Case report discussed by experts

Type 2 diabetes and metformin intolerance

Diabetes tipo 2 e intolerancia a la metformina

Male aged 73, with T2D of 5 years of evolution, who is being treated with glimepiride 6 mg/day and in the last analytic he shows a glycosylated hemoglobin (HbA1c) of 7.7%.

Personal history
Former truck driver, former smoker and drinker; He ensures that at present he only drinks wine with the meals. He always had good health, except for the several gastritis events after abundant meals that he treats with antiacids erratically. He has been operated on herniated disc. He did not tolerate the metformin due to abdominal upsets, reason why he started a glimepiride treatment. He hardly goes to see the physician; he does not perform the glycemic controls and refused to take medication for cholesterol and for arterial pressure (AP). He accepted to be treated on his diabetes because his father died due to this disease. He recognizes that he does less physical exercise every time and since he “left the truck”, he did not do anything but to gain weight.

Data corresponding to the last revision
Weigh 108 kg, height 174 cm, AP 155/95 mmHg, and abdominal waist 112 cm. No peripheral vascular disorder can be observed nor signs of peripheral neuropathy. In the differed analytic the following results appear: creatinine 1.5 mg/dL, basal glycemia 169 mg/dL, HbA1c 7.7, uric acid 8.4 mg/dL, total cholesterol 311 mg/dL, triglycerides 197 mg/dL, cholesterol bound to high density lipoproteins (cHDL) 59 mg/dL, AST 46.7, U/L ALT 44.3 U/L. Though he was requested for a urine sample, he did not submit it.

Which is the approach you would give to the global treatment of this patient?
It has to do with an obese patient (body mass index [BMI] 36), non reliable, with multiple risk factors (arterial hypertension, hypercholesterolemia, abdominal perimiter >102 cm) that complies with metabolic syndrome criteria and mild renal disorder (creatinine 1.5 mg/dL, creatinine clearance 67 mL/min [Cockcroft-Gault], glomerular filtration rate [GFR] 48.49 mL/min, MDRD [Modification of Diet in Renal Disease Study equation]). Moreover, he shows a hypertransaminasemia indicative of non-alcoholic fatty liver disease (NAFLD). He started the treatment with sulphonylureas (glimepiride) due to intolerance to the metformin; in spite of that, the patient keeps an inadequate metabolic control (glycosylated hemoglobin [HbA1c] of 7.7%.

The first impression is that he is a patient who does not help much, with a high cardiovascular risk and a slender control of the risk factors. We shall assess the complica-
Case report discussed by experts
Type 2 diabetes and metformin intolerance. M. Seguí Díaz, M.ª J. Goñi

The microangiopathic complications should be assessed, insisting on carrying out an ophthalmologic evaluation (funduscopy) and assessing the presence of proteins in urine (albumin/creatinine index). The condition of the micro-macro vascular complications provides strong arguments with which to determine therapeutic objectives according to international recommendations (HbA₁c <7%) (table 1), and to apply decision trees according to the recent algorithms. Sensu stricto, considering his physiopathology, we should introduce drugs for his metabolic control that shall act on the peripheral insulin resistance, affecting on the real causes of his current condition and on the insulin-resistance signs (arterial hypertension, dyslipidemia, obesity, non-alcoholic fatty liver disease [NAFLD], etc.). Such is the case of the metformin (as regards to the one to which the patient showed intolerance) and, though in a different manner, of the glitazones.

Which is the approach you would give to the diabetologic treatment?

Though it is true that the unique use of the diet and the exercise previous to the treatment with metformin is not collected in all the international consensus, following the reasoning of our team it would be convenient, with the collaboration of the nursing staff, its early introduction to educate and hold the patient responsible of his own disease. The gastric intolerance of the metformin is a matter that unfortunately obliges to withdraw several treatments, though sometimes it is exclusively due to an inadequate introduction of the medication and a final excessive dose. As the last consensus of the ADA/EASD indicates, it has to be started with a low dose of 500 mg (1-2 times a day) and increase it each week until achieving the optimal dose or the tolerated dose by the patient.

Assuming a completely resistant intolerance to the slow and scheduled re-introduction of the metformin, there are several alternatives according to the target of keeping the normoglycemia. All the therapies would be contraindicated with renal dysfunction, except for the strict insulin-therapy. A glomerular filtration (GF) of 48 mL/m would be the limit of them all and would constitute a datum against the use of secretagogues, as the sulphonylureas (glimepiride). Other data against it would the hypoglycemia risk, considering the used doses and taking into account his ponderal condition, as well as the pancreatic exhaustion risk; therefore in my opinion they would not be recommendable, at first. In this sense, the use of glinides (repaglinide), before or after the insulin-therapy, would increase the safety vs. the renal function.

**Table 1. Control targets in the diabetic patient**

<table>
<thead>
<tr>
<th>Target</th>
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<tr>
<td>HbA₁c (%)</td>
<td>&lt;7.0</td>
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<tr>
<td>Basal/pre-prandial glycemia (mg/dL)</td>
<td>70-130</td>
</tr>
<tr>
<td>Postprandial glycemia (mg/dL)</td>
<td>&lt;180</td>
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<tr>
<td>LDL cholesterol (mg/dL)</td>
<td>&lt;100</td>
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<tr>
<td>HDL cholesterol (mg/dL)</td>
<td>&gt;50</td>
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<tr>
<td>Triglycerides (mg/dL)</td>
<td>&lt;150</td>
</tr>
<tr>
<td>AP (mmHg)</td>
<td>&lt;130/80</td>
</tr>
<tr>
<td>Tobacco</td>
<td>No</td>
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Modified of the American Diabetes Association 2009.
and would reduce the hypoglycemia risk with a slight lower weight gain, though its doses (3 tablets), in this case, would not be adequate for a non compliant patient.

In the previous algorithms of the ADA/EASD, that is to say, from 2006, after a first step with modification of the life styles and metformin, the night insulin and the metformin were put in the same level (the cheapest ones) or the glitazones (lower risk of hypoglycemia). In the current algorithm, the new drugs are introduced and the decision is divided according to the highest or lowest evidence degree.

Therefore, in this case, and considering this exclusive objective of glycemic control in a patient with intolerance to the treatment with metformin, it would not be misconceived the use of NPH night insulin or a slow analogue (glargine, detemir) in an obese patient who has not lost the pancreatic beta-cell function, as he would improve his metabolic behavior quickly, and at the same time he would keep pancreatic beta cells and would represent an affordable economic cost. The Treat-to-Target trial showed that the dosage of night insulin associated to the oral therapy was safe and fast in obese patients with a slight increase of weight. However, he is a non-collaborative patient.

The use of some drugs or others, as regards to patients with overweight or not - (metformin in overweight and sulphonylureas in normal weight) has been left aside some years ago. The BMI informs the degree of insulin-resistance of the patient. From this point we shall assess the therapies that in their action mechanism do not increase the insulin levels, taking into account its relation with the increase of the body weight (secretagogues). On this regard, the drugs that reduce the insulin resistance in the peripheral system would avoid the early exhaustion of pancreatic beta cells and, therefore, the secondary increase of the circulating insulin. Thus, in general, the possibility of using metformin initially, together with other therapies like glitazones, should be taken into account. In this sense, the ADOPT study showed that the rosiglitazone when used alone in monotherapy, was able to keep the glycemic control during more time in comparison with the glibenclamide and metformin. Consequently, the use of glitazones would be the alternative therapy that in the absence of metformin would be adjusted better to the physiopathology mechanism involved in this patient, and would improve the symptoms that depend of the insulin resistance, as the non-alcoholic steatohepatitis. Its use might delay the starting of the insulin treatment. Certain use contradictions should be ruled out before starting the treatment, as the acute coronary syndrome, the peripheral arteriopathy and the heart disorder. The main side effect that has to be considered with the glitazones in this patient would be the possibility of edema onset and a probable weight increase (3-4 kg mean).

Other therapies that should not induce to an increase of weight and with a few side effects, but with a higher cost, are those based on incretin. The Food and Drug Administration have approved the gliptins, the DPP-4 enzyme inhibitors, in monotherapy. They are able to produce a level of metabolic control similar to other drugs, with fewer side effects (up to present) and absence of hypoglycemia. Other drugs, also based on the strengthening of the incretin effect, are the GLP-1 receptor agonists, like the exenatide, and seem to contribute to the conservation of pancreatic beta cells. The exenatide, of recent introduction in the Spanish market, stimulates the insulin secretion and inhibits the glucagon secretion, and has the beneficial feature of inhibiting the gastric emptiness in obese patients increasing the sensation of satiety and allowing the loss of weight. As counterpoint, its administration route is parenteral, b.i.d, and has frequent gastrointestinal side effects (nausea in 10-20% of the patients).

In conclusion, in this patient it should be insisted on the therapeutic compliance and on the diabetologic education before implementing (or at the same time) any pharmacologic treatment. Among them, the use of drugs with hypoglycemiatic effect that do not alter pancreatic beta-cells and that have demonstrated its safety in the mild renal disorder would be a good alternative to the metformin. Thus, the night NPH insulin, or its slow analogues (glargine, detemir), and the glitazones would be good therapeutic options.

**Which are the medical controls you would recommend?**

The controls would be the usual ones that the international guidelines recommend, among them; it should be ensured the measurement of the HbA1c on a three-month basis until achieving the adequate control and every six months after reaching the objective (table 2). The involvement of the nursing staff by means of scheduled
information and training sessions is relevant to demonstrate the negativism of this patient, to motivate him in order to introduce the necessary changes, and at the same time, to educate him until certain self-responsibility is achieved as regards to the handling of his disease. Thus, after the first information/motivation period, and after reaching the adequate metabolic control, the visits should be spaced out every 3 months, alternating with the visit to the physician, which would take place twice a year.

The self-analysis is controversial in patients under oral treatment with drugs without hypoglycemia risk, considering the limited cost-efficacy that has been found with the measurement. In turn, we would choose this in case of indicating insulin-therapy. In the same way, it is worthwhile encouraging the home controls of his AP.

**Would you do any complementary test?**

In this case, the general condition of the patient has to be assessed as regards to the possible existence of micro-macro vascular complications. Thus, the ophthalmologic revision with the inclusion of a funduscopy and the GF determination, the creatinine clearance, the microalbuminuria, albumin/creatinine quotient, the creatinine in plasma, and the electrocardiogram would be performed.

<table>
<thead>
<tr>
<th>Table 2. Follow-up of the patients with T2D</th>
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<td><strong>Activities</strong></td>
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<td>--------------------------------------------</td>
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<tr>
<td><strong>Basic medical chart</strong></td>
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<tr>
<td>Life habits</td>
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<td>Diabetes clinic</td>
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<tr>
<td>Complications</td>
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<td>Family history</td>
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<tr>
<td>Pharmacology history</td>
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<tr>
<td><strong>Physical exploration</strong></td>
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<tr>
<td>Weight/body mass index</td>
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<td>Arterial pressure/cardiac frequency</td>
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<td>Feet examination: monofilament, vibratory</td>
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<tr>
<td>Pulse exploration</td>
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<tr>
<td>Eye exploration (funduscopy, tonometry)</td>
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<tr>
<td>General exploration</td>
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<tr>
<td><strong>Complementary explorations</strong></td>
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<tr>
<td>HbA1c</td>
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<td>Lipid profile</td>
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<td>Microalbuminuria, albumin/creatinine quotient</td>
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<td>Creatinine in plasma</td>
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<tr>
<td>Electrocardiogram</td>
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<td><strong>Education evaluation</strong></td>
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<td>Pharmacology compliance</td>
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<td>Diet compliance</td>
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<td>Physical exercise compliance</td>
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<td>Feet care</td>
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<td>Hypoglycemia</td>
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<td>Self-analysis</td>
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<td>Self-control</td>
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*Modified of GEPAD5 and Seguí Díaz.*

*Activities preferably in charge of nursing.*
minuria and the albumin/creatinine quotient are relevant to be able to give an idea of the condition of his small vessels. The medication of the AP, the performance of an electrocardiogram, the measurement of the ankle/arm index and the estimation of a cardiovascular irrigation would help in order to obtain an approximate idea of his cardiovascular condition. Likewise, it would be convenient to perform an analytic follow-up of the transaminases (especially if we use glitazones), a study of the hepatic markets and an echographic assessment of his hepatopathy.

Declaration of potential conflict of interest
M. Seguí Díaz states that there are no conflicts of interests as regards to the content of this article.

References

Which is the approach you would give to the global treatment of this patient?
It is presented the case of a patient aged 73 with T2D, who besides gathers the diagnosis criteria of metabolic syndrome, according to the definition of the Third Report of the National Cholesterol Education Program (ATP-III), and the later of the International Diabetes Federation (IDF): obesity of degree 2 (BMI of 35.67), abdominal perimeter of 112 cm, hypertriglyceridemia and hypercholesterolemia with cLDL of 212 mg/dL, estimated with the Friedewald formula. Moreover, the patient shows mild renal disorder (creatinine clearance estimated with the Cockroft-Gault formula: 67 mL/min/1.73 m², that corresponds to a phase 2 according to the National Kidney Foundation guidelines), hyperuricemia (considered a vascular risk factor) and increase of the transaminases (possible due to an hepatic steatosis).

Before determining concrete therapeutic objectives it is convenient to estimate the patient’s cardiovascular risk (CV). Considering that the European SCORE scales and the American ones of the Framingham study seem to underestimate the risk in diabetic patients, it is advisable to use the UKPDS4 risk equation. The application of the estimated with the Cockroft-Gault formula: 67 mL/min/1.73 m², that corresponds to a phase 2 according to the National Kidney Foundation guidelines), hyperuricemia (considered a vascular risk factor) and increase of the transaminases (possible due to an hepatic steatosis).
formula indicates a risk of coronary disease after 10 years of 48.3%, death by coronary disease of 36.8% (high risk) and cerebro-vascular stroke of 22.8% (moderate risk).

Important studies that have been published during the last year demonstrate the importance of the intensive multifactor approach of the patient with T2D in the reduction of vascular events, and not only of hyperglycemia. These results led the American Diabetes Association (ADA), the American Heart Association (AHA) and the American College of Cardiology (ACC) to set out again the recommendations of the glycemic control in T2D. The recently published clinical trials Action to Control Cardiovascular Risk in Diabetes (ACCORD), Action in Diabetes and Vascular Disease-Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) and the Veterans Affair Diabetes Trial (VADT), do not demonstrate a relevant reduction of the serious macrovascular complications in the patients who achieved the target of a HbA1c level <7%. In the ACCORD study, the increase of mortality in the intensive treatment group motivated the interruption of the study before the foreseen termination date. However, it has to be taken into account that in these studies the number of CV events in both treatment groups was lower than the foreseen, given to the intensive treatment of the other risk factors (statins, antihypertensive and platelet antiaggregants) that was performed in both groups in a similar manner. It has been speculated about the causes of the major mortality of the ACCORD study. Though I could explain the highest number of hypoglycemias, there is only a relation between the serious hypoglycemia and the mortality in the participants of the conventional treatment group of the three trials. For many authors, the major importance falls on in the used therapeutic strategy and the speed of reaching the control.

The characteristics of the patient as regards to his age, HbA1c level and the high vascular risk coincide with the profile of the patients included in these studies; thereby the conclusions are applicable to this special case. In this sense, it is important to consider that in the participants without previous vascular event, with lower time of evolution and HbA1c <8% (characteristics that this patient has), it is indeed stated that a reduction of the risk of having a first CV event is determined. On the other hand, the trials follow-up studies, as the Steno-29 and the UKPDS, show a reduction at long-term of the macrovascular disease when the intensive treatment is implemented as early as possible after the diabetes diagnosis, as it has previously been demonstrated in T1D.11

Moreover, it is firmly demonstrated that the intensive treatment with the aim of reaching a HbA1c <7% reduces the onset and/or the evolution of the microangiopathic complications, both in T1D and in T2D. In this particular patient, we do not know the ophthalmologic assessment datum but he shows nephropathy. This datum reinforces the importance of optimizing the glycemic control. The intervention studies, as the ADVANCE study, show a reduction of 21% in nephropathy onset risk or worsening.7

Therefore, it should be set out a therapeutic strategy of all the modifiable risk factors, through measurements of life style change and an adequate pharmacological approach.

Which is the approach you would give to the diabetologic treatment?

In this particular case, taken in account the characteristics of the patient (lack of motivation and non-compliance of the previously indicated treatments), his inclusion in a continuous program of diabetology education reaches a special importance, with the aim of not only providing knowledge, but also to encourage a change of attitude to help him to assume the determined recommendations.

The specific objectives of these educational interventions should include:

- Diet modifications, with reduction of caloric reduction, restriction of saturated fats (<7%) and limitation of protein intake of 0.8-1.0 g/kg/day.
- Indications addressed to achieve an increase of the physical activity, as walks during 150 min/week.
- Training in the monitoring of the capillary glycemia, provided that, though that there are controversial data about the efficacy in patients who have not been treated with insulin, turns out to be useful in the adjustment of the pharmacologic treatment. In case of having a group education, the patients could have a benefit as regards to this program.

As regards to the modification of the pharmacologic treatment, several practical clinical guidelines (PCG)
have been published recently about T2D, as the one of the Canadian Diabetes Association,12 the NICE13 and the Ministry of Health and Consumption,14 besides the new consensus about the starting and adjustment of the treatment in T2D of the ADA-EASD.15 Though they might coincide in the need of the frequent monitoring in order to perform the treatment adjustments with the aim of achieving a HbA1c level <7% (≤6.5% in the case of NICE), they differ in the set out strategy in the different handling algorithms.

In this patient, two aspects have to be taken into account. On one hand, the obesity suggests the existence of insulin resistance that might be assessed through the determination of the C-peptide and the HOMA index (homeostasis model assessment). The use of metformin is limited by the previous gastric intolerance and the nephropathy, which advised its use with precaution. The pioglitazone could be the alternative, once the cardiac dysfunction and/or hypertensive cardiopathy is ruled out; with the inconvenience of weight increase that entails its use. However, the HbA1c that the patient shows allows us to suppose that the postprandial hyperglycemia is the main responsible of the inadequate glycemic control. Therefore, the drugs with a higher postprandial effect could be more efficacious in this case (meglitinides, alpha-glucosidase inhibitors, drugs based on the incretin effect, analogues of fast insulin). Recently, the IDF determined the postprandial hyperglycemia as a factor risk regardless of macrovascular disease.16 The ascorbate has a scarce efficacy and a high incidence of gastrointestinal effects, and the substitution of glimepiride by meglitinides would limit the combination with other drugs without adding higher hypoglycemiant strength. The best option seems to be the association of sulphonylureas with drugs that act through the incretin effect, as the GLP-1 agonists or the DPP-4 inhibitors.

The GLP-1 agonists reproduce the actions of this peptide (to stimulate the insulin secretion and to inhibit the glucagon after the intake), acting in the GLP-1 receptor. Two drugs are known up to date, exenatide and liraglutide (this last one has not been commercialized yet). Exenatide should be administered subcutaneously, starting with 5 µg bid during one month, to continue with 10 µg bid. From its association with glimepiride, a reduction of approximately 1% in the HbA1c can be expected and a loss of weight of 3-5 kg. It has the inconvenience of nausea in a 50% of the patients and the possibility of hypoglycemias (would oblige to reduce the dose of glimepiride).

The DPP-4 inhibitors, through the inhibition of the enzyme, also increase the action of the endogenous GLP-1. At present, we count with sitagliptine and vildagliptine. They have the advantage of oral administration, in one dose (100 mg of sitagliptine and 50 mg of vildagliptine in association to sulphonylureas) or 2 bid (vildagliptine 50 mg associated to metformin or glitazones) and the absence of gastrointestinal effects. On the contrary, they have a neutral effect on the weight, and lack of safety studies at long term and efficiency in the reduction of the CV risk. After the association to glimepiride (previously studied),17 a reduction of the HbA1c of 0.6-0.7% can be expected.

It does not seem necessary at the moment to add basal or pre-prandial insulin but it might be later. To summarize I suggest to combine the actual treatment with glimepiride, exenatide (due to the advantage on the weight) or the DPP-4 inhibitors in case of intolerance or rejection to the subcutaneous administration of exenatide.

Which are the medical controls you would recommend?
Taking in account that the initial approach is addressed to reduce the CV risk, the controls have to be the necessary ones until reaching the set out objectives for each of the risk factors. As regards to the AP control, considering that the values that the patient shows are over 140/90 mmHg, together with the indications about the changes in the lifestyle, the pharmacologic treatment should be started with an ARA II, given its demonstrated effect to reduce CV events in diabetic patients with nephropathy19 and slow down its progression rate.20 Once the treatment has been started, controls in each medical visit are recommended. In case the target is not achieved, it is indicated to associate a tiazidic diuretic, as this association is efficient to delay the nephropathy evolution.7 A control of the creatinine is recommended as well as the control of the plasma potassium 15 days after having started the treatment, and if the patient shows an acute intercurrent process. In case of requiring more drugs, a calcium antagonist or a beta-blocker should be chosen. The association ACEI-ARA II can cause a worsening of the renal function and hyperkalemia.21
In the treatment of dyslipidemia it is a priority to achieve a level of cLDL lower than 100 mg/dL, for which a pharmacological treatment is recommended with high doses of statins.\textsuperscript{22} If the objective is not achieved, an association with ezetimibe shall be set out. It should be expected to reduce the hypertriglyceridemia (to values <150 mg/dL) with the improvement of the glycemic control and the compliance of the diet recommendations. Once the treatment started, an analytical control should be performed after 3 months in order to determine an assessment and an adjustment of the dose, as well as to rule out the hepatic and muscular toxicity. After reaching the target, controls every six-month shall be determined. An antiaggregant treatment should be recommended with acetylsalicylic acid in primary prevention doses of 75-162 mg/day, once the values of the systolic AP are lower than 145 mmHg.\textsuperscript{22}

As it has already been mentioned, in this case there is a special importance on the consultations on diabetologic education, both initial and follow-up. The frequency of the consultations shall depend on the evolution and attitude of the patient. The last recommendations of the ADA include the glycemic self-control as part of the therapeutic intervention,\textsuperscript{22} agreeing with each patient the self-analysis frequency. The other main parameter in the follow-up of the glycemic control is the determination of the HbA\textsubscript{1c}. As it is collected in the CPG, controls on a three-month basis is recommended, in order to indicate the changes in the therapy, until reaching the control objective, with subsequent six-months determinations.

Would you do any complementary test?
For a correct assessment of the patient, it would be necessary to complete the study through tests that allow the determination of possible vascular complications of the diabetes, that probably might have an evolution time longer that the one known:
• Ophthalmology assessment. If there is not a previous assessment, it is recommended that the first examination, with pupil dilatation be performed by an ophthalmologist (funduscopy, ocular pressure and campimetry). In case no injuries are detected, an assessment will be done each 1-2 years by the ophthalmologist, or a non mydriatic retinography.\textsuperscript{22}
• Renal function. The determination of the microalbuminuria through the albumin/creatinine index in a sample of urine. Considering the level of the patient’s creatinine, it is probable that he has microalbuminuria, though it should be pointed out that an important percentage of patients have diabetic nephropathy without detectable albuminuria. Then, periodical controls should be determined in order to assess the response to the treatment.
• For the study of peripheral neuropathy, the vibratory exploration has to be registered with the tuning fork of 128 Hz, the sensitivity to the pressure with monofilament and the osteotendinous reflexes. The combination of more than one test has a diagnostic sensitivity >87%.\textsuperscript{22} The electrophysiological study should be indicated only if there are diagnosis doubts. The anamnesis should be completed with a questionnaire in order to detect the symptoms of autonomous dysfunction, and a basic exploration to rule out an autonomous cardiac neuropathy (tachycardia at rest, ortostatism, etc.).
• To assess the subclinical arterial ischemia of the lower limbs with the inspection of possible trophic signs, palpation of peripheral pulses and determination of the ankle-arm index. In case of a pathological result, an arterial echo-Doppler should be indicated.
• As regards to the ischemic cardiopathy screening, it is still controversial if other diagnosis tests are necessary besides the performance of an electrocardiogram (ECG). In the last studies, it has not been stated the usefulness of other tests in asymptomatic patients with a normal ECG.\textsuperscript{22}
• Finally, the performance of an abdominal echography will enhance the suspicion of hepatic steatosis and assess the need of ruling out other hypertransaminase causes.

In conclusion, in this patient, after completing the diagnostic study, a multifactor approach should be set out as well as intensive of this last multiple risk factors, with the aim of reducing the high CV risk that he shows.

Declaration of potential conflict of interest
M.J. Goñi states that there is no conflict of interests as regards to the content of this paper.

References