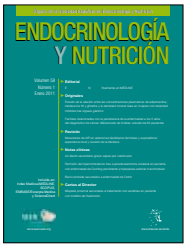
Endocrinol Nutr. 2011;**58(3):**112–120

ENDOCRINOLOGÍA Y NUTRICIÓN

www.elsevier.es/endo



CONSENSUS DOCUMENT

Recommendations for the pharmacological treatment of hyperglycemia in type 2 diabetes☆,☆☆

Recomendaciones para el tratamiento farmacológico de la hiperglucemia en la diabetes tipo 2

Edelmiro Menéndez Torre[a,*], Francisco Javier Lafita Tejedor[a], Sara Artola Menéndez[a], Jesús Millán Núñez-Cortés[b], Ángeles Alonso García[c], Manuel Puig Domingo[d], José Ramón García Solans[e], Fernando Álvarez Guisasola[f], Javier García Alegría[g], Javier Mediavilla Bravo[h], Carlos Miranda Fernández-Santos[i], Ramón Romero González[j]

[a]*On behalf of the Working Group for Consensus and Clinical Guidelines of the Sociedad Española de Diabetes, Spain*
[b]*Sociedad Española de Arteriosclerosis (SEA), Spain*
[c]*Sociedad Española de Cardiología (SEC), Spain*
[d]*Sociedad Española de Endocrinología y Nutrición (SEEN), Spain*
[e]*Sociedad Española de Farmacia Comunitaria (SEFAC), Spain*
[f]*Sociedad Española de Medicina Familiar y Comunitaria (SEMFYC), Spain*
[g]*Sociedad Española de Medicina Interna (SEMI), Spain*
[h]*Sociedad Española de Médicos de Atención Primaria (SEMERGEN), Spain*
[i]*Sociedad Española de Médicos Generales y de Familia (SEMG), Spain*
[j]*Sociedad Española de Nefrología (SEN), Spain*

Received 28 June 2010; accepted 16 July 2010

Introduction

Type 2 diabetes is a condition characterized by chronic hyperglycemia secondary to a dual pathogenetic mechanism: resistance to insulin action associated with progressive failure in pancreatic insulin secretion. Insulin resistance usually continues throughout the course of the disease, but may be improved with lifestyle changes (nutritional therapy and exercise), the achievement of more favorable anthropometric characteristics, and some drugs. Progressive failure in pancreatic insulin secretion should lead to early and active action being taken, with a gradual increase in

☆See Annex at the end of the article.

☆☆In agreement with authors and editors, this article is published in whole in the following publications: Avances en Diabetología (Av Diabetol. 2010;26:331-8), Atención Primaria (Aten Primaria. 2011. doi:10.1016/j.aprim.2010.07.012), Semergen (Semergen. 2011.doi:10.1016/j.semerg.2010.11.002) and Clínica e Investigación en Arteriosclerosis (Clin Invest Arterioscl. 2011. doi: 10.1016/j.arteri.2011.01.007) and Revista Clínica Española (Rev Clin Esp. 2011. 10.1016/j.rce.2010.11.006).

*Corresponding author.
E-mail address: edelmiro.menendez@sespa.princast.es (E. Menéndez Torre).

both the dosage and number of drugs to maintain control objectives.

Some scientific societies[1-6] have prepared consensus documents with recommendations regarding control objectives, stepped use of the different drugs, and the adaptation of both to the patient's characteristics. Such documents show both similarities and discrepancies because of the difficulties resulting from the lack of randomized, adequately powered clinical trials directly comparing the different treatment schemes recommended. The Board of the Spanish Society of Diabetes (SED) thus decided to commission our Working Group to prepare a document in which the available evidence and the different recommendations were adapted to the situation in Spain, taking into account that the final therapeutic decision will always depend on the physician, who must consider the specific characteristics of each patient. The Working Group considered that this document should be dynamic and regularly updated to take account of incoming evidence and on suggestions from SED members.

Control objectives

The achievement of good metabolic control may prevent or delay the occurrence of microvascular and macrovascular complications, as has been shown by various studies with long-term follow-up times in patients with both type 1 (DCCT/EDIC)[7] and type 2 diabetes (United Kingdom Prospective Diabetes Study [UKPDS])[8]. By contrast, if strict glycemic control is performed in patients with long-standing diabetes, advanced complications, or severe associated diseases, not only is a greater cardiovascular prevention not achieved (Action in Diabetes and Vascular disease: preterAx DiamicroN MR Controlled Evaluation [ADVANCE][9] and Veterans Affairs Diabetes Trial [VADT][10]), but mortality may even increase (Action to Control Cardiovascular Risk in Diabetes [ACCORD])[11]. Very strict control is therefore recommended in the early phases of diabetes treatment (glycosylated hemoglobin [HbA_{1c}] < 6.5%), provided that the patient is not older than 70 years and has no advanced microvascular or macrovascular complications at the time of diagnosis or any associated diseases that make it advisable to avoid hypoglycemia. In this case, the recommended control HbA_{1c} value would be < 7.5% or the best possible that would ensure treatment safety, adapted to the patient's condition and compatibility with concurrent drugs. It is generally admitted that approximately 10 years after disease onset, monotherapy is usually inadequate, and most patients will require combined treatment, often with insulin. When this occurs, it may be advisable to increase the control goal to HbA_{1c} < 7.5% unless the traditional 7% goal is feasible and safe.

It should be borne in mind that hyperglycemia is only one of the cardiovascular risk factors in diabetic patients and that there are other associated risk factors such as dyslipidemia, hypertension, obesity, and smoking. These will greatly condition the potential occurrence of complications and patient survival. Thus, although it is beyond the scope of this document, the monitoring of these risk factors is expressly recommended as it has been shown to be highly effective (STENO-2)[12].

Therapeutic inertia

After treatment has been started, or if it has been changed, a number of aspects, such as metabolic control, should be assessed by measuring HbA_{1c} and evaluating capillary blood glucose profiles (when appropriate), tolerability of changes made, and the course of associated complications and diseases.

This must be done approximately every 3 months following the acute phase of treatment adjustment, and at least until the condition stabilizes. Then, when goals have been achieved, all patients must be monitored at least twice every year. If the changes made have not been effective in achieving the control objective in the initial 3 months and such failure has not been due to intercurrent diseases or use of drugs, treatment should be intensified and decision taking should not be delayed. It is extremely important to maintain good metabolic control, particularly in patients with recent onset of the disease, who may be asymptomatic despite failure to achieve the control objectives. The main barriers to treatment intensification may occur when a change in treatment requires an additional diabetological education process, as may occur for instance when secretagogues or insulin are started. These situations should be anticipated so as to avoid unnecessary delay.

It is important to plan medical and nursing action guidelines and drug treatment monitoring by the pharmacist for dose intensification, but it is equally important to plan the changes in treatment required by acute intercurrent conditions that may cause some degree of dehydration or difficult intake (febrile syndrome, vomiting, diarrhea, and so on). These conditions may make the current treatment of the patient unsafe and require its urgent modification[13].

Stepwise treatment

A number of drugs are currently available for the treatment of diabetes, including metformin, sulfonylureas, glinides, thiazolidinediones, disaccharidase inhibitors, dipeptidyl-peptidase 4 (DPP-4) inhibitors, and glucagon-like peptide-1 (GLP-1) receptor agonists, which, together with insulin, may be used as monotherapy or in combination. These drugs should be used after consideration of their respective prescribing information; some combinations have been shown to be safe, others are not recommended, and for still others long-term safety is unknown. The choice of treatment will depend on its potency to decrease HbA_{1c}, the risk of inducing hypoglycemia and the degree of prior control, its influence on body weight and dyslipidemia, its preferential impact on basal or post-prandial blood glucose, any associated complications or diseases of the patient, the risk of drug-related adverse effects, tolerability, and cost (Table 1).

Initial drug treatment will vary depending on the prior degree of control, age, the presence of concurrent diseases, and the concomitant use of other drugs. As shown in the algorithm (Fig. 1), treatment will usually start with a single

Table 1 Main characteristics of oral antidiabetic drugs

	Risk of hypoglycemia	Advantages	Disadvantages	Contraindications
Metformin	No	• No weight increase • Improves lipid profile and other cardiovascular risk markers • Decreased mortality and macrovascular complications in obese patients (UKPDS)	• GI adverse effects (titrate dose) • Lactic acidosis (very rare) • Interferes with vitamin B12 absorption	• GFR <60 mL/min • Severe heart failure • Liver insufficiency • Respiratory insufficiency • Alcoholism • Use of iodinated contrasts
Sulfonylureas	• Glibenclamide (significant) • Gliclazide (moderate/minimum) • Glimepiride (moderate)	• Decreased microvascular complications (UKPDS/ADVANCE)	• Weight increase • Shortened duration of hypoglycemic efficacy as compared to metformin and glitazones	• Severe renal failure (GFR < 30 mL/min) • Severe liver insufficiency • Allergy to sulfonamides
Glinides	• Repaglinide (moderate) • Nateglinide (minimum)	• Not contraindicated in mild to moderate renal failure • Reduce post-prandial blood glucose	• Weight increase • Do not combine repaglinide with gemfibrozil	• Severe liver insufficiency
Thiazolidinediones or glitazones	No	• Not contraindicated in moderate renal failure • Pioglitazone improves lipid profile and other cardiovascular risk markers • Longer glycemic control (as compared to metformin or sulfonylureas)	• Weight increase • Edema • Increased incidence of heart failure • Increase limb fractures in females • 6-12 weeks are required for maximum effect	• Heart failure • Liver insufficiency • Rosiglitazone: - Ischemic heart disease - Peripheral vascular disease - Combined with insulin
Alpha-glycosidase inhibitors	No	• No weight increase • Reduce post-prandial blood glucose	• GI adverse effects • Low efficacy if diet poor in CHs • Decreased mortality and cardiovascular complications • Hypoglycemia should be treated with pure glucose	• Miglitol - GFR < 60 mL/min • Acarbose - GFR < 30 mL/min • Severe liver insufficiency • Chronic intestinal disease
DPP-4 inhibitors	No	• No weight increase • Mainly reduce post-prandial blood glucose	• Acute pancreatitis has been reported • Unknown long-term benefits and safety • Vildagliptin: not indicated with insulin, as monotherapy, or in triple therapy	• GFR < 50 mL/min • Vildagliptin: - Liver insufficiency or ALT or AST > 3 x UNL
GLP-1 agonists	No	• Weight decrease • BP decrease • Lipid improvement • Mainly reduce post-prandial blood glucose	• Subcutaneous administration • GI adverse effects (nausea, vomiting, diarrhea) • Acute pancreatitis has been reported • Unknown long-term benefits and safety • Not indicated with insulin, as monotherapy, or in triple therapy	• GFR < 30 mL/min • Severe GI disease

CHs, carbohydrates; GFR, glomerular filtration rate; GI, gastrointestinal.

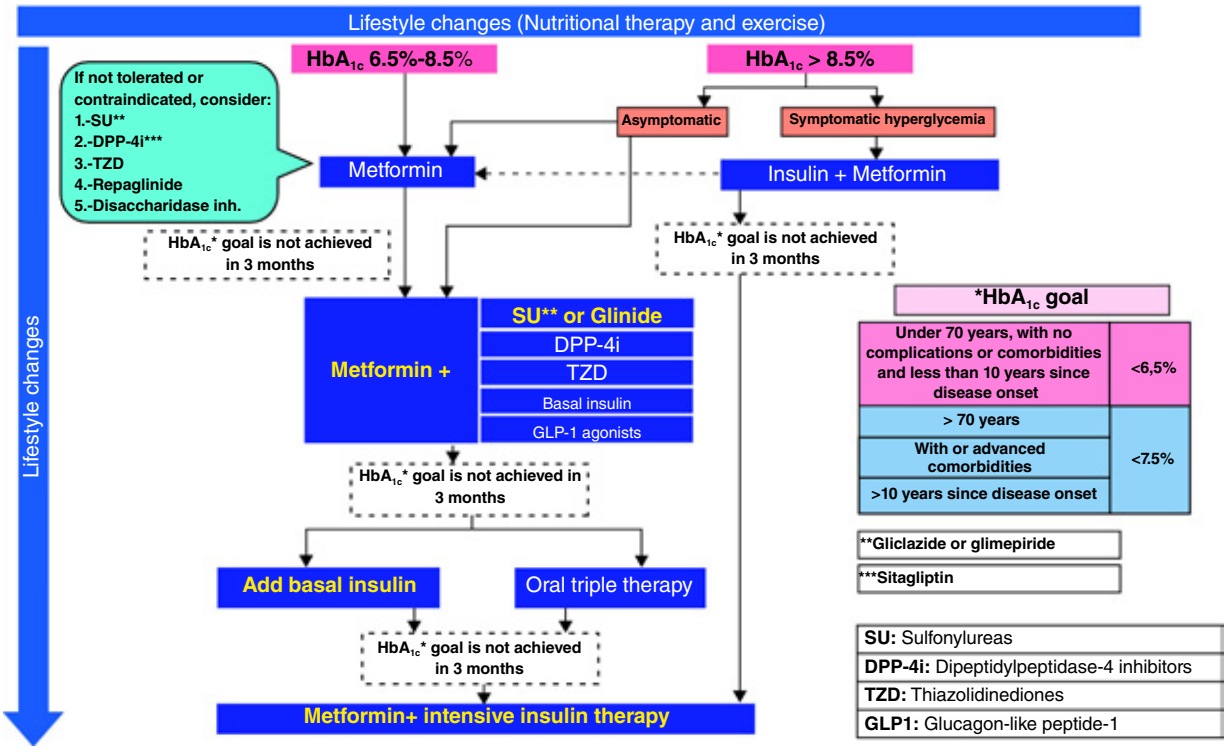


Figure 1 2010 algorithm of the Spanish Society of Diabetes for drug treatment of hyperglycemia in type 2 diabetes.

drug, and two-drug treatment will be considered as a second step. Insulin or triple therapy may finally be required if the degree of control in the patient makes it advisable.

First step

Patients with HbA_{1c} values ranging from 6.5% to 8.5%

The control goal (HbA_{1c} < 6.5%) may be achieved in some patients with some lifestyle changes[14], but this approach is not always effective because it depends on the patient's characteristics and how well the patient follows the recommendations made. The SED thus recommends concomitant administration of metformin from the start in most patients[15,16]. In any case, the introduction of metformin should not be delayed for longer than 3 months if the control goal has not been achieved. To improve metformin tolerability, gradual dose titration is advised[17]. For example, half an 850-1,000 mg tablet may initially be given, which is increased to half a tablet every 12 h at 4-5 days if tolerability is good, and so on until a dose of 850-1,000 mg every 12 h is reached. If intolerance occurs, the drug should be reduced to the prior dose tolerated and dose increase should be attempted again with a longer time interval.

Alternatives to treatment with metformin if this is contraindicated or not tolerated include:

- *First alternative: sulfonylureas.* With a control goal of HbA_{1c} < 6.5%, as potent secretagogues they involve a significant risk of hypoglycemia, but the risk is different depending on the active ingredient used[18-20]. A very careful dose titration and the preferential use of sustained release gliclazide or glimepiride should be considered. The use of glibenclamide or chlorpropamide is not recommended. Some studies suggest that sulfonylureas induce secondary beta cell failure sooner than metformin or glitazones[21]. They are also associated with a 1-3 kg weight increase[22,23]. Some guidelines do not recommend them in this treatment step.
- *Second alternative: DPP-4 (dipeptidylpeptidase-4) inhibitors*. These have clear advantages for use in this treatment step as an alternative to metformin if this is not tolerated. They involve a minimum risk of hypoglycemia when given as monotherapy and have no impact on patient weight[24,25]. Today, the main limitations on their use are the lack of studies showing their long-term efficacy and safety, and their high price. To date, only sitagliptine[26] has been approved for this indication, although other active ingredients of the same class are pending authorization[27,28].
- *Third alternative: glinides.* The option in this step is repaglinide[29]. Nateglinide should be used in combination because of its pharmacodynamic characteristics and potency[30]. In principle, it has the same limitations as sulfonylureas, but because of its characteristics and form of administration it may be suitable for patients with irregularities in diet and physical activity[31,32].
- *Fourth alternative: thiazolidinediones or glitazones*. These require 10 to 12 weeks for maximum efficacy, and have a potency in terms of HbA_{1c} reduction similar to

metformin and sulfonylureas. Their potential side effects include weight increase, edema, anemia, fractures, and heart failure in some patient groups[33-35], which have limited their indication. In addition, it has not been clearly elucidated whether differences exist between rosiglitazone and pioglitazone, as has been suggested by some observational studies[36], and the question thus remains open until studies directly comparing both molecules are completed. These drugs may have a more relevant role in patients with severe metabolic syndrome[37] and/or non-alcoholic steatohepatitis[38].

- *Fifth alternative: disaccharidase inhibitors.* These are less potent than the drugs mentioned above and are not associated with hypoglycemia when given as monotherapy. Their greatest limitation is intestinal intolerance, which requires treatment discontinuation in a high proportion of patients[39]. Their greatest benefit is that they appear to significantly improve cardiovascular risk (STOP-NIDDM)[40]. Two preparations have been marketed, acarbose and miglitol.
- *Sixth alternative: basal insulin.* In this step, insulin is reserved for patients in whom oral drugs are contraindicated.

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

In patients with significant clinical signs of hyperglycemia (cardinal clinical signs and/or weight loss) at disease onset, treatment with insulin[41-43], alone or combined with metformin, is usually required. After initial control and improvements in glucotoxicity and lipotoxicity, insulin requirements are likely to gradually decrease, and control may be maintained in some cases with oral drugs, either as monotherapy or in combination.

In asymptomatic patients, it is advisable to start with metformin using a faster titration and, depending on response, to add a second drug[44], with monitoring of its course in the short term in order to adjust final treatment.

Second step

In patients in whom control goals have not been achieved or who, after a period of adequate control, experience impairment due to the course of their diabetes (in the absence of any associated disease or drug increasing glycemia), a second drug should be added.

Long-term comparative studies are lacking for most drug combinations, which makes taking decisions difficult. In principle, it is recommended that associated drugs have different and complementary action mechanisms. Based on the response, dosage should be increased to the maximum effective dose, somewhat lower than the maximum dose allowed. It should also be borne in mind that the contraindications, limitations for use. and potential side effects are the same as those of both drugs separately.

Combinations with metformin

- *Sulfonylureas and glinides.* Metformin-sulfonylurea combinations are the most widely tested and have been shown to be effective and safe[42-45], although doubt still exists about the increased mortality in a subgroup of patients seen in the UKPDS[46] who started treatment with sulfonylureas and had metformin added in a second step. Various observational studies have addressed this issue[47-51] and reported somewhat conflicting results, which moreover may not be superimposable on those obtained with more recent preparations. The risks for the control goal (HbA_{1c} < 6.5%) are similar to those seen in monotherapy, and the same recommendations are therefore made. Glinides represents a viable alternative to sulfonylureas for patients with more irregular intake because of their short action period, and also for patients allergic to sulfonamides or, in the case of repaglinide, for patients with moderate renal failure[52]. As regards the risk of hypoglycemia and weight increase, they may be considered as superimposable, with a potency lower than nateglinide[53] and quite similar to repaglinide[54].
- *DPP-4 inhibitors.* These drugs, together with GLP-1 receptor agonists, form a novel group of secretagogues acting on both insulin and glucagon secretion. They have obvious advantages over sulfonylureas and glinides, including a low risk of hypoglycemia and weight neutrality[55] and[56]. However, their long-term safety and their impact on the course of diabetes and its complications are unknown. Their potency does not appear to be lower than that of sulfonylureas in terms of HbA_{1c} reduction[57,58]. They could be a preferential option in patients in whom hypoglycemia is unacceptable.
- *GLP-1 receptor agonists.* These are parenteral preparations achieving a stronger and longer effect on GLP-1 receptors than DPP-4 inhibitors. In the short-term studies published, they have been shown to improve glycemic control, especially post-prandial blood glucose, and partly also basal blood glucose[59]. They slow gastric emptying, creating a sensation of satiety, which results in a sustained weight reduction in a substantial proportion of patients[60,61]. They also achieve improvements in some vascular risk factors[62]. In Spain, exenatide has been marketed for parenteral administration twice daily (before main meals, with an interval of at least 6 h between them) associated with metformin and/or sulfonylureas and with metformin plus glitazone[63], in patients with a body mass index greater than 30 kg/m^2. The marketing of liraglutide is pending at the time of writing these guidelines[64]. We therefore recommend reading its prescribing information to assess its indications and limitations for use. This may be a highly useful drug class in patients in whom obesity is an essential problem, but its role as compared to other drugs or treatment approaches, such as surgery, has still to be defined.
- *Thiazolidinediones.* These drugs act by increasing insulin sensitivity by a different mechanism as compared to metformin, and are therefore frequently used in combination[65-68]. In principle, they should mainly be indicated for patients with good post-prandial glucose control and elevated basal blood glucose not totally corrected with metformin. Their side effects are similar to those of each drug alone, and the same limitations as in monotherapy therefore apply.
- *Basal insulin.* The combination of basal insulin with metformin is a good therapeutic option of proven safety and efficacy[69-71]. It is mainly indicated for patients with

good post-prandial control but with HbA_{1c} above the recommended objective. Although this approach increases the rate of hyperglycemia, this is still much lower than that found in patients with multiple insulin doses. It is a good alternative for patients with in whom treatment with glitazones is not appropriate.

- *Disaccharidase inhibitors.* Their combination with metformin is safe, as no hypoglycemia will occur, but they have a limited efficacy, with HbA_{1c} decreases hardly exceeding 0.5%[72]. Their main limitation is gastrointestinal intolerance. They are therefore not recommended as an alternative to a second drug in this therapeutic step.

Third step

In patients treated with two drugs with poor metabolic control, the next step is insulin therapy. Except in patients resistant to insulin therapy, there are no «advantages» in delaying insulin introduction in the treatment regimen after dual combined therapy has failed. The long-term benefit and safety of an oral triple therapy as compared to insulin use is uncertain because follow-up in the different clinical trials is not longer than 12 months.

Combinations including no insulin

Among the different and valid combinations of oral agents, the combination of metformin, sulfonylurea, and glitazone is the most widely tested and most commonly used in clinical practice. It would thus be the one recommended in most patients with type 2 diabetes and poor control with dual therapy[73-77]. In elderly patients[78], the combination of metformin, repaglinide, and glitazone may be safer. In patients with limitations on the use of glitazones, the most reasonable alternatives would be metformin plus sulfonylureas plus DPP-4i[79] or metformin plus repaglinide plus DPP4i[80], although these have the disadvantage that they have been less widely tested.

Combinations including insulin

Most patients will have been treated with combinations of metformin and secretagogues. To these, basal insulin is added. If time since diabetes onset is longer than 10 years and/or complications or intercurrent diseases have occurred, the control goal will be revised to less than 7.5% or the best possible that is considered safe for the patient. This scheme may achieve a period of good control, but not an excessively long one, to judge from the results of the 4T study (Treating-To-Target in Type 2 diabetes)[81]. Hence, most patients will require an intensified insulin regimen within approximately 3 years. If this occurs, it is advisable to continue treatment with metformin combined with insulin, and to discontinue all other oral antidiabetic treatment.

Fourth step

As regards the possibility of quadruple therapy, which is a feasible approach (due to the different pathophysiological pathways from the pharmacological viewpoint), we think that this is currently an investigational approach, rather than a possibility in clinical practice.

Conclusions

Once lifestyle changes have been implemented, the goal of drug treatment for type 2 diabetes will be to achieve an optimized degree of metabolic control with the maximum possible safety. The goal should be an HbA_{1c} value < 6.5% in the early stages of disease and < 7.5% in more advanced stages or when there is a risk of hypoglycemia.

Treatment is divided into 3 steps. In the first step, and if hyperglycemia is not too high (HbA_{1c}, 6.5%-8.5%), metformin is the drug of choice. Other alternative drugs will only be used if metformin is not tolerated or is contraindicated. If hyperglycemia is high (HbA_{1c} > 8.5%), initial treatment should consist of several oral drugs combined, or insulin therapy should be started. The second step consists of the addition of a second drug with a synergistic action. Various options are available for this, and should be individualized,based on the characteristics of each patient. Finally, the third step implies the introduction of basal insulin as a preferred option to oral triple therapy, which must be reserved for insulin-resistant patients only.

Conflict of interest

The authors state that they have no conflict of interest.

Annex A.

Study promoted by the Spanish Society of Diabetes (SED) in collaboration with:

Spanish Society of Atherosclerosis (SEA).
Spanish Society of Cardiology (SEC).
Spanish Society of Endocrinology and Nutrition (SEEN).
Spanish Society of Community Pharmacy (SEFAC)
Spanish Society of Family and Community Medicine (SEMFYC).
Spanish Society of Internal Medicine (SEMI).
Spanish Society of Primary Care Physicians (SEMERGEN).
Spanish Society of General and Family Physicians (SEMG)
Spanish Society of Nephrology (SEN).

Members of the Working Group for Consensus and Clinical Guidelines of the Spanish Society of Diabetes:

Jose Juan Alemán Sánchez, Ramiro Antuña de Aláiz, Francisco Javier Escalada San Martín, Fernando Escobar Jiménez, Juan Carlos Ferrer García, José Antonio Fornos Pérez, Ricardo García Mayor, Sonia Gaztambide Sáenz, María Luisa López Fernández, José Luis Martín Manzano, Javier Martínez Martín, Juan Carlos Méndez Segovia, Jorge Navarro Pérez, Eduard Montanya Mías, Carlos Ortega Millán, Itxaso Rica Etxebarría, and Teresa Tartón García.

Addendum to the Consensus Document «Recommendations for pharmacological treatment of hyperglycemia in type 2 diabetes»

As of September 23, 2010 the EMA decided to withdraw from the market all medicinal products containing rosiglitazone as an active ingredient (Avandia®, Avandamet® y Avaglim®) because the benefits of the drug were not considered to outweigh its potential risks. In this context, the FDA decided not to withdraw such products from the market, but proposed a number of pharmacovigilance measures. The FDA thinks that data suggesting a potential increase in cardiovascular risk associated with rosiglitazone are controversial and not definitive. Independent verification of the results of the RECORD study has been requested.

References

1. Nathan DM, Buse JB, Davidson MB, Ferrannini E, Holman RR, Sherwin R, et al. Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy. A consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care. 2009;32:193-203.
2. Canadian Diabetes Association 2008.Clinical Practice Guidelines for the prevention and management of diabetes in Canada. Can J Diabetes. 2008;32(Suppl 1):S1-S201.
3. Algoritmo de tratamiento de la diabetes tipo 2. Guía de práctica clínica sobre diabetes tipo 2. Ministerio de Sanidad y Consumo, 2008. Available from: http://www9.euskadi.net/sanidad/osteba/datos/e_06_06_Diabetes_tipo_2.pdf.
4. GEDAPS 2009. Algoritmo de tratamiento de la diabetes tipo 2. Available from: http://www. redgedaps.org/.
5. National Collaborating Centre for Chronic Conditions. Type 2 diabetes: national clinical guideline for management in primary and secondary care (update). London: Royal College of Physicians; 2009. Available from: http://www.nice. org.uk/nicemedia/live/12165/44318/44318.pdf.
6. AACE/ACE Consensus Statement. Statement by an American Association of Clinical Endocrinologist/American College of Endocrinology Consensus Panel on type 2 diabetes mellitus: an algorithm for glycemic control. Endocr Pract. 2009;15:540-59.
7. The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC). Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. N Engl J Med. 2005;353:2643-53.
8. Holman R, Paul SK, Bethel MA, Matthews DR, Neil HAW. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med. 2008;359:1577-89.
9. The ADVANCE collaborative group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med. 2008;358:2560-72.
10. Duckworth W, Abraira C, Moritz T, Reda D, Emanuele N, Reaven PD, et al, for the VADT Investigators. Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med. 2009;360:129-39.
11. The Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med. 2008;358:2545-59.
12. Gaede P, Lund-Andersen H, Parving HH, Pedersen O. Effect of a multifactorial intervention on mortality and in type 2 diabetes. N Engl J Med. 2008;358:580-91.
13. Kitabchi AE, Umpierrez GE, Miles JM, Fisher JN. Hyperglycemic crises in adult patients with diabetes. Diabetes Care. 2009;32:1335-43.
14. Look AHEAD Research Group. Reduction in weight and cardiovascular disease risk factors in individuals with type 2 diabetes: one-year results of the Look AHEAD trial. Diabetes Care. 2007;30:1374-83.
15. DeFronzo R, Goodman A. Eficacy of metformin in patients with non-insulin-dependent diabetes mellitus. The Multicenter Metformin Study Group. N Engl J Med. 1995;333:541-9.
16. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood glucose control with metformin on complication in overweight patients with type 2 diabetes (UKPDS 34). Lancet. 1998;352:854-65.
17. Krentz AJ, Ferner RE, Bailey CJ. Comparative tolerability profiles of oral antidiabetic agents. Drug Saf. 1994;11:223-41.
18. Holstein A, Plaschke A, Egberts EH. Lower incidence of severe hypoglycemia in patients with type 2 diabetes treated with glimepiride versus glibenclamide. Diabetes Metab Res Rev. 2001;17:467-73.
19. Gangji AS, Cukierman T, Gerstein HC, Goldsmith CH, Clase CM. A systematic review and meta-analysis of hipoglicemia and cardiovascular events: a comparison of glyburide with other secretagogues and with insulin. Diabetes Care. 2007;30:389-94.
20. Holstein A, Plaschke A, Egberts EH. Lower incidence of severe hypoglycaemia in patients with type 2 diabetes treated with glimepiride versus glibenclamide. Diabetes Metab Res Rev. 2001;17:467-73.
21. Kahn SE, Haffner SM, Heise MA, Herman WH, Holman RR, Jones NP, et al, ADOPT Study Group. Glycemic durability of rosiglitazone, metformin or glyburide monotherapy. N Engl J Med. 2006;355:2427-43.
22. Belcher G, Lambert C, Edwards G, Urquhart R, Matthews DR. Safety and tolerability of pioglitazone, metformin and gliclazide in the treatment of type 2 diabetes. Diab Res Clin Pract. 2005;70:53-62.
23. Campbell IW, Menzies DG, Chalmers J, McBain AM, Brown IR. One year comparative trial of metformin and glipizide in type 2 diabetes mellitus. Diabet Metab. 1994;20:394-400.
24. Scott R, Wu L, Sánchez M, Stein P. Efficacy and tolerability of the dipeptidyl peptidase-4 inhibitor sitagliptin as monotherapy over 12 weeks in patients with type 2 diabetes. Int J Clin Pract. 2007;61:171-80.
25. Aschner P, Kipnes MS, Lunceford JK, Sánchez M, Mickel C, Williams-Herman DE. Effect of the dipeptidyl peptidase-4 inhibitor sitagliptin as monotherapy on glycemic control in patients with type 2 diabetes. Diabetes Care. 2006;29:2632-7.
26. Mohan V, Yang W, Son HY, Xu L, Noble L, Langdon RB, et al. Efficacy and safety of sitagliptin in the treatment of patients with type 2 diabetes in China, India and Korea. Diabetes Res Clin Pract. 2009;83:106-16.
27. Göke B, Hershon K, Kerr D, Calle Pascual A, Schweizer A, Foley J, et al. Efficacy and safety of vildagliptin monotherapy during 2-year treatment of drug-naïve patients with type 2 diabetes: comparison with Metformin. Horm Metab Res. 2008;40:892-5.
28. Rosenstock J, Aguilar-Salinas C, Klein E, Nepal S, List J, Chen R, CV181-011 Study Investigators. Effect of saxagliptin monotherapy in treatment-naïve patients with type 2 diabetes. Curr Med Res Opin. 2009;25:2401-11.
29. Johansen OE, Birkeland KI. Defining the role of repaglinide in the management of type 2 diabetes mellitus: a review. Am J Cardiovasc Drugs. 2007;7:319-35.
30. Rosenstock J, Hassman DR, Madder RD, Brazinsky SA, Farrell J, Khutoryansky N, et al. Repaglinide versus nateglinide monotherapy: a randomized, multicenter study. Diabetes Care. 2004;27:1265-70.

31. Black C, Donnelly P, McIntyre L, Royle PL, Shepherd JP, Thomas S. Meglitinide analogues for type 2 diabetes mellitus. Cochrane Database Syst Rev. 2007;2:CD004654.
32. Blicklé JF. Meglitinide analogues: a review of clinical data focused on recent trials. Diabetes Metab. 2006;32:113-20.
33. Waugh J, Keating GM, Plosker GL, Easthope S, Robinson DM. Pioglitazone: a review of its use in type 2 diabetes mellitus. Drugs. 2006;66:85-109.
34. Home PD, Pocock SJ, Beck-Nielsen H, Curtis PS, Gomis R, Hanefeld M, et al. Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomised, open-label trial. Lancet. 2009;373:2125-35.
35. Dormandy JA, Charbonnel B, Eckland DJ, Erdmann E, Massi-Benedetti M, Moules IK, et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macro Vascular Events): a randomized controlled trial. Lancet. 2005;366:1279-89.
36. Graham DJ, Ouellet-Hellstrom R, Macurdy TE, Ali F, Sholley C, Worrall C, et al. Risk of acute myocardial infarction, stroke, heart failure, and death in elderly medicare patients treated with rosiglitazone or pioglitazone. JAMA. 2010;304:411-8.
37. Lebovitz HE, Banerji MA. Insulin resistance and its treatment by thiazolidinediones. Recent Prog Horm Res. 2001;56:265-94.
38. Belfort R, Harrison SA, Brown K, et al. A placebo-controlled trial of pioglitazone in subjects with nonalcoholic steatohepatitis. N Engl J Med. 2006;355:2297-307.
39. Van de Laar FA, Lucassen PL, Akkermans RP, Van de Lisdonk EH, De Grauw WJ. Alphaglucosidase inhibitors for type 2 diabetes mellitus. Cochrane Database Syst Rev. 2005;2:CD003639.
40. Chiasson JL, Josse RG, Gomis R, Hanefeld M, Karasik A, Laakso M, STOP-NIDDM Trial Research Group. Acarbose for prevention of type 2 diabetes mellitus: the STOP-NIDDM randomised trial. Lancet. 2002;359:2072-7.
41. Ryan EA, Imes S, Wallace C. Short-term intensive insulin therapy in newly diagnosed type 2 diabetes. Diabetes Care. 2004;27:1028-32.
42. Bloomgarden ZT. Exploring treatment strategies for type 2 diabetes. Diabetes Care. 2007;30:2737-45.
43. Lingvay I, Legendre JL, Kaloyanova PF, Zhang S, Adams-Huet B, Raskin P. Insulin-based versus triple oral therapy for newly diagnosed type 2 diabetes: which is better?. Diabetes Care. 2009;32:1789-95.
44. Garber AJ, Larsen J, Schneider SH, Piper BA, Henry D. Simultaneous glyburide/metformin therapy is superior to component monotherapy as an initial pharmacological treatment for type 2 diabetes. Diabetes Obes Metab. 2002;4:201-8.
45. Hermann LS, Scherstén B, Bitzén PO, Kjellström T, Lindgärde F, Melander A. Therapeutic comparison of metformin and sulfonylurea, alone and in various combinations. A double-blind controlled study. Diabetes Care. 1994;17:1100-9.
46. UK Prospective Diabetes Stud-54y (UKPDS) Group: intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet. 1998;352:837-853.
47. Olsson J, Lindberg G, Gottsater M, Lindwall K, Sjostrand A, Tisell A, et al. Increased mortality in type II diabetic patients using sulphonylurea and metformin in combination: a population based observational study. Diabetologia. 2000;43:558-60.
48. Mannucci E, Monami M, Masotti G, Marchionni N. All-cause mortality in diabetic patients treated with combinations of sulfonylureas and biguanides. Diabetes Metab Res Rev. 2004;20:44-7.
49. Fisman EZ, Tenenbaum A, Boyko V, Benderly M, Adler Y, Friedensohn A, et al. Oral antidiabetic treatment in patients with coronary disease: time-related increased mortality on combined glyburide/metformin therapy over a 7. 7-year follow-up. Clin Cardiol. 2001;24:151-8.
50. Kahler KH, Rajan M, Rhoads G, Safford MM, Demissie K, Lu SE. Impact of oral antihyperglycemic therapy on all-cause mortality among patients with diabetes in the Veterans Health Administration. Diabetes Care. 2007;30:1689-93.
51. Johnson JA, Majumdar SR, Simpson SH, Toth EL. Decreased mortality associated with the use of metformin compared with sulfonylurea monotherapy in type 2 diabetes. Diabetes Care. 2002;25:2244-8.
52. Moses R, Slobodniuk R, Boyages S, Colagiuri S, Kidson W, Carter J, et al. Effect of repaglinide addition to metformin monotherapy on glycemic control in patients with type 2 diabetes. Diabetes Care. 1999;22:119-24.
53. Raskin P, Klaff L, McGill J, South SA, Hollander P, Khutoryansky N, et al. Efficacy and safety of combination therapy: repaglinide plus metformin versus nateglinide plus metformin. Diabetes Care. 2003;26:2063-8.
54. Raskin P. Oral combination therapy: repaglinide plus metformin for treatment of type 2 diabetes. Diabetes Obes Metab. 2008;10:1167-77.
55. Ahrén B. Clinical results of treating type 2 diabetic patients with sitagliptin, vildagliptin or saxagliptin –diabetes control and potential adverse events. Best Pract Res Clin Endocrinol Metab. 2009;23:487-98.
56. Bosi E, Camisasca RP, Collober C, Rochotte E, Garber AJ. Effects of vildagliptin on glucose control over 24 weeks in patients with type 2 diabetes inadequately controlled with metformin. Diabetes Care. 2007;30:890-5.
57. Nauck MA, Meininger G, Sheng D, Terranella L, Stein PP, Sitagliptin Study 024 Group. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, compared with the sulfonylurea, glipizide, in patients with type 2 diabetes inadequately controlled on metformin alone: a randomized, double-blind, non-inferiority trial. Diabetes Obes Metab. 2007;9:194-205.
58. Ferrannini E, Fonseca V, Zinman B, Matthews D, Ahrén B, Byiers S, et al. Fifty-two-week ef.cacy and safety of vildagliptin vs. glimepiride in patients with type 2 diabetes mellitus inadequately controlled on metformin monotherapy. Diabetes Obes Metab. 2009;11:157-66.
59. DeFronzo RA, Ratner RE, Han J, Kim DD, Fineman MS, Baron AD. Effects of exenatide (exendin-4) on glycemic control and weight over 30 weeks in metformin-treated patients with type 2 diabetes. Diabetes Care. 2005;28:1092-100.
60. Monami M, Marchionni N, Mannucci E. Glucagon-like peptide-1 receptor agonists in type 2 diabetes: a meta-analysis of randomized clinical trials. Eur J Endocrinol. 2009;160:909-17.
61. Van Gaal LF, Gutkin SW, Nauck MA. Exploiting the antidiabetic properties of incretins to treat type 2 diabetes mellitus: glucagon-like peptide 1 receptor agonists or insulin for patients with inadequate glycemic control? Eur J Endocrinol. 2008;158:773-84.
62. Klonoff DC, Buse JB, Nielsen LL, Guan X, Bowlus CL, Holcombe JH, et al. Exenatide effects on diabetes, obesity, cardiovascular risk factors and hepatic biomarkers in patients with type 2 diabetes treated for at least 3 years. Curr Med Res Opin. 2008;24:275-86.
63. Zinman B, Hoogwerf BJ, Durán García S, Milton DR, Giaconia JM, Kim DD, et al. The effect of adding exenatide to a thiazolidinedione in suboptimally controlled type 2 diabetes: a randomized trial. Ann Int Med. 2007;146:477-85.
64. Montanya E, Sesti G. A review of ef.cacy and safety data regarding the use of liraglutide, a once-daily human glucagon-

like peptide 1 analogue, in the treatment of type 2 diabetes mellitus. Clin Ther. 2009;31:2472-88.
65. Rosenstock J, Rood J, Cobitz A, Huang C, Garber A. Improvement in glycaemic control with rosiglitazone/metformin .xed-dose combination therapy in patients with type 2 diabetes with very poor glycaemic control. Diabetes Obes Metab. 2006;8:643-9.
66. Bolli G, Dotta F, Colin L, Minic B, Goodman M. Comparison of vildagliptin and pioglitazone in patients with type 2 diabetes inadequately controlled with metformin. Diabetes Obes Metab. 2009;11:589-95.
67. Rajagopalan R, Iyer S, Khan M. Effect of pioglitazone on metabolic syndrome risk factors: results of double-blind, multicenter, randomized clinical trials. Curr Med Res Opin. 2005;21:163-72.
68. Ceriello A, Johns D, Widel M, Eckland DJ, Gilmore KJ, Tan MH. Comparison of effect of pioglitazone with metformin or sulfonylurea (monotherapy and combination therapy) on postload glycemia and composite insulin sensitivity index during an oral glucose tolerance test in patients with type 2 diabetes. Diabetes Care. 2005;28:266-72.
69. Yki-Jarvinen H, Ryysy L, Nikkila K, Tulokas T, Vanamo R, Heikkila M. Comparison of bedtime insulin regimens in patients with type 2 diabetes mellitus. Ann Int Med. 1999;130:389-96.
70. Riddle MC, Rosenstock J, Gerich J, Insulin Glargine 4002 Study Investigators. The treat-to-target trial: randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients. Diabetes Care. 2003;26:3080-6.
71. Swinnen SG, Dain MP, Aronson R, Davies M, Gerstein HC, Pfeiffer AF, et al. A 24-week, randomized, treat-to-target trial comparing initiation of insulin glargine once-daily with insulin detemir twice-daily in patients with type 2 diabetes inadequately controlled on oral glucose-lowering drugs. Diabetes Care. 2010;33:1176-8.
72. Chiasson JL, Naditch L, Miglitol Canadian University Investigator Group. The synergistic effect of miglitol plus metformin combination therapy in the treatment of type 2 diabetes. Diabetes Care. 2001;24:989-94.
73. Kiayias JA, Vlachou ED, Theodosopoulou E, Lakka-Papadodima E. Rosiglitazone in combination with glimepiride plus metformin in type 2 diabetic patients. Diabetes Care. 2002;25:1251-2.
74. Dailey GE, Noor MA, Park JS, Bruce S, Fiedorek FT. Glycemic control with glyburide/metformin tablets in combination with rosiglitazone in patients with type 2 diabetes: a randomized, double-blind trial. Am J Med. 2004;116:223-9.
75. Roy R, Navar M, Palomeno G, Davidson MB. Real world effectiveness of rosiglitazone added to maximal (tolerated) doses of metformin and a sulfonylurea agent. Diabetes Care. 2004;27:1741-2.
76. Charpentier G, Halimi S. Earlier triple therapy with pioglitazone in patients with type 2 diabetes. Diabetes Obes Metab. 2009;11:844-54.
77. Scheen AJ, Tan MH, Betteridge DJ, Birkeland K, Schmitz O, Charbonnel B, PROactive investigators. Long-term glycaemic control with metformin-sulphonylurea-pioglitazone triple therapy in PROactive (PROactive 17). Diabet Med. 2009;26: 1033-9.
78. Papa G, Fedele V, Rizzo MR, Fioravanti M, Leotta C, Solerte SB, et al. Safety of type 2 diabetes treatment with repaglinide compared with glibenclamide in elderly people: a randomized, open-label, two-period, cross-over trial. Diabetes Care. 2006;29:1918-20.
79. Hermansen K, Kipnes M, Luo E, Fanurik D, Khatami H, Stein P. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, in patients with type 2 diabetes mellitus inadequately controlled on glimepiride alone or on glimepiride and metformin. Sitagliptin Study 035 Group. Diabetes Obes Metab. 2007;9:733-45.
80. Tran MT, Navar MD, Davidson MB. Comparison of the glycemic effects of rosiglitazone and pioglitazone in triple oral therapy in type 2 diabetes. Diabetes Care. 2006;29:1395-6.
81. Holman RR, Farmer AJ, Davies MJ, Levy JC, Darbyshire JL, Keenan JF, Paul SK, 4-T Study Group. Three-year efficacy of complex insulin regimens in type 2 diabetes. N Engl J Med. 2009;361:1736-47.