pathologies suffered by the patient; the risk of side effects related to the drug; its tolerance; and the cost (Table 1).

The initial drug treatment will vary depending on the previous degree of control, the patient's age, whether there are associated diseases, and the concomitant use of other medication. As the algorithm shows (Figure 1), treatment will begin with one drug, with two drugs being considered in a second step. Lastly, insulinisation or triple therapy may be necessary if the patient's degree of control makes it recommendable.

FIRST STEP

Patients with HbA1c between 6.5% and 8.5%

In some cases glucose control goals (HbA_{1c}<6.5%) can be achieved with some changes in lifestyle,[14] although this is not always effective, since it depends on the characteristics of the patients and their level of compliance with the recommendations. For this reason, the SED recommends combining lifestyle changes with metformin treatment as a

Table 1. Main characteristics of oral antidiabetic drugs

	Risk of hypoglycaemia	Advantages	Disadvantages	Contraindications
Metformin	No	• No weight gain • Improves lipid profile and other cardiovascular risk markers • Reduction of mortality and marcrovasuclar complications in obese patients (UKPDS)	•Digestive side effects (titrate dose) • Lactic acidosis (very uncommon) • Interferes with absorption of vitamin B12	• GFR<60ml/min • Severe heart failure • Liver failure • Respiratory failure • Alcoholism • Use of iodine contrasts
Sulphonylureas	• Glibenclamide (significant) • Gliclazide (moderate/minimal) • Glimepiride (moderate)	• Reduction of microvascular complications (UKPDS/ADVANCE)	• Weight gain • Reduced duration of a hypoglycaemic effect compared with metformin and glitazones	• Severe kidney failure (GFR<30ml/min) • Severe liver failure • Sulphonamide allergy
Glinides	• Repaglinide (moderate) • Nateglinide (minimal)	• No contraindications for mild-moderate kidney failure • Reduces postprandial glucose levels	• Weight gain • Do not combine repaglinide with gemphibrozil	• Severe liver failure
Thiazolidinediones or glitazones	No	• No contraindications for moderate kidney failure • Pioglitazone improves lipid profile and other cardiovascular risk markers • Longer-lasting glucose control (compared with metformin and sulphonylureas)	• Weight gain • Oedemas • Increased incidence of heart failure • Increase in limb fractures in women • 6-12 weeks are needed to assess the maximum effect	• Heart failure • Liver failure • Rosiglitazone: - Ischaemic cardiomyopathy - Peripheral vascular disease - In combination with insulin
Alpha-glycosidase inhibitors	No	• No weight gain • Reduce postprandial glucose levels • Reduction in mortality and cardiovascular complications	• Adverse GI effects • Low efficacy if diet is low in CH • Hypoglycaemia must be treated with pure glucose	• Miglitol - GFR<60ml/min • Acarbose - GFR<30ml/min • Severe liver failure • Chronic intestinal disease
DPP-4 inhibitors	No	• No weight gain • Reduce above all postprandial glucose levels	• Cases of acute pancreatitis have been reported • Unknown long-term benefits and safety • Vildagliptin: contraindicated with insulin, monotherapy and triple therapy	• GFR<50ml/min • Vildagliptin: - Liver failure or ALT or AST>3xULN
GLP-1 receptor agonists	No	• Weight loss • Reduction in BP • Improved lipid profile • Reduce above all postprandial glucose levels	• Subcutaneous administration • Digestive side effects (nausea, vomiting, diarrhoea) • Cases of acute pancreatitis have been reported • Unknown long-term benefits and safety • Contraindicated with insulin, and in monotherapy and triple therapy	• GFR<30ml/min • Severe gastrointestinal disease

GFR: glomerular FILTRATION RATE; GI: gastro intestinal; CH: Carbohydrates.

first step in most patients.[15,16] In any case, delaying the introduction of metformin by over 3 months is not recommendable if control goals have not been reached. To improve tolerance to this drug, a progressive titration of the dose is recommended[17]; for example, half a 850-1000mg pill at first, increasing to half a pill every 12 hours after 4-5 days if it is well tolerated until reaching a dose of 850 to 1000mg every 12 hours. If intolerance is observed, the dose must be

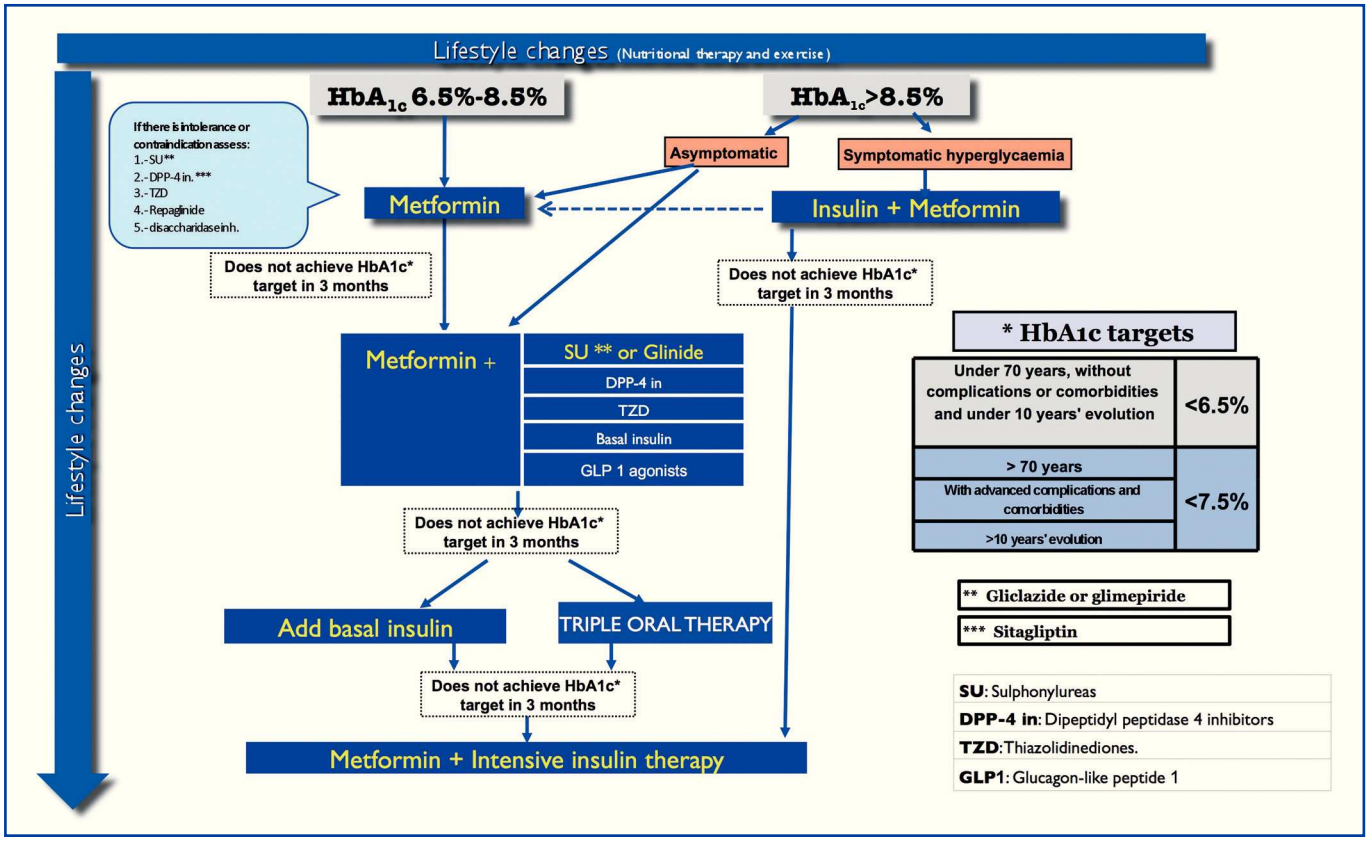

Figure 1. 2010 algorithm of the Spanish Diabetes Society for the pharmacological treatment of hyperglycaemia in type 2 diabetes

lowered again to the previously tolerated level, then increasing the dose again more gradually.

The following alternatives are proposed to treatment with metformin in the event of contraindication or intolerance:

First alternative: sulphonylureas. With the control goal of HbA_{1c}<6.5%, these potent secretagogues pose a significant risk for hypoglycaemia, although this risk differs depending on the active ingredient used.[18-20] For this reason, a very careful dose titration is recommended, preferably using slow-release gliclazide or glimepiride. The use of glibenclamide or chlorpropamide is not recommended. Some studies show that sulphonylureas cause secondary beta-cell failure earlier than metformin or glitazones.[21] They have also been associated with a 1-3kg increase in bodyweight.[22-23] Some guidelines do not recommend them in this treatment step.

Second alternative: DPP-4 inhibitors. Their use has obvious advantages in this treatment stage as an alternative when metformin is not well tolerated. The risk of hypoglycaemia is minimal in monotherapy and they do not affect the patients' bodyweight.[24-25] Nowadays, their main limitations are based on the lack of studies showing their long-term efficacy and safety, as well as their high cost. To date, only sitagliptin has been approved for this indication,[26] although other active principles of the same family are awaiting authorisation.[27,28]

Third alternative: glinides. The option in this step is repaglinide.[29] Nateglinide must be used in combination due to it pharmacodynamic profile and potency.[30] In principle, repaglinide has the same limitations as sulphonylureas, but due to its characteristics and method of administration, it can have a stronger effect on patients with irregularities in diet and physical activity.[31,32]

Fourth alternative: thiazolidinediones or glitazones. Between 10 and 12 weeks are needed for them to reach their maximum efficacy, and they have an HbA_{1c}-lowering potency similar to metformin and sulphonylureas. Of note among their possible side effects are weight gain, the onset of oedemas, anaemia, fractures, and heart failure in some groups of patients,[33-35] which have limited their indications. It is not totally clear if there are differences between rosiglitazone and pioglitazone, as several observational studies have suggested.[36] Thus the matter will remain open until studies specifically comparing the two molecules have been performed. They may play a more relevant role in patients with severe metabolic syndrome[37] and/or those with non-alcoholic liver steatosis.[38]

Fifth alternative: disaccharidase inhibitors. They have less potency than the drugs mentioned above and, in monotherapy, they are not associated with hypoglycaemias. Their biggest limitation is intestinal intolerance, which makes it necessary to suspend treatment in a high percentage of patients.[39] Their biggest advantage is that they seem to significantly reduce cardiovascular risk (STOP-NIDDM[40]). There are two preparations on the market: acarbose and miglitol.

Sixth alternative: basal insulin. This is reserved in this step for patients with contraindications for oral drugs.

Initial treatment for patients with HbA_{1c}>8.5%

In patients with severe hyperglycaemia (cardinal symptoms and/or weight loss) on the onset, it is often necessary to begin insulin treatment,[41-43] alone or in combination with metformin. After the initial control and improvements in glucotoxicity and lipotoxicity, there will be a progressive decrease in the need for insulin, and in some cases control can be maintained with oral medication, either in monotherapy or in combination.

With asymptomatic patients, treatment should begin with metformin, with a faster titration and, depending on the response, combine this with another drug.[44] The short-term outcome should be monitored to modify the definitive treatment.

SECOND STEP

It is necessary to combine a second drug with patients who have not met the control goals or whose condition deteriorates after a period of good control due to the evolution of the diabetes (if there is no associated pathology or drug that increases blood glucose).

There is a lack of long-term comparative studies for most drug combinations, which makes decision-making difficult. In principle, combinations of drugs should be used which have different and complimentary mechanisms of action. Depending on the response, increased amounts of the drug should be given until reaching the maximum effective dose, just below than the maximum allowed. It is also necessary to bear in mind that the contraindications, limitations of use and possible side effects are the same as those for both drugs separately.

Combinations with metformin

Sulphonylureas and glinides. The association of metformin and sulphonylureas is the most widely studied combination and has proven efficacy and safety[42-45] although a doubt still lingers about the increase in mortality observed in subgroups such as the UKPDS[46] in patients who began treatment with sulphonylureas and combined that treatment with metformin in a second step. There are several observational studies which have considered this matter,[47-51] with some discrepancies between the results. However, these are results which may be different to those obtained with more recent pharmacological preparations. The risks for the control target (HbA_{1c}<6.5%) are similar to those observed in monotherapy, so the same recommendations apply. Glinides are a good alternative to sulphonylureas in patients with a more irregular food intake, due to their short action profile, and also in patients allergic to sulphamides or, in the case of repaglinide, in patients with moderate kidney failure.[52] Regarding the risk of hypoglycaemia and weight gain, both drugs can be considered superposable, with a lower potency than nateglinide[53] and similar to repaglinide.[54]

DPP-4 inhibitors. Together with GLP-1 receptor agonists, they form a new group of secretagogues which act upon both the secretion of insulin and glucagon. The obvious advantages compared with sulphonylureas and glinides are a low risk of hypoglycaemia and their neutral effect on weight.[55,56] However, neither their long-term safety nor their influence on the outcome of diabetes and its complications are known. Their potency does not seem to be lower than that of sulphonylureas in terms of the reduction of HbA_{1c}.[57,58] They could be the treatment of choice for patients that cannot undergo hypoglycaemia.

GLP-1 receptor agonists. These are parenteral drugs which achieve a more intense and prolonged effect on GLP-1 receptors than that of DPP-4 inhibitors. Published studies have reported that they achieve short-term improvements in glucose control, above all of prandial glucose, but also basal glucose levels.[59] They slow down gastric emptying causing a feeling of satiety, obtaining sustained weight loss in a high percentage of patients.[60,61] Furthermore, they improve some vascular risk factors.[62] In Spain, exenatide has been authorised for sale for parenteral administration twice a day (before main meals with a time interval between each of at least 6 hours) in combination with metformin and/or sulphonylureas; and combined with metformin with glitazones[63] in patients with a body mass index over 30kg/m^2. At the time of writing this guide, the marketing authorisation for liraglutide[64] is pending, so we recommend studying its data sheet to assess its indications and limitations of use. They can be a very useful group of drugs in patients with significant obesity problems, but their effectiveness compared with other drugs or other treatment approaches such as surgery has still to be defined.

Thiazolidinediones. These drugs increase sensitivity to insulin via a different mechanism to metformin, so they are commonly used in combination.[65-68] In principle, they are

mainly indicated in patients with good prandial glucose control and with an increase in basal blood glucose which is not totally corrected by metformin. The side effects are similar to those of each drug separately, so the limitations remain the same as in monotherapy.

Basal insulin. Combination therapy with basal insulin and metformin is a good, safe option with proven efficacy.[69-71] It is preferably indicated in patients with good prandial control, but with HbA_{1c} levels above the target. Although there is an increase in the number of hypoglycaemic events with this regimen, these are still much less frequent than in patients with multiple doses of insulin. It is a good alternative for patients with whom treatment with glitazones has limitations.

Disaccharidase inhibitors. They are safe in combination with metformin as no hypoglycaemic events will occur, but their efficacy is very limited, with reductions in HbA_{1c} which barely exceed 0.5%.[72] Their main limitation is digestive intolerance. Thus, they are not recommended as an alternative to a second drug in this treatment step.

THIRD STEP

In patients treated with 2 drugs and with poor metabolic control, the next treatment step is insulinisation. Except in cases of insulin resistance, there are no reasons for delaying the introduction of insulin in the treatment regime after double combination therapy has failed. The long-term benefit and safety of a triple oral therapy compared with insulin treatment are unclear, as monitoring in clinical trials has not exceeded 12 months.

Combinations without insulin

Among the different valid combinations of oral drugs, the combination of metformin, sulphonylurea and glitazone has been most widely studied and is the most commonly used in clinical practice. Therefore, it would be the recommended combination for most patients with type 2 diabetes and poor control with a dual drug therapy.[73-77] With elderly patients,[78] the combination of metformin, repaglinide and glitazone may be the safest option. In those patients for whom there are limitations to the use of glitazones, the most reasonable alternatives are metformin together with sulphonylureas and DPP-4 inhibitors,[79] or metformin with repaglinide and DPP-4 inhibitors.[80] The drawback of these combinations is that they have been less studied.

Combinations with insulin

Most patients will have received treatment with combinations of metformin and insulin secretagogues. In these cases basal insulin will be added in combination. If the clinical course is over 10 years and/or there are complications or intercurrent pathologies, the control target for HbA_{1c} will be revised to below 7.5% or as low as possible, bearing in mind patients safety. This regimen may lead to a period of good, but not excessively prolonged, glucose control, according to the results of the 4T study.[81] Therefore, at around 3 years most patients will require a more intense insulin regimen. In this instance, maintaining treatment with metformin in combination with insulin is recommended, and the rest of the oral diabetes treatment will be suspended.

FOURTH STEP

Although a quadruple therapy regimen is a possible approach (due to the different pathophysiological pathways from a pharmacological viewpoint), we consider that this belongs more to the field of research than to clinical practice.

CONCLUSIONS

Once lifestyle changes have been established, the target of the pharmacological treatment of type 2 diabetes will be to achieve optimal metabolic control with the maximum possible safety. The target should be HbA_{1c}<6.5% in the early stages of the disease and <7.5% in the more advanced stages, or in patients with a risk of hypoglycaemic events.

The treatment is divided into three treatment steps. First, if the hyperglycaemia is not severe (HbA_{1c}: 6.5%-8.5%), metformin is the medication of choice. Alternative drugs will only be used in patients with intolerance or contraindications. If blood glucose levels are high (HbA_{1c}>8.5%), the initial treatment must begin with several oral drugs in combination or with insulin. The second step involves adding a second synergistic drug. Several options are available for this, but patients must receive personalized treatment in accordance with their characteristics. Lastly, the third step involves introducing basal insulin as the option of choice rather than triple oral therapy, which is reserved only for cases of resistance to insulin.

ADDENDUM TO THE CONSENSUS DOCUMENT "RECOMMENDATIONS FOR THE PHARMACOLOGICAL TREATMENT OF HYPERGLYCAEMIA IN TYPE 2 DIABETES"

On 23rd September 2010, the EMEA decided to suspend the marketing authorisations for rosiglitazone-containing anti-diabetes medications (Avandia®, Avandamet® y Avaglim®) as

it considers that the possible risks outweigh the pharmacological benefits. In this context, the FDA has decided to maintain its marketing authorisations, but has proposed a series of measures of pharmacovigilance. The FDA considers that the data about the possible increase in cardiovascular risk associated with rosiglitazone are controversial and not definitive. An independent verification of the results of the RECORD study has been requested.

List of acronyms included in the text:

4T: Treating-To-Target in Type 2 diabetes; ACCORD: Action to Control Cardiovascular Risk in Diabetes; ADVANCE: Action in Diabetes and Vascular disease: preterAx DiamicroN MR Controlled Evaluation; DPP-4: dipeptidyl peptidase 4; GLP-1: glucagon-like peptide 1); HbA1c: glycosylated haemoglobin; SED: Spanish diabetes society; STENO-2: Steno-2 Study; STOP-NIDDM: Study to prevent NIDDM; UKPDS: United Kingdom Prospective Diabetes Study; VADT: Veterans Affairs Diabetes Trial.

Sponsored by the Spanish diabetes society (SED) in collaboration with:

- Spanish atherosclerosis society (SEA)
- Spanish cardiology society (SEC)
- Spanish society of endocrinology and nutrition (SEEN)
- Spanish society of community pharmacy (SEFAC)
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- Spanish nephrology society (S.E.N.)

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