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Pharmacological management of type 2 diabetes. A pending solution

resumen

Objective. To review the recommendations on the medical management options of type 2 diabetes. **Material and methods.** A review of the main clinical trials, long-term prospective cohort studies published in Medline since 1995 upto now, and national and international guidelines that provide management protocols was carried out. The most habitual recommendations on the management of type 2 diabetes were evaluated, and the role of the new drugs now available on the market. **Results and conclusions.** Diet, physical activity and an adequate escalation of the classical medications (metformin, sulfonylureas and insulin) are the cornerstone of management of an ample majority of patients with type 2 diabetes. The objective of control should be individualized and the patients stage of the disease and present complications should be taken into account. New agents present attractive action mechanisms and characteristics, but there are still a lot of unanswered questions with regard to their efficacy in reducing morbi-mortality, their safety and their combination with other hypoglycemic agents.

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Introduction

Within the concept of type 2 diabetes mellitus, we include a heterogenous group of patients who present different levels of insulin resistance. There is moreover a gradual reduction in the capacity of the pancreatic islets to secrete a sufficient amount of insulin to adapt to the situation. This demands certain dynamism on the part of the practitioner when recommending treatment to each patient, according to the evolutive stage of these factors.

Type 2 diabetes is associated with an elevated risk of complications, even at the time of diagnosis, as was appreciated in the inclusion phase of the UKPDS trial[1]. At the microvascular level, retinopathy and neuropathy was observed in 21% and 7% of patients respectively. The most frequent macrovascular complications included: acute myocardial infarction (2%), angor (2%), ECG EKG abnormalities (18%), intermitent claudication (3%), stroke (1%) and absence of pulse in lower extremities (14%). It must be mentioned that glycemic levels employed in the study as criteria for hyperglycemia were more elevated than those used currently.

Intensifying glycemic controls in this trial demonstrated a reduction in the incidence in microvascular complications (RR = 25 %, 95%CI, 7 – 40%; p = 0.009). This result was obtained, above all, at the expense of a reduction in retinal laser photocoagulation, while no decrease in the rate of macrovascular complications or mortality was observed after a median follow up of 10 years. An increase in the incidence of hypoglycemia was also observed in the group under intensive therapy. The conclusions of the UKPDS trial, given its design and statistical power, were a clarification of some pending controversial issues, on the safety and efficacy of the available treatments at the time. However the study left other questions unanswered, which conditioned investigations on the management of type 2 diabetes henceforth:

· Could a lower HbA1c level prove effective in preventing macrovascular complications? If so, are the drugs available effective and safe?

· Is a longer study period necessary to appreciate any benefits?

· Is a substantial increase in macrovacular risk of diabetes patients due primarily to hyperglycemia or to associated risk factors: obesity, dyslipemia, hypertension, smoking?

· In order to attain maximum prevention safely, what would be the ideal escalation of treatment with drugs, given the evolutionary characteristic of the disease?

There is no adequate evidence that responds to these questions given that investigations that directly compare drugs and that employ hard endpoints of morbi-mortality are scarce, especially with reference to combined treaments. While new agents appear on the market that require long-term evaluation, doubts have been raised on some classical treaments and some studies designed to respond to these questions have been unable to show an improvement with regard to the previous situation. Thus, it is not surpising that there exists diversity in recent *consensus´* published on the treatment of type 2 diabetus mellitus. With coincidences and discrepancies, the guidelines are based more on clinical experience of the panel members than on solid evidence.
On the whole, this clearly makes clinical decision making difficult, a key aspect in the management of diabetes patients.

What are the goals of management for the type 2 diabetes patient?

As mentioned the results of the UKPDS trial showed that better metabolic control of type 2 diabetes patients prevented or delayed microvas-

cular complications taken as a whole[2]. However, there are controversies with regard to the real magnitude of this prevention[3]. In the case of type 1 diabetes patients with a long-term follow up in the DCCT trial, there was a 42% reduction (95%CI, 9-63%, p = 0.02) in relative risk for any cardiovascular event[4,5].

It was still yet to be demonstrated that metabolic control could achieve beneficial effects on **cardiovascular prevention** in type 2 diabetes patients. The differences observed in the UKPDS between the groups of intensive therapy and conventional treatment was unable to establish significant conclusions after a follow up period of 10 years. This opened up a debate on whether it was necessary to reduce even further the HbA1c goals or prolong the follow up period.

Meta-analyses carried out posteriorly have shown that there is a relation between metabolic control and vascular risk[6]. The recent publication regarding the continuation of the UKPDS trial[7] sheds light, at least in part, on some of the pending questions. On prolonging treatment, the level of control of the patients under conventional treatment improved with no other significant differences with the group under intensive therapy throughout the rest of the follow up period. In these circumstances, the magnitude of efficacy in prevention of microvascular complications was maintained around 9% (95%CI, 1-17%; p = 0.04). A reducton of 15 % in the incidence of myocardial infarction (95CI%, 3-26%; p = 0.01) and 13% mortality (95CI%, 4-21%; p = 0.01) was observed. This finding was attributed to a metabolic memory effect that would condition the increased vascular risk of hyperglycemia in the long-term in patients with worse control, even though their metabolic control improved during the second part of the trial. This effect was not observed in the hypertension arm of the study[8]. It should be taken into account that the elevated number of dropouts during the follow up would condition any solid conclusions.

Nevertheless when the results were applied to clinical practice and intensive therapy, some limitations were found. This was made manifest in three studies published during the course of last year with some surprising results: the ADVANCE (*Action in Diabetes and Vascular Disease – Preterax and Diamicron Modified Release Controlled Evaluation* study, VADT (*Veterans Affairs Diabetes Trial*), and the ACCORD trial (*The Action to Control Cardiovascular Risk in Diabetes Study Group*).

The ADVANCE trial[9] included 11,140 patients (42% women) diagnosed with type 2 diabetes and above 55 years (mean = 66 years on inclusion to the study). Known vascular disease or at least one other cardiovascular risk factor associated with diabetes was present in 32% of the cases, while significant microvascular disease in 10.5% of patients was recorded. The mean time of evolution was 8 years. The group under intensive therapy received glicazide associated with additional medication when necessary to achieve HbA1c values of $\leq$ 6.5%. The group under conventional therapy had the aim to achieve the control targets marked by the local guidelines (Europe, Asia, Australia/New Zealand and Canada), without using glicazide which was the drug assessed in the trial. The main result under evaluation was the composite of micro and macrovascular outcomes (infarction, non-fatal stroke or cardiovascular mortality). Patients with contraindications for the treatments under study or who were candidates for insulin therapy in the long term were excluded.

The latest trials available show that intensive therapy (HbA1c < 7) does not reduce morbimortality.

The VADT study[10] included 1,791 patients with a mean age of 60 years (97% men), and with no adequate metabolic control achieved under therapy with oral antidiabetic agents or insulin (median HbA1c = 9.4%). The group under intensive therapy were set to achieve an HbA1c goal of <6%, while the goal for the group under conventional treatment was an HbA1c value of at least 1.5% more than that obtained by those under intensive control. The mean follow up period was 11.5 years. At the moment of inclusion, 40% of the patients had suffered from a cardiovascular event. The main result evaluated was a composite endpoint of non-fatal infarction, non-fatal stroke, cardiovascular death, admission to hospital due to heart faliure or revascularization procedures and/or amputation.

Patients participating in the ACCORD trial were also concomitantly treated with antihypertensive agents and hypolipidemic agents. In the ADVANCE trial the efficacy of an antihypertensive drug was also under evaluation, and in the VADT

study, a protocol of intensive tretament of risk factors was employed in both arms.

The ACCORD study[11] was discontinued after 3.5 years when an increase in mortality was found among the intensive treatment group. Currently this trial continues, but only the arms that evaluated the efficacy of the treatment of dyslipemia and hypertension. The increment in mortality associated with intensive control of diabetes has not been appreciated in the other two trials. In the subgroup analysis carried out, no motive was established for the increased mortality.

The most relevant characteristics of the trials are shown in table 1.

The participants included in the 3 trials were somewhat different, the ADVANCE study including patients from Europe, Australia, Asia and North America, while participation in the other two studies was limited to the USA. Patients in the ADVANCE study had a shorter evolution of disease, a lower body mass index, and had clearly lower insulin requirements, which could have influenced the low rate of hypoglycemias observed. Nevertheless the results of the trials were quite homogenous, given that they concurred in demonstrating that intensive therapy in patients with advanced disease and a high percentage of chronic complications did not reduce the mortality rate and more so, as in the case of the ACCORD trial, increased that rate.

Neither was there any improvement in the reduction of cardiovascular events, at least in this group of patients, already under treatment for other risk factors.

These trials have shown the lack of efficacy of intensive therapy in patients with severe disease or with long term diabetes mellitus. The conclusion of the hypothesis raised after the publication of the prolongation of the UKPDS trial[7] is still pending: if intensive control is carried out at the early stages of diabetes, before the appearance of chronic complications, would there be a reduction in cardiovascular events and mortality? This is based on the fact that a metabolic memory effect may limit our efficacy in treatment posteriorly[12], a phase in which a multifactorial approach to management has been shown to be effective[13,14]. However good quality studies are necessary to evaluate this hypothesis.

Following this line of thought, the ADA (*American Diabetes Association*) and the ACC – AHA (*American College of Cardiology Foundation - American*

Table 1. Summary of the baseline characteristics and main outcomes in the ADVANCE, VADT and ACCORD trials.

	ADVANCE	VADT	ACCORD
Length (median in years)	5	5,6	3.5
Proportion of men	58	97	62
Initial BMI (mean +/- SD)	28 ± 5	31.3 ± 3	32.2 ± 5
Initial median HbA1c (%)	7,2	9.4	8,1
Final median HbA1c (intensive vs control groups)	6.3 vs 7	6.9 vs 8.5	6.4 vs 7.5
Insulin treated patients at the beginning (%)	1,5	52	35
Insulin treated patients at the end (intensive vs control groups) (%)	40 vs 24	89 vs 74	77 vs 55
TZD* at the end (% patients) (intensive vs control groups)	17 vs 11	53 vs 42	91 vs 58
Change in weight (Kg):			
Intensive therapy	- 0.1	+ 7.8	+ 3.5
Conventional therapy	- 1.0	+ 3.4	+ 0.4
Severe hypoglycaemia % (a)			
Intensive therapy	2.7	21.2	16.1
Conventional therapy	1.5	9.9	5.1
Outcomes			
Primary endpoint HR	0.90	0.88	0,90
(95%CI)	(0.82-0.98)	(0.74-1.05)	(0.78-1.04)
Mortality HR	0.93	1.07	1.22
(95%CI)	(0.83-1.06)	(0.81-1.42)	(1.01-1.46)

(*) TZD: thiazolidinediones.

(a): proportion of patients with at least one severe hypoglycaemia.

Heart Association) have taken a joint position with regard to management and recently published the following recommendations[15]:

· Maintain the objective goal of HbA1c <7% for the majority of patients.

· In some patients a lower target could be attempted, if this is achieved with no significant hypoglycemias or other adverse effects of treatment. This group includes diabetes patients with a short length of disease, long term life expectancy, and with no significant cardiovascular disease.

· On the contrary, in some patients the target for HbA1c could be set to more than the 7% recommended for most patients. This mainly affects patients with a history of severe hypoglycemias, limited life expectancy, and advanced micro and macrovascular complications. Other candidates for this approach include diabetes patients with severe disease associated with poor metabolic control obtained despite educational measures, self control, and effective hypoglycemic medication, including insulin.

An observational study recently published including patients with heart failure showed lower mortality in patients with moderate HbA1c control (between 7.1-7.9%) than in those under intensive therapy[16].

What is the most recommended treatment for the initial management of type 2 diabetes mellitus?

The limitations and problems posed by current clinical guidelines have already been mentioned. However the aim of this publication is not to substitute their study or implementation, but rather, it is an attempt to underline common aspects and the ground for possible discrepancy. Our aim is fundamentally didactic. To do so, we refer to the most employed guidelines employed internationally: the ADA-EAS[17], NICE guidelines[18], the guidelines from the *Canadian Diabetes Association*[19], the *Roadmap of the AACE (American Association of Clinical Endocrinologysts)*[20] and the 2005 IDF (*International Diabetes Federation)*[21]. We also include the main Spanish national guidelines: the practical guide for type 2 diabetes mellitus from the Spanish Ministry of Health[22] and the treatment algorithm of the REDGEDAPS, recently updated[23].

The HbA1c targets should be individualized.

At the time of diagnosis of type 2 diabetes, two essential questions are raised when deciding on management: what grade of descompensation does the patient present? Is it necessary to start with drugs from the time of diagnosis?

In order to respond to both questions, we will refer to the algorithm proposed by the *Canadian Diabetes Association*[19] (figure 1), possibly the best structured guideline based on the available evidence and reviewed by the greatest number of professionals.

Initial treatment will depend on the characteristics and the clinical condition of the patient at the time of diagnosis.

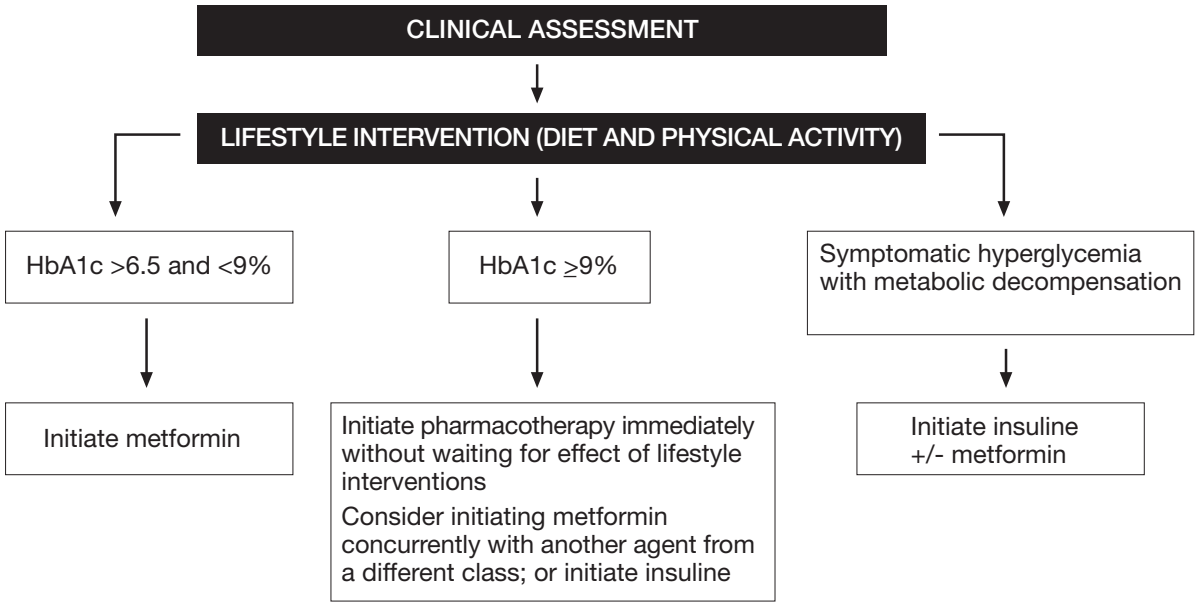
One of the characteristics of the UKPDS trial was that 50% of the patients with type 2 diabetes at the time of diagnosis presented chronic complications, reflecting a late diagnosis that obliged the prescription of a more intensive regimen of treatment adapted to that stage of disease. By reducing the level of glycemia to 126 mg/dL (7.0 mmol/L) as diagnostic criteria for diabetes[24,25]*, and implementing the recommendation of regular monitoring of blood glucose in risk populations[26], the diagnosis of diabetes was even more frequent in asymptomatic patients with HbA1c levels quite close to normality.

Initial non pharmacological management

Asymptomatic patients with HbA1c values near to normality can clearly benefit from self-management education and the implementation of measures related to both diet and physical activity, both essential throughout the entire evolution of the disease. It is the ideal moment to outline the importance of these two measures. They have been shown useful in both diabetes patients and in the prevention of diabetes in risk populations and in patients with impaired basal glycemia. There are

* An international panel of experts has recently proposed that the diagnosis of diabetes should be based on the presence of HbA1c levels over 6.5% (Diabetes Care 2009;32:1-8), though the main medical associations have not published any position statement about it until now.

Figure 1. Initial treatment of hyperglycemia (CDA 2008 modified).



no studies available that directly compare this strategy to the initiation of pharmacological treatment at the time of diagnosis.

Initial pharmacological management

Metformin

All consensus are unanimous in recommending metformin as initial pharmacotherapy. There is clear evidence for its use in overweight patients. In monotherapy initial targets of HbA1c levels should be between >6.5% and <9%, when initiating medication after diet and physical activity have been implemented over a reasonable period and glycemic targets have not been achieved. According to the baseline values, a reduction of HbA1c levels of 1-2% should be expected with a very low risk of hypoglycemias and least weight gain when compared to the majority of the alternatives.

Definitive support for clinical use stems from the clear improvement in survival and cardiovascular prevention in the subgroup of obese patients treated with metformin in the UKPDS trial[27], both in the initial trial and in the prolonged study. However its use presents some limitations. On the one hand, it is contraindicated in patients with renal faliure (CrCl <30 ml/min) and liver failure. The balance between risk and benefits should be considered before prescribing it to patients with moderate heart or respiratory failure, while it is prohibited in patients in advanced stages of these conditions. Metformin inteferes with the absorption of vitamin B_{12}[28] and has traditionally been associated with cases of lactic acidosis. Nevertheless in recent publications its implication in causing lactic acidosis seems lower than other antihyperglycemic agents[29]. Its main side effects include digestive discomfort, which rarely requires suspension of treatment and which can be limited if progressive doses of the product are introduced to the patient as recommended by the 2009 ADA consensus.

ADA recommendations for metformin

1. Start with a low dose: 500 mg /12-24 h or 850 mg/24 h.
2. After 5-7 days, once gastric tolerance is confirmed, increase doses to 2 pills of 850 mg per day OR 2 pills of 500 mg twice daily (breakfast and dinner).
3. In case gastrointestinal side effects appear then return to previous doses and attempt to increase the dose again at a further date.
4. The maximum effective doses is 1000 mg every 12 hours (most frequently 850 mg/12 h). There are modest increments in efficacy at 2,500 mg per day, but the gastrointestinal side effects can limit their use at such doses.

In a percentage that oscillates between 5–20%, according to some series, despite a correct progressive introduction, metformin was discontinued due to gastrointestinal intolerance. In this case, or if contraindicated, then an alternative should be considered.

Initial treatment of patients with HbAc1 values near normal should consist of diet and physical activity.

Alternative agents to metformin in initial management

Second generation **sulfonylureas** were tested in the UKPDS trial[2], resolving doubts from the UGDP trial[30] with regard to the increment in mortality induced by treament with tolbutamide. They proved safe and effective in monotherapy, constituing the first alternative to metfomin in case of intolerance or contraindication of the latter.

They are effective drugs (reductions in HbA1c values of 1-2%) though they are associated with a clear increase in the incidence of hypoglycemia and present the inconvenience of contributing to the progressive deterioration in the secretion of insulin by beta cells. Consequently, this provokes secondary failure in treatment during a limited period of time and conditions the increase in weight.

In the case of chlorpropamide, the risk of hypoglycemia increases due to its long half life and it is asociated with hyponatremia. Posteriorly, when comparing treatment with glibenclamide against more recent sulfonylureas (glimepiride), it was found that the former could alter the adaptation of the miocardium to ischemic situations[31], which made it seem more reasonable to use glimepiride, which could be administered once daily.

In the ADVANCE trial the use of prolonged release glicazide was tested showing a good safety profile especially with reference to the low incidence of hypoglycemias. Like glimepiride, glicazide is administered once daily.

It is necessary to gradually titrate the dose of secretagogues, especially in early stages of the disease, when patients have near normal glycemias due to the elevated risk of producing hypoglycemias.

Repaglinide shares some of the characteristics of sulfonylureas. It binds in a different manner to the sulfonyl receptor, adjacent to the potassium canals, but shares the induction of secondary failure of sulfonylureas (by a crossover mechanism). Consequently change in treatment does not produce any better response by the beta cell. Given its half-life, it should be administered before each main meal and it appears to present a similar incidence of hypoglycemias as sulfonylureas, although less severe in elderly patients[32]. It also provokes weight gain, but as an added advantage, it can be used in cases of moderate renal failure, as it is metabolised mainly through biliary elimination. Its action is intensified by the concomitant use of fibrates, and therefore its association with the latter is not recommended.

Whenever early insulinization is not expected and in cases where the main problem of treatment is caused by insulin resistance, the logical alternative to metformin would be the use of the **glitazones** (rosiglitazone and pioglitazone). They are similar drugs, with some differences yet to be confirmed. Their effectiveness is similar to metformin as far as the reduction in HbA1c values. The lapse of time until maximum efficacy is approximately three months. The risk of hypoglycemias is low, but these agents are limited by the risk of producing or worsening an already present heart failure condition, increasing the incidence of bone fractures, producing weght gain and oedemas.

A controversy exists concerning the effectiveness of these drugs in cardiovascular prevention, as we described in a previous publication of this bulletin[33]. They present the advantage of delaying the need for starting insulin more than any other agent[34,35]. After the publication of the Nissen meta-analysis[36], the cardiovascular safety of rosiglitazone became questionable, and some consensus, like the ADA recommended not using it. Recently the RECORD study[37] showed that the group under treatment with rosiglitazone had a higher incidence of heart failure and bone fractures, with no increase in cardiovascular morbidity or mortality. Today the evidence is not definitive, thus it seems more reasonable to limit the prescription of these agents to the group of patients that would clearly benefit from them, that is in early stages of the disease with severe insulin resistance when met-

The elective agent is metformin; if not sufficient, then sulfonylureas or insulin should be added.

formin cannot be used. Glitazones are contraindicated in patients with previous cardiac faliure and rosiglitazone is also contraindicated in patients with acute coronary syndromes.

Lastly, some agents used in monotherapy that reduce the intestinal absorption of glucose can also be considered. These are the alpha glucosidase (disaccharide) inhibitors and the main substances available are **acarbose** and **miglitol**. They are less powerful than the previous treatments, with HbA1c reductions of 0.5-1.0%, and their digestive intolerance is important given the significant number of patients abandoning tretament. In the STOP-NIDDM trial[38], in patients with impaired glucose tolerance, these agents seemed useful in cardiovascular prevention. However these results should be considered preliminary as confirmation of this should be made from further studies.

Recently, the indication of sitagliptin in monotherapy has been approved when metformin is contraindicated or if the patient shows intolerance. Drugs based on the system of incretins theoretically could prove a good alternative, but for now we should wait for further evidence. We will refer to them later in the section on combined treatment.

Early insulinization may be a good alternative to maintain the pancreatic reserves of insulin, especially in patients with clear limitations for oral treatment. These patients could benefit from the addition of metformin, as it contributes to less weight gain, reduces the needs for insulin, and can even reduce macrovascular complications[39].

Systematic reviews which evaluate the different treatments have not made any definitive conclusions on the differences in cardiovascular mortality and morbidity, fundamentally due to the scarcity of trials that directly study these effects. Instead, these studies have focussed directly on more intermediate objectives, like metabolic control, and therefore there is very little information regarding the combination of drugs in management.

Thus it seems that metabolic control achieved with metformin, second generation sulfonylureas and thiazolidinediones is superimposable with reductions on HbA1c of upto nearly 1%. Repaglinide has the least number of studies compared to the rest of the drugs. The evidence available on the control of vascular risk factors are of moderate to low range. There is clear evidence that thiazolidinediones or second generation sulfonylureas combined with metformin increase body weight by 1-5 kg compared to metformin alone. The incidence of hypoglcemia is more frequent with sulfonylureas, especially glibenclamide (with an absolute risk of 2% compared to other second generation sulfonylureas). For this reason some consensus do not recommend the use of glibenclamide given the availablity of other safer sulfonylureas[40].

A controversy exists concerning the effectiveness of these drugs in cardiovascular prevention, as we outlined in a previous publication of this bulletin. They present the advantage of delaying the need for starting insulin more than any other agent. After the publication of the Nissen meta-analysis, the cardiovascular safety of rosiglitazone became questionable, and some consensus, like the ADA´s recommended not using it. Recently the RECORD study showed that the group under treatment with rosiglitazone had a higher incidence of heart failure and bone fractures, with no increase in cardiovascular morbidity or mortality. Today the evidence is not definitive, thus it seems more reasonable to limit the prescription of these agents to the group of patients that would clearly benefit from them, that is in early stages of the disease with severe insulin resistance when metformin cannot be used. Gllitazones are contraindicated in patients with previous cardiac faliure and rosiglitazone is also contraindicated in patients with acute coronary syndromes.

Glitazones produce an increase in the incidence of heart faliure and bone fractures.

When should other treatments be combined with metformin in initial management? What are the most indicated combinations?

The evidence regarding these questions is quite scarce and the following affirmations originate in good part from theoretically based clinical principles. The 2009 ADA guideline[17] establishes two possible options of implementing intensified management:

· Combination of drugs with the most clinical experience, less cost and with solid support from the scientific evidence available.

· Other options not validated as yet.

THE MOST VALIDATED OPTIONS (figure 2)

In the first step there are two treatment options:

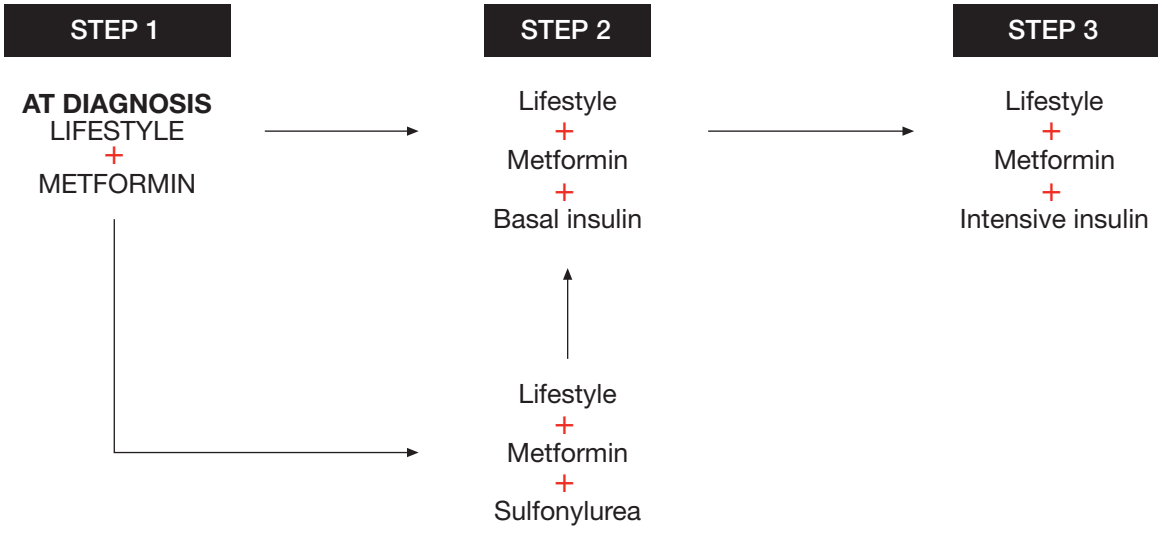
Combination with sulfonylureas. This option is by far the most employed. It is effective with reductions in HbA1c equivalent to the sum of the expected individual drugs and is very economical. It should be considered in patients who present postprandial hyperglycemia in monotherapy. Logically the combination presents the risk of hypoglycemia, which should be carefully considered when adjusting the dose of the sulfonylurea. Nevertheless, despite the experience up to now, there is still doubts on the safety of this combination[41]. In some subgroup of patients in the UKPDS trial an increase in mortality was observed and in recent meta-analyses questions arose with regard to its safety. The action of the glinides seems to be very similar to sulfoylureas, with the exceptions we have commented in monotherapy.

Combination of basal insulin (intermediate or a long-acting insulin analog) and metformin. This is a good therapeutic option given that the combination can limit weight gain derived from insulin, the deterioration of secretion of insulin from beta cells is slower and it could be the only option if the patients main problem is insulin resistance and is not a good candidate for the use of glitazones. Patients that could most benefit are those with high basal glycemias with good postprandial profiles. (See BIT on insulin therapy)[42].

If the objective goals are not achieved with the combination of metformin and secretagogues then a basal insulin could be added (intermediate or a prolonged insulin analog). In the same way, in case of inadequate control with the combination of metformin and insulin, then a secretagogue could be added. Here once again there is very little evidence on the effcacy of these combinations in the long-term.

In case the above regimens fail to achieve the set targets, then intensive insulin therapy combined with metformin is the recommended approach to management. The various possibilities of insulinization (premixed insulin, basal-bolus regimen, etc.) which have been commented on previously.

Figure 2. Algorithm on initial management and adjustments of treatment according to the 2009 ADA-EASD statement. Validated treatment.



LESS VALIDATED OPTIONS (figure 3)

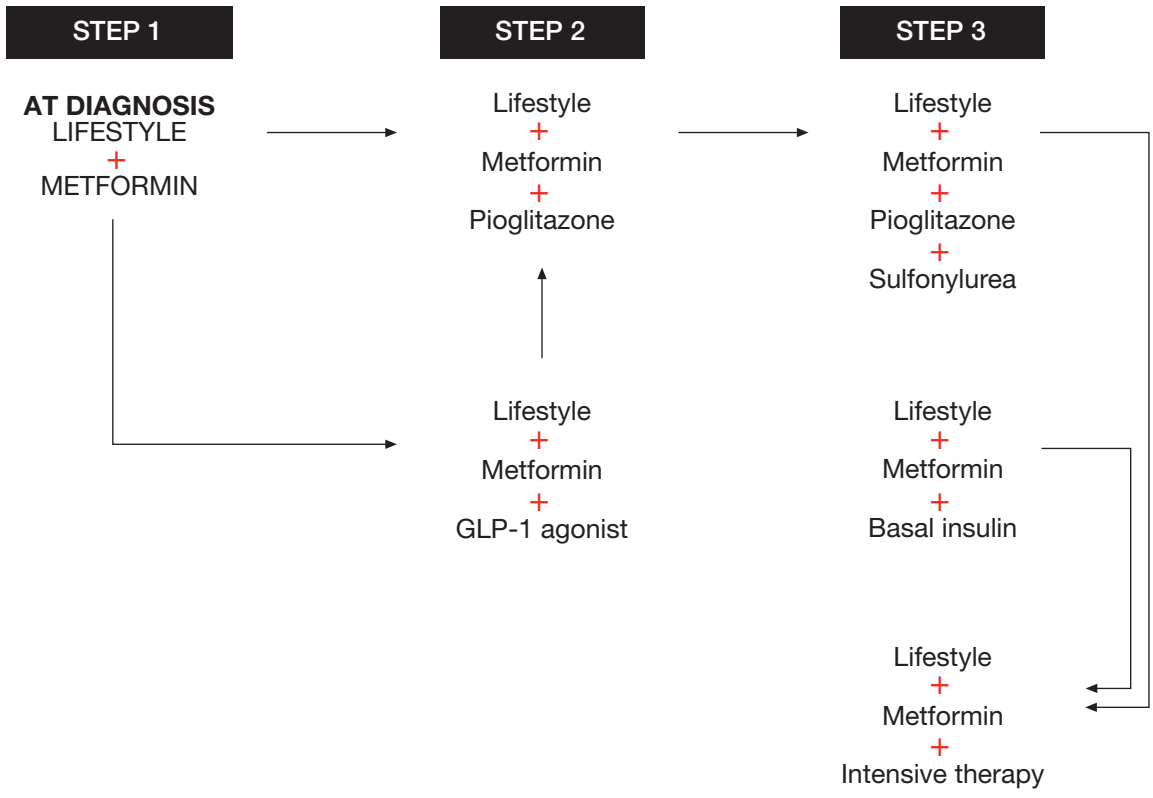
In this group the options included require further investigation. The motive for designating this option as "less validated" is that they are new drugs whose profiles are still little known, both in use in monotherapy or combined with one or two other antihyperglycemic agents.

This chapter most supports our stance that a definite solution to the management of type 2 diabetes is still pending.

Combination of metformin and pioglitazone. This is a logical combination for patients whose main problem is insulin resistance and do not require any rapid control of glycemia, given that the full effect of the glitazone is appreciated after 9-12 weeks. The consensus statement clearly inclines to the use of pioglitazone, after the Nissen meta-analyses[35] raised doubts on the the cardiovascular safety profile of rosiglitazone. Despite other contrary evidence, its use is not recomended until investgations now underway define clearly its role, profile of the ideal patient, and safety. The combination presents the same problems for each drug separately, therefore close monitoring of patients is absolutely necessary, especially with regard to gastrointestinal intolerance, cardiac function, oedemas, bone fractures, anaemia, etc.

In case the regimens fails to meet the targets, two possibilities can be offered: either associate a secretagogue, which could be the case when the combination is well tolerated and effective, but the problem now lies with the management of postprandial glycemias; or in the case of no tolerance to the combination or inadequate control, then the most recomendable approach would be to discontinue pioglitazone and combine metformin with basal insulin, with the possibility of adding a secretagogue.

Figure 3. Algorithm on initial treatment and adjustments according to the 2009 ADA-EASD consensus statement. Less validated treatments.



Treatments based on the incretin hormones. Incretins, (GIP and GLP-1) are gastrointestinal hormones secreted during the postprandial period. They induce the secretion of insulin from beta cells while inhibiting glucagon release by alpha cells in the pacreatic islets, especially GLP-1. They play an important physiological role in glycemic control after food ingestion, and have therefore been considered a potential alternative in the management of type 2 diabetes, classified within the group of secretagogues[43].

The short half-life of these peptides is a drawback to their use, so much so that it has been necessary to elaborate long-acting analogs (exenatide, which is currently on the market) and to reduce the action of the enzyme responsible for its metabolism, dipeptidyl-peptidase 4 (DPP-4).

GLP-1 analogs

In Spain, exenatide has been commercialised for parenteral administration before breakfast and dinner. It mainly reduces postprandial glycemia, with reductions in HbA1c values by 0.5-1.0%, and can be combined with either metformin and/or sulfonylureas. It presents a low risk of hypoglycemias, except in association with sulfonylureas, and has shown to be very effective in losing weight. Therefore it is ideal for patients whose main priority is weight reduction. Its drawbacks include gastrointestinal side effects in up to 30-40%, mainly nausea and vomiting, that in some cases can be tolerated with the titration of the recommended dose initially. Some cases of pancreatitis have been documented (1 case/2,000 patients per year)[44] which makes it necessary for patients to learn to recognize signs and symptoms of acute pancreatitis so that an early diagnosis and treatment of this mishap may be carried out.

The short period of its commercialisation conditions our knowledge regarding its safety profile in the mid to long term, its role in the survival of the pancreatic islets, and its effectiveness in monotherapy or in combination with insulin, for which it has no indication as yet. The profile of the patient suitable for this agent is the obese diabetes patient (BMI > 30 kg/m^2), with inadequate control despite metformin or combined metformin and sulfonylureas.

DPP-4 inhibitors

The first commercialised drug of this class in Spain is sitagliptin and more recently vildagliptin.

There are still many information gaps with regard to GPL-1 analogs and DPP-4 inhibitors.

Both are administered orally and its use has been approved in combination with metformin, thiazolidinediones, or sulfonylureas. Their combination with insulin has not for the moment been indicated. Efficacy in postprandial glycemic management is comparable with sulfonylureas Their use has a low risk of hypoglycemias, except when associated with sulfonylureas. With regard to side effects, these agents present less digestive intolerance than the analogs, but they are less effectve in weight modification, which in theory they do not increase weight, but rather should reduce it slightly.

There is some difference between both drugs, for example, sitagliptine is administered in one single dose, while vildagliptine is taken twice daily, and what is more important, the latter requires initial monitoring of liver transaminases due to the possibility of toxicity. There are no comparative studies between the two available as yet. The inhibition of DPP-4, an ubiquitous enzyme in many substrates (hormones, immune system mediators, etc.) is now an area of concern. Laboratory studies on the safety of sitagliptin carried out by the manufacturer evaluating the previous studies in the last three years, the majority short-term, showed that the drug is safe[45].

However long-term studies are not available as yet. The ideal candidate for this agent is the patient with poor postprandial glycemic control, whose goal is to avoid increases in weight and whose main limiting factor in management is the possibility of hypoglycemias.

Although theoretical, both GLP-1 agonists and DPP-4 inhibitors possess attractive characteristics for the management of type 2 diabetes with an acceptable safety profile and efficacy in the short term. However a lot of questions regarding their long-term safety and efficacy in reducing macro and microvascular complications, and mortality remain unanswered[46,47]. Therefore careful selection and monitoring of the ideal candidates are necessary when they are employed.

Table 3. Glycemic control of type 2 diabetes patients.

	MEAN	SD	25th PERCENTILE	50th PERCENTILE	75th PERCENTILE
HbA1c > 8	11.3	5.5	7.5	11.0	14.8
HbA1c < 7	33.3	13.2	24.3	33.3	42.6
HbA1c not determined	44.2	19.6	30.0	41.2	55.2
No antidiabetic drugs	21.1	9.7	14.0	19.0	26.3

In summary, we have outlined the current regimens recommended in the management of type 2 diabetes, supported by clinical experience and observational studies rather than solid evidence, especially with respect to combined treatments and new agents. There are still issues yet to be resolved including the degree of metabolic control needed to intensely reduce the development of micro-macrovascular complications and the most adequate combination of drugs given the stage of the disease. Some well designed studies like the STENO 2[13,14], propose that while glycemic management is a necessary but not sufficient condition for managing type 2 diabetes patients with high vascular risk, a multifactorial approach to management is much more effective. This does not necessarily challenge any of the other evidence on the metabolic memory effect of hyperglycemia in the development of complications and the need for adequate management from the initial stages of the disease.

The situation in Navarre

An evaluation of glycemic control in primary care consultancies show that in an important percentage of type 2 diabetes patients (mean = 44%) the computer based clinical records (OMI) did not register the determination of glycated hemoglobin (HbA1c) during the last year (1 April 2008 - 31 March 2009). The percentage of patients with HbA1c >8% in the last determination was low (mean, 11%). In a third of the cases in each consultancy, the last determination of HbA1c values was less than 7% (Table 3 and Figure 4).

Approximately one fifth of the type 2 diabetes patients did not require medical treatment in the last year (table 3). Data obtained from the automatic dispensation of the prescriptions (from January to March 2009), showed that 66% of the patients under treatment with oral hypoglycemic agents were in monotherapy, 28% in combined therapy with two agents while 6% were prescribed more than two agents.

Table 4. Proportion of patients treated with antidiabetic drugs*.

	% PATIENTS
Metformin	75.0%
Sulfonylurea	40.4%
Repaglinide	12.0%
Alpha glucosidase inhibitor	6.0%
Glitazone	4.8%
DPP-4 inhibitor	5.3%
Exenatide	0.1%

(*) A patient can be treated with more than one antidiabetic drug.

Management of diabetes with hypoglycemic agents is highly alligned to the recommendations. Seventy-five percent of the patients under oral medication collected at least one pack of metformin, and 44% sulfonylurea (table 4). Patients with combined oral medication and insulin represented 17% of all the cases.

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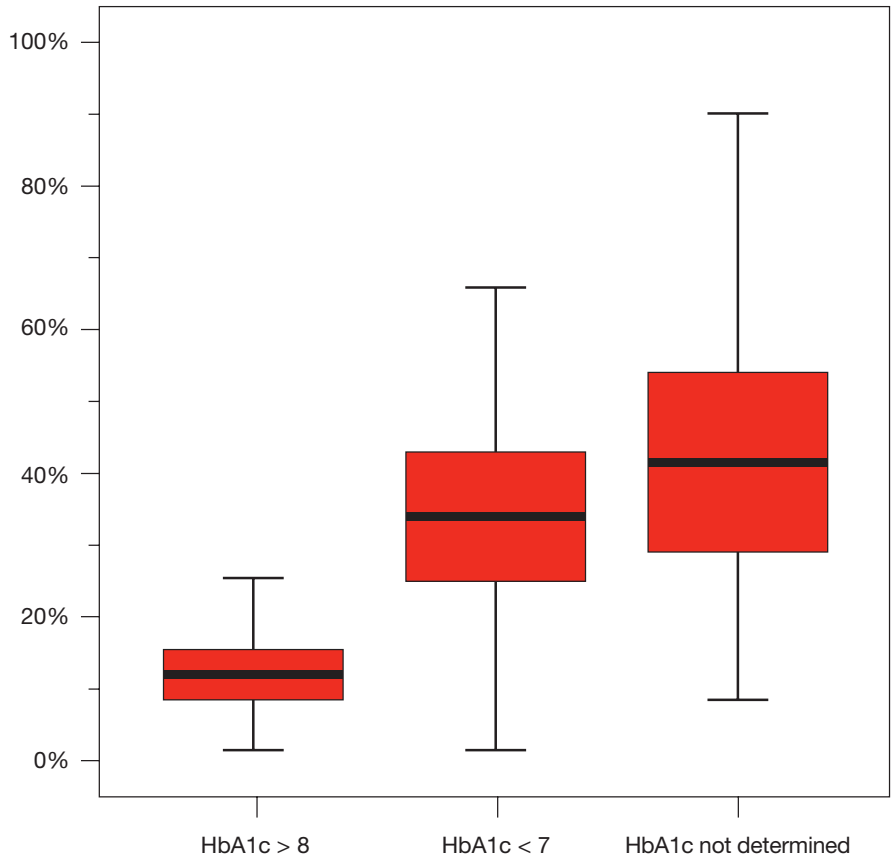
Figure 4. Proportion of patients according to different levels of HbA1c.



Conclusions

The consensus on the management of type 2 diabetes has rationalised the use of the different agents, but we are still far from a definitive solution.

Diet, physical activity and adequate progression in prescribing the classical agents (metformin, sulfonylureas and insulin) constitute the cornerstone of management for an ample majority of type 2 diabetes patients.

Strict control is not always the most beneficial approach for the patient.

New agents present attractive action mechanisms and characteristics, but there are still a lot of unanswered questions with regard to their efficacy in reducing morbi-mortality, their safety and their combination with other hypoglycemic agents.

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