Clinical Practice Guideline on type 2 Diabetes

NOTE:

More than 5 years have passed since the publication of this Clinical Practice Guideline, and **its validity has not been reviewed**.

Therefore, **it is unclear whether its recommendations remain valid**; they should therefore be treated with caution and applied in accordance with **clinical judgement and the individual circumstances of each patient**.

CLINICAL PRACTICE GUIDELINES IN THE SPANISH NHS
MINISTRY OF HEALTH AND CONSUMER AFFAIRS

GOBIERNO DE ESPAÑA
MINISTERIO DE SANIDAD Y CONSUMO

Plan de Calidad para el Sistema Nacional de Salud

EUSKO JAURLARITZA
GOBIERNO VASCO
OSASUN SAILA
DEPARTAMENTO DE SANIDAD

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Eusko Jaurlaritzaren Argitalpen Zerbitzu Nagusia
Servicio Central de Publicaciones del Gobierno Vasco

Vitoria-Gasteiz, 2008

A bibliographic record of this work can be consulted in the catalogue of the General Library of the Basque Government:
http://www.euskadi.net/ejgvbiblioteka

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This CPG is healthcare decision aid. It is not mandatory, and it is not a substitute for the clinical judgement of healthcare personnel.

Version:	1 July 2008
Print run:	100 copies
Internet:	http//publicaciones.administraciones.es
Published by:	Eusko Jaurlaritzaren Argitalpen Zerbitzu Nagusia Central Publications Service of the Basque Government c/ Donostia-San Sebastián, 1 - 01010 Vitoria-Gasteiz
Photocomposiition:	Composiciones RALI, S.A. Particular de Costa, 8-10, 7.ª - 48010 Bilbao
Printed by:	Estudios Gráficos ZURE, S.A. Carretera Lutxana-Asua, 24-A - Erandio Goikoa (Bizkaia)
ISBN:	978-84-457-2753-3
INOP:	354-07-051-4
Copyright:	BI-2207-08

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This CPG has been funded through the agreement signed by the Carlos III Health Institute, an independent body of the Ministry of Health and Consumer Affairs, and the Health Technologies Assessment Agency of the Basque Country-Osteba, within the framework of cooperation provided for in the National Health System Quality Plan.

This guideline must be quoted:

Working group of the Clinical Practice Guideline for type 2 Diabetes. Clinical Practice Guideline on type 2 Diabetes. Madrid: National Plan for the NHS of the MSC. Health Technologies Assessment Agency of the Basque Country; 2008. Clinical Practice Guidelines in the Spanish NHS: OSTEBA No. 2006/08.

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Presentation

Care practice is becoming more and more complicated due to many different factors. One of the most relevant factors is the exponential increase of scientific information.

To make clinical decisions that are adequate, safe and effective, practitioners need to devote a lot of effort in continuously updating their knowledge.

In 2003, the Interterritorial Council of the Spanish NHS created the GuiaSalud Project whose final aim is to improve clinical decision-making based on scientific evidence, via training activities and the configuration of a registry of Clinical Practice Guidelines (CPG). Since then, the GuiaSalud project has assessed dozens of CPGs in agreement with explicit criteria stipulated by its scientific committee. It has registered them and has disseminated them over the Internet.

At the beginning of 2006, the D.G. of the Quality Agency of the National Health System prepared the Quality Plan for the National Health System, which was divided into in 12 strategies.

The purpose of this Plan is to increase the cohesion of the National Health System and help guarantee maximum quality health care for all citizens regardless of their place of residence.

As part of the Plan, different agencies and expert groups in prevalent pathologies related to health strategies were entrusted with the preparation of eight CPGs. This type 2 Diabetes guideline is the fruit of this assignment.

The definition of a common methodology to prepare the CPGs for the NHS was also requested, and this has been prepared as a collective effort of consensus and coordination among the Spanish CPG expert groups.

In 2007, the GuíaSalud project was renewed and the Clinical Practice Guideline Library was created. This project developed into the preparation of the CPGs and included other Evidence-Based Medicine services and products. It also aims to favour the implementation and assessment of the use of CPGs within the National Health System.

This CPG deals with type 2 Diabetes mellitus (DM 2), a disease with serious implications as regards the morbidity and mortality of our population. It has been prepared by a multidisciplinary team, comprised of medical, nursing and pharmaceutical practitioners from fields such as primary care and endocrinology. The patients' point of view has been taken into consideration through their involvement in a specific focus group. Likewise, the opinion of scientific societies and the Spanish Diabetes Federation has also been included.

The CPG answers 40 questions on the health care provided for patients who suffer diabetes type 2. Special emphasis is placed on aspects such as education and self-care, the new pharmacological strategies, the prevention of macro- and microvascular complications and the pre-diabetic stages. The evidence, which supports most of the recommendations, is solid and coherent.

We are sure that this project will result in better quality health care for the diabetic patient.

Dr. Alberto Infante Campos
D. G. of the NHS Quality Agency

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Acknowledgements

To the executive team of the Gipuzkoa Est District – Ekialde (Osakidetza) for the logistic facilities provided to prepare the CPG

Collaborating Societies

Spanish Diabetes Federation (FED)

Spanish Society of Primary health care Pharmacists (SEFAP)

Spanish Society of Family and Community Medicine (SEMFYC)

Spanish Society of Primary Care Physicians (SEMERGEN)

Members of these societies have taken part in the authorship and expert collaboration of the CPG.

Declaration of interests

A declaration of interests has been requested from all the members of the Working Group, as well as from professionals who have participated as expert collaborators (appendix 12).

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Questions to be answered

Definition, natural history, diagnostic criteria and screening of DM 2

1. What is the definition of diabetes? Diagnostic criteria, tests to be carried out and cut-points
2. Which are the risk factors to develop DM 2?
3. For which risk groups is diabetes screening recommended?
4. Which is the most reliable test for diabetes screening: fasting blood glucose, oral glucose tolerance test, glycosylated haemoglobin (HbA_1c)? How frequently are the screenings to be carried out on the population at risk?
5. What is the diagnosis validity of HbA_1c 1c in patients with fasting plasma glucose between 110 and 126 mg/dl?
6. What is the diagnosis validity of capillary blood glucose in comparison with venous plasma glucose and oral glucose tolerance test to the diagnosis and screening of diabetes?

Prevention of diabetes in patients with intermediate hyperglycaemia

7. Which interventions are efficient to prevent the development of diabetes in patients with imparired fasting glucose or impaired oral glucose tolerance test (diet, exercise, pharmacological treatment)?

Diet and exercise

8. What is the most appropriate diet for a diabetic patient?
9. What are the effects of physical exercise on DM 2 patients? What type of exercise is recommended?

Glycemic control

10. Which are the targetss for HbA_1c?
11. What is the initial pharmacological treatment for patients with diabetes who do not reach the appropriate glycemic control criteria?
12. Which is the most appropriate treatment in case of failure with the initial therapy?

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13. Which drug combination strategies are recommendable to treat patients with diabetes with poor glycemic control?

14. Which drug combination strategies are recommendable to treat patients with diabetes with poor glycemic control after using double oral therapy (triple oral therapy vs. insulin)?

15. Should the treatment with oral antidiabetic drugs be maintained in patients who start treatment with insulin?

16. What initial insulin regimen is the most appropriate for patients who failed with oral drugs?

17. Which is the efficacy and safety of insulin analogues in comparison to conventional insulin for patients with DM 2 who require the use of insulin?

Screening and treatment of macrovascular complications

18. Is the cardiovascular risk for diabetic patients comparable to the risk for those patients who have suffered a myocardial infarction? What risk table is recommended for patients with DM 2?

19. Should a coronary hearte disease screening be carried out in adults with DM 2?

Which is the method to develop a coronary heart disease screening?

20. Should diabetic patients be treated with aspirin?

21. Does the treatment with statins reduce cardiovascular complications in diabetes? When is it appropriate to use treatment with statins for patients with diabetes?

22. Which are the targets for blood pressure within the treatment of the diabetic hypertense patient?

23. Which is the preferred hypertensive treatment in patients with diabetes and high blood pressure?

Screening and treatment of microvascular complications[1]

24. Should a screening of the diabetic retinopathy be carried out? With which technique and how often?

[1] The question on peripheral arteriopathy has been included in the section on diabetic foot as there is no randomized clinical trial on screening efficacy as isolated intervention (only evidence has been found when the peripheral arteriopathy screening was done within the context of a diabetic foot screening).

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25. Is a diabetic nephropathy screening to be done? How often should it be carried out? What methods are to be used?

26. Which is the treatment for patients with DM 2 and microalbuminuria?

27. Which is the treatment for painful diabetic neuropathy?

28. Which is the treatment for erectile dysfunction in a type 2 diabetic patient?

Diabetic foot. Assessment, prevention and treatment

29. Should a diabetic foot screening be done? How often? What method?

30. Which are the most effective preventive measures to avoid diabetic foot complications?

31. What is the efficacy of the interventions to treat diabetic foot ulcers?

Diabetologic education

32. Which are the goals and contents of the education addressed to patients with DM 2?

33. Is the education addressed to patients with DM 2 effective?

34. How should education be addressed to patients with DM 2 in primary care and in specialist care?

35. Is self-management effectivet for patients with DM 2 (with components such as weight self-control, self-monitoring of blood glucose, foot or blood pressure)? What should the content of the self-management program include?

36. Is self-monitoring of blood glucose effective in patients with DM 2, treated with insulin and not treated with insulin?

Organization of the visit of a DM 2 patient

37. Which are the referral criteria to a specialized consultation proposed?

38. Which is the initial treatment for adults with DM 2?

39. Which are the good control criteria proposed for patients with diabetes?

40. Which is the content of the periodic control in medical and nursing consultation?

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Summary of recommendations

Definition, natural history, diagnostic criteria and DM 2 screening

B	The use of HbA_1c is not recommended as a diagnostic criteria in patients with impaired fasting glucose.
√	The development of studies within our field is recommended to assess the diagnostic validity of HbA_1c in these situations.
D	Annual screening of diabetes through fasting plasma glucose in the population at risk, defined by hypertension, hyperlipemia, obesity, gestational diabetes or obstetric pathology (macrosomia, repeated miscarriages, malformations), impaired blood glucose, and impaired glucose tolerance at any age; and every three years in patients aged 45 or more, within a structured program on cardiovascular prevention.
C	Capillary blood glucose is not recommended as diagnosis test in population at risk.

Prevention of diabetes in patients with intermediate hyperglycaemia

A	In patients with impaired glucose tolerance or impaired fasting glucose, the structured programs recommended are those, which foster physical exercise and diet.
A	The use of pharmacological treatments is not recommended for patients with impaired glucose tolerance or impaired fasting glucose.

Diet and exercise

Diet

D	The distribution of the intake of carbohydrates during the day to enable glycemic control, adjusting this to pharmacological treatment is recommended.
A	The use of phaStructured programs which combine physical exercise and dietary advice, reducing the intake of fat (<30% of daily energy), carbohydrates between 55%-60% of daily energy and 20-30g of fibre intake are recommended. Patients with BMI ≥25 kg/m^2, must follow a low-caloric diet. rmacological treatments is not recommended for patients with impaired glucose tolerance or impaired fasting glucose.
B	Widespread use of obesity-related diabetes pharmacological treatment is not recommended (orlistat, sibutramine). It can be used in specific cases, taking into consideration the associated pathology and the possible interactions, contraindications of the different drugs.
B	Bariatric surgery in diabetic patients with morbid obesity may be recommended in specific cases, taking into consideration the risks and benefits, the patient's preferences, his comorbidity and the technical availability.
B	The use of omega 3 fatty acid supplements is not recommended for the diabetic population in general.

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C	The use of omega 3 fatty acids could be considered for diabetic patients with severe hypertriglyceridemia who do not respond satisfactorily to other means (diet and drugs).
B	It is not necessary to contraindicate the moderate consumption of alcohol in diabetic patients with this habit, unless there are other medical criteria which require it. In any case, it is recommendable to limit the intake of alcohol to a maximum of two-three units per day in the case of men and one-two units in the case of women.
D	Fixed menu diets can be used, or portion exchange diets or those based on simplified guidelines, depending on the patient, the specialist or the health environment.

Exercise

A	In DM 2 patients, the practice of regular and continuous physical exercise is recommended, of aerobic or anaerobic intensity, or preferably a combination of both. The recommended frequency is three sessions per week on alternate days, progressive in duration and intensity and preferably under supervision.

Glycemic control

Glycemic control with oral antidiabetic drugs

HbA_1c targets

D	In general, orientative targets under 7% for HbA_1c are recommended. However, the target should be based on an individual assessment of the diabetes risk complications, comorbidity, life expectancy and patients' preferences. A more intensive control is recommended for patients with microalbuminuria within the context of a multifaceted intervention to reduce cardiovascular risks. Likewise, less strict targets can be appropriate for patients with a limited life expectancy, elderly or individuals with comorbidity conditions, with a previous hypoglycaemia history or patients with long-term diabetes.

Initial treatment with monotherapy

D	If after a three-six months treatment with non-pharmacological measures glycaemic targets are not achieved, it is recommended to start pharmacological treatment.
D	Oral glucose lowering drugs should be prescribed within a trial period and its effects should be monitored according to HbA_1c levels.
A	Metformin is the preferred drug for people overweight or suffering from obesity (BMI ≥25,0 kg/m^2).
B	Metformin is also the first line option for people not overweight.
C	Metformin is contraindicated for patients with renal failure (serum creatinine over 1,5 mg/dl for men and 1,4 mg/dl for women).
A	Sulfonylureas should be considered as initial treatment when mwtformin is not tolerated or is contraindicated and it can be used on patients not overweight.

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D[CPG]	A daily single dose of sulfonylurea can be useful when there is a suspicion of a problem of therapeutic non-compliance.
B	Glinides can play a role to improve glycemic control in patients with non-routine models (no regular meals or missed meals).
B	Acarbose can be considered an alternative therapy when there is intolerance or contraindication to the rest of oral antidiabetic drugs.
B	Thiazolidinediones should not be used as first line drugs. Rosiglitazone has been recently withdrawn from the market because of its negative cardiovascular profile.
B	Should the use of a thiazolidinediones, be considered necessary, it is recommended to use pioglitazone due to its more favourable safety profile.
√	Additional trials are required with morbimortality and safety variables to establish the role of the incretin therapy in DM 2.

Combination therapy after failure of initial monotherapy

B	When glycemic control is not appropriate in monotherapy, a second drug should be added.
A	Sulfonylureas should be added to metformin when glycemic control is not appropriate.
A	When glycemic control is not satisfactory with a sulfonylurea in monotherapy, metformin should be added.
B	Should there be intolerance to sulfonylureas or in patients with non-routine intake models, meglitinides can be used.
B	Acarbose as alternative treatment for patients who cannot use other oral antidiabetic drugs could be considered.
B	Thiazolidinediones, are second line drugs within a combined therapy. Their use could be considered individually when there is poor glycemic control as well as intolerance or contraindication to other oral antidiabetic drugs. In this case, the use of pioglitazone is recommended.
B	Thiazolidinediones, should not be used in diabetic patients with heart failure.

Treatment after the failure with a two drug associated therapy

A	Should there be an inadequate control of glycaemia despite using a double optimized oral therapy, the use of treatment with insulin is recommended.
B	Triple oral therapy can be recommended after an evaluation of the potential cardiovascular risks in specific patients with insulinization problems.
B	Should the use of thiazolidinediones,be considered necessary, it is recommended to use pioglitazone due to its more favourable safety profile. Rosiglitazone has been recently withdrawn from the market because of its negative cardiovascular profile.

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Insulin therapy

A	When an insulin treatment is started, it is recommended to maintain the metformin and/or sulfonylureas therapy.
√	The need to continue with sulfonylurea or to reduce its dose due to hypoglycaemia risk must be monitored.
A	In patients with DM 2 who require insulinization the generalized use of insulin analogues is not recommended. On the contrary, slow-acting insulin analogues should be used for patients with an increasing risk to night hypoglycaemias. In patients with DM 2, when intensive insulinization is required, fast-acting analogues have no advantages.
D^{CPG}	DCPC When choosing the initial insulin regimen, the preferences of the patient, the risk of adverse effects (especially hypoglycaemia) and costs should be taken into consideration.

Screening and treatment of macrovascular complications

Cardiovascular risk and statin treatment

D	Localized evidence does not provide a recommendation favouring coronary heart disease screening in the general asymptomatic diabetic population. More research is required for selected groups at high risk.
C	Treating the general diabetic population with the same means as the population that has suffered an myocardial infarction is not recommended.
C	Whenever necessary, a risk table should be used to calculate the coronary risk in diabetic patients. The risk tables recommended are those from the REGICOR project.
C	In patients with diabetes for more than 15 years, especially in the case of women, it is recommended to use an acetylsalicylic acid and statin treatment, due to its high cardiovascular risk.
B	A statin treatment is recommended for diabetic patients with coronary risk ≥10% according to the REGICOR table.
D	The evidence relating the effectiveness of aspirin in diabetic patients is controversial. The use of aspirin treatment can be considered for diabetic patients with coronary risk ≥10%, according to the REGICOR table, but risk benefict assessment is needed.
B	In type 2 diabetic patients with cardiovascular risk ≥10% in the REGICOR table and for those where statins are contraindicated or are not tolerated, the use of fibrates can be considered.

High blood pressure treatment

B/D	Patients with high blood pressure and DM 2 without nephropathy should receive treatment to reduce their blood pressure until achieving an diastolic blood pressure (DBP) <80 mmHg (B) and systolic blood pressure (SBP) <140 mmHg (D).

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A	Hypertense patients with DM 2 without nephropathy should be treated firstly with an angiotensin converting enzyme (ACE) inhibitor or a thiazide; or both when blood pressure is to be controlled. Dihydropiridinic calcium antagonists are the alternative treatment.
B[CPG]	Beta-blockers are not recommended unless there is any other firm indication for its use, such as ischemic cardiopathy or heart failure.

Screening and treatment of microvascular complications

Diabetic retinopathy screening

B	The use of a 45º non-mydriatic retinal camera with a single photograph is recommended as a diabetic retinopathy screening method.
B	In DM 2 patients without retinopathy, the recommendation is for a control to be carried out every three years and every two years in the case of patients with non-proliferative mild retinopathy.

Diabetic nephropathy

C	Microalbuminuria screening is recommended during the initial diagnose of type 2 diabetic patients and afterwards on an annual basis.
D[CPG]	The morning albumin-to creatinine ratio is the method recommended.
D[CPG]	Should this method not be available, the determination of microalbuminuria during periods of time of 12 or 24 hours, or the use of morning urine dipsticks could be useful.
A	Patients with DM and nephropathy (hypertense and normotensive) should be treated with an angiotensin converting enzyme (ACE) inhibitor. The angiotensin II receptor blockerst (ARB II) is the alternative treatment when ACE-Inhibitors are not tolerated.
A	The use of the combination ACE-Inhibitor – ARB II is not recommended.
D[CPG]	ACE-Inhibitor -ARB IIs must be used with caution in patients with suspicion of renal artery stenosis. Plasma creatinine and potassium monitoring is recommended two weeks after the start of the treatment.
A	In patients with DM 2 and nephropathy a multifactorial intervention is recommended (measures considering the patient's life style and pharmacological therapy) monitored by a multidisciplinary team with appropriate training.

Diabetic peripheral neuropathy

A	Tricyclic anti-depressants and traditional anticonvulsants are the preferred drugs to treat neuropathic pain in diabetic patients. As second line drugs (when there are contraindications for the previously mentioned treatments or these are not tolerated), the use of new anticonvulsants (gabapentin or pregabalin), opioids (such as morphine, oxycodone or tramadol) or duloxetine is recommended.

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B	When the response to the treatment is not sufficient, other drugs with different action mechanisms can be associated, monitoring the response and any adverse effects.
B	In milder cases, topical treatment with capsaicin can be used, assessing the response and its local adverse effects.

Erectile dysfunction

A	5-FDE inhibitors are the preferred drugs to treat erectile dysfunction in men with DM 2.
B	In case of contraindication or intolerance to 5-FDE inhibitors, the following drugs can be used alternatively: intracavernous alprostadil (tolerance and acceptability problems) or apomorphine (doubtful efficacy). The patient's preferences and response to the treatment are to be assessed.
B	In specific patients where it is not possible or desirable to use pharmacological therapy, psychotherapy can be recommended.
√	5FDE inhibitors are contraindicated for patients who use nitrates for angina.

Diabetic foot. Assessment, prevention and treatment

A	In diabetic patients, screening, risk stratification, prevention and treatment for risk foot structured programs are recommended.
D^{CPG}	Professionals who deal with diabetic patients should assess the risk to develop diabetic foot ulcers during the control visits. An annual check-up is recommended in low-risk patients, every three to six months for mild risk patients and between one and three months for high-risk patients.
B	Diabetic foot screening must include: foot and soft tissue check-up, footwear assessment, skeletal muscle scan, symptoms of peripheral artery disease assessment complete with the determination of the ankle-brachial index in some cases and assessment of sensitivity through a monofilament or turning fork.
D^{CPG}	More in depth monitoring is recommended for elderly patients (>70 years), with long-term diabetes, residential patients, suffering from sight problems, smokers, those with social problems or who live alone.
B	Education on the appropriate care for diabetic foot, within a structured educational program which includes different elements is recommended, in order to improve knowledge, foster self-management and reduce the risk of complications.
B	Patients with prior ulcer without severe deformities can use common footwear (well adjusted and well made), while those who suffer foot deformities could use therapeutic footwear.
√	Training on how to deal with diabetic foot should be developed among the professionals who deal with these patients.

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Treatment for diabetic foot ulcers

D	In diabetic foot ulcers, the necrotic tissue should be removed with surgery for better healing. The use of hydrogel dressings as debriding agents can be recommendable for better healing. In case of severe ischemia, the patient should be referred.
A	Contact splints are the devices chosen to reduce plantar pressure in diabetic patients with non-infected and non-ischemic foot ulcers.
B	Fixed fibreglass splints are an alternative to contact splints, as they require less time and professional staff.
C	Routine culture in diabetic foot ulcers is not recommended as it has a limited diagnosis value.
D[CPG]	Patients with progressive ulcers, which do not heal, and with clinical symptoms of active infection, should receive systemic antibiotic treatment.
D[CPG]	If an antibiotic is to be used, the most probable microorganisms as well as the local resistance patterns should be considered, with broad-spectrum antibiotics that cover anaerobes and aerobes.
D[CPG]	Should there be no solid evidence of clinical efficacy or cost-effectiveness, the health professionals should use the dressings which adapt best to their clinical expertise, the patient's preference or infection location as well as cost.
B	More research is required to determine the role of colony-stimulating factors in patients with diabetic foot infections.

Diabetologic education

A	People with diabetes should be given a structured education program based on their regularly checked needs during the diagnosis stage and subsequently, on a regular basis.
D	The use of several learning techniques adapted to the patient's personal preferences and integrated within his daily care routine on the long term are recommended.
B	Primary and specialist care teams should foster programs directly aimed to encourage patient participation, adapted to their preferences and aims and which include contents related to their personal experience.
A	Self-management should be recommended to people with DM 2, by fostering the patient's participation.
B	Self-management components may vary, though in general, these should include knowledge of the disease (definition, diagnosis, importance of good control) dietetic and pharmacological treatment, physical exercise, ways to approach any complications, self-care of feet and self-monitoring of blood glucose with adaptation of the treatment in selected patients.
A	It is highly recommended that group education on self-management be directed by skilled professionals.

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D	Within the medical context we recommend that these programs are carried out by nurses, both in primary and specialist care.
C	Self-monitoring of blood glucose is recommended for the insulinised patient in order to adjust the insulin dose.
D	The frequency of self-monitoring in insulinised patients depends on the characteristics of the patient, the aims to be achieved and the type of insulin.
A	Non-insulinised DM 2 patients with an acceptable metabolic control and those recently diagnosed should not carry out self-monitoring of blood glucose.
B	Selected patients with inappropriate glycemic control can be offered a self-monitoring of blood glucose within a structured educational and self-management program, which includes regular follow-up. The patient's level of motivation, his capacities and preferences, the frequency of hypoglycaemias, the type of medication used and the costs are to be taken into consideration.
D^{CPG}	Self-analysis can be offered to non-insulinised DM 2 patients in order to provide information on hypoglycaemias, assess glycemic control after changing treatment or life style and monitor changes during intercurrent diseases.

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1. Introduction

Effective care for diabetic patients implies coordinated and multidisciplinary work where primary and also specialised care are involved.

Type 2 diabetes mellitus is a disease where medical advances are constantly taking place, both in the diagnosis as well as its handling and treatment. Changes in the diagnostic criteria, marketing of new drugs for glycemic control and the permanent publication of new studies on the efficacy of cardiovascular risk factors must be assessed and incorporated to clinical practice as appropriate by those professionals responsible for the care of diabetic patients.

The existence of an updated Clinical Practice Guideline can be a useful tool to provide answers to those questions posed when dealing with a diabetic patient.

One of the proposals of the strategy on diabetes of the National Health System (1) is to "guarantee that the treatment and follow-up of diabetic patients complies with the best criteria and quality standards as regards health care". Thus, it is recommended to "create, adapt or adopt and subsequently implement, within the Autonomous Communities, integrated guides on clinical practice according to the priorities and quality criteria established by the National Health System".

This is one of the reasons for choosing diabetes as a topic for one of the Clinical Practice Guidelines of the program to create clinical practice guidelines based on evidence and which will help the decision-making processes within the Spanish National Health System (NHS).

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2. Scope and objectives

The main aim of this Clinical Practice Guideline is to provide the sanitary professionals in charge of diabetic patient care with a tool which will allow them to make better decisions on the problems that the caring of this disease may involve.

This Clinical Practice Guideline focuses on the patient's care within the outpatient context and does not deal with gestational diabetes or the acute metabolic complications of the disease. As regards micro- and macroangiopathic complications, the Clinical Practice Guideline approaches its screening, prevention, diagnosis and partial aspects of the treatment. There are treatments for these complications which are dealt with at primary care and thus justify their approach in this guide. These are the treatments of microalbuminuria, some aspects of neuropathy and diabetic foot.

During the editing process of this Clinical Practice Guideline, inhaled insulin was withdrawn from the market and for this reason this section has been removed.

This guideline is addressed to: diabetes educators, family physicians, primary care and specialised nursing professionals, endocrinologists and other professionals who attend these patients in outpatient visits (ophthalmologists, internists, cardiologists, nephrologists, chiropodists, general and vascular surgeons, etc.). In the Annexes, both patients and relatives can find educational material about the disease.

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3. Methodology

Methodology. Evidence levels and formulation of recommendations.

The methodology used is recorded in the "Manual de elaboración de GPC" (Manual on how to create a Clinical Practice Guideline) from the Ministry of Health and Consumer Affairs[1].

The steps followed were:

- Setting up the group in charge of creating the guide, which included the following professionals from: primary care (medicine, nursing, pharmacy), specialised care (endocrinologists and nursing educators on diabetes) and professionals experienced in the creation of a Clinical Practice Guideline.
- Creating of clinical questions following the Patient / Intervention / Comparison / Outcome format.
- Developing a qualitative study with diabetic patients (focal group and personal interviews) in order to validate and complete the list of questions.
- Bibliographic review:
  - Data bases: Cochrane Library, DARE, Medline Pubmed, Evidence Based Review, Embase, CINHAL, Clinical Evidence, IME, IBECS.
  - Languages: English, French and Spanish.
  - Research structure: in a first phase, preliminary research of Clinical Practice Guidelines and systematic reviews was carried out. As a secondary evidence resource, a Clinical Practice Guideline on glycemic control[2] and specific Clinical Practice Guidelines on retinopathy, diabetic foot and nephropathy have been included[3, 4, 5].
  - The Clinical Practice Guideline from the GEDAPS group has been used as additional reference material. (2).
  - In a second phase, wide research on original studies (randomised clinical trials, observational studies, studies of diagnosis and prognosis tests and clinical prediction rules) was carried out.
  - Research period: the research deadline was January 2008. However, a service of bibliographic alert was kept active until May 2008 to include the most relevant updated literature.

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[1] Grupo de trabajo sobre GPC, Elaboración de Guías de Práctica Clínica en el Sistema Nacional de Salud. Manual Metodológico. Madrid: Plan Nacional para el SNS del MSC. Instituto Aragonés de Ciencias de la Salud -I+CS; 2007. Guías de Práctica Clínica en el SNS: I+CS Nº 2006/0I.

[2] NICE. Clinical Guideline. Management of type 2 diabetes: Management of blood glucose. London: National Institute for Clinical Excellence; 2002.

[3] NICE. Clinical Guideline. Management of type 2 diabetes: Retinopathy, screening and early management. London: National Institute for Clinical Excellence; 2002.

[4] NICE. Clinical Guideline. Management of type 2 diabetes: Prevention and management of foot problems. London: National Institute for Clinical Excellence; 2003.

[5] National Institute for Clinical Excellence. Clinical Guideline F. Management of type 2 diabetes. Renal disease- prevention and early management. London: National Institute for Clinical Excellence; 2002.

- Assessment of the quality of the studies and evidence summary for each question, following the recommendations of the Scottish Intercollegiate Guidelines Network (SIGN).
- Formulation of recommendations based on the "considered judgement." by SIGN. The evidence classification and rating of the recommendations have been developed with a mixed system which uses the centre's proposal on medicine based on the Oxford evidence for the diagnosis questions and the SIGN evidence for the rest (annex 1). Controversial recommendations or those lacking evidence have been discussed and decided on by consensus among the production team in a meeting.
- Selection of a panel of national collaborator experts in the area of DM 2 to elaborate the initial phase of the questions and review the first draft of the Clinical Practice Guideline.
- Different Scientific Associations involved have been contacted: Spanish Federation of Diabetes, Spanish Society of Primary Care Pharmacists (SEFAP), Spanish Society of Family and Community Medicine (SEMFYC), Spanish Society of Primary Care Physicians (SEMERGEN), which are also represented by the production team and expert collaboration.
- The update of the Clinical Practice Guideline is due every five years, however, there may be an electronic update issued sooner.
- The recommendations adapted from other guidelines have been identified with the index «[CPG]».
- The tables of the Levels of Evidence and Grades of Recommendation can be consulted in Annex 1.

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4. Epidemiology and sanitary impact of type 2 diabetes mellitus

4.1. Epidemiology of DM 2

The epidemiologic situation of type 2 diabetes mellitus (DM 2) in Spain has recently been reviewed in the report Estrategia en diabetes del Sistema Nacional de Salud (Strategy on diabetes of the National Health System) from the Ministry of Health and Consumer Affairs (1). According to this report, the prevalence of DM 2 is around 6.5% for the population between 30 – 65 years old, though this figure may vary between 6% and 12% (1; 3; 4) depending on the different studies, groups of population and methods used for diagnosis. The National Health Survey states that in the period 1993-2003, the prevalence of diabetes mellitus (DM) declared by the respondents increased from 4.1% to 5.9%, 16.7% in the age range between 65 and 74 and 19.3% for those over 75. (1)

This prevalence increase can be due to several causes; on the one hand, the change in the DM diagnosis criterion (reduction from 140 mg/dl to 126 mg/dl) (5), and, on the other, the gradual ageing of the population as well as the changes in lifestyle, characterised by less physical activity and diabetic habits with pathologies such as obesity (1; 6).

The data from different prevalence studies in Spain state that the use of diagnostic criteria based on blood glucose (ADA, 1997) instead of on the Oral Glucose Tolerance Test (OGTT) (WHO, 1999) undervalue the prevalence of diabetes. It is believed that the prevalence of unknown diabetes is similar to that of the known diabetes (6%-10%) (4).

The DM 2 mortality rate ranges between 12.75 and 30.37 deaths for every one thousand inhabitants, according to the different Autonomous Communities. 75% of the diabetic patients die from cardiovascular disease, mainly due to coronary disease (1).

Diabetic microangiopathy (retinopathy, nephropathy and neuropathy) is mainly determined by the level of glycemic control, while the development of macrovascular complications (coronary heart disease, stroke and peripheral arteriopathy) is attributed to the existence of risk factors in the diabetic patient (hypertension, dislypemia, smoking and obesity).

Macroangiopathy or macrovascular disorder has an earlier start, a more aggressive evolution and it affects women more. The diabetic population has a greater adjusted risk than the non-diabetic (2.6 in the case of women and 1.7 in the case of men) to suffer coronary heart disease (angina, silent ischemic cardiopathy, acute myocardial infarction (AMI) or sudden death) (2).

The prevalence of macroangiopathy in type 2 diabetics ranges between 22% and 33% in the different studies. It is worth highlighting: 30% of electrocardiogram alterations; 12.4% of coronary heart disease; 9.8% of stroke; 14.1% with signs of peripheral arteriopathy; 8% of intermittent claudication and ; 1.4% of amputations, according to a study carried out in the Basque Country (3).

Up to 20% of type 2 diabetics present diabetic retinopathy when diagnosed. In the GEDAPS study from the year 2000, retinopathy prevalence was 31% and that of amaurosis, 3%. After 20 years of evolution, 60% of DM 2 patients have diabetic retinopathy (1).

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The studies carried out in Spain state in type 2 diabetics a prevalence of microalbuminuria of 23%; 5% for proteinuria; and between 4.8% and 8.4% for renal failure. Microalbuminuria is a determining factor of renal failure as well as an indicator of coronary heart disease and cardiovascular mortality (1; 2).

Currently, diabetes mellitus is the first cause of inclusion in the renal replacement therapy programs which includes haemodialysis, peritoneal dialysis and renal transplant (1).

Diabetic neuropathy is another microvascular complication of diabetes. It can appear as somatic neuropathy, where diabetic foot is included and its most common pathology is symmetric distal polyneuropathy, which affects at least 24.1% of the DM 2 population. Autonomous neuropathy affects between 20% and 40% of type 2 diabetics. The most frequent forms are digestive neuropathy (gastroparesia, diarrhoea), cardiovascular neuropathy (orthostatic hypotension) and impotence.

Diabetic foot is the consequence of loss of sensitivity due to neuropathy or the existence of deformities. The existence of peripheral arteriopathy aggravates the prognosis. The amputation prevalence is from 0.8% to 1.4%; the incidence of ulcers is 2.67% (2).

The appropriate assessment of cardiovascular risk, with the integrated action it conveys on all the risk factors, not only on hyperglycaemia, is a priority strategy to reduce the morbimortality of DM 2 patients (1).

4.2. Costs for DM 2

For DM 2 patients assisted in primary care, the average direct cost was 1.305€ per patient on an annual basis, according to the CODE-2 study. From this total estimation, 42% corresponds to pharmaceutical expenses, 32% to hospitalization costs and 26% to outpatient health care (1).

According to a study held in Spain in 2002, between 6.2 and 7.4% of health care expenses were from diabetes. The direct expense of a diabetic patient almost doubles that of a non-diabetic patient (7).

The average of annual visits of a diabetic patient to the family physician is estimated in nine visits, and between a third and a half of the visits to the endocrinologist are related to diabetes (7).

4.3. Organization and assistance to DM 2 patients in the Spanish National Health System

Diabetes is diagnosed and seen mainly by primary care physicians and by referred endocrinologists; these two physicians deal with this disease depending on its severity and the complexity of the treatments.

Strategy (1) states that 68.5% of the Autonomous Communities have standardised coordination between primary and specialist care, mainly through agreed protocols, improvement committees, clinical sessions and training activities. There are specific information or registration systems on diabetes in primary care in 73.7% of the Autonomous Communities, 15% in specialist care and 31.6% in public health. Variability is very wide.

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However, the quality of the assistance provided to people with diabetes and the health results are aspects which are difficult to evaluate. Most studies have been carried out in specific and hardly representative areas of the diabetic population as a whole or with methodological problems (i.e., the sampling was not randomized).

A recent report carried out within a wide population, which included 430 health centres throughout Spain (8) and 1,907 diabetic patients, stated that 22.6% of the patients smoke, 49.4% have glycosylated haemoglobin beyond 7% and 31.5% present >30 kg/m2 body mass index (BMI). As regards other more controversial indicators, 61.3% suffer from cardiovascular risk, according to Framingham original [3]20%; 5.6% reach LDL <100 mg/dl levels and 7.8% <130/80 blood pressure levels.

The GEDAPS group, pioneer in the assessment of diabetes assistance in primary care in Spain, offers data from 1998 to 2002, including both the process and the result of a sample performed in 8,000 patients. In its 2002 assessment, the glycosylated haemoglobin (HbA_1c) average was 7.2% ± 1.5; the BMI was 29.8 ± 4.9 kg/m2; systolic blood pressure (SBP) 139 ± 4.9 mmHg; diastolic blood pressure (DBP) 79 ± 9 mmHg; and total cholesterol 205 ± 40 mg/dl (9). The tendency of all these indicators, both during the process and at the result stage is the improvement of the period analysed.

To conclude, all the indicators and data mentioned show that it is still necessary to continue improving assistance provided for diabetes within the Spanish National Health System.

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5. Definition, natural history, criteria, diagnoses and screening of DM 2

The questions to be answered are the following:

- What is the definition of diabetes? Diagnostic criteria, tests to be carried out and cut-points
- Which are the risk factors to develop DM 2?
- For which risk groups is diabetes screening recommended?
- Which is the most reliable test for diabetes screening: fasting blood glucose, glucose overload, glycosylated haemoglobin (HbA_1c)? How frequently are the screenings to be carried out on the population at risk?
- What is the diagnosis validity of HbA_1c in patients with blood glucosea between 110 and 126 mg/dl?
- What is the diagnosis validity of capillary blood glucose in comparison to venous blood glucose and glucose tolerance test to the diagnosisa and screening of diabetes?

5.1. Definition of diabetes mellitus

The term *diabetes mellitus* (DM) defines metabolic alterations of different etiologies characterized by chronic hyperglycaemia and carbohydrate, fats and protein disorders in the metabolism as a result of the defects in the secretion of insulin, in its action or in both (WHO, 1999) (6).

DM can appear with characteristic symptoms, such as thirst, polyuria, blurred vision and weight loss. Frequently, the symptoms are not serious or are barely noticeable. Thus, hyperglycaemia can provoke functional and pathological changes for a long period before the diagnosis.

The chronic complications of DM include gradual development of retinopathy, with potential blindness: nephropathy which can lead to renal failure; peripheral neuropathy with risk for plant ulcers, amputation or Charcot foot; several infections; dental alterations, autonomous neuropathy; and cardiovascular diseases such as ischemic heart disease, stroke or peripheral arteriopathy.

DM 2 accounts for 90% of the diabetic cases.

Most of type 2 diabetics suffer from overweight or obesity, which leads to an increase in the resistance to insulin. It is a type of diabetes that presents variable levels of insulinic deficit and peripheral resistance to the action of insulin. Frequently, in DM 2 there are high levels of compensatory initial insulinemia, provoking insufficient insulinic secretion in the long term to compensate the resistance to insulin. Ketoacidosis is uncommon.

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5.2. Risk factors for the development of diabetes

5.2.1. Age and sex

The prevalence of diabetes increases with age. It is below 10% in people under 60 and between 10%-20% for people between 60 and 79 years old (10). There is a higher prevalence in males aged between 30 and 69 and in females over 70.

Prevalence studies 3

5.2.2. Race

The Nurses' Health Study (11) (n 78.419 patients) concludes, after 20 years of follow-up, that the risk to develop diabetes was lower among Caucasians than among the rest of the races assessed (black race, Asians and Hispanics)

Cohort study 2 +

5.2.3. Genetic susceptibility

Most genetic risk for the development of DM 2 diabetes is based on a complex interaction between different polygenic and environmental factors.

Cohort study 2 +

A cohort study (12) which lasted for 20 years concludes that there is a greater risk to suffer from DM in people who descend from diabetic patients; the risk is similar if either the mother or the father are diabetic [Relative risk (RR) 3.5 (CI 95%: 2.3-5.2]) and more so when both parents are diabetic [(RR 6.1(CI 95%: 2.9-13.0)].

If a homozygous twin suffers from diabetes, his brother or sister will develop diabetes in 90% of the cases (13). Several studies (14; 15) consider that the gene variant 2 TCF7L2 conveys a risk to suffer from DM 2.

5.2.4. Gestational diabetes

The risk to develop DM 2 is higher in women with gestational diabetes antecedents (16).

SR of cohort studies 2 +

The incidence to develop DM 2 in women with gestational diabetes was higher during the first five years after delivery; its increase was much slower ten years after delivery (17).

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5.2.5. Low weight at birth

The relation between low weight at birth and DM incidence is not yet clear. In a 14-study high quality meta-analysis (18) (n 132.180) the odds ratio (OR) was 1.49 (CI 95%: 1.36-1.64). The results of this study are heterogeneous and are determined by the influence of a single study (19); if this study is not taken into consideration, the statistic relevance disappears. This meta-analysis also associates a DM 2 risk increase when there is high weight at birth (>4 kg) [OR 1.25 (CI 95%: 1.12-1.42)]. The authors conclude that it is difficult to acknowledge the real impact of the confusion factors in the relation between low weight at birth and DM 2.

SR of cohort studies 2 +

5.2.6. Breast-feeding

A systematic review (SR) (20) concludes that there could exist an association between mother's milk and the decrease of DM 2 incidence [OR: 0.61 (CI 95%: 0.44-0.85)]; however, the result can be overestimated as it is not adjusted by the confusion factors in all the studies. These results coincide with those stated in the Nurses' Health Study (21) where the beneficial effect took place after 11 months of breast-feeding.

SR of cohort studies 2 +

5.2.7. Obesity

A cohort study (22) carried out among women (n 84.991) with an average follow-up of 16 years concluded that the most important risk factor for DM 2 was high body mass index (BMI). Relative risk for women with a 23-24.9 BMI was 2.67 (CI 95%: 2.13-3.34); BMI 25-29.9, RR 7.59 (CI 95%: 6.27-9.19); BMI 30-34.9, RR 20.1 (CI 95%: 16.6-24.4), BMI >35, RR 38.8 (CI 95%: 31.9-47.2).In the case of men, a cohort study was carried out (23) and, after a five-year follow-up, it concluded that men with a >35 BMI had a 42.1 (CI 95%: 22-80.6) RR compared with a <23 BMI.

Cohort studies 2 +

Abdominal obesity (waist-hip index >0.95) increased the risk of diabetes [RR: 42.2 (CI 95% 22-80.6)] in a male cohort (24). In another cohort study (25) carried out among the general German population in general, the DM highest risk was in the case of men with a high BMI in combination with a high waist-hip index.

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5.2.8. Diet and alcohol

Type of diet

The dietary pattern influences the risk to suffer from DM 2.

Cohort studies 2 +

From a 20 year-long cohort study, after having carried out a multivariate adjustment (age, BMI, race), it can be stated that a healthy diet (high in polyunsaturated fibre and low in trans fatty acids and sugars) has a stronger impact on risk for diabetes in some ethnic groups (black race, Asians and Hispanics) than on the white race (RR 0.54 (CI 95%: 0.39-0.73) vs. RR 0.77 (0.72-0.84)) (11).

In another study (26) performed among 42.000 male health professionals, a diet consisting of a high intake of red meat, processed meat, fatty dairy products, sweets and desserts was associated with an increase in the risk of diabetes regardless of the BMI, physical activity, age or family background [RR 1.6 (CI 95%: 1.3-1.9)] (26).The risk was even higher [RR 11.2 (CI 95%: 8.07-15.6)] if the patients were obese (BMI >30 kg/m2). On the other hand, the males who followed a diet with a high intake of vegetables, fruit, fish and poultry had a reduction of the risk which verged upon the statistic significance [RR 0.8 (CI 95%: 0.7-1.0)]. These results are similar in the case of females (27).

Dairy products

The intake of low fat dairy products is associated with a lower DM 2 risk (regardless of the BMI) in men [RR 0.77 (CI 95%: 0.62-0.95)] (28) and women [RR 0.79 (CI 95%: 0.67-0.94) (29).

Dried fruits

According to a cohort study (30) with 83,000 women (Nurses' Health Study), the increase of nut intake is inversely associated with the risk to suffer from DM 2 (intake of $^{3}5$ units per week vs. no intake), the relative risk adjusted by other risk products was RR 0.73 (CI 95%: 0.6-0.89).

Cohort studies 2 +

Coffee

Long-term intake of coffee can be associated with a fall in DM 2 risk. In an SR (31) of nine cohort studies (n 193,473), the risk of diabetes was lower in people with a high coffee intake.

SR of cohort studies 2+

A prospective study (32) with 88,000 females aged between 26 and 46, revealed that the risk of diabetes was lower for higher coffee intakes. The RR was 0.87 (CI 95%: 0.73-1.03) for a cup a day; 0.58 (CI 95%: 0.49-0.68) for two cups a day; and 0.53 (CI 95% 0.41-0.68) for four cups or more a day, in comparison to non-consumers.

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Green tea

In a study (33) with 17,000 Japanese aged between 40 and 65, the common intake of green tea (six or more cups a day) was associated [OR 0.67 (CI 95%: 0.47 – 0.94)] with a lower risk to develop diabetes after five years of follow-up.

These data do not show a cause-effect relation, therefore it is difficult to recommend an increase in the intake of coffee or green tea as a preventive strategy.

Sweetened drinks

A cohort study among adult women (n 91.249) (34), after an eight-year follow-up, states that a daily intake of one or more sweetened drinks (cola drinks, sweetened carbonated drinks and fruit nectars) is associated with a higher overweight risk and DM 2 [RR 1.83 (CI 95%: 1.42-2.36)].

Cohort studies 2+

Alcohol

A meta-analysis and an SR (36) concluded that a moderate intake of alcohol (5-30 g of alcohol per day) reduces the risk of DM 2; people who take around three drinks a day have between a 33% and 56% reduction in the risk to suffer from diabetes (36). Conclusions cannot be drawn between a high alcohol intake (>30 g of alcohol per day) and DM 2 risk.

SR of cohort studies 2+

5.2.9. Physical activity

Moderate physical exercise (intensity ³5.5 MET, Metabolic Equivalent T, and for more than 40 minutes/week) reduces the incidence of new DM 2 cases (37-39).

Cohort studies 2+

5.2.10. Tobacco

A cohort study (40) (n 41.372) assessed the association between tobacco and DM 2 risk. After a 21-year follow-up it stated that smoking less than 20 cigarettes a day increases 30% the risk to suffer from DM 2 and smoking more than 20 cigarettes a day, implies this increase rises to 65%.

Cohort Studies 2+

5.2.11. Polycystic ovary syndrome

A descriptivel study carried out in Italy (n 121) (41) in patients with polycystic ovary syndrome, DM prevalence and carbohydrates intolerance was higher than that corresponding to the general population of the same age.

Descriptive studies 3

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5.2.12. Heart failure

The association between heart failure and increase in DM 2 risk has been assessed (42) in 2,616 non-diabetic patients with coronary disease (myocardial infarction and stable angina).

Cohort Studies 2+

The subgroup with advanced heart failure (class III from NYHA) had a higher risk to develop diabetes [RR 1.7 (CI 95%: 1.1- 2.6)]; this was not the case for class II from NYHA. The study was initially not designed for this target group and neither did it consider the patients' physical exercise.

5.2.13. Drugs

Atypical antipsychotic drugs

Some studies (43) suggest that patients with schizophrenia present a higher DM prevalence than the general population, though its cause has not been fully established.

SR of different types of studies 1+/3

A review of 17 studies (44) states that the treatment with olanzapine and clozapine is associated with a higher risk to develop DM, in comparison to those patients who are not being treated or who receive treatment with classic antipsychotic drugs. It also concludes that more comparative studies are required among the different antipsychotic drugs.

Diuretics and beta-blockers

The *HTA Clinical Practice Guideline* from the National Institute for Clinical Excellence (NICE) states that there is a higher risk to develop diabetes when a combination of beta-blockers and thiazidic diuretics (45) is used.

SR of RCT 1 +

An SR (46) assessed the effect of the different types of antihypertensives in the incidence of DM, including very heterogeneous studies. It concluded that the ARBII blockers and ACE inhibitors were the antihypertensives less associated with diabetes, followed by calcium channel blockers and placebo , beta-blockers and diuretics.

Other drugs

Other drugs (47) involved in the development of diabetes are: glucocorticoids, oral contraceptives, tacrolimus, cyclosporine, nicotinic acid, protease inhibitor antiretroviral agents, gonadotropin agonist hormones, clonidine and pentamidine.

RCT, cohort, case series 1+/2+/3

More than 5 years have passed since the publication of this Clinical Practice Guideline, and its validity has not been reviewed

5.3. DM 2 diagnosis

5.3.1. Diagnostic criteria

The diagnostic criteria endorsed by the American Diabetes Association (ADA) in 1997 (48) and by the World Health Organisation (WHO) in 1999 (6) try to avoid the delay in the diagnosis in three possible ways; each one must be confirmed in the days to follow, if there is no unequivocal hyperglycaemia (see table 1).

Table 1. **DM 2 diagnostic criteria**

1. Diabetes symptoms (polyuria, polydipsia and weight loss) and a casual plasma glucose (any time of the day) >200 mg/dl.
2. Two determinations of fasting plasma glucose >126 mg/dl.. Lack of caloric intake in the previous eight hours.
3. Two determinations of plasma glucose >200 mg/dl two fours after the oral glucose tolerance test with 75 g (OGTT).

Cohort Studies 2+

It is important to highlight that the current diagnostic thresholds to define diabetes are especially based on the increase of risk to suffer from microvascular complications (mainly retinopathy) (48). Glycaemia thresholds to define an increase in mortality and cardiovascular diseases are not established (49-51). Neither are there sufficient data to define normal glycaemia levels.

5.3.2. Diagnostic methods

Fasting plasma glucose

This is the recommended method to diagnose diabetes and to perform population studies. It is a detailed, low cost, reproducible and easy-to use test. Glucose measure in plasma is approximately 11% higher than glucose measured in total blood in a fasting or basal stage. In non-basal stages (postprandial), both determinations are practically the same.

Oral Glucose Tolerance Test (OGTT)

This involves the determination of glycaemia in venous plasma two hours after a 75 g glucose intake in adults. Although it is a valid method to diagnose diabetes, recommendations on its use differ.

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The ADA does not recommend it for common practice, unlike the WHO, which proposes its use to diagnose asymptomatic diabetes. The test is not quite reproducible (due to the difficulty to comply during its preparatory stages), more expensive and uncomfortable (see table 2). Nevertheless, it should be taken into consideration that it can be considered valid in some cases. Only with the fasting plasma glucose (FPG), 30% of the diabetic population is not diagnosed (unknown diabetes) (52). This figure is higher if the population group is elderly and even more so if they are women. According to several studies, diagnose through plasma glucose two hours after the OGTT is related to higher cardiovascular morbimortality and diabetes microvascular complications than fasting plasma glucose(54). The impaired glucose tolerance (IGT) stage can only be diagnosed by glycaemia two hours after the OGTT.

Therefore, the OGTT is recommended in the following cases:

• When there is a strong suspicion of diabetes (microvascular complications, symptoms, contradictory or doubtful results, etc.) and there are normal fasting plasma glucose levels.

• In patients with repeatedly impaired fasting glucose (IFG) (110-125 mg/dl), to check the diagnosis of diabetes, or with impaired glucose tolerance (IGT), especially among the elderly and female population.

Table 2. Conditions to develop the Oral Glucose Tolerance Test (OGTT)

Do not carry out the test in case of	Fasting plasma glucose >126 mg/dl. Acute disease or post-surgical stress (delay for three months). Pharmacological treatment which cannot be interrupted.
Preparation	At least three days before follow a free and rich in carbohydrates diet (at least 150 g /day) and do as much physical exercise as desired.
Method	Absolute fasting for 8-12 hours (except water). Carry out a test in the morning (between 8-10 am). Oral administration of 75 g of glucose in 250 ml of water (100 g in the case of pregnant women and 1, 75 g/kg for children). The patient shall remain seated and will not smoke during the test. For the general population, a determination after two hours is enough. Pregnant women will undergo three extractions (1, 2 and 3 hours after taking 100 g of anhydrous glucose).

Glycosylated haemoglobin (HbA_1c)

This shows the average of the glycaemia determinations in the last two-three months in a single measure and it can be carried out at any time of the day, without any prior preparation nor fasting. It is the test recommended to control diabetes.

More than 5 years have passed since the publication of this Clinical Practice Guideline, and its validity has not been reviewed

HbA_1c could be used to diagnose diabetes in patients with impaired fasting glucose (110-125 mg/dl), as if there was a positive result due to a high specificity or a negative result due to high sensitivity, the carrying out of the OGTT could be avoided. This way, the interventions of this group of patients could be individualized better.

In the five localized studies (55-59) on this issue, the OGTT was used or the medical diagnosis after six years can be used as diagnostic gold standard. Only two of the studies provided data on the population associated with this matter (58; 59).

Diagnostic test study II

The study carried out among the Chinese population (58) only considers 39 patients with altered basal glycaemia, thus it has not been taken into consideration. A French study (59) was performed on a cohort of 3,627 white race patients among the general population with low diabetes prevalence and 272 patients with altered basal glycaemia. The aim of the study was to assess the predictive capacity of HbA_1c in the development of diabetes among the general population. This study has two limitations: loss of patients and assessment of gold standard. From the initial cohort, 2,820 patients are assessed six years after (77%). The study does not specify if the physicians carrying out the trial knew the initial classification of patients.

The glycosylated haemoglobin values from 5.9% patients with Impaired Fastng Glucose have a 64% sensitivity and 77% specificity, a 2.78 positive likelihood ratio (+LH) and a 0.46 negative likelihood ratio (-LR). For the diabetes prevalence of the study (22%) a positive predictive value (PPV) of 44% and a negative predictive value (NPV) of 88% is achieved.

To summarise, the scarce evidence available cannot give an accurate answer to our question and thus has some methodological limitations.

An additional limitation of this technique is that, until very recently, no consensus has been reached (60) on the standardisation of the method and the values differ according to the technique used by each laboratory.

Evidence summary

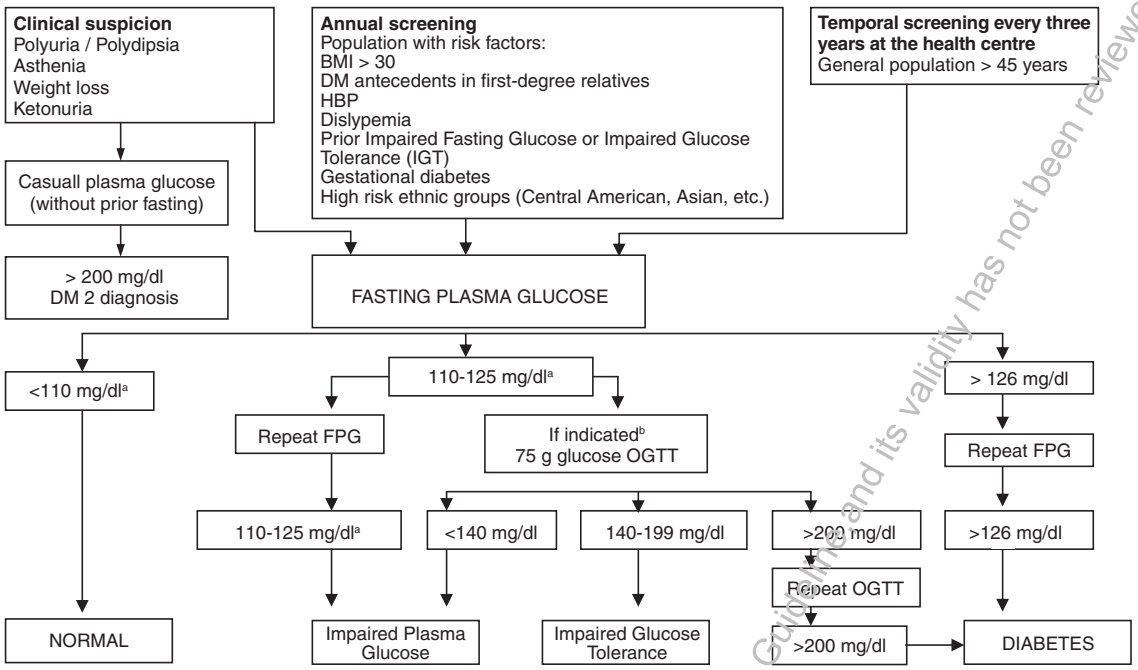
II	In a study with methodological flaws, the glycosylated haemoglobin values in 5.9% of patients with impaired fasting glucose (IFG had a 64% of sensitivity and 77% of specificity, 2.78 +LR and 0.46 -LR in the prediction of diabetes (59).

Recommendations

B	The use of HbA_1c is not recommended as a diagnostic test for patients with impaired fasting glucose.
√	The performance of studies within our field to assess the diagnostic performance of HbA_1c in these situations is recommended.

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Figure 1. DM 2 diagnostic algorithm and screening



[a] WHO / IDF Criteria 2006.

[b] Indicated in case of suspicion of diabetes with normal basal glycaemias and in some cases of patients with repeated Altered Basal Glycaemias, especially among the elderly and female population.

OGTT: Oral Glucose Tolerance Test; FPG: Fasting Plasma Glucose; IFG: Impaired Fasting Glucose ; IGT: Impaired Glucose Tolerance.

5.4. DM 2 screening

There is no evidence to support DM 2 universal screening. It is worth highlighting that the best evidence to support screening is that provided by randomized clinical trials (RCTs) where the intervention performed is the screening and the result variables are the fall of the morbi-mortality rates attributed to the condition to be screened. If these are not available, screening can be justified by indirect evidence which shows the existence of effective interventions for the disease to be screened. At a lower evidence level, an increase in the risk to develop the disease in different groups at risk may justify the screening.

SR of RCT 1+

CPG and Expert opinion 4

The Systematic Reviews taken into consideration recommend screening in groups at risk though they disagree in the classification of these groups. The US Preventive Services Task Force (61; 69) recommends screening in hypertensive patients and those suffering from dyslipidemia. Recent research carried out in the UK extends the screening indications to obesity (62). Different national initiatives agree on the recommendation to develop a screening in other groups at risk in addition to those already mentioned: adults over 45 years old, within a cardiovascular preventive structured activity program; diabetes antecedents in first degree relatives; prior Impaired Fasting Glucose or Impaired Glucose Tolerance diagnosis,

More than 5 years have passed since the publication of this Clinical Practice Guideline and its validity has not been reviewed

and certain ethnic groups (Asian, Central American, etc.) (1; 2; 63). The screening frequency is determined by consensus; screening is recommended every three years for people over 45 years old and on an annual basis for patients suffering from other risk factors (hypertension, dyslipidemia, pre-diabetic stages, etc.) (64).

As regards the screening technique, the reviews and Clinical Practice Guidelines analysed recommend fasting plasma glucose. Determination through capillary glucose in total blood, could simplify the diagnosis. Although there are multiple studies published on capillary glucose on the diagnosis of diabetes (65-68), none of them complies with the quality standards demanded for a study on diagnostic tests, therefore the located evidence does allow its recommendation for this purpose.

CPG

Evidence summary

1+	Diabetes universal screening is not cost-effective (61; 62; 69).

Recommendations

D	An annual diabetes screening is recommended through fasting plasma glucosein the population at risk, defined by hypertension, hyperlidemia, obesity, gestational diabetes or obstetric pathology (macrosomia, repeated miscarriages, malformations), Impaired Fasing Glucose and Impaired Glucose Tolerance at any age; and every three years in patients aged 45 or over, within a cardiovascular preventive structured program.
C	Capillary glucose in total blood cannot be recommended as a diagnostic test in the population groups at risk.

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6. Diabetes prevention in patients with intermediate hyperglycaemia

The questions to be answered are:

- Which interventions are effective to prevent the development of diabetes in patients with impaired fasting glucose or intolerance to glucose (diet, exercise, pharmacological treatment)?

Intermediate hyperglycaemias (or *pre-diabetic stages*) refer to two concepts, Impaired Fasting Glucose (IFG) and Impaired Glucose Tolerance (IGT), which overlap and whose definition has changed a lot in the last years, depending on the levels selected to define normoglycaemia.

Both the American Diabetes Association, the WHO and the IDF (International Diabetes Federation) establish a category of hyperglycaemic stages between glycemic normality and the diagnose of diabetes by the determination of fasting plasma glucose (FPG or the venous plasma glucose considering the 75 g OGTT after two hours.

These organizations differ in the level of fasting plasma glucosethat is considered impaired fasting glucose (see table 3). A broad and thorough SR on the diagnostic and prognostic implications of impaired fasting glucose and impaired glucose tolerance (70) has been published recently. This report uses the WHO and IDF criteria, so these are the criteria adopted in this CPG.

The criteria are as follows:

Table 3. Diabetes and intermediate glycaemia diagnostic criteria (WHO and IDF)

	Basal Glycaemia	2 h- OGTT	Glycaemia at random
Normal	<110 mg/dl	<140 mg/dl	–
Impaired Fasting Glucose	110-125 mg/dl*	–	–
Impaired Glucose Tolerance	–	>140 mg/dl	–
DIABETES	>126 mg/dl	≥200 mg/dl	≥200 mg/dl

* ADA considers impaired fasting glucose between 100-125 mg/dl. The determinations are carried out in venous plasma.

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6.1. Impaired Fating Glucoseucose (IFG)

Impaired fasting glucose is the stage used to define fasting plasma glucose between normal glycaemia and diabetes. It is defined between the 110-125 mg/dl margins, according to WHO and IDF.

According to the WHO and IDF criteria, a 5% or higher prevalence is stated, which increases with age; according to the ADA criteria, its prevalence triples or quadruples (71).

The classification as impaired fasting glucose can be hardly reproducible. If glycaemia repeats after six weeks, impaired fasting glucoseis confirmed in 51% to 64% of the cases; 10% of the cases are classified as diabetic and the rest as normal (70).

SR of cohort studies 2+

These patients have a five-fold risk to develop diabetes (70). Their cardiovascular risk (AMI, stroke, non-fatal strode) is higher (RR 1.19), and likewise is mortality higher (RR 1.28) (70).

6.2. Impaired Glucose Tolerance (IGT)

IGT is the stage defined by a plasma glycaemia in venous blood between 140 mg/dl and 200 mg/dl two hours after the 75g glucose tolerance test.

It is more frequent in women. Its prevalence is around 10%; it increases with age and varies depending on race.

IGT reproducibility after six weeks is low. It is confirmed in 33% to 48% of the cases; 36% to 48% are reclassified as normal and 6% to 13% as diabetic (2; 70).

IGT is associated with a higher risk than altered basal glycaemia to develop diabetes. This risk is 6 times higher than in normoglycaemic patients [RR 6.02 (CI 95%: 4.66 a 7.38)], and up to 12 times more if both are associated [RR 12.21 (CI 95%: 4.32 a 20.10)] (70).

SR of cohort studies 2+

IGT also implies a higher cardiovascular mortality risk (RR 1.48) and overall mortality risk (RR 1.66) (70).

6.3. Preventive interventions in patients with intermediate hyperglycaemia

There are several SRs (72-74), evidence summaries (70) and a recent RCT (75) not included in the SR, which analyse the pharmacological and non-pharmacological intervention effectiveness in the prevention of diabetes and cardiovascular morbimortality in diabetic stages. There is no uniformity in the inclusion criteria of patients in the studies.

SR of RCT 1+

More than 5 years have passed since the publication of this Clinical Practice Guideline, and its validity has not been reviewed

An SR (72) only includes patients with intolerance while the rest include mixed population groups. The Agency for Healthcare Research and Quality (AHRQ) (70) report analyses the risks to develop diabetes, cardiovascular and general morbimortality through a meta-analysis of cohort studies.

The assessed evidence is of high quality and all the editions are based on the same RCT group. The grouping of these varies depending on the aim of the SR. There are isolated Cochrane SRs for acarbose and to lose weight through diet and exercise (73; 74; 76). The other two reviews assess all the measures.

The most recent SR includes all the pharmacological measures (metformin, glitazones, orlistat, acarbose) and non-pharmacological (diet and exercise) and carries out a meta-analysis. It does not compare the measures among them. However, the AHRQ report does develop this analysis based on a single RCT (77) where the non-pharmacological measures proved to be more efficient than metformin. **SR of RCT 1++**

There is coherence between the evidence analysed on the effectiveness to prevent diabetes both through diet and exercise as through drugs.

Life styles and oral antidiabetic drugs (acarbose, rosiglitazone and metformin) and orlistat are effective in the prevention of diabetes. Life styles have a greater impact according to the patients' initial weight: for each 0.04 BMI increase, the preventive effect of the diet increases 7.3%.

In the DREAM study performed on 5,269 people suffering from Impaired Glucose Tolerance or Impaired Fasting Glucose without cardiovascular disease antecedents, rosiglitazone showed to be effective to prevent diabetes [RR 0.38 (CI 95%: 0.33-0.40); NNT 7], though it increased the oedemas incidence [RR 1.41 (CI 95%: 1.13- 1.76); NNH 51], the BMI and heart failure frequency [RR 7.03 (CI 95%: 1.6-30.9); NNH 250] (75). The study follow-up period was three years. Recently rosiglitazone has ben withdrawn from the market because of its negative cardiovascular profile. **RCT 1++**

Adverse effects are more frequent in the group following pharmacological treatment (gastrointestinal effects and diarrhoea). The effect of the diet is coherent at all risk levels to develop diabetes. On the other hand, hypoglycaemic-agents do not have any approved indication to be used in pre-diabetic stages.

The effect on cardiovascular morbimortality has not been proved conclusive, due to the length of the studies. Acarbose proved to be efficient in the decrease of cardiovascular complications only in an RCT included in the reviews (78). This finding is based on only 48 events and it must be interpreted with caution, as the aim of the study was not the effect on cardiovascular morbimortality. **RCT 1+/-**

Evidence summary

1++	The structured interventions which enable physical exercise and diet reduce the risk to develop diabetes [RR 0.51 (CI 95%: 0.44-0.60); NNT 6.4] in patients with pre-diabetes (70; 72; 73).
1++	The interventions with anti-diabetic drugs (metformin and acarbose) reduce the risk to develop diabetes [RR 0.70 (CI 95%: 0.62-0.79); NNT 11 (8 to 15)] (70; 72; 74).

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1++	An intensive intervention on life style – hypocaloric diet, low in fat, physical exercise (at least two hours per week) and a program of educational sessions- is more effective than metformin to prevent diabetes (70; 77).
1++	Anti-diabetic drugs increase side effects significantly (gastrointestinal, hypoglycaemias) in patients with pre-diabetes (72).
1++	Rosiglitazone prevents the appearance of diabetes [RR 0.38 (CI 95%: 0.33-0.40); NNT 7], though it increases the incidence of oedemas [RR 1.41 (CI 95%: 1.13-1.76); NNH 51 (33-143)] as well as heart failure frequency and BMI [RR 7.03 (1.6- 30.9); NNH 250] (75).

Recommendations

A	Structured programs which foster physical exercise and diet are advised for patients with Impaired Glucose Tolerance or Impaired Fasting Glucose.
A	The use of pharmacological treatments in patients with Impaired Glucose Tolerance or or Impaired Fasting Glucose is not recommended.

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7. Diet and exercise

The questions to be answered are:

- What is the most appropriate diet for a diabetic patient?
- What are the effects of physical exercise on DM 2 patients? What type of exercise is recommended?

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7.1. Diet

7.1.1. Introduction

Diet is the basic pillar to treat DM 2. However, evidence on the type of diet (total calories, composition through immediate principles, menus, portions, exchanges, etc.) and the way to achieve the patients' commitment to this is still an area which requires solid evidence to present solid recommendations.

The aims of the dietary treatment in diabetes include the attainment of an appropriate weight with the maintenance of glucose levels close to normality level and the improvement of the lipid profile and blood pressure; all this taking into consideration the personal and cultural preferences of the patients.

Expert opinion 4

Considering that 80% of type 2 diabetic patients suffer from overweight or obesity, the first aspect to be considered is whether the patient needs a hypocaloric diet.

The general recommendations on the proportion of immediate principles in the diet, both for patients overweight as normoweight are not different from those of the general population. The recommendation panels of the different guidelines state for diabetic patients, the proportion of 50%-60% intake of energy needs through carbohydrates, 15% through proteins and less than 30% through fats (79).

The initial estimate of the caloric needs is performed taking into account basal calories (10 Kcal/0.45 kg of desired body weight) and the number of calories depending on the physical exercise performed (Appendix 2).

7.1.2. Effectiveness of the interventions to lose weight

CPGs recommend reducing weight in order to maintain a desired weight (79). In general, the BMI values recommended are between 19-25 kg/m2. Obese and overweight patients are recommended to lose around 5%-7% of the current weight (2; 80) and to do it gradually (between 0.5 – 1 kg per week).

CPG 4

Different SRs (81-84) have assessed the effectiveness of non-pharmacological (81; 82; 84) and pharmacological (83) interventions on the loss of weight in type 2 diabetic patients. The reviews cannot assess morbimortality due to the short duration of the RCTs included.

CPG 4

The cohort studies associate intentional loss weight in obese diabetic patients with a fall in the mortality rate in the long-term (85).

Cohort studies 2+

The first SR (84) is based on 22 studies, with an at least 12-month follow-up, which assesses dietary interventions (diets low in calories or diets very low in calories), encouraging physical exercise and behavioural therapies. Overall, the measures achieve a slight reduction of weight: 1.7 kg (CI 95%: 0.3 to 3.2). In the RCTs where several simultaneous strategies were used, for example, a combination of diet, exercise and behavioural therapies, the loss of weight was higher: 4.1 kg (CI 95%: 2.9 to 5.4).The weight difference observed between diets on low calories and very low calories was not statistically significant.

SR of RCT 1+

The second review (82) assessed the effects of the different types of guidance. There is coherence in that the association of diet and exercise conveys more weight loss. Another aspect stated in this review is the effect of the modification in the proportion of immediate principles of the diet. The five RCTs which compared the effect of the low fat diets in contrast to others with moderate fat or reductions in the amount of carbohydrates showed a higher reduction in weight with the low fat diet.

SR of RCT 1+

The third SR (81) states that hypocaloric diets with around 55% to 60% of carbohydrates together with a high amount of fibre (>20 g/day), increase moderate loss weight and improve glycemic control as well as the lipid profile. There is no study performed with low carbohydrate diets (<30%). These diets should not be recommended as their long-term effects are not established (86).

SR of RCT 1+

This SR attempts to approach the differing effectiveness of diets according to the food glycemic index. This index consists of the relation between the area of the 50 g glucose intake curve throughout time, where the maximum value would be 100. In the eight RCTs where the diets with low glycemic index food are compared to those with a high glycemic index, there is an insignificant tendency to reduce glycosylated haemoglobin and a more favourable lipid profile for low glycemic index diets.

A Cochrane SR (83) assessed the efficacy of obesity pharmacological treatment associated with DM 2. The pharmacological treatment in combination with the diet for overweight diabetic patients produces moderate weight losses: fluoxetine [5.1 kg (CI 95%: 3.3 to 6.9)] after a 26-week follow-up, orlistat [2.0 kg (CI 95%: 1.3 to 2.8 kg)] and sibutramine [5.1 kg (CI 95%: 3.2 to 7.0)] after a 12 to 57-week follow-up. Weight loss in all these groups also includes an improvement of glycemic control as well as the lipid profile and blood pressure. 20% of patients who took orlistat showed gastrointestinal side effects. Sibutramine provoked tachycardia and an increase of cardiac frequency.

SR of RCT 1+

There is not enough data to develop an analysis for groups divided by age, sex, obesity levels and pharmacological treatment (oral anti-diabetic drugs, insulin, etc.).

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An RCT analysed the effectiveness of rimonabant in comparison to placebo in DM 2 overweight patients not appropriately controlled with metformin or sulfonylureas (87). Together with a diet and exercise intervention, a 20 mg/day dose of rimonabant was effective to reduce annual weight (-5.3 kg with rimonabant vs. -1.4 kg with placebo). The interruption of the treatment due to adverse effects was more frequent with rimonabant due to depressive disorders, nauseas and dizziness. Recently rimonabant has been withdrawn from the market because of its adverse effects.

RCT 1+

The population groups included in the trials with drugs are very specific, as patients with severe complications have been excluded. The follow-up period is very short to assess the long-term safety of the treatments. It must be taken into account that diabetic patients are polymedicated and frequently suffer from high comorbidity levels, so the use of a pharmacological treatment cannot be recommended for the obese diabetic population. This fact has to be taken into consideration especially when using sibutramine due to its cardiovascular side effects.

The surgical treatment of DM 2 and morbid obesity patients is effective for weight loss and improvement of glycemic control in specific cases (88).

SR of RCT, observational studies and case series 1+/2+/3

7.1.3. Composition of fat in the diet

A higher proportion of polyunsaturated /saturated fats has been associated with a reduction in the mortality risk due to coronary heart disease (89).

Cohort study 2+

The recommendations for the diabetic population are the same as those for the general population: reduce the intake of saturated fat to <10% of total energy and cholesterol intake <300 mg/day or <200 mg/day if the LDL-cholesterol is over 100 mg/dl (90).

As in the case of the general population, the substitution of saturated fatty acids by unsaturated can reduce LDL levels and improve the sensitivity to insulin among the diabetic population. The Garg meta-analysis (91) shows the benefit of diets with a high amount of monounsaturated fat on the very low-density lipoprotein and triglycerides levels (VLDL) (between 19% and 22% reductions) without modifying the concentrations of high-density lipoprotein (HDL) and low-density lipoproteins (LDL).

SR of RCT 1+

The effect of omega-3 fatty acids on the diabetic population is assessed in a Cochrane SR (92). The intake of fish oil significantly reduces the levels of triglycerides, especially among hypertriglyceridemic diabetic patients and it produces a low increase in LDL cholesterol, without modifying glycemic control parameters. There is no data on a cardiovascular event reduction.

SR of RCT 1+

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7.1.4. Other dietary interventions

Protein intake contributes to a 15% to 20% of the total energy consumed, which corresponds to 0.8-1.3 g/kg of weight needs. The protein intake within a normal range in diabetic patients has no effect on the development of proteinuria.

Salt intake

As for the general population, the intake of salt should be limited to less than 6 g/day. For people with high blood pressure, a higher limitation of salt intake is recommendable.

Alcohol

A recent SR has assessed the effect of alcohol on total and coronary morbimortality. It classifies the alcohol intake in g/day into four categories: abstemious, <6 g, 6-17 and ³18 g. An intake below 6 g is associated with a reduction in total and coronary morbimortality while the rest of the categories show a reduction in coronary morbimortality but not on total morbimortality (93). This alcohol protective effect on coronary morbimortality is higher among the diabetic population than the general one.

SR of cohort studies 2+

The effect of alcohol intake over other relevant diabetes variables (glycemic control, microangiopathy, etc.) has not been fully analysed. Howard (36) carried out a review of the effects of alcohol on diabetes. It confirms the previous findings about coronary disease and states how a moderate alcohol intake does not affect glycemic control. No quality evidence on the moderate intake and microangiopathy was found.

Alcohol intake can foster the development of hypoglycaemias through the inhibition of the hepatic neoglycogenesis, hypoglycaemias which do not react to glucagon (36). Alcohol intake should be accompanied by food to prevent hypoglycaemias.

Expert opinion 4

There is coherence on the beneficial effect of moderate alcohol intake in diabetic people, so it should not be contraindicated for those diabetic patients with this habit. Alcohol intake should be limited to a maximum of two to three units/day in men and one to two units for women 1.

7.1.5. Diet planning methods

There are different alternatives to plan meals to achieve changes in the diet. In a British review (94) a description of the main methods is presented. The most frequent educational method is carried out by qualitative recommendations and to a less extent, by semi-quantitative methods (diet by portions) and by an exchange diet, mainly followed by the American population.

Expert opinion 4

More than 5 years have passed since the publication of this Clinical Practice Guideline, and its validity has not been reviewed

The evidence on efficacy of the different methods described hereafter are scarce, therefore the characteristics of the patients and their preferences together with the professionals' experience and skills, as well as the availability of the means, will determine the most convenient diet for each patient (Appendix 2).

Method based on meals

It is the basis of all the methods and it shows how meals can be designed to adapt to the patient's preferences and life style, while maintaining appropriate nutritional parameters. The menus can be specific or can include several alternatives.

Method based on guidelines

It is based on simplified guidelines which allow the identification of the representative ingredients of each of the immediate principles. General rules are provided that reduce the global carbohydrates intake. A short list of simplified and abbreviated food to be exchanged can be provided.

Carbohydrates counting method

The amount of carbohydrates included in the diet is the main nutrient which affects the postprandial glycaemia level, in the same way that the amount of carbohydrates and its distribution can improve metabolic control. Thus, in order to have a high performance in terms of metabolic control, carbohydrate counting is considered basic within the educational aspects related to the diet. A portion is equivalent to 10 g of carbohydrates (6).

Expert opinion 4

The educational system of this method for patients comprises of three levels (95):

• The first or basic level introduces the concept of carbohydrates as the meal component which can increase glucose levels.

• The second or intermediate level trains the patient how to identify the causes of hyperglycaemia as a consequence of the variables of exercise, carbohydrates intake or pharmacological treatment, and how to make changes in the diet to correct hyperglycaemia.

• The third or advanced level is addressed to people with insulin pumps or multi-doses. The patient is trained on the adjustment of the insulin dose according to the glycaemia level and the amount of portions to be consumed.

[1] SDU: standard drinking unit

Units of alcohol consumption:

1 SDU: 200 ml of beer (small glass or small bottle of approximately 200 ml; 100 ml of wine (small glass); 50 ml of strong wine (sherry); 50 ml of sparkling wine (one glass); or 25 ml of liquor (strong spirits).

2 SDU: 1 glass of brandy (50 ml); 1 cocktail (50 ml); 1 vermouth (100 ml); or 1 whisky (50 ml).

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Exchange system

This system is based on the classification of the main food groups: carbohydrates (starches, fruit, milk, vegetables), meat and fish (proteins) and fat. Food tables are provided which include the proportion for 100 g of the different active principles. The food with similar nutrient values are numbered together and these can be exchanged for any other belonging to the same list. The common portions of each food are numbered, including its weight in grams. The exchange lists are used to achieve an appropriate nutrient contribution and provide a variety when planning the meals.

An SR (82) compared the effectiveness of the exchange diets in contrast to a standard diet with low fat reduction. No conclusion was established due to the lack of evidence available. **SR of RCT 1+**

In an RCT not included in the SR no differences were found between the exchange diet recommended by the ADA and a weekly planned diet. Both improved weight loss, glycemic control and the lipid profile (96). **RCT 1+**

The CPG recommends the mid-night snack to avoid night hypoglycaemia in patients on pharmacological treatment (79), though no studies have been found on this issue. **Expert opinion 4**

Evidence summary

1+	Dietary changes, exercise and behavioural therapies are effective in DM 2 weight loss and glycemic control. Their combination increases efficacy (73; 82).
1+	Diets with high amount of fibre and a 55% to 60% of carbohydrates are more efficient for glycemic control than the diets with moderate amounts of carbohydrates (30%-54%) and a low or moderate amount of fibre (81).
1+	Diets based on food with low glycemic indexes show a favourable tendency in glycemic control (81).
1+	Diets where the amount of fat consists of polyunsaturated fatty acids improve the lipid profile in diabetic patients (91).
1+	Drugs for obesity (orlistat, sibutramine, rimonabant) are effective for weight loss and improve glycemic control. Nevertheless, the frequent or potentially severe adverse effects limit their use (83; 87). Sibutramine can provoke adverse effects at cardiovascular level (83). Rimonabant has been withdrawn form the market.
1+/2+/3	Surgical treatment for DM 2 patients and those with morbid obesity is effective to reduce weight and to improve the glycemic profile in specific cases (88).
1+	Omega 3 fatty acid supplements reduce triglycerides and produce a slight increase in LDL levels (92).
2+	Moderate alcohol intake is associated with a reduction of cardiovascular morbimortality risk without presenting any effect on glycemic control (36; 93).
4	There are several useful systems to plan diets (based on meals, guidelines, carbohydrates count, exchange). Their effectiveness has not been compared (79).

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Recommendations

D	The carbohydrate intake should be distributed throughout the day in order to maintain glycemic control, adjusting it to pharmacological treatment.
A	Structured programs which combine physical exercise with dietary guidance, fat intake reduction (<30% of daily energy), between 55% to 60% of carbohydrates of daily energy and between 20 and 30 g of fibre are recommended. Patients with BMI $^{3}25$ kg/m^2, must follow a hypocaloric diet.
B	General use of pharmacological treatment for obesity associated with diabetes (orlistat, sibutramine, rimonabant) is not recommended. It can be used for specific cases, taking into consideration the associated pathology as well as the possible interactions, contraindications and adverse effects of the different treatments.
B	Morbid obesity surgery in diabetic patients with morbid obesity can be recommended in specific cases, taking into consideration the risks and benefits, the patient's preferences, his comorbidity and the technical availability.
B	Omega 3 fatty acid supplements are not recommended in general terms for the diabetic population.
C	The use of omega 3 fatty acids could be used for diabetic patients who suffer from severe hypertriglyceridemia and do not respond to other measures (diet and drugs).
B	It is not necessary to contraindicate moderate alcohol intake in diabetic patients who have this habit, unless there are medical criteria to do so. In any case, its intake should be limited to a maximum of two to three units per day for men and one to two units per day in the case of women.
D	Diets based on meals, portion exchange and on simplified guidelines can be used, depending on the patient, the professionals and the sanitary environment.

7.2. Exercise

According to the results of an SR (97), the physical exercise programs proved to be efficient to improve glycemic control, with 0.6% (CI 95%: 0.3 to 0.9) of HbA_1c reductions, improve the response to insulin (a single RCT) and the reduction of the triglycerides levels (TG). No beneficial effects were observed on weight loss, cholesterol levels and arterial pressure. The RCT lasted between 8 and 12 months and most of the interventions included three exercise sessions per week in non consecutive days; the exercises were varied both as regards anaerobic and moderate aerobic intensity.

SR of RCT 1+

A subsequent RCT (98) assessed the effect of combining aerobic and anaerobic intensity exercise in comparison with each modality individually and to no exercise at all (control group), in DM 2 patients aged between 39 and 70. The trial excluded patients on insulin treatment or with advanced complications. The adherence to the intervention was high (86%). The intervention consisted of three weekly sessions during six months with supervised and gradual exercises (both in

RCT 1++

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duration and intensity). Performing aerobic and anaerobic intensity exercise improved glycemic control (0.51% and 0.38% of HbA_1c reductions) in comparison to the control group, respectively), though the improvement was better when both were combined (additional 0.46% reduction).

The group assigned to the aerobic intensity training showed a higher weight reduction as well as BMI reduction in comparison with the control group; the combination of both types of exercise was not higher than that in each of the interventions performed individually. The adverse effects were more frequent in those patients who did exercise (musculoskeletal pain or traumatisms), though no differences were observed as regards the hypoglycaemia stages. Although it is a high quality trial, it does present extrapolation problems to other contexts.

Cohort studies 2+

The effects of exercise on morbimortality have been assessed in several long-term cohort studies involving a wide range of population groups (99; 103). The inclusion criteria are variable as regards risk factors, cardiovascular disease antecedents or pharmacological treatments followed. The interventions vary as regards type and intensity of the exercise performed. The performance of continuous aerobic physical exercise for more than 120 minutes per week reduces the risk of coronary and cerebrovascular disease, both in women (100) and men (103). Improved physical condition, associated with higher exercise intensity reduces death risk (101), regardless of the obesity level (99).

Evidence summary

2+	Physical exercise performed on a regular basis reduces the risk of coronary and cerebrovascular disease (100; 103). Improved physical condition, associated with higher exercise intensity reduces death risk (101), regardless of the obesity level (99).
1+	The aerobic and anaerobic intensity physical exercise programs are effective to improve glycemic control (0.6% of HbA_1c reductions) and can improve the response to insulin and TG levels (97; 98).
1++	In DM 2 patients who are motivated and without severe complications, the combination of aerobic and anaerobic intensity exercise is higher in each of the modalities individually as regards the improvement of glycemic control (98).
1+	Most of the interventions consist of three sessions per week in non-consecutive days; the exercise is performed under supervision and gradually (97; 98).

Recommendations

A	DM 2 patients are recommended to perform regular and continuous aerobic and anaerobic intensive physical exercise, or preferably a combination of both. The recommended frequency is three weekly sessions on alternate days, gradual as regards duration and intensity and preferably, under supervision.

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8. Glycemic control

The questions to be answered are as follows:

- Which are the targets for HbA_1c?
- What is the initial pharmacological treatment for patients with diabetes who do not reach the appropriate glycemic control criteria?
- Which is the most appropriate treatment in case of failure with the initial therapy?
- Which drug combination strategies are recommendable to treat patients with diabetes with a poor glycemic control?
- Which drug combination strategies are recommendable to treat patients with diabetes with a poor glycemic control after using double oral therapy (triple oral therapy vs. insulin)?
- Should the treatment with oral antidiabetic drugs be maintained in patients who begin treatment with insulin?
- What initial insulin regimen is the most appropriate for patients who failed with oral drugs?
- Which is the efficacy and safety of insulin analogues in comparison to conventional insulin for patients with DM 2 who require the use of insulin?

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8.1. Glycemic control with oral antidiabetic drugs

8.1.1. HbA_1c targets

Cohort studies 2++

The incidence of clinical diabetes complications, especially microvascular, is related to HbA_1c basal levels. The observational trial UKPDS 35 (104) assessed the micro- and macrovascular complication risk according to the long-term HbA_1c levels, adjusting by potential confusion factors. Each 1% reduction of HbA_1c was associated with a 21% risk decrease for any problem related to diabetes, 21% for deaths related to diabetes, 14% for AMI and 37% for microvascular complications. The lowest risk was for those patients with HbA_1c levels closer to normality (<6.0%). The results of a meta-analysis of prospective cohort studies performed on DM 2 patients (105) concluded that, for every 1% increase in HbA_1c, the cardiovascular risk increased in 18% [RR 1.18 (CI 95%: 1.10-1.26)].

RCT 1+

On the other hand, the clinical trial UKPDS 33 which lasted 10 years showed that intensive therapy reduced the complications provoked by diabetes (106) for DM 2 patients. The HbA_1c levels were 7% for the group within the intensive treatment and 7.9% for the control group. The intensive treatment was associated with a 12% reduction in the aggregated variable which included death related to diabetes, macrovascular and microvascular complications. It is worth highlighting that this effect was mainly due to the reduction of microvascular complications

[RR 0.75 (CI 95%: 0.60-0.93)], and in particular, due to the reduction of photocoagulation. Likewise, an insignificant tendency in the decrease of other events, such as AMI or amputations, was observed. The main adverse effect found was the imperative increase of severe hypoglycaemia stages; this is one of the reasons why glycemic aims must be individualised. Only 50% of the patients assigned to the intensive treatment, achieved figures below 7%.

CPG and RCT 1+

Therefore the HbA_1c targets have to take into consideration the benefits of intensive control as regards the risk of hypoglycaemia, and the incovenience of the treatment for the patient and his family. The guidelines examined agree on the importance of glycemic targets for HbA_1c between 6.5% and 7.5% mainly based on the aforementioned studies. An edition was issued recently on this matter in the main CPGs on diabetes (107). The authors state that targets below 7% for HbA_1c are considered reasonable for many patients, though not for all. The target for the HbA_1c level should be based on the individualised assessment of the risk for diabetes complications, comorbidity, life style and the patient's preferences. The aims of the treatment should be set after having debated with the patient on the advantages and the risks of the specific levels of glycemic control. In general, lower HbA_1c figures are recommended for patients with microalbuminuria within the context of a multifactorial intervention to reduce cardiovascular risk (108). Likewise, less strict levels can be appropriate for patients with limited life expectancy, comorbidity or a prior hypoglycaemia history (2).

Recently, the ACCORD trial has compared strict glycemic control (HbA_1c <6% with oral drugs and if required, insulin) to a less strict control (HbA_1c 7%-7.9%) for DM 2 patients after many years of evolution (an average of 10 years) and two risk factors, or diabetic patients with cardiovascular disease. The trial was interrupted prematurely due to a higher mortality rate in the group assigned to intensive glycemic control (109).

Descriptive studies 3

On the other hand, it is important to take into consideration that the assessment of the different studies performed in different countries and in our field (8), state that glycemic control of DM 2 patients is still inadequate despite the progress achieved in the treatments. These data, together with the UKPDS 33 findings, have made some authors (110) support more realistic and individualised aims depending on the patients' characteristics, both as regards glycemic control as well as other risk factors.

Evidence summary

2++	The incidence of clinical complications in DM 2 patients depends on the HbA_1c basal levels. It is stated that for every HbA_1c 1% increase, the cardiovascular increase would be an 18% (105).
1+	In the UKPDS 33 (106) clinical trial, intensive therapy was associated with a significant 12% reduction of microvascular complications (especially in the reduction of the need for laser photocoagulation). The aim to a 7% HbA_1c was achieved in 50% of the cases, at the expense of a higher hypoglycaemia incidence.

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4	The guidelines examined agree to state that HbA_1c aims below 7% are for guidance (107). A more strict control is recommended for people with high cardiovascular risk (79) or microalbuminuria (108).
1+	Patients with long-term diabetes and high risk to have cardiovascular events, the HbA_1c control <6% created a mortality increase in comparison to the aims of 7%-7.9% (109).

Recommendations

D	In general, guidance target s under 7% for HbA_1c are recommendable. However, the target should be based on an individualised assessment of the diabetes complications risk, comorbidity, life expectancy and the patient's preferences. A more intensive control is recommended for people with microalbuminuria within the multifactorial intervention context to reduce CVR. Likewise, less strict targets can be appropriate for patients with a limited life expectancy, elderly people or individuals with comorbidity conditions, a prior hypoglycaemia history or patients with long-term diabetes.

8.1.2. Initial treatment with monotherapy

If after a three-to-six month period with non-pharmacological treatment, no glycemic control has been achieved, the use of a pharmacological treatment should be considered. Hypoglycaemic-agent treatments should be prescribed as monotherapy during a trial period, supervising its reaction and using HbA_1c as a measure.

Expert opinion 4

Metformin is the drug recommended as first line by the NICE CPG (79).

SR of RCT 1+

Metformin has proved to be efficient to reduce glycaemia / HbA_1c in the same way as other oral anti-diabetic agents, with HbA_1c reductions between 1% and 2% (111; 112). This is the treatment chosen for diabetic patients who suffer from overweight or obesity.

According to the UKPDS 34 (113) results, patients overweight or obese on metformin intensive treatment showed a 32% significant risk reduction in the combined result of events related to diabetes (sudden death, death due to hyperglycaemia or hypoglycaemia, fatal or non-fatal myocardial infarction, angina pectoris, heart failure, stroke, renal failure, amputation of at least one finger, vitreous haemorrhage, retinopathy which required photocoagulation, blindness in one eye or cataract extraction) and a significant reduction of total mortality and attributable to diabetes.

RCT 1+

Moreover, in comparison with sulfonylureas and insulin, the treatment with metformin produces weight loss (~1-5 kg) without increasing the risk for hypoglycaemia (111; 113).

SR of RCT 1+

In recent retrospective studies, metformin achieved similar HbA_1c reductions in obese and non-obese patients (114; 115). According to its authors, these findings suggest that metformin is a valid option as initial therapy for non-obese type 2 patients.

Cohort studies 2+

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The optimum dose in most patients is around 2,000 mg/day (116). **RCT 1+**

Metformin's most common adverse effects are gastrointestinal (abdominal pain, nausea and diarrhoea) which can appear in 2% to 63% of cases in comparison to the 0% to 32% with second generation sulfonylureas and 0% to 36% with thiazolidinediones (111). These symptoms can be reduced by consuming food and the slow dose titration. In less than 5% of patients, it is necessary to withdraw the drug (117).

Lactic acidosis is another important and severe adverse effect which has been recently assessed in an SR (118), and which has not objectified an excess of cases in the group treated with metformin. The incidence of lactic acidosis in the group treated with metformin was 6.3 cases for every 100,000 patients/years in comparison to 7.8 cases in the group without it. **SR of RCT 1+**

Nevertheless, the SR includes an insufficient number of patients with renal or hepatic failure, which makes it difficult to assess the risk in these groups. According to the technical specifications, the use of metformin is contraindicated for patients with serum creatinine over 1.5 mg/dl for men and 1.4 mg/dl for women. The safety of metformin has nor been analysed in patients with severe renal failure, with creatinine clearance below 30 ml/min.

The insulinsecretagogues (sulfonylureas and metiglinides) work by stimulating the release of insulin through beta cells from the pancreas, so a certain insulin reserve is required. They are effective to reduce HbA_1c.

The sulfonylureas proved effective to reduce morbidity related to diabetes and in microangiopathy (106), while metiglinides have no studies on morbimortality (119). **RCT 1+**

Sulfonylureas should be considered first line alternative treatment when metformin is not tolerated or it is contraindicated, or for people who are not overweight. Sulfonylureas and glinides provoke weight increase as well as an increase in the risk of hypoglycaemia. **SR of RCT 1+**

A sulfonylurea should be chosen as a first option as, although they are not better than the new oral antidiabetic drugs as regards glycemic control, there is a wider usage experience and they have proved to be effective and much cheaper in long-term RCTs (111).

Gliclazide and glimepiride could be useful for elderly patients or when there is mild-moderate renal failure due to less severe hypoglycaemias risk (120); moreover, sulfonylureas on a single daily dose (gliclazide and glimepiride) can be useful when there is suspicion of therapeutic compliance problems (79; 120). **CPG, Expert opinion 4**

Metiglinides (repaglinide and nateglinide) have a quick action onset and short-term activity; it is recommended to be taken before each main meal.

These drugs can play a role in glycaemia control in patients with non-routine daily models (patients with irregular meals or who omit some meals) (79). **Expert opinion 4**

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Its effectiveness has been recently assessed in a Cochrane SR. Repaglinide reduces HbA_1c between 0.1-2.1% in comparison to placebo, while nateglinide does so between 0.2% and 0.6%. Repaglinide reduces HbA_1c more than nateglinide. In comparison to metformin, repaglinide achieved an HbA_1c similar reduction though with a higher weight increase (up to 3 kg in three months) (121). **SR of RCT 1+**

Repaglinide, compared with sulfonylureas, presents a similar hypoglycaemias frequency, although less severe in some subgroups, such as elderly or people who omit some meal (111).

The alpha-glucosidase inhibitors (acarbose and miglitol) inhibit in a competitive and reversible way alpha-glucosidases of intestinal microvilli, delaying the complex carbohydrate absorption and reducing the postprandial glycemic peak. Acarbose reduces HbA_1c in relation to placebo in an -0.8% (CI 95%: -0.9 to -0.7) (122). **SR of RCT 1+ RCT 1+**

In comparison to sulfonylureas, the alpha-glucosidases are inferior as regards glycemic control and produce adverse effects more frequently. Acarbose doses over 50 mg three times a day do not produce additional effects on the HbA_1c and increase adverse effects, mainly gastrointestinal (flatulence in 30% to 60% of the cases and diarrhoea) thus provoking the interruption of the treatment. In the UKPDS (123) study, the rate of interruption was 58% with acarbose in comparison to 39% with placebo.

In the last few years, thiazolidinediones (pioglitazone, rosiglitazone) have been marketed. Their main action mechanism involves the increase of the uptake and use of glucose in the tissues, in the muscles and the fat tissue without stimulating the secretion of insulin. Recently rosiglitazone has been withawn from the market. **SR of RCT 1++**

In two Cochrane SRs, pioglitazone (124) and rosiglitazone (125) proved to be effective to improve glycemic control (HbA_1c), though with not enough data on morbimortality. The effectiveness of both glitazones as regards the reduction of HbA_1c is similar to that of other antidiabetic drugs (111; 112).

The cardiovascular safety of glitazones has been questioned. Several SRs have been issued which describe the unfavourable effects of rosiglitazone (126-128) and pioglitazone (129).

There is coherence between both SRs on rosiglitazone in highlighting the significant risk increase to develop heart failure [RR 2.09 (CI 95%: 1.52-2.88)] (127; 128), AMI [RR 1.42 (CI 95%: 1.06-1.91)] (126; 128), without increasing total mortality (128).

Pioglitazone has been assessed in two recent SRs (127; 129). Both are coherent in showing the risk increase in heart failure RR 1.41 (129). As regards other cardiovascular events, the evidence is more controversial.

The second SR includes primary and secondary prevention studies (patients with ischemic cardiopathy) performed with pioglitazone and presents a risk decrease in a combined death result CVA and AMI [RR 0.82 (CI 95%: 0.72-0.94)] (129). The determining relevance in these findings corresponds to the Proactive study (130) carried out on patients with ischemic cardiovascular disease though

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without heart failure. In this study, there were no favourable differences to pioglitazone within the main variable, though they did arise in the compound variable performed in the SR, so caution is required in the interpretation of these findings (131).

These results are recorded in a safety specification in the Spanish Medicines Agency (132).

The use of thiazolidinediones can result in an increase in fracture risk in women. According to the analyses carried out by the manufacturer (130), the use of pioglitazone presents a fracture excess of 0.8 cases/year for every 100 women under treatment. This excess is similar to that observed for rosiglitazone in the ADOPT study (133). Most of the fractures took place in the extremities. The mechanism is still unknown.

RCT
1+

These data have been recorded in the pharmacological warnings of the FDA (134) and the Spanish Medicines Agency (135). Recently rosiglitazone has been withdrawn from the market.

The incretin effect is the increase of insulin secretion stimulated by the increase of glucose, through intestinal peptides. The incretin system consists of two peptides, the GLP-1 (glucagon-like peptide 1) and GIP (glucose-dependent insulinotropic polypeptide). The incretins are quickly inactivated by the DPP4 (dipeptidyl peptidase 4) enzyme. Analogue drugs to the GLP-1 (exenatide) receptors have been developed recently. They interact with the GLP-1 receptor and are resistant to be degraded by the DPP4 enzyme. These drugs require parenteral administration. Exenatide and liraglutide can be administered once or twice a day, subcutaneously and even only once a week (exenatide).

Another group of drugs includes the DPP4 inhibitors, which are administered orally (sitagliptin, vildagliptin and others).

A recent SR (119) has analysed the 29 RCTs which compared the addition of these new drugs in comparison to placebo, showing a 0.97% (CI 95%: 0.81-1.13) reduction for HbA_1c for the GLP-1 analogues and 0.74% (CI 95%: 0.62-0.85) for the DPP4 inhibitors, so they are not inferior to other hypoglycaemic agents. The GLP-1 analogues produce weight loss (1.4 kg and 4.8 kg in comparison to placebo and insulin, respectively), while the DPP4 inhibitors have no effect on weight. The GLP-1 analogues have gastrointestinal adverse effects (RR 2.9 for nauseas and 3.2 for vomits). The DPP4 inhibitors have a higher infection risk (RR of 1.2 for nasopharyngitis and 1.5 for urinary infection) and headaches. Most RCTs last 30 weeks maximum, therefore long-term safety has not yet been assessed.

Evidence summary

1++	Metformin, second generation sulfonylureas, repaglinide and thiazolidinediones c are similar in effectiveness as regards HbA_1c reduction (nateglinide and alpha-glucosidases inhibitors seem to be less effective (111;112).
1+	In obese diabetics, the treatment with metformin, in comparison with conventional therapy (sulfonylureas or insulin), reduces the risk of any event related with diabetes (113).

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2+	Glycemic control, achieved with metformin, measured as the HbA_1c, reduction in non-obese patients is similar to that of obese patients (114; 115).
1++	The treatment with metformin produces a greater weight loss than thiazolidinediones or sulfonylureas, though it presents more gastrointestinal adverse effects (111).
1+	Metformin has not shown any increase of lactic acidosis among the general diabetic population, though there is still data missing to treat patients with renal or hepatic failure (118).
1++	Sulfonylureas produce more hypoglycaemias than metformin or thiazolidinediones c (111).
1++	Glibenclamide has a higher hypoglycaemia risk than the rest of sulfonylureas (111).
1+	The incidence of hypoglycaemias with repaglinide and sulfonylureas is similar, although repaglinide produces less severe hypoglycaemias in elderly patients or those who omit some meal (111).
1+	Acarbose frequently produces gastrointestinal adverse effects which can cause an interruption of the treatment (123).
1+	Pioglitazone and rosiglitazone increase the risk of heart failure both in high and low doses (127-129).
1+	Rosiglitazone increases the risk of myocardial infarction (126; 128). It has been wihtdrawn fron the market.
1++	Therapy with incretins is effective in the improvement of glycemic control measured as a decrease of HbA_1c (119). GLP-1 analogues produce weight loss, while the GPP4 inhibitors have no effect on weight. The GLP-1 analogues have frequent gastrointestinal adverse effects. The GPP4 inhibitors have a higher infection risk (nasopharyngitis, urinary infection) and headaches. There is no data on long-term safety.

Recommendations

D	If after three to six months under treatment with non-pharmacological measures HbA_1c targets are not achieved, it is recommended to begin using a pharmacological treatment.
D	The hypoglycaemic agent treatment should be prescribed with a trial period and its response should be supervised using HbA_1c as a measure.
A	Metformin is the drug chosen for people overweight or obese (BMI³25.0 kg/m^2).
B	Metformin is also the first line option for people who are not overweight.
C	Metformin is contraindicated for patients with renal failure (serum creatinine over 1.5 mg/dl for men and 1.4 mg/dl for women).
A	Sulfonylureas should be considered as initial treatment when metformin is not tolerated or it is contraindicated, and can be prescribed for people not overweight.
D^{CPG}	DCPG A single daily dose of sulfonylurea can be useful when there is a suspicion of therapeutic incompliance problems.

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B	Metillinides can play a role in the improvement of glycemic control in patients with non-routine daily models (irregular or omitted meals).
B	Acarbose can be considered an alternative therapy when there is intolerance or contraindication to the rest of oral anti-diabetic drugs.
B	Thiazolidinediones should not be used as first option drugs.
B	Should the use of a glitazone be considered necessary, it is recommended to choose pioglitazone due to its more favourable safety profile.
√	Additional trials with morbimortality and long-term safety variables are required to establish the role of incretins therapy on DM 2.

8.1.3. Combination therapy after inadequate control with initial monotherapy

In the UKPDS 49 study, three years after the DM 2 diagnose, approximately 50% of the patients required more than one oral antibiotic to maintain an HbA_1c below 7%, a percentage which increases up to 75% after nine years (79). Due to a gradual deterioration of diabetes control, most patients required combined therapies to maintain long-term glycemic aims.

Cohort studies 2+

The combination metformin-sulfonylurea is the association of oral anti-diabetic drugs with more usage experience; however, it is not yet clear whether the effect of this association on cardiovascular and total mortality is different to that of metformin or the sulfonylureas as monodrug as there are no RCTs on this matter. There are some cohort studies which analyse this issue, but they are adjusted by the main confusion factors and therefore no conclusions can be settled to take clinical decisions (111).

RCT 1+

As regards glycemic control, the UKPDS 28 study (136) states that in patients who are not controlled with sulfonylureas, the addition of metformin is more effective than continuing with the maximum dose of sulfonylureas.

RCT 1+

There is no information available on the morbimortality results with the rest of the oral anti-diabetic combinations (111).

SR of RCT 1+

According to a recent SR (111), combined therapies have an additive effect and manage to reduce HbA_1c more than monotherapy (1% total reduction). However, the incidence and severity of the adverse effects also increases, unless oral anti-diabetic drugs are used in smaller doses.

SR of RCT 1+

This SR states that the mild and severe hypoglycaemia frequency is higher with those combinations which include sulfonylureas in comparison to monotherapy (absolute risk differences between 8% and 14%) (111).

SR of RCT 1+

The combination of metformin with rosiglitazone has a similar mild hypoglycaemia risk in comparison with the metformin monotherapy; in this treatment group, no severe hypoglycaemias were detected (111).

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On the other hand, the combined therapy of metformin with sulfonylureas or glitazones has associated less gastrointestinal adverse effects than higher doses of metformin monotherapy (metformin + sulfonylurea 1%-35%, metformin + thiazolidinediones 17%, metformin as monotherapy 2%-63%) (111). **SR of RCT 1+**

The Cochrane SRs on pioglitazone (124), rosiglitazone (125), metiglinides (121) and alpha-glucosidase inhibitors (122) offer drug global results and do not focus on specific guidelines. Their results do not differ from those found in the AHRQ SR (111). **SR of RCT 1+**

After the SR (15; 111), two new clinical trials have been issued where glycemic control and the adverse effects of the association of metformin and rosiglitazone in contrast to metformin and a sulfonylurea are compared. The results from the first of these trials (137) are coherent with the SRs previously mentioned. **RCT 1+**

Nevertheless, the data on the safety of glitazones in cardiovascular morbidity (126-129) and bone morbidity recommend a cautious attitude also when used in a combined therapy.

In the second trial (138), the association metformin 2,000 mg and glibenclamide 10 mg reduced HbA_1c more than the combination of metformin 2,000 mg and rosiglitazone 8 mg (-1.5 vs. -1.1%, p <0.001). 4% of patients under the metformin-glibenclamide treatment abandoned it due to hypoglycaemia, in contrast to the 3% of interruptions by hyperglycaemia with the combination metformin-rosiglitazone. **RCT 1+**

Evidence summary

1+	Combined therapies have an additive effect and reduce HbA_1c more than monotherapy (1% global reduction) (111).
1+	The data on the comparisons of the different oral anti-diabetic drugs are not conclusive, due to the methodological diversity and the lack of sufficient RCTs (111).
1+	In patients who are not controlled with sulfonylureas, the addition of metformin is more effective in glycemic control than continuing with the maximum doses of sulfonylureas (136).
1+	The frequency of mild and severe hypoglycaemia is higher in the combinations which include sulfonylureas in contrast to monotherapy (111).
1+	The combination of metformin with rosiglitazone has a similar risk of mild hypoglycaemia in comparison with the metformin monotherapy (111).
1+	The combination of metformin with sulfonylureas or thiazolidinediones has been associated with fewer gastrointestinal adverse effects than metformin monotherapy (metformin + sulfonylureas 1%-35%, metformin + thiazolidinediones 17%, metformin as monotherapy 2%-63%), if metformin is administered at doses inferior to those used in monotherapy (111).
1+	Thiazolidinediones and sulfonylureas provoke a similar weight increase (around 3 kg) when used in monotherapy or in combination with other oral anti-diabetic drugs (111).
1++	Acarbose reduces glycaemia in monotherapy or as combined treatment, though it produces a high incidence of gastrointestinal adverse effects (122).

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Recommendations

B	When glycemic control is not appropriate in monotherapy, a second drug should be added.
A	Sulfonylureas should be added to metformin when glycemic control is not appropriate.
A	When glycemic control is not satisfactory with a sulfonylurea in monotherapy, metformin should be added.
B	In case of intolerance to sulfonylureas or in patients with non-routine intake models, metoglinides can be used.
B	Adding acarbose could be considered as an alternative treatment for people who cannot take other oral anti-diabetic drugs.
B	Thiazolidinediones are second option drugs in a combined therapy. Its use could be used on an individual basis when glycemic control is poor, or there is intolerance or contraindication to the other oral antidiabetic drugs. In this case, the use of pioglitazone is recommended.
B	Thiazolidinediones should not be used for diabetic patients suffering from heart failure.

8.1.4. Treatment after two-drug combination therapy failure

Before triple oral therapy authorisation, the use of insulin was the only option left for patients who did not achieve a good glycemic control with double oral therapy. In the UKPDS (106) study, insulin was one of the hypoglycaemic-agent therapies which, considered as a whole, reduced vascular complications in comparison with simply interventions on life style, so the use of a triple oral therapy was required instead of continuing with the double therapy or administering insulin (79). **RCT 1+**

The RCTs available so far which compare triple therapy to double oral therapy or the use of insulin, assess glycemic control and adverse effects. Its design and duration do not make it possible to assess its effects on morbimortality.

The triple oral therapy has proved to be more efficient as regards glycemic control than double oral therapy, though it also provokes more adverse effects. Two clinical trials have been carried out which compare triple oral therapy with sulfonylurea, metformin and thiazolidinediones with double oral therapy with sulfonylurea and metformin (139) or with metformin and thiazolidinediones (140). Both trials show that better glycemic control is achieved (1.0% additional HbA_1c reduction) with triple therapy, though hypoglycaemia incidence and weight increase are also higher. Triple therapy presents an oedema incidence, which is higher than that with the metformin and a sulfonylurea association (139). **RCT 1+**

In several clinical trials (141-143) glycemic control and the adverse effects of triple oral therapy (metformin + secretagogues + thiazolidinediones) are compared to adding insulin to metformin or the association of metformin and a sulfonylurea. No trial presented any significant differences as regards glycemic control, measured as the reduction of HbA_1c, between triple oral therapy and the associa- **RCT 1+**

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tion of insulin and oral diabetic drugs. In three trials, more hypoglycaemia events in the association of insulin with oral anti-diabetic drugs in comparison to triple oral therapy were observed. Rosiglitazone provoked more adverse effects than insulin glargine (143), especially due to the high incidence of oedemas (12.5% in contrast to no case with insulin).

As regards thiazolidinediones, the evidence on its effectiveness and safety (cardiovascular and bone) has already been mentioned in the chapter on monotherapy and associated therapy and its conclusions are also applicable to the use of combined therapy with three drugs.

SR or RCT
1+

Evidence summary

1++	Insulin improves glycemic control and reduces morbidity risk associated with diabetes (79; 106).
1+	Triple oral therapy with a sulfonylurea, metformin and a glitazone achieves more HbA_1c reductions than double oral therapy with sulfonylurea and metformin (139) or with metformin and a thiazolidinediones (140), although there is a higher incidence of hypoglycaemia and more weight increase.
	Triple oral therapy with a sulfonylurea, metformin and a thiazolidinediones provokes more oedema incidence than the association of metformin and a sulfonylurea (139).
1+	Triple oral therapy (metformin + secretagogue + thiazolidinediones) achieves a similar glycemic control measured as the reduction of HbA_1c, to the obtained with insulin associated with metformin or a sulfonylurea (139; 141-143). More hypoglycaemia events are observed with the association of insulin and oral antidiabetic drugs than with the triple oral therapy. No comparative data exists on morbimortality (141-143).

Recommendations

A	In case of inappropriate glycaemia control, despite using an optimized double oral therapy guideline, the use of insulin treatment is recommended.
B	Triple oral therapy can be recommended after having assessed its possible cardiovascular risks, for specific patients who have insulinization problems.
B	Should the use of a thiazolidinediones be considered necessary, it is recommended to use pioglitazone due to its more favourable safety profile.

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8.2. Insulin therapy

8.2.1. Association of insulin with oral antidiabetic drugs

SR or RCT and RCT 1+

A Cochrane (144) SR and several subsequent clinical trials (145-147) have assessed the effect of the combination of insulin with oral anti-diabetic drugs in contrast to monotherapy with insulin. All the trials assess glycemic control and the adverse effects, though they do not assess the effect on morbimortality. The guidelines and types of insulin used differ in diverse trials. In the SR (144), the combination of NPH (Neutral Protamine Hagedorn) insulin on a single night dose associated with an oral anti-diabetic drug presented a glycemic control comparable to monotherapy with human insulin (no analogues) every 12 hours or on a multiple schedule. Weight increase was much less with the night schedules of insulin associated with metformin (with or without sulfonylureas) in contrast to monotherapy with insulin (144).

The results of the subsequent studies follow the same lines; in general, the association of metformin with insulin improves glycemic control (expressed in HbA_1c reduction) (146-148), with less weight gained (145-147). The results in relation to the frequency of hypoglycaemias vary among the different studies; in the SR (144) no differences were observed as regards hypoglycaemia events, though in other studies (145; 148) the treatment combined with a dose of insulin plus metformin was associated with less hypoglycaemias in comparison with insulin taken twice on a daily basis.

In the Douek (146) study more hypoglycaemias were observed than in the group with insulin plus metformin in comparison to insulin with placebo.

In general, the more intense the treatment is, the better the achievement of glycemic control and the higher the incidence of hypoglycaemia. Should there be no conclusive evidence on which guideline is better, then the patient's preferences (79) and the risk of adverse effects, mainly hypoglycaemia, should be taken into consideration.

8.2.2. Insulin analogues

There are many possible insulinization schedules, both as regards dosage frequency as the type of insulin: fast-acting insulin, intermediate or mixed human insulin or fast-acting analogues of human insulin (lispro, aspart and glulisine) or slow-acting insulin analogues (glargine and detemir).

Fast-acting insulin analogues are absorbed faster and manage to double the concentrations of insulin in plasma in half the time in comparison to human insulin, due to their pharmacokinetics. This characteristic creates lower glucose levels after the meals. Another advantage of fast-acting insulin analogues would be the possibility to inject insulin just before the meals.

While fast-acting insulin analogues are used to imitate the response of eNdogenous insulin to the intake or to improve or prevent «inter-intake» hyper-

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glycaemia, slow or intermediate acting insulin is used to provide a continuous amount of insulin, regardless of the meal and can regulate lipolysis and the hepatic production of glucose.

Studies on the use of insulin on DM 2 should provide valid information on: the effectiveness of the different insulins on the reduction of micro- and macrovascular complications, glycemic control, hypoglycaemias and the impact on the quality of life, long-term safety (mitogenic effects), the patient's preferences and the cost.

Quick/fast acting insulin analogues vs. human insulin

CPG 4

The NICE CPG, due to a lack of evidence which compares the different insulinization strategies, recommends following local experience, the patients' experience and the cost.

SR of RCT 1+

The strategies of the treatment with fast-acting insulin consist of an intensified treatment with insulin (fast-acting insulin before meals, basal insulin before going to bed or twice a day, even an adjustment of the insulin dose based on the intake of carbohydrates) instead of a treatment with conventional insulin (basal or pre-mixed insulin three times a day with or without oral hypoglycaemic drugs).

There are two SRs which have assessed this matter (149; 150). The Cochrane SR is based on eight RCTs which include lispro, aspart and glulisine insulin. There are no differences in glycemic control assessed through HbA_1c. There was no difference in the global hypoglycaemia events (difference of averages measured per patient and per month -0.2; CI 95%: -0.5 to 0.1). The incidence of severe hypoglycaemia varied from 0 to 30.3 (average 0.3) events for 100 people/year for insulin analogues and from 0 to 50.4 (average 1.4) with conventional insulin. There was variability in the definition of severe hypoglycaemic events: from the need of other people to coma or the use of glucagon or glucose.

The other review (149), after the Cochrane review, aims to compare the effectiveness of fast-acting analogues in contrast to any other hypoglycaemic agent drug in DM 1, type 2 or gestational patients, thus there were more studies included. In DM 2, 26 RCTs were analysed; most compare insulin analogues to human analogues with or without oral anti-diabetic drugs. Its results are coherent with the Cochrane review: there are no differences in glycemic control or hypoglycaemia events.

The use of fast-acting insulin regimen using conventional insulins or analogues is just as effective. Nevertheless, in DM 2, the need for multiple jabs limits its application to very specific patients.

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Slow-acting insulin analogues vs. NPH insulin

SR of RCT
1+

There are three SRs (151-153) and a report from a Canadian agency with an SR and a meta-analysis (154) which have assessed the effectiveness and safety of the different types of insulin. Three of them assess insulins glargine and detemir in comparison to NPH insulin, while the third type (152), funded by the manufacturer, aims to assess only the hypoglycaemia events of insulin glargine.

The studies included in the reviews compare single night insulin glargine doses in contrast to one or two doses of NPH insulin, while the comparison of insulin detemir in contrast to NPH insulin is with one or two doses of both. The duration of the studies is limited in time (24-52 weeks), which makes it difficult to detect differences in variables such as micro- and macroangiopathy. The variables assessed are glycemic control measured as glycosylated haemoglobin values and the hypoglycaemias as safety variables. The latter are assessed as total night and severe hypoglycaemias without any standardization of their definition and their recording. In some studies, these are referred by the patients themselves, without masking of the treatment received.

There are no differences in glycemic control between insulin glargine or detemir in contrast to NPH insulin. There are no differences either between the number of severe hypoglycaemias, though there is in the total number of hypoglycaemias, especially at the expense of night hypoglycaemias, which are less than with analogues. The number of severe hypoglycaemias is seldom found in the RCTs included in the SRs.

Appendix 3 describes the guidelines to begin the insulinization process and the use of hypoglycaemic drugs. Appendix 4 records the hypoglycaemia treatment.

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Evidence summary

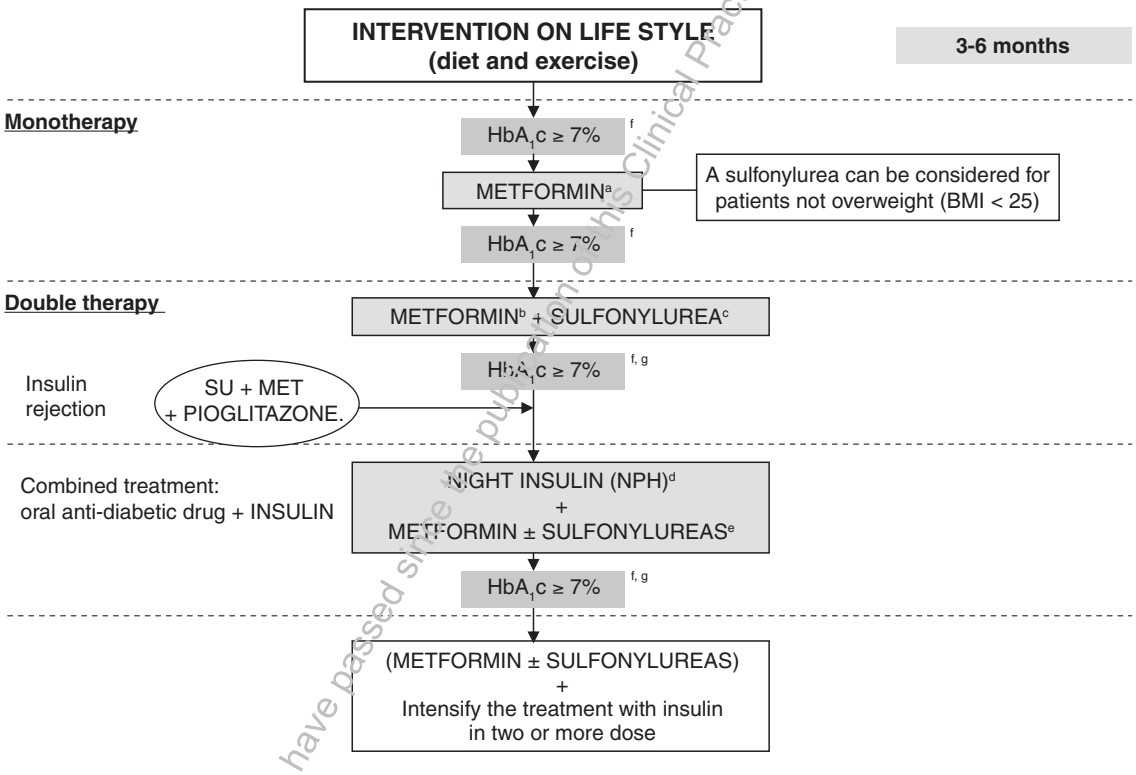
1+	The combination of single night dose NPH insulin associated with an oral anti-diabetic drug provides glycemic control comparable to monotherapy with insulin every 12 hours or on a multiple schedule (144).
1+	In comparison with the insulin monotherapy, the combination of metformin with insulin improves glycemic control (reduction of HbA_1c) with less weight gain (145-147). The results on the frequency of hypoglycaemias are contradictory (144-146; 148), though a higher incidence has been proved as the treatment intensifies. There are no data on morbimortality.
1+	The studies which compare the different insulins are not designed to show differences in micro- and macrovascular complications and they do not provide data on quality of life or patients' preferences (151-154).
1+	There are no significant differences as regards glycemic control assessed by means of glycosylated haemoglobin between the slow-acting insulin analogues and NPH insulin. Slow acting insulin analogues are associated with a lower risk of hypoglycaemias at the expense of the reduction of night hypoglycaemias (151-154).

1+	There are no significant differences as regards glycemic control assessed by means of glycosylated haemoglobin between fast-acting insulin analogues and fast-acting human insulin. There are no differences in the frequency of hypoglycaemias (149; 150).

Recommendations

A	When treatment with insulin is started, it is recommendable to keep up the therapy with metformin and/or sulfonylureas.
√	The need to continue with sulfonylureas or to reduce their dosage due to the risk of hypoglycaemias is to be reviewed.
A	In DM 2 patients who require insulinization, the general use of insulin analogues is recommended. The use of slow-acting insulin analogues in patients with increased risk of night hypoglycaemias is recommended. DM 2 patients who require intensive insulinization, are not recommended the use of fast-acting analogues, as they present no advantages.
D^{CPG}	DCPG When selecting an initial insulin schedule, the patient's preference, the adverse effects risks (mainly hypoglycaemia) and the costs are to be taken into consideration.

Figure 2. DM 2 treatment algorithm



[a] If intolerance to Metformin, use Sulfonylureas.
[b] If intolerance to Metformin, Pioglitazone.
[c] If Sulfonylureas are contraindicated or the patient follows irregular meals, use metiglinides (Repaglinide, Nateglinide).
[d] If the patient suffers night-time hypoglycaemias, use slow-acting insulin analogue (Glargine or Detemir).
[e] Review the need to continue with sulfonylureas or reduce the dose due to risk of hypoglycaemias.
[f] The HbA_1c ≤7% target is for guidance. The aim is to be set individually, depending on cardiovascular risk, comorbidity, disease evolution time, life expectancy and the patients' preferences.
[g] Before insulinization start and during the intensification process, less strict aims can be considered.

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9. Screening and treatment of macrovascular complications

The questions to be answered are the following:

- Is the cardiovascular risk for diabetic patients comparable to the risk for those patients who have suffered a myocardial infarction? What risk table is recommended for patients with DM 2?
- Should an coronary heart diseasescreening be carried out in adults with DM 2? Which is the method to develop a coronary heart disease screening?
- Should diabetic patients be treated with aspirin?
- Does the treatment with statins reduce cardiovascular complications in diabetes? When is it appropriate to use treatment with statins for patients with diabetes?
- Which are the targes for blood pressure within the treatment of the diabetic hypertense patient?
- Which is the prferred hypertensive treatmentin patients with diabetes and high blood pressure?

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9.1. Cardiovascular risk in diabetic patients

Diabetes is associated with an increase in cardiovascular disease. In order to adopt therapeutic decisions or to intensify treatment (glycemic control, antiplatelet therapy, lipid-lowering drugs, etc.) it is important to identify which groups of patients present higher cardiovascular risk and could benefit more from the above-mentioned treatments.

There are different RCTs which provide evidence of effective interventions on patients with individual risk factors, such as high blood pressure or the presence of microalbuminuria.

For patients who do not present any of these risk factors, different approaches can be considered. Some experts suggest that diabetes ought to be treated as a cardiovascular disease (secondary prevention). This assumption is based on prognosis studies that compare the risk of cardiovascular events in DM 2 patients with patients who have suffered from acute myocardial infarction (AMI).

Another option is to use *equations or cardiovascular or coronary risk tables* to select the patients who can benefit most from the cardiovascular primary prevention interventions.

In any case, these approaches should be supported by clinical trials which endorse the effectiveness of the different interventions (antiplatelet therapy, statins, etc.) in the decrease of cardiovascular events in DM 2 patients.

9.1.1. Comparison of cardiovascular morbimortality in diabetic patients and patients who have suffered from a previous acute myocardial infarction

Cohort studies 2+

Fifteen cohort studies (155-169) have been found that compare the risk of coronary events in diabetic patients to that of patients with ischemic cardiopathy antecedents and the population in general. All the studies present a higher coronary risk for the diabetic patient than the general population. However, the coronary mortality comparative results between the diabetic population and the people with coronary heart disease antecedents are contradictory. The differences in these results could be justified through several causes: inclusion criteria differences, lack of uniformity when defining diabetes and coronary heart disease, the way to collect the data, inclusion of incident or prevalent cases, characteristics of the patients (age group, gender, time of diabetes evolution) or methodological aspects (differences in the confusion factors considered, cohorts taken on a population basis or not, different result variables, lack of follow-up, etc.)

The studies which analyse their results according to gender agree that diabetes in women involves a relatively higher risk for coronary disease than in diabetic male patients (155-157; 159) and in some cases, this risk is the same (155; 157) or higher (155; 158) to that of women with coronary heart disease antecedents.

Some studies have assessed the duration of DM and conclude that it is an independent risk factor (22) and that, after 15 years developing the disease, coronary risk is similar to that of patients with ischemic cardiopathy antecedents (22; 159; 160).

Therefore, stating that the same risk exists for both population groups and extending all the interventions tested through RCTs in cardiovascular secondary prevention to primary prevention for all diabetic patients is a statement which cannot be considered as based on proven evidence.

For this reason, it seems necessary to use other criteria to select the patients. An evolution longer than 15 years can be one of them.

9.1.2. Cardiovascular risk tables

Clinical prediction rules 2+

As has already been mentioned, another widely used tool to classify diabetic patients is cardiovascular or coronary risk tables. The cardiovascular or coronary risk tables differ between them depending on the events taken into consideration.

The original Framingham risk table and its adaptations consider only coronary risk which includes non-fatal AMI (symptomatic and silent), angina and fatal AMI. The tables that calculate the total cardiovascular risk add to coronary risk that of suffering from a fatal or non-fatal cerebrovascular disease.

Both estimate the probability to suffer cardiovascular or coronary events during a certain time depending on the existence or inexistence of different risk factors. The risks are based on a special type of follow up study: clinical prediction rules (CPRs).

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The validity and applicability of a CPR for a certain population group requires, firstly, the creation of a group in a cohort through a multivariate analysis and after a validation process, first, in the population of origin and afterwards on different population groups where the rule is to be applied (170). Currently, there is the REGICOR equation (also known as Framingham calibrated), which is the rule with the highest validation for our population (171-173).

There is a risk function which is exclusive for diabetic patients based on the results of the UKPDS study (174). It has the advantage that it considers the diabetes evolution years and the HbA_1c levels as independent risk factors and it provides, apart from coronary risk, the stroke risk. When this function is validated for our population (175; 176) it can be used as a very useful tool for cardiovascular education and prevention.

The VERIFICA study (173), performed on 5,732 patients of whom 941 (16.4%) were diabetic, found no significant differences between the rate of events expected from the calibrated Framingham equation with those closely observed during the follow-up of the cohort of the different risk categories. The population group in the study was fairly young (the average age was 56.3), so probably the diabetes had had a relatively short evolution.

The REGICOR equation is the one recommended to calculate coronary risk among the diabetic population within our scope. Appendix 5 includes the REGICOR risk tables.

9.2. Coronary heart disease screening

RCT 1+/-

There have been no studies carried out across the general diabetic population on the effectiveness of coronary heart disease screening. Only one pilot RCT (177) has been found across a very specific population group which assesses the effectiveness of coronary heart diseasescreening on 144 patients with high risk DM 2, without heart disease, asymptomatic and aged between 46 and 75. The patients had at least two risk factors: 1) total cholesterol ³240 mg/dl or HDL <35 mg/dl or pharmacological treatment, 2) blood pressure ³140/90 mmHg or pharmacological treatment, 3) active smokers, 4) albuminuria ³30 mg/24 h, 5) family history of coronary heart diseasein first-degree relatives, before the age of 55 in men and 65 in women. These were randomised to the screening group (stress test and stress echocardiography with dipiridamol) in contrast to no intervention. During the follow-up period (53 months) fewer cardiac events (stroke, cardiac death and angina) were observed in the group assigned for the screening [OR 0.22 (CI 95%: 0.07-0.93)], at the expense of major events (stroke and cardiac death). The study contains some limitations, such as being carried out on a very small number of patients and events, not being able to perform a stress test on enough patients and the limited generalization (high-risk patients coming from a specialized centre). The authors of the study suggest the screening to be carried out through a stress echocardiography due to its high sensitivity (85%) and specificity (93%) and its acceptable cost. The stress test could not be done on many diabetic patients, especially on those suffering from high cardiovascular risk, due to the existence of severe hypertension, hemorrhagic retinopathy, peripheral vascular disease or obesity.

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More studies with more patients are required to achieve a firm recommendation on this matter.

9.3. Antiplatelett treatment

The decision to prescribe aspirin a in primary care of DM 2 patients must take into consideration the benefits of the drug as it reduces the number of cardiovascular events and the risk of adverse effects (mainly, digestive and haemorrhage). **SR of RCT 1+**

The results of the RCT meta-analysis in primary care show that the benefit of aspirin is closely related to baseline cardiovascular risk (178), thus the patients with higher baselinel cardiovascular risk are those who benefit more from the treatment. The meta-analysis includes five RCTs in primary care which also contain a minority of diabetic patients (between 2% and 17%); the HOT (179) and PPP (180) studies are the ones which include more diabetic patients (8% and 17%, respectively, in contrast to the 2% of other studies. However, the meta-analysis does not provide data on the effectiveness of aspirin in the diabetic patient's subgroup.

The SIGN guide, based on the results of this study (178) and another meta-analysis (181) has specified the cut-off of cardiovascular risk to be over 15% to consider primary prevention with aspirin (182). **CPG 4**

The only specific study on aspirin in DM is the ETDRS study (183) which included 3,711 patients suffering from DM types 1 and 2 with retinopathy, half of whom were under secondary prevention. The treatment with aspirin during seven years did not reduce the incidence of AMI, strode or cardiovascular death in these patients. **RCT 1+**

A meta-analysis on the effectiveness of aspirin in contrast to placebo in primary prevention (184) included a total of nine RCTs which provided data on diabetic patients. In this subgroup no statistically significant differences were found in the incidence of severe vascular events (non-fatal AMI, non-fatal stroke or vascular death), [RRR 7% (CI 95%: -1% to +15%)]. **SR of RCT 1+**

Two RCTs were later published in primary prevention that include diabetic patients.

In the analysis of the PPP diabetic population subgroup (180) (1,031 diabetics aged ³50 without prior cardiovascular disease), a slight and insignificant reduction of severe vascular events was observed [RR 0.90 (CI 95%: 0.50-1.62%)], far smaller than that observed in primary prevention of patients with other risk factors, though where a significant reduction of the risk was observed (185). The authors state that due to the limitations of the study (open and with a limited number of patients, as it was interrupted prematurely), the results are not conclusive.

In another RCT carried out in primary prevention on women (186), which included approximately a 10% of diabetic women, a reduction of cerebrovascular disease was observed, though none related to AMI nor the main variable of cardiovascular events. **RCT 1+**

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The RCTs and the meta-analysis are coherent as regards the increase of the bleeding risk with the aspirin treatment (178; 184).

SR of RCT and RCT 1+

As regards diabetic patients with microalbuminuria, a population with higher cardiovascular mortality than the diabetic population without microalbuminuria, a clinical trial stated that an intensive long-term treatment which included habit changes and a pluripharmacological treatment (aspirin and statins, among others), was beneficial for these patients (108).

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9.4. Treatment with statins

In the evidence evaluation three SRs (187-189) and two subsequent clinical trials (190; 191) have been taken into consideration.

The reviews (187; 188) include diabetic and non-diabetic patients as well as an analysis of diabetic subgroups.

The first SR (187) includes four RCTs in primary prevention (AFCAPS, ALLHAT-LLT, HHS, ASCOT-LLA) and two in mixed populations (PROSPER and HPS). It observed a risk difference in the main variable (combined result of cardiovascular mortality, stroke, cerebrovascular accident and global mortality) favourable to the treatment with statins [ARR -0.03 (CI 95%: -0.04 to -0.01)]. The results are highly influenced by the HPS study, carried out across high-risk patients.

SR of RCT (Subgroups) 1+

The second SR (188) includes the same studies, though the variable assessed is coronary events (coronary mortality, non-fatal myocardial infarction or coronary revascularization, with a favourable effect to the treatment with statins [RR 0.79 (CI 95%: 0.7-0.89) NNT 37 (24-75) to 4.5 years].

The third review (189) analyses only the effects of fibrates and combines trials carried out only across diabetic patients with other trials that have mixed population groups (diabetic and non-diabetic patients), although it does analyse diabetic subgroups. It also combines primary prevention studies with secondary prevention studies. The global result of the review (combining all the studies) shows a relative risk for coronary events of 0.84 (CI 95%: 0.74-0.96). Analysing only the studies of primary prevention, an HR favourable to fibrates of 0.79 (NNT 26 after 10 years), although it does not offer confidence intervals and in one of the primary prevention studies, the diabetic patients belong to a subgroup.

SR of RCT (subgroups) 1+

The FIELD study (192), included in the systematic review, is the only clinical trial carried out with fenofibrate in type 2 diabetic population in primary and secondary prevention, with low HDL values (38.5 mg/dl) and slightly high triglycerides values (170 mg/dl). It includes a 22% of patients with prior cardiovascular disease. No differences were observed in the main variable of the study (coronary mortality or non-fatal AMI), although there were differences in a secondary variable of total global cardiovascular events, at the expense mainly of non-fatal AMI and revascularization procedures. These differences in the secondary variable were more evident in the primary prevention patients. Nevertheless,

RCT 1+

it is worth mentioning, that 19.2% of the patients assigned to the fenofibrate group and 36% of the control group started taking statins during the study. On the other hand, a significant increase of adverse effects took place, NNH of 250 for pulmonary embolism and 330 for pancreatitis.

The two subsequent RCTs carried out in DM 2 patients with relatively low cholesterol levels (LDL cholesterol below 160 mg/dl) showed different results (190; 191). The CARDS study (190) carried out in primary prevention was stopped prematurely (4) when a reduction of the main result was observed (combined variable or acute coronary event, coronary revascularization or stroke) favourable to atorvastatin [HR 0.63 (CI 95%: 0.48-0.83); NNT 4 years after of 27 (CI 95%: 20-62)]. The patients included were diabetics aged between 40 and 75, without prior cardiovascular disease, with moderate LDL cholesterol levels and at least one of the following risk factors: HBP, retinopathy, smoking or micro-or macroalbuminuria. It is worth mentioning that the results of this study present implementation problems for countries such as Spain, where there is a lower coronary disease risk and where the number of patients required to try to prevent a cardiovascular event would be clearly higher (in the CARDS study, with an event rate of 9% in the control group, the NNT was 14; considering a 4% rate in our field, the NNT would be 40).

RCT 1+

The second RCT contains bias (191) and thus no firm conclusions can be obtained. Initially it had been designed as secondary prevention and afterwards, patients from primary prevention were included. No differences were found in the main result between atorvastatin and placebo.

RCT 1–

On the other hand, the treatment with statins conveys a slight increase in the risk of hepatic disease (193-195). However, statins are reasonably safe in low to moderate doses. Moderate doses are the following: atorvastatin 10 mg/day, simvastatin 40 mg/day or equivalent.

Evidence summary

1+/–	There is not enough evidence on the effectiveness coronary heart diseasescreening in the reduction of coronary morbimortality among the general diabetic population. Additional studies are required for patients at risk (177).
2+	The general diabetic population has higher coronary risk than the general population (22; 156-163; 166), though this risk is lower than that of the population with coronary heart disease antecedents (156; 158-169).
2+	The diabetic population with more than 15 years of evolution of the disease (159; 160; 162; 168) tends to balance their coronary risk with that of the population with prior coronary heart disease. The risk is higher for women (155-159).
2+	The REGICOR equation is the risk table with more validation for the Spanish general and diabetic population (173).
1+	Aspirin did not reduce the AMI, stroke or cardiovascular death incidence in an RCT with patients with DM types 1 and 2 with retinopathy, half of whom were in secondary prevention (183).

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1+	In primary prevention, aspirin benefit depends on the baseline cardiovascular risk (178). In a meta-analysis on the effectiveness of aspirin in primary prevention (184), no statistically significant differences were found in cardiovascular morbidity in the subgroup of diabetic patients.
1+	Two subsequent RCTs in primary prevention (180; 186) show contradictory results in the subgroup of diabetic patients. Only a study carried out across women (186) offered favourable results in the reduction of stroke, though no differences were observed in coronary disease nor in cardiovascular events as a whole.
1+	Aspirin increases the bleeding risk among the diabetic population (178; 180; 184; 186).
1+	In diabetic patients with microalbuminuria, an RCT observed that an intensive treatment with habit changes, strict glycemic control and aggressive pharmacological treatment (which included aspirin and statins) reduced cardiovascular morbimortality (180).
1++	Statins reduce coronary (188) and cardiovascular events (190). Atorvastatin at 10 mg doses is effective to reduce cardiovascular events in primary prevention in type 2 diabetic patients with no prior cardiovascular disease, with LDL-cholesterol below 160 mg/dl and with an additional risk factor (equivalent to a moderate coronary risk): high blood pressure, retinopathy, micro-or macroalbuminuria or smoking (190).
1+	In an RCT carried out with fenofibrate in DM 2 patients in primary and secondary prevention with low HDL–c levels and slightly high triglycerides, no differences were observed in the study's main variable (coronary mortality and non-fatal AMI) nor in the overall survival, though there were differences in a secondary variable of total cardiovascular events (especially at the expense of revascularization procedures) (189).

Recommendations

D	The located evidence does not permit the provision of a recommendation in favour of ischemic cardiopathy screening among the general asymptomatic diabetic population. More studies are required in selected high-risk population groups.
C	The same measures are not recommended when treating the general diabetic population and the population group which has suffered an AMI.
C	When the use of a risk table is required to calculate coronary risk in diabetic patients, the tables of the REGICOR project are recommended.
C	Diabetic patients with more than 15 years of evolution, and in particular if they are women, should consider a treatment with statins, due to its high cardiovascular risk.
B	A treatment with statins is recommended for diabetic patients with coronary risk ³10% according to the REGICOR table.
D	A treatment with aspirin can be considered for diabetic patients with coronary risk ³10% according to the REGICOR table.
B	In type 2 diabetic patients with cardiovascular risk ³10% in the REGICOR table and for whom statins are contraindicated or not tolerated, the administration of fibrates can be considered.

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9.5. Treatment for high blood pressure

9.5.1. Target blood pressure

The NICE CPG on diabetic nephropathy recommends blood pressure (BP) lower than 140/80 mmHg for the general diabetic population. Several CPGs in the cardiovascular field do not agree with these figures and recommend others which range between 130-140 mmHg for systolic blood pressure (SBP) and 80-90 mmHg for diastolic blood pressure (DBP). This variability can be explained due to the different evaluations and interpretations of the scarce evidence there is on this matter.

CPG 4

There are no quality trials with a specific design and appropriate selection result variable to respond to this matter in a clear way. The two main studies generally mentioned by the CPG and consensus are the UKPDS 38 (196) and the HOT (179) studies. The editing team of this CPG has not considered the ABCD (197) study due to its poor quality. In the UKPDS 38 study, the patients assigned to a strict blood pressure control (target <150/85 mmHg; achieved: 144/82 mmHg) present less risk to suffer any event related to diabetes [RR 0.76 (CI 95%: 0.62-0.92)] and a lower mortality related to diabetes [RR 0.68 (CI 95%: 0.49-0.94)] than the patients assigned to a less strict blood pressure (target: <180/105 mmHg; achieved: 154/87 mmHg). A non pre-specified analysis of diabetic patients in the HOT study shows that there are differences in the subgroup assigned to a diastolic blood pressure whose target was lower than 80 mmHg (achieved value 81 mmHg in the general population) in comparison to a subgroup assigned to a diastolic blood pressure whose target was lower than 90 mmHg. Although there are no differences in the overall mortality, the patients with a less strict control on their blood pressure target have an increased cardiovascular mortality risk [RR 3.0 (CI 95%: 1.28-7.08)].

RCT 1+

A meta-analysis (198) suggests that there is limited evidence that the intensive control of blood pressure in contrast to a less intensive control can be more beneficial for the diabetic population than the non-diabetic population.

SR of RCT 1+

In a recent review (199), it was stated that the evidence is scarce in order to recommend specific figures and thus the authors chose 140 mmHg for SBP and 80 mmHg for DBP.

CPGs are designed to help professionals and patients when taking decisions. The cooperation team of this CPG agrees on the need to create realistic recommendations based on best evidence and that can be achieved in clinical practice (110). Assessments on the control level of the blood pressure targets in our field for hypertense patients with diabetes show that at least 15% of the patients reach SBP and DBP levels lower than 135/80 mmHg (8; 200).

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9.5.2. Pharmacological treatment of high blood pressure

The benefits of antihypertensive treatment observed in the diabetic subpopulation of the major trials do not differ from those of the general population (198).

The ALLHAT (102) trial, where the analysis across the diabetic population was to be carried out at the beginning of the study, is the trial which has incorporated the highest number of diabetic patients (13,101 patients). No differences were found between chlorthalidone vs. lisinopril or chlorthalidone vs. amlodipine in the main result variable of cardiocoronary disease. The only variable which presented significant differences was the secondary variable on heart failure, where chlorthalidone was higher than amlodipine [RR 1.39 (CI 95%: 1.22-1.59)] and lisinopril [RR 1.15 (CI 95%:1.00-1.32)]. **RCT 1++**

For calcium channel blockers there are, apart from the ALLHAT study, other minor and less qualitative studies (202; 203), carried out only across diabetic population, where some unfavourable results on cardiovascular morbimortality were observed in comparison to the ACE inhibitors. **RCT 1+/-**

In the analysis of the diabetic subgroup of the INSIGHT trial (204) there were no differences between the diuretic (hydrochlorothiazide/ amiloride) and nifedipine GITS in the main result variable on cardiovascular morbimortality. On the other hand, the results of the two meta-analysis (198; 205), although of poor quality, are coherent as regards unfavourable results for calcium channel blockers in the result variable on heart failure in comparison to the conventional treatment (diuretic / beta-blocker) [OR 1.33 (CI 95 %: 1.17- 1.50)] or ACE inhibitor/ARB II [OR 1.43 (CI 95 %: 1.10-1.84)] (205). **RCT 1+ SR of RCT 1+/-**

As regards the ARB II, the evidence is derived from the diabetic subgroup of the LIFE trial (106), carried out in patients with left ventricular hypertrophy (LVH) and high cardiovascular risk, where losartan reduced cardiovascular morbimortality more than atenolol, even though this drug was not the most appropriate comparator according to the current evidence (207). It is difficult to achieve practical conclusions of the study a part from the fact that Losartan is better than atenolol for these patients. **RCT 1++**

The ONTARGET study was published recently and it includes a 38% of diabetic patients; telmisartan was similar to ramipril 10 mg in the prevention of death for cardiovascular reasons (208). **RCT 1++**

The results of the LIFE trial, together with the latest evidence taken from systematic reviews on the general population (208), suggest not recommending beta-blockers as a treatment for HBP in DM 2 unless there are other firm indications for its use, such as the existence of ischemic cardiopathy or heart failure. **RCT 1+**

The association of Perindopril with Indapamide reduced the incidence of events (added variable of micro- and macrovascular events) in DM 2 patients (209). **RCT 1+**

Lastly, the HOPE trial shows that adding ramipril 10 mg to the conventional treatment for diabetic patients over 55 with another cardiovascular risk, including HBP, reduces cardiovascular morbimortality (210). **RCT 1++**

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Regarding renal results, the slow progression of the renal disease would require long-term trials with a high number of patients to identify its clinical benefits, thus what are normally used are intermediate result variables, such as moving from microalbuminuria to macroalbuminuria or the doubling of serum creatinine to assess the progression of nephropathy. Most of type 2 diabetic patients with or without microalbuminuria will die before due to cardiovascular reasons rather than to renal causes. In fact, the greatest benefit of treating these patients is achieved through the reduction of cardiovascular events (211).

A Cochrane review (212) concludes that only the ACE-inhibitors have proved to prevent the development of microalbuminuria (NNT 25), although it is not yet clear if there are differentiating effects with other anti-hypertensive drugs with the exception of calcium antagonists, which in this review, have proved to be less effective than the ACE-inhibitors. **SR of RCT 1+**

On the other hand, the independent nephroprotector effects of the ACE-inhibitors or ARB-II, beyond blood pressure reduction, have been questioned by a recent meta-analysis (213). In the ALLHAT trial, after a 4.9-year follow-up, no differences were observed between lisinopril, amlodipine and chlorthalidone in the renal result variables, taking into consideration the limitations that nephropathy was not the study's main aim and that the patients were selected as they had high cardiovascular risk (214).

Evidence summary

1+	There is limited evidence that an intensive blood pressure control is more beneficial among the diabetic population than the non-diabetic (179; 196).
1+	In the subgroup of hypertense DM 2 patients, reducing DBP to less than 80 mmHg implies a reduction of cardiovascular morbimortality (179).
1++	There are no significant differences in cardiovascular mortality among hypertense diabetics treated with chlorthalidone, amlodipine or lisinopril (201). Chlorthalidone has proved to be more effective than lisinopril and amlodipine in the prevention of heart failure.
1+/–	ACE-inhibitors have proved to be more effective than calcium channel blockers in the prevention of cardiovascular morbimortality (202; 203).
1+	ARB II is not better than the ACE-inhibitors when reducing cardiovascular mortality among the diabetic population (208).
1++	In hypertense diabetic patients aged between 55 and 80 and with LVH electrocardiographic signs, losartan reduces cardiovascular mortality much more than atenolol (206).
1++	In diabetic patients over 55 years old with another cardiovascular risk factor (including HBP), the use of ramipril 10 mg, added to conventional treatment, reduces cardiovascular morbimortality (210).
1++	ACE-inhibitors are more effective than placebo and than calciumchannel blockers to prevent microalbuminuria (212).

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Recommendations

B/D	Patients with essential HBP and DM 2 without retinopathy should receive treatment to reduce blood pressure (BP) until they achieve diastolic blood pressure (DBP) _80 mmHg (B) and systolic blood pressure (SBP) _140 mmHg (D).
A	DM 2 hypertense patients without nephropathy should be treated firstly with an angiotensin converting enzyme-inhibitor (ACE) or a thiazide; or both when it is considered necessary to control blood pressure. An alternative treatment are dihydropyridines calcium channel blockers.
B^{CPG}	The use of beta-blockers is not recommended unless there is a firm indication for their use, such as coronary heart disease or heart failure.

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10. Screening and treatment of microvascular complications

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The questions to be answered are the following:

- Should a screening of the diabetic retinopathy be carried out? With which technique and how often?
- Is a diabetic nephropathy screening to be done? How often should it be carried out? What methods are to be used?
- Which is the treatment for patients with DM 2 and microalbuminuria?
- Which is the treatment for painful diabetic neuropathy?
- Which is the treatment for erectile dysfunction in a type 2 diabetic patient?

10.1. Diabetic retinopathy screening

Diabetic retinopathy is the first cause of blindness for people under 60 and one of the main causes of blindness among the elderly. 20 years after diabetes is diagnosed, more than 60% of type 2 diabetic patients will suffer from retinopathy. In type 2 diabetics, maculopathy is the main cause of sight loss (215).

The risk of sight loss and blindness can be reduced through programs which combine methods for screening with diabetic retinopathy effective treatment (215). It is essential, both to determine which technique is best and how often the retinopathy screening is to be carried out.

Studies of diagnostic tests II

The effectiveness of the non-mydriatic retinal camera as a screening method to detect the presence and severity of diabetic retinopathy has been described in several studies (216; 217). The technique requires only one photograph which includes the papilla and the macula, and is interpreted by professionals. In a study carried out in our field (218), the non-mydriatic 45º retinal camera showed 91.1% of sensitivity and 89.7% of specificity, in contrast to the standard method (biomicroscopic technique with an ophthalmoscope with a 78D lens) and was cheaper for the patient. The non-mydriatic retinal camera is more sensitive than the screening with an ophthalmoscope when compared with seven standardised photographs (217).

Cohort study 2++

In order to establish the optimal interval for retinopathy screening through a photograph from a non-mydriatic camera, a cohort study was carried out across 4,770 type 2 diabetic patients derived from primary care (219). The accumulated incidence of sight-threatening retinopathy, according to the initial level of retinopathy (without retinopathy, mild preproliferative retinopathy, severe retinopathy) was assessed. In patients without initial retinopathy, the retinopathy-accumulated

incidence was 0.3% after the first year and 1.6% after the third year. In patients treated with insulin and those with more than a 20-year evolution of the diseases, the risk was higher. In patients with mild preproliferative retinopathy and severe retinopathy, the incidence after one year was 5% and 16%, respectively, and after three years, 15% and 41.1%, respectively. Based on the 95% probability of remaining free from retinopathy, the authors recommended a periodic control every three years and more frequent controls for those patients treated on insulin or with a more than 20-year long evolution of the disease, as well as for patients with initial retinopathy.

Cohort study 2++

Another retrospective cohort study was carried out within our field with type 1 and type 2 outpatient diabetics, with a non-mydriatic camera in order to establish the optimal screening intervals (220). The type 2 diabetics from this study (n 141) had, in general, a much more advanced diabetes than those from the previous study, as 60% of them presented some degree of initial retinopathy, 69.1% were treated with insulin and the average time of the evolution of diabetes was 13.6 years. In the case of type 2 diabetics without initial retinopathy, the probability of remaining free from high-risk retinopathy was 100% after the first year, 97% (CI 95%: 86-99) at the end of the third year and 92% (CI 95%: 70-98) at the end of the fourth year. In type 2 diabetics with mild non-proliferative initial retinopathy, the probability to remain free from high-risk retinopathy was 100% after the first year, 92% (CI 95%: 78-97) at the end of the second year and 66% (CI 95%: 45-80) at the end of the third year. The retinopathy risk was higher for patients with a more than 10-year long evolution of the disease and for those with poor glycemic control. Based on the results from the study, the authors recommend a three-year periodicity for type 2 patients without retinopathy and two years for patients with mild non-proliferative initial retinopathy. The study contains limitation of the small sample for type 2 diabetics and the difficulty to generalize the results to a population at lower risk.

Cohort study 2+

It must be made clear that it is not possible to discard a macular oedema through a single photograph if there are no other signs, such as hard exudates or haemorrhages. For this reason, stereoscopic assessment with a slit lamp can be required to detect early macular oedemas.

Appendix 6 contains the diagnose algorithms and the treatment of macro- and microangiopathy.

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Evidence summary

2+	The 45º non-mydriatic retinal camera has a higher sensitivity and specificity in comparison to direct ophthalmoscopy (216-218).
2++	In type 2 diabetics who come from primary care and have no retinopathy, the high-risk retinopathy accumulated incidence was 0.3% after the first year and 1.6% after the third year (219).
	In patients without retinopathy coming from hospital, with a longer evolution period and treated with insulin in 58.3% of the cases, the probability of remaining free from high-risk retinopathy was 100% after the first year and 97% at the end of the third year (220).

Recommendations

B	The 45º non-mydriatic retinal camera with a single photograph is recommended as screening method for diabetic retinopathy.
B	For DM 2 patients without retinopathy, a three-year periodicity control is recommended and a two-year periodicity control for patients with mild non-proliferative retinopathy.

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10.2. Diabetic nephropathy

This CPG only deals with patients suffering from nephropathy at a micro- and macroalbuminuria stage; the treatment of advanced renal failure is not considered.

10.2.1. Diabetic nephropathy screening

There have been no clinical trials carried out to assess the impact of microalbuminuria screening in the diabetic population. The NICE CPG (221) recommends screening based on two assumptions: **CPG 4**

- The evidence that the presence of microalbuminuria increases both general and cardiovascular mortality among diabetic patients.
- The benefit of possible interventions in this group at risk, for example, the antihypertensive treatment and glycemic control.

A further SR carried out after the NICE CPG with rigorous methodology, recommends the use of screening based on the same criteria (222). This review contains a meta-analysis of cohort studies proving that diabetes with microalbuminuria implies an increase of general mortality risk [RR 1.9 (CI 95%: 1.7 to 2.1)], cardiovascular mortality risk [RR 2.0 (CI 95%:1.7 to 2.3)] and coronary mortality risk [RR 1.9 (CI 95%: 1.5 to 2.3)]. **SR of cohort studies 2+**

There are no specific assessments on the different screening methods for the clinical evolution of diabetic patients. The reports which have analysed the risk associated with this condition have used different methods (urine in different periods of time) and cut-off points (even according to genre) to define microalbuminuria.

The gold standard diagnosis consists of a 24-hour urine sample under standard conditions, discarding other possible causes which can produce microalbuminuria. The NICE CPG defines microalbuminuria by levels between 30-300 mg/24 hours or 20-200 μg/min in night urine. Higher figures define frank diabetic nephropathy. **CPG 4**

The urine sample during prolonged periods can be cumbersome for patients, thus simpler alternatives are proposed, based on the determination of morning urine, under the same standardized principles as the 24-hour sample. For the screening, the determination of the albumin/creatinine ratio in the first morning urine through laboratory methods or dipsticks is recommended. With this method,

it is believed that microalbuminuria exists with the following figures: [3]2.5-30 mg/mmol in men and 3.5-30 mg/mmol in women (221).

In the case of a positive result, once other possible causes have been excluded (such as urinary infections), it is recommended to repeat the test twice with a monthly interval. Should this method not be available, the NICE CPG recommends the use of specific dipsticks.

Table 8. Classification of diabetic nephropathy

	Albumin in 24-hour urine (mg)	Albumin/creatinine ratio (mg/g)
Normal	<30	<30
Microalbuminuria	30-299	30-299
Proteinuria	≥300	≥300

Summary of evidence

2+	The presence of microalbuminuria in patients with diabetes implies an increase in general mortality [RR 1.9 (CI 95%: 1.7 to 2.1)] and cardiovascular mortality [RR 2 (CI 95%: 1.7 to 2.3)] (222).
4	The NICE CPG recommends an annual screening for microalbuminuria, measured in a morning urine sample through the albumin/creatinine ratio (221).

Recommendations

C	The screening for microalbuminuria at the moment of the initial diagnosis of type 2 diabetic patients is recommended, as well as annual periodicity.
D^{CPG}	The recommended method is the morning albumin/creatinine ratio.
D^{CPG}	Should this method not be available, the determination of microalbuminuria during 12 or 24-hour periods or the use of dipsticks in the morning urine can be useful.

10.2.2. Treatment for diabetic microalbuminuria

Diabetic nephropathy can evolve from the early stage (determined by microalbuminuria) to more advanced stages, developing HBP, macroalbuminuria, renal function decrease and finally, renal failure.

There is conclusive evidence that drugs which block the renin-angiotensin system (ACE-inhibitors or ARB-II) delay the progression to renal failure (223), although a recent meta-analysis states that it might be due to an independent effect of its hypotensive effect (213).

The benefit of ACE-inhibitors has been proved mainly on patients with nephropathy and DM type 1 (both in hypertense and normotensive patients) and in DM type 2 patients with microalbuminuria (223).

SR of RCT
1+

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Regarding the ARB-II, in a clinical trial, irbesartan 300 mg reduced the risk of developing macroalbuminuria in patients with microalbuminuria (224) and in patients with frank proteinuria. In two other trials, losartan and irbesartan reduced the risk of progression to renal failure in patients with microalbuminuria (225; 226). **RCT 1+**

No trials have been found which compare ACE-inhibitors with ARB-II and whose aim is to assess definitive result variables such as death or renal failure.

In a recent Cochrane review (223), it was stated that ACE-inhibitors and ARB-II are effective as regards renal results (terminal renal failure, duplication of serum creatinine, progression from micro- to macroalbuminuria and regression from macro- to microalbuminuria). There seem to be no differences between both drug groups in these results, though there were no direct comparisons between them. ACE-inhibitors and ARB-II did not reduce mortality in contrast to placebo. When analyzed separately, the studies that used full doses of ACE-inhibitors did show a significant mortality reduction [RR 0.78 (CI 95%: 0.61-0.98)], though this did not happen in the studies which used low doses of ACE-inhibitors. As regards the combination of ACE-inhibitors and ARB-II, the studies carried out included few patients and have only assessed intermediate variables such as proteinuria and glomerular filtration, instead of doubling the amounts of creatinine or evolution to renal failure. These RCTs have been recorded in a recent meta-analysis (227) which shows a short-term improvement (12 weeks) of proteinuria with a slight increase in potassium levels. The meta-analysis is heterogeneous in the results and the sensitivity studies carried out indicate that the benefits become visible with suboptimal doses of ACE-inhibitors: they are associated with higher initial proteinuria levels and are related to the decrease rate of blood pressure achieved. **SR of RCT 1+**

In the ONTARGET study (208), which includes diabetic patients with target organ impairment and with microalbuminuria, telmisartan was similar to ramipril. The association of telmisartan with ramipril was not higher than that of each of them separately as regards the reduction of cardiovascular events. The association was worse tolerated and produced a greater frequency of renal deterioration. **RCT 1++**

If, despite everything, a patient is considered eligible for this treatment, he should be referred to specialized care.

As mentioned previously, there is solid evidence on the increased risk in patients with diabetes and maintained microalbuminuria. These patients can be prioritised to receive multifactorial interventions in order to reduce their cardiovascular morbidity. There is a trial (108) which shows that a multifactorial intervention that includes diet, moderate exercise, a therapy to stop smoking, ACE-inhibitors (a dose equivalent to 100 mg of captopril) and losartan in case of intolerance, aspirin 100 mg, blood pressure control with target figures of 130 mmHg, glycemic control with a target of 6.5% of HbA 1c and cholesterol <175 mg/dl, reduces the risk of a combined variable which consists of cardiovascular death, non-fatal AMI, by-pass, angioplasty, strode, amputation and surgery for peripheral arteriopathy [adjusted HR : 0.47 (CI 95%: 0.22-0.74) NNT 5]. **RCT 1++**

This intervention was carried out by a multidisciplinary team (physician, nurse and dietician) at a hospital specialised in diabetes.

Appendix 6 includes the diagnose algorithms as well as the treatment of macro- and microangiopathy.

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Summary of evidence

1++	In hypertense patients with diabetic nephropathy, the treatment with ACE-inhibitors or ARB-II (in comparison with placebo) reduces the risk of progression towards renal impairment (223).
1++	In hypertense patients with diabetic nephropathy, the treatment with ACE-inhibitors at full dosage reduces mortality (223).
1+	The combination ACE-inhibitors + ARB-II has only proved to reduce proteinuria and improve short-term glomerular filtering (12 weeks) in patients with nephropathy and lower creatinine at the expense of producing a slight increase in potassium levels (227).
1++	A multidisciplinary and multifactorial intervention on the different cardiovascular risk factors (HbA 1c <6.5%, systolic blood pressure <130 mmHg, cholesterol <175 mg/dl, aspirin, smoking cessation, diet and exercise) reduces the morbimortality associated with diabetes (108).
1++	In the ONTARGET study (208), which includes diabetic patients with microalbuminuria, telmisartan was similar to ramipril. The association of telmisartan with ramipril did not improve the morbimortality results and provoked more adverse effects, such as renal impairment.

Recommendations

A	Patients with DM and nephropathy (hypertense and normotensive) should be treated with an ACE-inhibitor. The angiotensin receptor blocker - II (ARB-II) is the alternative treatment when ACE-inhibitors are not tolerated.
A	The use of the combination ACE-inhibitor + ARB-II is not recommended.
D^{CPG}	The ACE-inhibitors and ARB-II must be used with caution in patients where there is suspicion of stenosis of the renal artery. Monitorization of the plasma creatinine and potassium should be carried out two weeks after beginning a treatment.
A	Patients with DM 2 and nephropathy are recommended a multifactorial intervention (measures on life style and pharmacological therapy) under the supervision of a multidisciplinary team with appropriate training.

10.3. Diabetic peripheral nephropathy

Diabetic peripheral neuropathy is a symmetric sensorimotor neuropathy which affects mainly lower extremities (foot and ankle) and, on some occasions, upper extremities. It is a frequent complication of DM 2. It is characterized by symptoms such as burning, pressing pain, tingling and allodynia. The main predictors for its occurrence are the duration of diabetes, age and the level of glycemic control (228).

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SR of RCT
1++

The effectiveness of antidepressive drugs, anticonvulsants, opioids, N-Metil-D-Aspartic antagonists, Tramadol and capsaicin was compared in an SR (229) to placebo to assess pain relief. The SR carried out exhaustive research up to October 2006 where it evaluated the quality of the trials and heterogeneity. The review did not consider some comparative studies. The main result was expressed as the OR to achieve approximately 50% relief or a moderate decrease of the pain. These studies lasted less than six months, and for this reason no conclusions can be confirmed on its long-term effectiveness.

Tricyclic antidepressants (amitriptyline, desimipramin, imipramine) or traditional anticonvulsants (carbamazepine, lamotrigin, sodium valproic acid) proved to be more effective in comparison with placebo than SSRI antidepressants (citalopram) or duloxetine and that new anticonvulsants (oxcarbazepine, gabapentin, pregabalin), with a moderate risk of interrupting the treatment due to adverse effects. These are the drugs which have undergone most research. There were three studies with opioids, two minor cross-over studies that assessed the effectiveness of oxycodone and a trial with a parallel design with tramadol. There was only one study for topic capsaicin at 0.075%.

Table 9. **Drugs for painful neuropathy in a diabetic patient (229)**

Drug (N = Number of trials performed)	OR for 50% of pain relief or moderate effectiveness (CI 95%)	OR for interruption due to adverse effects (CI 95%)
Traditional anticonvulsants (carbamazepine, lamotrigin, sodium valproic acid) (N = 4)	5.33 (1.77 to 16.02)	1.51 (0.33 to 6.96)
New generation anticonvulsants (oxcarbazepine, gabapentin, pregabalin) (N = 4)	3.25 (2.27 to 4.66)	2.98 (1.75 to 5.07)
Tricyclic antidepressants (amitriptyline, desimipramin, imipramine) (N = 3)	22.24 (5.83 to 84.75)	2.32 (0.59 to 9.69)
Citalopram (N = 1)	3.5 (0.3 to 38.2)	5.6 (0.3 to 125.5)
Duloxetine 60 mg (N = 1)	2.36 (1.05 to 5.35)	
Duloxetine 120 mg (N = 1)	2.10 (1.03 to 4.27)	4.65 (2.18 to 9.94)
Opioids (oxycodone and tramadol) (N = 3)	4.25 (2.33 to 7.77)	4.06 (1.16 to 14.21)
Capsaicin 0,075% (N = 1)	2.37 (1.32 to 4.26)	4.02 (1.45 to 11.16)

SR of RCT
1+

There are several systematic reviews prior to the Wong review which assess the effectiveness of gabapentin, carbamazepine and opioids (230-233) in neuropathic pain, not only in diabetic polyneuropathy, the results of which are very similar. In the SR on opioids (233), the mid-term studies (from eight days to eight weeks) showed that oxycodone, morphine, methadone and levorfanol were effective in the reduction of neuropathic pain.

However, there are few comparative trials among the different drugs, so the recommendations are mainly based on trials compared to placebo.

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An SR on drugs to treat diabetic neuropathic pain searched for studies where they were compared with placebo as well as comparative studies (the search was carried out up to December 2004), and only five comparative RCTs were found (228). These studies had a reduced number of patients and they lasted between two and six weeks, therefore any possible conclusion is quite limited in terms of validity. The drugs compared were tricyclic antidepressants in contrast to gabapentin, carbamazepine and SSRI antidepressants. No differences were found as regards pain intensity nor in the percentage of patients who gave up the treatment due to adverse effects, with the exception of a study which compared paroxetine with imipramine (plus discontinuance with imipramine).

SR of RCT 1+

Another three further comparative RCTs have been found. A trial done in India compared amitriptyline with lamotrigin on a cross-over study which lasted two weeks (234). No differences were found as regards effectiveness; the adverse effects were more frequent and predictable with amitriptyline (somnolence, anticholinergic effects), while lamotrigin created an increase in the serum creatinine which lead to four patients interrupting the treatment.

RCT 1+

An extension study (235) compared duloxetine 60 mg to the common treatment (mainly gabapentin, amitriptyline and venlafaxine) for 52 weeks, after a double blind period of 13 weeks. No differences in effectiveness or quality of life were observed; duloxetine was well tolerated.

RCT 1-

An RCT (236) compared the combination of morphine with gabapentin to each of the drugs. Pain relief was higher with the association of drugs; the most frequent adverse effects of the combination were constipation, sedation and dry mouth.

RCT 1+

Appendix 7 includes the dosage and most frequent adverse effects of common drugs for neuropathic pain (237).

Summary of evidence

1++	In painful diabetic neuropathy, tricyclic antidepressants (amitriptyline, desimipramin, imipramine) and traditional anticonvulsants (carbamazepine, lamotrigin, sodium valproic acid) have proved to be more effective in contrast to placebo than SSRI antidepressants (citalopram) or duloxetine and that new anticonvulsants (oxcarbazepine, gabapentin, pregabalin), with a moderate risk of interrupting the treatment due to adverse effects. Opioids (oxycodone, tramadol) have proved to be moderately effective, although their adverse effects profile can limit their use in the long-term. Capsaicin proved to be effective in a study (229).
1+	There are few comparative trials between the different drugs and moreover, they contain methodological flaws (low statistical power, short duration, cross-over design). In the comparisons carried out (tricyclic antidepressants vs. gabapentin, carbamazepine, SSRI (228) and lamotrigin (234) or duloxetine in contrast to the common treatment (235)) no differences were observed as regards effectiveness, and, in general, the adverse effects of tricyclic antidepressants were frequent and predictable.
1+	There is limited evidence that the treatment of combined drugs with different action mechanisms can improve its response though it also increases adverse effects (236).

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Recommendations

A	Tricyclic antidepressants and traditional anticonvulsants are the drugs of choice to treat neuropathic pain in diabetic patients. As an alternative (when there is a contraindication of these or they are not tolerated), the use of new anticonvulsants (gabapentin or pregabalin), opioids (such as morphine, oxycodone or tramadol) or duloxetine are recommended.
B	When the response to the treatment is not satisfactory, drugs with different action mechanisms, which monitor the response and adverse effects, can be associated.
B	For milder cases, a topical treatment with capsaicin can be used, assessing its response and the local adverse effects.

10.4. Erectile dysfunction

Erectile dysfunction affects approximately between 34 and 45% of men with diabetes. Risk factors include: old age, inappropriate glycemic control, smoking habit, hypertension, dyslipidemia and cardiovascular disease. Organic causes include: micro- and macrovascular disease and neuropathy. Psychological factors and the drugs prescribed for diabetes can also have an influence (238).

10.4.1. Phosphodiesterase inhibitors

SR of RCT 1++

A recent SR identified eight RCTs on the effectiveness of the phosphodiesterase type 5 inhibitors (FDE-5) vs. placebo in patients with diabetes, 80% of whom suffered from DM 2 (239).

There is solid evidence that FDE-5 inhibitors (sildenafil, tadalafil and vardenafil) are very effective in the improvement of erectile dysfunction in men with diabetes.

The most frequent adverse effect is headache, followed by flush, disorder of the upper respiratory pathways and symptoms similar to flu, dyspepsia, myalgia, abnormal vision and lumbar pain. The risk to suffer adverse effects was 4.8 times higher in patients treated with FDE-5 inhibitors. No significant differences were found as regards stroke frequency.

10.4.2. Apomorphine

RS of RCT 1+

A review in which research lasted until September 2005 (204) found four RCTs vs. placebo, one of which was carried out on diabetic patients (241) and two open comparative trials vs. sildenafil. Sublingual apomorphine is more effective than placebo; 45% of men have normal erections in contrast to 29% in the placebo group [RR 1.4 (CI 95%: 1.3 to 1.7), NNT 6.6 (5.0 to 9.6)]. It is far less efficient in comparison with sildenafil. In a study carried out across 130 diabetic patients

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(241), the response rate to placebo was 17% in contrast to 22% with apomorphine, a difference which is not significantly relevant, and therefore, this drug has a limited use for these patients.

The most frequent adverse effects were nausea, dizziness, headache and somnolence, which tend to improve with continuous use of the treatment (242; 243). A study assessed specifically its cardiovascular safety in patients treated with antihypertensive drugs or nitrates. There were no clinically relevant changes in blood pressure nor in cardiac frequency in those patients taking short-acting nitrates. Men who were taking long-acting nitrates underwent changes in their blood pressure when seated, though not when in a supine position. Apomorphine could be safer than FDE-5 inhibitors in men treated with nitrates (242).

10.4.3. Intracavernosal alprostadil

Intracavernosal alprostadil is effective vs. placebo in that it improves erectile dysfunction. A minor study showed no differences between intracavernosal alprostadil and sildenafil. The most frequent adverse effect of alprostadil is penile pain, which affects 40% of the patients (242).

RCT 1+

10.4.4. Psychosocial interventions

A recent Cochrane review has analysed the randomised or quasirandomised studies which assess the effectiveness of psychosocial interventions in erectile dysfunction among the general population and this included diabetic patients.

SR of randomised and quasi-randomised studies 1+/2+

Statistical heterogeneity was found. The authors stated that psychotherapy can be more effective, but the response to the treatment varies among the subgroups. Group therapy proved to be more effective than the waiting list control. The combination of sildenafil with group therapy was more effective than that with sildenafil alone (244).

Evidence summary

1++	There is solid evidence that phosphodiesterase inhibitors (sildenafil, tadalafil and vardenafil) are very effective in the improvement of erectile dysfunction for men who suffer from DM 2 (239).
1+	Sublingual apomorphine is more effective than placebo among the general population with erectile dysfunction, though far less effective in comparison to sildenafil (240). In the only study carried out in diabetic patients, apomorphine did not prove to be more effective than placebo (241).
1+	Intracavernosal alprostadil is effective vs. placebo in the improvement of erectile dysfunction. A minor study showed no differences between intracavernosal alprostadil and sildenafil. The most frequent adverse effect was penile pain, which affects 40% of the patients (242).

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1+	Group psychotherapy can be more effective for specific people, as the response may vary. Group therapy is more effective than the waiting list control. The combination of sildenafil with group therapy is more effective than sildenafil alone (244).

Recommendations

A	FDE-5 inhibitors are the drugs of choice for erectile dysfunction in patients with DM 2.
B	In case of contraindication or intolerance to FDE-5 inhibitors, the alternative drugs are as follows: Intracavernosal alprostadil (tolerance and acceptability problems) or apomorphine (doubtful effectiveness). The patient's preferences and response to the treatment have to be taken into consideration.
B	In selected patients where it is not possible or desirable to use pharmacological therapy, psychotherapy can be recommended.
√	FDE-5 inhibitors are contraindicated for patients who take nitrates to treat angina.

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11. Diabetic foot. Assessment, prevention and treatment

The questions to be answered are the following:

- Should a diabetic foot screening take place? How often? Sith which method?
- Which are the most effective preventive measures to avoid diabetic foot complications?
- What is the efficacy of the interventions to treat diabetic foot ulcers?

11.1. Introduction. Risk factors

Diabetic foot comprises a group of syndromes where the presence of neuropathy, ischemia and infection provoke tissue wounds or ulcers due to minor traumatisms, thus increasing morbidity which can even lead to amputations.

Most of those suffering from diabetic foot also have peripheral arterial disease. Ischemia and infections can also exist (245).

Neuropathy is a microvascular complication which produces a loss of sensitivity in the foot, and fosters deformities, abnormal pressure, injuries and ulcers. Ischemia is produced by peripheral vascular disease. Generally, infection complicates both neuropathy and ischemia (245).

Diabetic foot ulcers can be predictable using an appropriate strategy which includes screening, risk classification and effective prevention and treatment measures (246).

Observational studies 2+

These are modifiable risk factors associated with the development of diabetic foot and their consequences are as follows: peripheral vascular disease, neuropathy, foot deformities, high plantar pressure, plantar callus or smoking habit (246).

Other ulcer risk factors in diabetic foot are: prior foot ulcer [RR 1.6], prior amputation of the lower extremity [RR 2.8], evolution time of diabetes (10 years) [OR 3.0)], poor glycemic control (HbA 1c >9%) [OR 3.2], and poor sight (visual acuity 20/40) [RR 1.9] (247).

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11.2. Methods to assess the foot at risk

11.2.1. Neuropathy

The studies of nerve conduction are considered the reference pattern to diagnose peripheral neuropathy, but this technique is not available for generalized use.

A recent SR (247) has analysed the diagnose capacity of other simpler and more accessible methods:

Monofilament

In three prospective studies, the monofilament identified patients with high ulceration risk, with a sensitivity from 66% to 91% and a specificity from 34% to 86%, a positive predictable value from 18% to 39% and a negative predictable value from 94% to 95% to predict the evolution to ulcer.

Studies of diagnostic tests
II

The test is carried out with the 5.07 SWM (10 g) monofilament pressing on four plantar points in each foot: first toe (distal phalanx) and the base of the first, third and fifth metatarsal (247; 248). The test is considered positive when there is at least one insensitive point (248).

The monofilament cannot be used in more than 10 patients without a 24-hour recovery period (247).

Appendix 8 describes the use of the monofilament.

Tuning fork

It is a simple and cheap method to measure vibratory sensation (247), though it has reliability problems. It is less accurate as regards ulcer prediction (248) than the monofilament. It can be used as an alternative if there is no monofilament available.

Biotensiometer

The biotensiometer exceeds the reliability limitations of the tuning fork as it can regulate the different vibration thresholds. A vibration threshold over 25V has 83% of sensitivity, 63% of specificity, a positive likelihood ratio (+LH) of 2.2 (CI 95%: 1.8-2.5), and negative likelihood ratio (-LH) of 0.27 (CI 95%: 0.14-0.48) to predict foot ulcer after four years (247). This technique is not available on a general basis within our field.

Studies of diagnostic tests
II

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11.2.2. Peripheral arterial disease

The methods most frequently used to diagnose peripheral artery disease are the ankle-arm index (AAI) by Doppler (or otherwise a sphygmomanometer) and clinical exploration.

An AAI at 0.09 or less suggests peripheral arterial disease, whereas an AAI at 1.1 can represent pressure which has been falsely increased due to arterial calcifications. The test is easy, objective and replicable (247). On some occasions an AAI cannot be done because there is no technical team available or there is not enough time or staff to do it.

SR of studies of diagnostic tests II

An SR has analysed the validity of the clinical and physical exploration assessment in the diagnose of peripheral arterial disease (PAD) in symptomatic patients (patients who consult due to symptoms which may suggest PAD) and asymptomatic (patients who do not consult on this issue) (249).

In symptomatic patients, the most useful clinical findings to confirm DAP are the existence of intermittent claudication [+LH 3.30], femoral murmur [+LH 4.80], or any abnormal pulse [+LH 3.10]. To discard PAD, the most useful findings were the inexistence of claudication [-LH 0.5] or normal pulse [-LH 0.44]. In symptomatic patients, the most useful findings were skin coldness [+LH 5.90], the existence of at least one murmur [+LH 5.60) or any pulse anomaly [+LH 4.70]. The inexistence of murmurs (iliacus, femoral, popliteal) [-LH 0.39] or normal pulse [-LH 0.38] reduce the probability of DAP. The combination of clinical findings does not improve the diagnostic performance of the individual findings to confirm the disease, though it can be useful to discard it (249).

When there are difficulties to carry out the AAI, it can be done only on patients with symptoms of abnormal physical exploration or those who have suffered a cardiovascular event.

11.3. Effectiveness of the screening and prevention programs for diabetic foot

RCT 1+

The NICE guideline recommends screening, based on a clinical trial (250) with a diabetic foot screening and protection program carried out in 2001 on DM 2 outpatients which identified 192 patients at high risk. These patients were randomised to receive an intervention program (weekly visits to the chiropodist and hygiene maintenance, protective footwear and education on daily care) in contrast to common care. In the intervention group a slightly significant trend was observed towards fewer ulcers and minor amputations as well as significant reductions in major amputations after two years. The patients who already had ulcers gradually had fewer amputations. The intervention was cost-effective.

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No subsequent RCTs have been found which analyse the impact on the complications of diabetic foot. In an RCT carried out in primary care centres (251), a structured program which was revised on an annual basis, identified and treated patients at high risk, improved the knowledge and attitudes of patients and professionals as well as the use of services.

Observational studies 2+

In contexts different to the one presented in this guideline, there are several studies with less solid design, such as before-after studies (252) or prospective studies (253) which assess the impact of programs that include screening, risk stratification, preventive and treatment measures depending on the risk and which have proved to reduce the incidence of amputations. In these studies screening is carried out by chiropodists and trained nursing staff, who normally belong to multidisciplinary teams, or by foot or diabetes specialized units with structured programs.

In the studies reviewed (250; 253), the following methods were used to identify patients at high risk:

- Close visual inspection of the foot to identify deformities, hyperkeratosis, inappropriate footwear or the existence of prior amputations.
- Arteriopathy evaluation: observation of the skin colouring, temperature, presence of pulses, pain when walking, determination of the ankle-arm index.
- Sensory neuropathy evaluation through the monofilament test.

The NICE guideline (246) recommends the classification of the risk into four categories depending on the risk factors.

CPG 4

Table 11. Classification of diabetic foot risk. Recommended frequency of inspection

Risk (Classification)	Characteristics	Frequency of inspection
Low risk	Maintained sensitivity, palpable pulses	Annual
Increased risk	Neuropathy, absence of pulses or any other risk factor	Every 3-6 months
High risk	Neuropathy or absent pulses together with deformity or changes in the skin Ulcerate foot	Every 1-3 months
Ulcerate foot		Individualized treatment, possible referral

In Spain, the implementation of these interventions can be limited. The screening and risk stratification activities are feasible, though there are no equivalent and structured facilities to refer to and treat the foot at risk, as these vary among the different Autonomous Communities. The current barriers to implement appropriate diabetic foot prevention and treatment are mainly a lack of organization and training.

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11.4. Other preventive measures

The most effective measure to prevent diabetic foot complications are the screening and treatment programs on the foot at risk. Other measures used are as follows:

11.4.1. Education

A Cochrane review (254) found nine methodologically poor RCTs on the effect education had on diabetes to prevent ulceration of the diabetic foot. Only one study which included patients at high risk presented a reduction in the incidence of ulcers [OR 0.28 (CI 95%: 0.13 to 0.59)] and in the amputation rate [OR 0.32 (CI 95%: 0.14 to 0.71)] after one year. The patient's short-term education seems to affect positively the acknowledgment on foot care and the patient's behaviour.

SR of RCT
1+

11.4.2. Smoking cessation

Some studies have proved a direct causal relation. Case-control studies and transversal studies have proved that smoking is an amputation indicator (247).

Observational studies
2+/3

11.4.3. Intensification of glycemic control

The UKPDS 33 study proved that intensive glycemic control was effective to reduce microvascular complications and lead to the reduction of amputations (106).

RCT
1+

11.4.4. Therapeutic footwear, orthopaedic material and measures to relieve pressure

A Cochrane SR (updated in May 2000), based on four RCTs, assessed the effectiveness of the measures which reduce plantar pressure for the prevention and treatment of diabetic foot. A trial stated that therapeutic footwear reduced the incidence of ulceration [RR 0.47 (CI 95%: 0.25- 0.87), NNT 4 (CI 95%: 2-14)]. Another study compared different corrective footwear with plantar padding or pads in the contact surface area without finding any differences as regards the incidence of callus or ulcers. A subsequent RCT carried out across 400 diabetic patients and with prior ulcer but no significant deformities in their feet, proved that therapeutic footwear did not reduce ulcer recurrence in comparison to conventional footwear (255). An observational study concluded that, in patients with prior ulceration, the relapse risk was lower if therapeutic footwear was used (256).

RCT and observational studies
1+/ 2+

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These inconsistencies suggest that patients at low complication risk (without relevant deformities) can use common footwear (well adjusted, and of good quality) while patients with severe foot deformities could benefit from therapeutic footwear (247).

Evidence summary

II	The monofilament test has a sensitivity which ranges from 66% to 91% and a specificity that ranges from 34% to 86% to predict ulcer risk (247).
II	The tuning fork is more inaccurate and has a lower predictive capacity for ulcer risk than the monofilament (247; 248).
II	Biotensiometer: a vibration threshold over 25V has an 83% of sensitivity, 63% of specificity, a 2.2 +LH and a 0.27 –LH to predict foot ulcer after four years (247).
II	In patients with symptoms which suggest the existence of PAD, the findings of absence of iliac, femoral or popliteal murmurs, normal pulse, as well as the combination of these symptoms, are useful to discard the disease (249).
II	The ankle-arm index of 0.90 or less suggests peripheral arterial disease (247).
1+	Screening within a foot care structured program reduces ulcers and minor amputations slightly, and major amputations after two years significantly; in patients with ulcers, the evolution to amputations decreases (250).
2+	In contexts different to the one presented in this guideline (252; 253), the programs which include screening, risk stratification and preventive and treatment measures depending on the risk, have managed to reduce the incidence of amputations.
1+	There is limited evidence that education addressed to the patient can improve his knowledge about foot care and his attitude. In a trial carried out in patients at high risk, education reduced ulcer and amputation incidences after a year. Other studies have not stated any benefits (254).
2+/3	Smoking is an amputation risk indicator (247).
1+	The UKPDS study proved that intensive glycemic control was effective to reduce microvascular complications and led to the reduction of amputations (106).
1+/2+	Therapeutic footwear and orthopaedic material can reduce the incidence of ulceration in patients at risk with prior ulcers and severe foot deformities (255; 256).

Recommendations

A	Screening, risk stratification and foot at risk prevention and treatment-structured programs are recommended for diabetic patients.
D^{CPG}	The professional staff that attends diabetic patients should assess the risk to develop diabetic foot in the control visits. Annual revision is recommended for patients at low risk, every three to six months for patients at moderate risk and every one to three months for high-risk patients.

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B	Diabetic foot screening must include: inspection of the foot and soft tissues, footwear assessment, musculoskeletal exploration, assessment of peripheral arterial disease complemented with the determination of the ankle-arm index in some cases and sensitivity assessment through the monofilament or alternatively, through the tuning fork.
D[CPG]	More control is recommended for elderly patients (>70 years), with long-term diabetes, residential patients, patients with sight problems, smokers, patients with social problems or who live alone.
B	Education on diabetic foot care is recommended, based on a structured educational program with different components in order to improve knowledge, enable self-care and reduce the complications risk.
B	Patients with prior ulcers without significant deformities can use common footwear (well adjusted and of good quality), while patients with deformities can benefit from therapeutic footwear.
√	Training on diabetic foot for professional staff that attend these patients should be encouraged.

11.5. Treatment for diabetic foot ulcers

Most foot ulcers appear in patients with neuropathy and ischemia.

The measures to treat these are based mainly on: how to cover the wound properly, treat the infection and relieve the pressure.

People with diabetes who have had prior ulceration should take special care in their foot hygiene and care as well as wear appropriate footwear (258). The great challenge is to prevent recurrences, as their rate in patients who have suffered ulcers is 66% after 5 years (257).

The Wagner ulcer classification is recommended (259).

11.5.1. Dressings

Dressings protect ulcers from possible traumas, absorb the exudate and can heal the infection. Ideally, these should be sterile and non-adherent, able to absorb the exudate, remain in place while walking and facilitate the wound inspection (260). **CPG 4**

Hydrogels, used as debridement agents, have proved to be significantly more effective than gauze or standard care as regards healing of diabetic foot ulcers (261). **SR of RCT 1+**

Despite the general use of dressings and topical agents which contain silver to treat diabetic foot ulcers, a Cochrane review did not find any RCT which assessed its effectiveness (262). **SR of RCT 1+**

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The new dressings (hydrocolloid dressings, polyurethane, sodium alginate, activated carbon and collagen dressings) have proved to be better than the classical saline gauze dressings in leg venous ulcers (263) though there are no adequate studies on diabetic foot ulcers.

There is an ongoing RCT, which compares simple dressings to iodine-impregnated dressings and hydrofiber dressings in 350 diabetic patients with chronic foot ulcers (264).

11.5.2. Debridement

In neuroischemic ulcers, the guidelines recommend the elimination of the necrotic tissue (246; 260). In the case of severe ischemia, debridement must be done very carefully as it is absolutely essential that the viable tissue remains undamaged (265). **CPG 4**

A Cochrane review (261) found five RCTs (amongst them three on hydrogels and one on surgical debridement). The RCT on surgical debridement was brief and its results were not conclusive. Hydrogels, used as debriding agents, are significantly more effective than gauze or standard care to heal diabetic foot ulcers. Other debridement methods, such as enzyme preparations or polysaccharide granules, have not been assessed on diabetic patients in an RCT. **SR of RCT 1+**

11.5.3. Off loading devices

An SR (258) found that total contact weight relieving splints were more effective to heal non-infected ulcers than traditional bandages [RR 2.87 (CI 95%: 1.46-5.63) NNT 2], without any differences in the incidence of hospitalization. Total contact splints seem to be effective to treat plantar ulceration. These may not be fully tolerated. In order to be reliable, they must be carried out by trained experts, apart from requiring revisions and frequent changes, thus limiting their usefulness. In the SR, no studies were found on non-fixed splints. **SR of RCT 1+**

Afterwards, two RCTs were found which compared fixed splints to non-fixed or pads (266; 267); fixed splints were more effective. Another trial (268) found no differences between total contact splints and non-fixed splints transformed into fixed splints by a fibreglass covering. In another trial, the weight-relieving splints covered with foam dressings were more effective than medium pads (269). Fixed splints are associated with a significant increase in infections which require the use of antibiotics and more maceration of the surrounding skin (266). Total contact splints are contraindicated in case of osteomielytis or infection. **RCT 1+**

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11.5.4. Antibiotic treatment for infected ulcers

Most chronic diabetic foot ulcers are colonized by microbiological flora, which includes aerobes (*S.aureus, S.epidermidis, Staphylococcus spp, Enterococcus spp, Pseudomonas aeruginosa, Proteus mirabilis* and others), anaerobes (*Bacteroides, Peptostreptococcus* and *Peptococcus*) as well as fungus (259). The relationship between ulcer bacterial colonization and healing has not yet been established, and most of the documentation released is related to venous ulcers (259).

SR of RCT 1+

The determination of infected diabetic foot ulcers requires several clinical aspects to be taken into consideration, such as the optimization of glycemic control, surgery (debridement, drainage or revascularization) as well as the treatment of infections associated with soft tissues or osteommielytis (259).

Infection diagnosis

An SR (259) includes minor studies on the relevance of clinical signs to diagnose an infection and on the importance of the culture, though these were carried out on venous ulcers in the legs rather than on diabetic foot ulcers, therefore their validity is limited.

SR of studies of diagnostic tests II

In comparison with the biopsy (reference test), no clinical infection sign can diagnose infection with certainty. It is worth mentioning the almost null value of the presence of pious exudate to classify an ulcer as infected.

The culture has a limited value in contrast to the biopsy. Its sensitivity is 70% and its specificity 60% (+LH 1.96, -LH 0.36).

Effectiveness of antibiotic treatment (ATB)

An SR includes 23 clinical trials, all of them on patients with diabetic foot ulcers – the studies had to include at least 80% of patients with diabetic foot ulcers- both outpatient and inpatient. In general, the quality of these studies was poor and some were statistically irrelevant.

SR of RCT 1+

Intravenous antibiotics (IV)

No studies were found which were compared to placebo or oral or topical ATBs. Eight RCTs compared different ATBs (imipenem/ cilastatin, penicillins associated with beta-lactamase inhibitors, cephalosporins, linezolid, piperacillin / clindamycin, etc.) with no solid evidence in any ATB schedule being superior to any other. In these studies, in general, the patients were offered debridement and standard dressings.

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Oral antibiotics

Five studies were found, some of them minor, one on amoxicillin-clavulanic vs. placebo, two between different oral ATBs and two vs. topical ATBs. There is not enough evidence to recommend an ATB in particular, as no significant differences were observed between the active treatments nor vs. placebo.

Topical antibiotics and antiseptics

Five studies were found. No differences were found between cadexomer iodide and the treatment with topical gentamycin and enzymes, nor between antiseptics and eosin, nor between topical sugar vs. systemic ATB. Hydrogels were more effective to heal ulcers in contrast to gauzes irrigated with chlorhexidine.

11.5.5. Colony stimulating factors

SR of RCT 1+

A meta-analysis (270) was found which includes five RCTs with a total of 167 diabetic patients with foot infections, most of them severe (extensive cellulitis, infections which affect the extremities) as well as minor ulcers (levels 2-3 from Wagner). The introduction of colony stimulating factors to the common treatment was not effective in the main outcome of the healing either of the wound or of the resolution of the infection. However, it reduced the amputation risk [RR 0.41 (CI 95%: 0.17-0.95), NNT 8.6] as well as invasive surgical interventions [RR 0.38 (CI 95%: 0.20-0.69)]. As regards the limitations, it was carried out on a small number of patients and the infections were severe in general (270).

The role of these factors within the diabetic foot treatment requires new studies, thus this is an area to be researched in the future.

Summary of evidence

1+	There is no trial that assesses the effectiveness of silver dressings (262).
4	Current evidence is insufficient to support the effectiveness of any type of protective dressing over another in diabetic foot ulcers (246).
1+	There are not few studies on the role of surgical debridement (261). Hydrogels used as debriding agents are significantly more effective than gauze or standard care as regards the healing of diabetic foot ulcers. Other debridement methods such as enzyme preparations or polysaccharide granules have not been analysed in RCTs with diabetic patients (261).
1+	Total contact splints or fixed fibreglass splints are more effective than traditional bandages, non-fixed splints, medium pads or special foot wear in the healing of ulcers (258; 266; 267; 269).
4	Total contact splints are associated with an unacceptable risk factor in patients with severe ischemia (246).

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2+	The culture has a limited value in contrast to the biopsy. Its sensitivity is 70% and its specificity 60% (+LH 1.96, -LH 0.36) (259).
1+	It has not been confirmed that systematic or local antibiotic treatment is effective in the healing of ulcers and if some ATBs or patterns are better than others (259).
1+	In diabetic patients with foot infections, most of them severe (extensive cellulitis, infections which affect the extremities), the introduction of colony-stimulating factors to common treatment was not effective in the main outcome of the healing of the wound nor the resolution of the infection. Amputation risks as well as invasive surgical interventions were reduced. These data require further confirmation (270).

Recommendations

D	In diabetic foot ulcers, the necrotic tissue should be removed through surgery for the healing process to be easier. The use of hydrogel dressings as debriding agents can be recommendable to make the healing easier. In case of severe ischemia, the patient should be referred.
A	Total contact splints are the devices chosen to reduce plantar pressure in diabetic patients with non-infected and non-ischemic foot ulcers.
B	Fixed fibreglass splints are an alternative to total contact splints, as they require less time and less professional staff.
C	Routine culture is not recommended for diabetic foot ulcers, as its diagnostic value is limited.
D^{CPG}	Patients with progressive ulcers which do not heal and with clinical signs of active infection, should receive systematic antibiotic treatment.
D^{CPG}	If an antibiotic is used, when choosing it, the potential microorganisms as well as the local resistance patterns should be taken into consideration, as regards broad-spectrum antibiotics which cover aerobes and anaerobes.
D^{CPG}	If there is no solid evidence of clinical effectiveness or cost-effectiveness, the health professionals should use dressings which adapt best to their clinical experience, the patients' preferences or the location of the infection, without forgetting the cost.
B	More studies are required to establish the role of colony-stimulating factors in patients with diabetic foot infections.

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12. Diabetologic education

The questions to be answered are the following:

- Which are the aims and contents of the education addressed to patients with DM 2?
- Is the education addressed to patients with DM 2 effiective?
- How should education be addressed to patients with DM 2 in primary care and in specialist care?
- Is self-management effiective for patients with DM 2 (with components such as weight self-control, self-monitoring of blood glucose, foot or blood pressure)? What should the content of the self-management program include?
- Is self-monitorin of blood glucoseg effectivet in patients with DM 2, treated with insulin and not treated with insulin?

Education is considered an essential element in the diabetic patient's care. People with diabetes, whether they use insulin or not, have to assume the responsibility of controlling this disease on a daily basis. Thus, it is vital that they understand the disease and know how to deal with its treatment (271).

Structured education for patients is understood as a planned and progressive program which is consistent with the aims to be achieved, flexible with the content, which covers the individual and psychological clinical needs and that is adaptable to the cultural context and literacy of each patient.

12.1. Aims of diabetologic education

The aim of education for people who suffer from diabetes is to improve their knowledge and abilities, empowering them to assume control over the disease and integrate self-management in their daily lives (271).

The specific aims of education are to achieve improvements in the following areas (6; 271):

- Control risk factors, including blood glucose, lipids, blood pressure and smoking.
- Manage those complications associated with diabetes.
- Diabetic foot care.
- Quality of life.
- Glycemic control.
- Involve the patient in his own care and encourage his autonomy (self-control).

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- Promote healthy lifestyles: diet, weight control and physical exercise.
- Adherence to the medical treatment.

12.2. Effectiveness of educational intervention and diabetes self-management

Many SRs have assessed the impact of education addressed to DM 2 patients. The duration of these conditions, the contents, the educational styles, the professionals and the contexts assessed vary a lot within the different studies, which hinders the drawing of conclusions on the really effective elements of education. Other SRs have focused on self-management evidence or on specific educational elements, beyond education.

12.2.1. Education

Generally speaking, education in diabetes improves glycemic control to a certain extent and can have a beneficial impact on other outcomes (weight loss, quality of life, etc.) (79; 272-274).

The interventions that consider the patients' active role to take informed decisions improve self-care and metabolic control (275). Most of the decisions which affect the diabetes outcomes take place in the patient's space (choosing the diet and exercise, adherence to the medical treatment, self-analysis, etc.). Therefore, if professionals take into consideration the aims of the treatments of the patients, and provide them with tools and support to solve their problems within their own space, then the clinical measures will be more successful (276).

SR of RCT 1+

12.2.2. Self-management: individual and group measures

Self-management of diabetes has shown to consistently improve glycemic control (277-279). The findings on other outcomes (weight, blood pressure, lipid profile, etc.) have been variable. The Chodosh review offered a clinically relevant effect in the reduction of HbA 1c (0.81%) among adult patients, with no differences as regards weight (278).

Group training in self-management of DM 2 patients has shown to be very effective to improve glycemic control, knowledge on diabetes, self-care abilities, BP reduction, weight and the need for mid and long-term medical treatment for diabetes (NNT 5). There was only one trial which compared individual education vs. group education and proved that the latter was more effective (280).

SR of RCT 1+

In a clinical trial which was not included in the previous review and which was carried out in Spain (281), with 78 DM 2 patients from primary care, both group and individual educational interventions proved to be effective to improve

RCT 1+

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metabolic control (with significant clinical improvements), blood pressure targets, knowledge on diabetes and the lipid profile after a year. The trial had lowr statistical power to detect differences between the two groups.

12.2.3. Self-monitoring of blood glucose

Patients treated with insulin

In the patient treated with insulin the evidence to recommend the use of self-monitoring and self-adjustment of insulin comes from observational studies (282; 283) as well as from the benefits observed in DM 1 patients, as the information on the glucose level is useful to adjust insulin dose, thus, managing to improve glycemic control.

Observational studies 2+

Patients not treated with insulin

In type 2 diabetic patients not using insulin , the use of SMBG is more controversial and the results of the trials are inconsistent. Two SRs and three RCTs have been selected.

The Cochrane review (284) carries out an SR which includes seven RCTs on non-insulin DM 2 patients. There is no meta-analysis. The authors conclude that there is moderate evidence to prove that SMBG can be effective to improve glycemic control; the results of the individual RCTs are quite different from each other. In general, these studies are carried out in highly motivated patients and within a self-management context with more elements than the SMBG.

SR of RCT 1+

An SR with meta-analysis (286), self-management with SMBGs was better than self-management without SMBG in the case of non-insulin DM 2 patients (reduction of 0.39% in the HbA 1c).

SR of RCT 1+

Recently, in a high quality RCT carried out in primary care (287) with 453 DM 2 patients with acceptable metabolic control (baseline average HbA1c of 7.5%) no significant differences were observed in HbA 1c after 12 months between standard care (HbA 1c controls every 3 months and treatment review), less intensive SMBG (self-monitoring, contacting the physician abnormal values) and intensive SMBG with self-management (additional training to interpret results and maintaining compliance with lifestyles, diet and exercise as well as with medical treatment). The frequency of SMBG was twice a week with two daily determinations. The average age of the patients was 65.7, with an average of three years of evolution of the disease, treated with diet or oral antidiabetics.

RCT 1++

In an RCT carried out in Spain (289) no statistically significant differences were found in the percentage of patients that improve glycemic control, although the trend was favourable for sSMBG. In the logistic regression, it was concluded that the number of years of evolution of the disease and poor control of the same, are signs which provide a positive response to self-analysis.

RCT 1+

The patients with the lowest HbA1c baseline levels could benefit more from SMBG (288).

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In another recent RCT (289), sMBG was not effective to reduce HbA1c in DM 2 patients who were newly diagnosed or under the age of 70. SMBGs was associated with worse outcomes in the depression subscale of a quality of life questionnaire.

RCT
1++

Appendix 9 provides information on the contents of diabetologic education as well as additional material for patients.

Summary of evidence

1+	Education in diabetes improves glycemic control to a certain extent and can have a beneficial impact on other outcome variables (weight loss, quality of life, etc.) (79; 272-274).
1+	The measures which include an active role of the patients to take informed decisions improve self-care and glycemic control (HbA 1c) (275).
1+	Group training on self-care strategies for DM 2 patients is very effective to improve glycemic control, knowledge on diabetes and self-care abilities, as well as to reduce blood pressure, body weight and the need to treat mid and long-term diabetes (280).
1+/1++	Self-management of patients with diabetes improves glycemic control (277-279). The findings on other results suffer more variations (weight, blood pressure, lipid profile, etc.). The Chodosh review (278) (of better quality), showed a clinically relevant effect on the reduction of HbA1c (0.81%), without any weight differences.
2+	In the insulinised patient, the evidence to recommend the use of SMBG and insulin dose self-adjustment comes from observational studies (283; 283), as the information on the glucose level is useful to adjust the insulin dose, thus providing better glycemic control (284).
1+	In diabetic patients not using insulin, the results are inconsistent. SMBG has shown some effectiveness in the improvement of glycemic control in some studies (284; 286). Normally, the studies are carried out across motivated population and within the context of self-managementl with more elements than SMBG (285).
1++	In DM 2 patients from primary care with acceptable glycemic control, no significant differences were observed in HbA1c between standard care (HbA1c controlwith treatment review every 3 months), less intensive SMBG (contacting the physician if any abnormal values) and intensive SMBG with self-management (additional training to interpret the results and maintain adherence to life styles, diet and exercise as well as to medical treatment) (283; 288).
2+	Patients with lower HbA 1c baseline levels could benefit more from SMBG (287; 289).
1++	Self-analysis has not proved to be more effective in the reduction of HbA1c in newly diagnosed DM 2 patients under 70 and it has been associated with a negative impact on their quality of life (289).

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Recommendations

A	People with diabetes should be provided with structured education when diagnosed and, afterwards, on a regular basis, depending on their needs which are to be revised regularly.
D	Different learning techniques are recommended, adapted to their personal preferences and integrated within their future everyday care.
B	Primary and specialized care teams should boost programs directly addressed to encourage the patients' participation, adapted to their preferences and aims and which include contents related to their personal experiences.
A	DM 2 patients should be recommended to carry out self-management of the disease by fostering the participation of the patient.
B	The components of self-management can vary; but, in general, it must include knowledge of the disease (definition, diagnose, importance of good control), dietary and pharmacological treatment, physical exercise, ways to approach complication, foot self-care and SMBG with an adjustment of the treatment in selected patients.
A	It is highly recommended that group education for self-care be carried out by trained professionals.
D	In our field, we recommend that these programs be carried out by the nursing staff, both in primary and specialized care.
C	SMBG is recommended for the diabetic patient using insulin to adjust insulin dose .
D	The frequency of SMBG in insulin patients depends on the characteristics of the patient, the aims to be achieved and the type of insulin.
A	SMBG is not recommended for non-insulin DM 2 patients with acceptable metabolic control and for newly diagnosed patients.
B	In specific patients with inadequate glycemic control, SMBG can be offered within an educational and self-management structured program with a regular follow-up. To this end, the patient's level of motivation, his abilities and preferences are to be taken into consideration, as well as the frequency of hypoglycaemias, the type of medical treatment used and the costs.
D^{CPG}	SMBG can be offered to non-insulinDM 2 patients in order to: provide information on hypoglycaemias, assess glycemic control after changes in medical treatment or life style and monitorize the changes during intercurrent diseases.

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12.3. Contents and methods of an educational program

The contents of educational programs must be adapted to the needs of each patient. Table 12 includes the components which a self-control program should include:

Table 12. Contents of a self-control educational program for diabetic patients (modified by GEDAPS) (6)

• Information on the disease (what is diabetes, types of diabetes, risk factors)
• Diet
• Physical exercise
• Severe and chronic complications of diabetes
• Tobacco
• Diabetic foot
• Oral drugs*: compliance with the treatment, dealing with adverse effects. Hypoglycaemia
• Insulin*: schedules, techniques, dose adjustment. Hypoglycaemia
• Self-monitoring of blood glucose (selected patients)
• Special situations: journeys, incurrent diseases, etc.

* Depending on the treatment followed by the patient.

Communication is the basis of the educational process and for this reason, the following points are to be considered (6):

- It is two-way communication, both verbal and non-verbal.
- The first step has to be the assessment of the knowledge, beliefs, attitudes and capacities of the patient.
- The educational content must be adapted to the learning capacity of the patient, without presenting more than three different concepts per session.
- The language used must be clear and adapted to the patient.
- The session must be complemented with supporting educational material.
- The content must be progressive depending on the needs of the patient, giving priority to the most relevant aspects which are to be modified.

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13. Organization of the medical consultations with a DM 2 patient

The questions to be answered are the following:

- Which are the referral criteria to a specialized consultation?
- Which is the initial treatment for adults with DM 2?
- Which are the acceptable control criteria proposed for patients with diabetes?
- Which is the content of the periodic control in medical and nursing consultation?

Expert opinion 4

The basic care unit of the diabetic patient consists of medical and nursing professionals. Both have to work together in coordination to formulate the aims and organize activities. The diabetic patient must perceive clearly the idea of a team, where each professional has different assigned tasks in order to guarantee global care.

13.1. Content of the nursing consultation

The nursing staff plays and essential role in the control and education of the diabetic patient.

The content of the nursing consultation is summarised in table 13.

Table 13. Content of the nursing consultation

Anamnesis • Hypoglycaemias (number and circumstances) • Symptoms of hyperglycaemia (polyuria, polydipsia) • Cramps and paresthesias • Intermittent claudication. Thoracic pain. • Feet wounds • Tobacco consumption
Compliance assessment • Diet • Exercise • Pharmacological treatment • Foot hygiene and care • Therapeutical aims (treatment and education)
Exploration • Weight (BMI) • Feett exploration • Blood pressure (decubitus and orthostatism) • Capillary blood glucose (only when necessary) • Assessment of the puncture areas

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Assessment of self-management record • Capillary blood glucose . SMBG: frequency and techniques • Record of hypoglycaemias • Weight
Diabetologic education • Initial educational program • Minimum advice to stop smoking • Annual enhancement interventions

13.2. Content of the medical consultation

An anamnesis, a full physical examination and an analytic determination are to be carried out on an annual basis to assess the existence of complications (see table 14).

Expert opinion 4

Every six months or every year, an assessment of the control and therapeutic plan aims, as well as an adaptation of these if so required, is to be carried out.

The frequency of the tasks to be performed with the diabetic patient is shown in table 14.

Table 14. Frequency of the tasks to be carried out in the medical consultation (modified by GEDAPS) (6)

	Initial visits Diagnosis	Control visits	Every six months	Annual
Weight/BMI	⊗	⊗	⊗	⊗
BP/ Heart Rate (HR)	⊗	⊗	⊗	⊗
HbA_1c	⊗		⊗	⊗
Lipid profile	⊗			⊗
Albumin/creatinine ratio	⊗			⊗
Creatinine (plasma)	⊗			⊗
Ocular exploration	⊗			1
Feet exploration (Inspection, monofilament or vibration and average pulse)	⊗			⊗
Electrocardiogram (ECG)	⊗			2
Diet compliance		⊗	⊗	⊗
Exercise compliance		⊗	⊗	⊗
Pharmacological compliance		⊗	⊗	⊗
Check SMBG record		⊗	⊗	⊗

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	Initial visits Diagnosis	Control visits	Every six months	Annual
Investigate hypoglycaemias		⊗	⊗	⊗
Educational interventions		⊗	⊗	⊗
DM diagnosis and classifications	⊗			
Chronic complication screening and assessment	⊗			⊗
Establish and assess therapeutic aims	⊗	⊗	⊗	⊗
Propose a therapeutic and educational plan	⊗			⊗
Complication anamnesis	⊗			⊗
Cardiovascularr risk calculation	⊗			⊗
Anti-tobacco advice	⊗	⊗		⊗
Influenza vaccine				⊗

1. According to the protocol on retinopathy. Every three years if there is no retinopathy and every two years if there is non-proliferative retinopathy.
2. In case of coronary heart disease or cardiac rhythm disorders.

13.3. Frequency of consultations

The consultations will be programmed depending on the level of metabolic control, the needs of the educational process and the time of evolution of diabetes.

Expert opinion 4

After the diagnose, every two weeks, the treatment is to be adjusted and the basic educational program developed. Insulinization requires a frequency of daily visits during the first week. After the first year of diagnose, stable diabetics or those without any changes in the treatment, will keep to the following frequency of consultations:

- One or two medical consultations per year (table 14).
- Three or four nursing visits per year, which include educational intervention (table 14).

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13.4. Referral criteria to medical consultation

The situations when the patient is to be referred to medical consultation are to be determined between the physician and the nursing professional. The following situations can arise:

Expert opinion 4

- Three succeeding blood glucose between 200-300 mg/dl or one of >300 mg/dl, or ketosis or any incurrent process.
- Frequent hypoglycaemia events.
- Adverse effects to drugs or drug interactions.
- Every six moths or every year, depending on the protocol and the organization of the health centre, request an analytical check-up, an ECG, or an ocular fundus check.

13.5. Referral criteria to specialized care

The consultation criteria with other specialized levels must maintain permanent contact with the diabetic patient. Training the different teams, the resources available in each health centre and the existence of protocols in combination with the specialized levels are to be taken into consideration. In general terms, the following criteria can be established:

Expert opinion 4

Endocrinology

- Suspicion of specific DM (genetic, exocrine pancreas diseases and endocrinopathies).
- Pregnancy in a diabetic patient.
- Any diabetic person with poor chronic metabolic control despite therapeutic modifications.
- Patient under 40 with possible DM 1 when diagnosed.

Nephrology

- Persistent clinical proteinuria (>200 mcg/min or 300 mg/day).
- Creatinine >2 mg/dl or creatinine clearance <50 ml/min/1.73 m^2.

Vascular surgery

- Peripheral arteriopathy with rest pain or nocturnal pain in lower limbs.
- Increase of intermittent claudication.
- Ulcers which do not heal.

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Cardiology

- Coronary heart disease suspicion or existence.

Neurology

- Transient ischemic attact.

Ophthalmology

- If there is no retinograph available (non-mydriatic digital camera) in primary care, refer in the first visit. Afterwards, if there is no retinopathy, every three years; if there is non-proliferative retinopathy, every two years.

Hospital emergencies

- Suggestive signsof hyperglycemic-hyperosmolar coma or diabetic ketoacidosis.
- Severe hypoglycaemia or hypoglycaemic coma, especially if it is secondary to a treatment with oral anti-diabetic agents (sulfonylureas).
- Severe hyperglycaemia which requires initial treatment with insulin and which cannot be done in primary care.

13.6. Registration systems

SR of RCT 1+

The interventions which use reminder systems or databases, flow diagrams and feedback of the information are considered more effective to improve the quality of the care process (290; 291).

Monitoring is recommended, especially by computed means, of the results both of the process and the outcomes, to remember and record the carrying out of explorations and to improve the quality of the care provided to diabetic patients.

A record system of diabetic patients is recommended, to have an estimate of the prevalence in each Autonomous Community, as well as reminder systems of opportunistic screening to be done during the medical consultations.

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Appendices

Appendix 1. Levels of Evidence and Grades of Recommendation

Table 1. Levels of evidence and grades of recommendation according to SIGN

Levels of evidence	
1++	High quality meta-analysis, systematic review of clinical trials or high quality low-bias risk clinical trials.
1+	Meta-analysis well conducted, systematic review of clinical trials or well conducted clinical trials with a very low risk of bias.
1-	Meta-analysis, systematic review of clinical trials or clinical trials with a very high risk of bias.
2++	High quality systematic reviews of cohort studies or case-control studies. Cohort or case-control studies with low-bias risk and a high probability that the relationship is casual.
2+	Well conducted cohort or case-control studies with low-bias risk and a moderate probability that the relationship is causal.
2-	Cohort or case-control studies with high-bias risk and a significant risk that the relationship is not causal.
3	Non-analytical studies, such as case reports, case series or descriptive studies.
4	Expert opinion.
Grades of recommendation	
A	At least one meta-analysis, a systematic review or a clinical trial rated as 1++ and directly applicable to the target population of the guideline; or a body of evidence consisting of studies rated as 1+ and demonstrating overall consistency between them.
B	A body of evidence composed of studies rated as 2++, directly applicable to the target population of the guideline and demonstrating overall consistency between them; or extrapolated evidence from studies rated as 1++ or 1+.
C	A body of evidence composed of studies rated as 2+ directly applicable to the target population of the guideline and demonstrating overall consistency between them; or extrapolated evidence from studies rated as 2++.
D	Evidence levels 3 or 4; or extrapolated evidence from studies rated as 2+.

Good practice points

√*	Recommended best practice based on clinical experience and the consensus of the development group.

* *On some occasions, the development group presents important practical cases which they consider relevant but that have no scientific evidence. In general, these cases are related to some aspect of the treatment which nobody would normally ask about and which are assessed as <good practice points>.*

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Table 2. **Levels of evidence and grades of recommendation according to OXFORD**

Levels of evidence	Type of evidence
Ia	Systematic review with homogeneity of **level 1** studies
Ib	**Level 1** studies
II	**Level 2** studies Systematic review of **level 2** studies
III	**Level 3** studies Systematic review of **level 3** studies
IV	Consensus, expert opinion without explicit critical appraisal
Level 1 studies	Follow: • Blinded comparison to a valid reference test (<gold standard>) • Appropriate spectrum of patients
Level 2 studies	• Present only one of these biases: • Non-representative population (the sample does not reflect the population group where the test will be implemented) • Comparison with an inappropriate reference standard («gold standard») (the test to be assessed is part of the gold standard or the outcome of the test to be assessed poses an influence on the carrying out of the gold standard • Non-blinded comparison • Case control studies
Level 3 studies	Present two or more criteria in level 2 studies

Recommendation	Evidence
A	Ia or Ib
B	II
C	III
D	IV

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Appendix 2. DM 2 diet

Estimating caloric needs

Caloric needs are calculated from the maximum weight acceptable, depending on the genre, according to the physical activities and the reductions are applied depending on the age and degree of overweight, applying the following formula:

(Maximum acceptable weight x physical activity) - age - overweight

Maximum acceptable weight:	Male	27 x size^2 (metres)
	Female	25 x size^2 (metres)

Energy needs depending on the physical activity		**Kcal/kg/day**
Basal metabolism		24
Bed rest or minimum activity		30
Light activity	*Male*	42
	Female	36
Moderate activity	*Male*	46
	Female	40
Intense activity	*Male*	54
	Female	47
Exceptionally intense activity	*Male*	62
	Female	55

Reduction by age	**Reduction by overweight**
19-49 years ..... 5% reduction 50-59 years ..... 10% reduction 60-69 years ..... 20% reduction ³ 70 years..... 30% reduction	10-20% if overweight (25 £ BMI < 30) 30-40% if obesity (BMI ³ 30) **BMI = weight (kg) / size2 (metres)**

Example of a diet estimate:	64-year old female, housewife, with the following size: 1.56 m and 70 kg.
BMI estimate:	70 / (1.56)^2 = 28.8 (overweight)
Acceptable weight estimate:	25 x (1.56)^2 = 60.7 Kg.
Type of activity: (WHO table)	60.7 x 36 (housewife) = 2.185 kcal/day
Age: (WHO table)	2.185 - 20% (64 years) = 1.748 kcal/day
Reduction according to current weight:	If she is **overweight**, a **10-20**% will be reduced to the kcal calculated If she is **obese**, a **30-40**% will be reduced In this example_® 1.748 - 20% = **1.400 kcal/day**

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Dieta 1500 kcal



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tomas	LÁCTEOS *	ALIMENTOS PROTEÍCOS	VERDURAS	ALIMENTOS HIDROCARBONADOS	FRUTAS	GRASAS
desayuno	1			1	1	0,5
media mañana		0,5		2		
comida		2	1	4	2	2
merienda	1			1	1	0,5
cena		2	1	4	2	2
antes de dormir	0,5					

* Desnatados

cantidad de alimento por unidad de intercambio

lácteos

- 200 ml de leche (desnatado)
- 2 yogures (naturales, sabores, bio, desnatados)
- 2 Actimel líquido (0% M.G.)



alimentos proteícos

- 50g de ternera magra, buey, pollo, conejo, cordero* o cerdo
- 60g de jamón de York*, pechuga de pavo
- 75g de pescado blanco, azul, marisco
- 40g de embutido*
- 40g de queso: fresco, cremoso, seco*
- 35g de jamón serrano
- 1 huevo



verduras

- 300g de escarola, lechuga, endibias, acelgas, espinacas, setas, espárragos, pepinos, tomates, pimientos, col, berenjenas, coliflor, calabacín, champiñón
- 200g de judías verdes, nabos, puerros
- 100g de alcachofas, coles de bruselas, zanahoria, remolacha, cebolla



alimentos hidrocarbonados

- 60g de guisantes, habas
- 50g de patatas, boniatos
- 20g de legumbres
- 20g de pan
- 20g de cereales de desayuno integrales
- 15g de tostadas, biscotes, cereales para desayuno, galletas
- 15g de arroz, sémola, harina
- 15g de pasta (fideos, macarrones, canelones)



frutas

- 150g de melón, sandía
- 100g de naranja, albaricoque, pera, mandarina, ciruelas, piña, kiwi, fresón, paraguayo
- 50g de plátano, uva, cerezas, higos, chirimoya, níspero, mango, caquis, frutos secos



grasas

- 1 cucharada de aceite de oliva, mahonesa
- 10g de mantequilla*, margarina
- 40g de aceitunas
- 30g de nata*

* Para calcular a qué cantidad de alimento (que no esté en nuestro listado) equivale un intercambio, se utiliza la siguiente fórmula: 1000 / gramos (por cada 100g de alimento) = gramos de alimento que equivale a un intercambio

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plan de alimentación por intercambios

desayuno

h.

1 taza de leche o 2 yogures

20g de pan o 15g de cereales

1 fruta mediana

media mañana

h.

Media taza de leche o 1 yogur o 20g de queso, jamón, atún...

1 fruta mediana

comida

h.

1 plato de verdura o ensalada

Escoger:

Pasta
Arroz
Patata
Guisante
Legumbre

2 cucharones sin pan

1 cucharón + 40g de pan

Sin cucharón + 80g de pan

100g de carne o 150g de pescado

1 fruta grande

merienda

h.

1 taza de leche o 2 yogures

20g de pan o 15g de cereales o tostadas

1 fruta mediana

cena

h.

Igual que en la comida. Variar los menús

antes de dormir

h.

Media taza de leche o 1 yogur

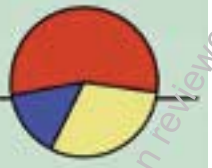
Aceite total /día 50 gramos (5 cucharadas soperas)

1 cucharón igual a 40g de pan

Barra de 200g

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dieta de 1500 kcal



TOMAS	Nº de intercambios	EJEMPLOS
desayuno y merienda		
Lácteos	1	1. Un vaso de leche desnatada, cereales "All Bran" (20g-1l), una pieza de fruta pequeña.
Alimento hidrocarbonado	1	2. Un vaso de leche desnatada con café, pan (20g-1l), una pieza de fruta pequeña.
Fruta	1	3. Dos yogures desnatados, galletas (2-1l), una fruta pequeña.
media mañana		
Alimento hidrocarbonado	2	1. Pan (40g-2l), jamón York (30g), café solo o infusión.
Alimento proteico o lácteo	0,5	2. Galletas (4 unidades-2l), medio vaso de leche o un yogur.
comida		
Verdura	1	1. Arroz blanco (30g-2l) con verduras (200g) y pollo (100g), pan (40g-2l), una pieza de fruta.
Alimento hidrocarbonado	4	2. Menestra de verduras (300g), albóndigas de ternera (100g) con arroz (30g-2l), pan (40g-2l), una pieza de fruta.
Alimento proteico	2	3. Ensalada de tomate (300g) con queso de Burgos (25g), pasta (30g-2l) con salsa de tomate casera, carne picada (50g) y queso rayado (25g), pan (40g-2l), una pieza de fruta.
Fruta	2	4. Espinacas rehogadas (300g) con patatas (100g-2l), chuleta de cerdo (100g), pan (40g-2l), una pieza de fruta.
		5. Pasta (30g-2l) con almejas y gambas (100g), pan (40g-2l), ensalada de lechuga (100g), tomate (50g) y cebolla (50g), una pieza de fruta.
		6. Cocido: garbanzos (40g-2l) con repollo (250g) y carne (100g), pan (40g-2l), una pieza de fruta.
cena		
Verdura	1	1. Puré de patata (100g-2l), trucha (100g), pan (40g-2l), una pieza de fruta.
Alimento hidrocarbonado	4	2. Pisto de verduras (300g), pechuga de pavo (120g) con arroz (30g-2l), pan (40g-2l), una pieza de fruta.
Alimento proteico	2	3. Espinacas (300g) con uvas pasas (25g) y piñones (25g), merluza (100g) con patatas (100g-2l), pan (40g-2l), una pieza de fruta.
Fruta	2	4. Sopa de fideos (30g-2l), Roti de pavo (120g) con zanahoria, pimiento verde y cebolla (200g) al horno, pan (40g-2l), una pieza de fruta.
		5. Alcachofas (100g), salmón a la plancha (100g) y puré de patatas (100g-2l), pan (40g-2l), una pieza de fruta.
		6. Ensalada, lechuga (100g), tomate (100g) y cebolla (100g), tortilla de patatas (100g- 2l patata y 2 huevos), pan (40g-2l), una pieza de fruta.
antes de dormir		
Lácteos	0,5	1. Medio vaso de leche o un yogur
Grasas total /día	50 gramos (5 cucharadas soperas de aceite)	

Los intercambios de alimentos hidrocarbonados de la media mañana pueden sustituirse por fruta.

En la dieta de 1500 kcal los lácteos son desnatados.

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Dieta 1750 kcal



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tomas	LÁCTEOS *	ALIMENTOS PROTEÍCOS	VERDURAS	ALIMENTOS HIDROCARBONADOS	FRUTAS	GRASAS
desayuno	1			2	1	1
media mañana		1		2		
comida		2	1	4	2	2
merienda	1			2	1	1
cena		2	1	4	2	2
antes de dormir	1					

* Desnatados

cantidad de alimento por unidad de intercambio

lácteos

- 200 ml de leche (entera, semi, desnatada)
- 2 yogures (naturales, sabores, bio, desnatados)
- 2 Actimel líquido (0% M.G.)



alimentos proteícos

- 50g de ternera magra, buey, pollo, conejo, cordero* o cerdo
- 60g de jamón de York*, pechuga de pavo
- 75g de pescado blanco, azul, marisco
- 40g de embutido*
- 40g de queso: fresco, cremoso, seco*
- 35g de jamón serrano
- 1 huevo



verduras

- 300g de escarola, lechuga, endibias, acelgas, espinacas, setas, espárragos, pepinos, tomates, pimientos, col, berenjenas, coliflor, calabacín, champiñón
- 200g de judías verdes, nabos, puerros
- 100g de alcachofas, coles de Bruselas, zanahoria, remolacha, cebolla



alimentos hidrocarbonados

- 60g de guisantes, habas
- 50g de patatas, boniatos
- 20g de legumbres
- 20g de pan
- 20g de cereales de desayuno integrales
- 15g de tostadas, biscotes, cereales para desayuno, galletas
- 15g de arroz, sémola, harina
- 15g de pasta (fideos, macarrones, canelones)



frutas

- 150g de melón, sandía
- 100g de naranja, albaricoque, pera, mandarina, ciruelas, piña, kiwi, fresón, paraguayo
- 50g de plátano, uva, cerezas, higos, chirimoya, níspero, mango, caquis, frutos secos



grasas

- 1 cucharada de aceite de oliva, mahonesa
- 10g de mantequilla*, margarina
- 40g de aceitunas
- 30g de nata*

* Para calcular a qué cantidad de alimento (que no esté en nuestro listado) equivale un intercambio, se utiliza la siguiente fórmula: 1000 / gramos (por cada 100g de alimento) = gramos de alimento que equivale a un intercambio

More than 5 years have passed since the publication of this Spanish Practice Guideline and its validity has not been reviewed

plan de alimentación por intercambios

desayuno

h.

1 taza de leche o 2 yogures

40g de pan o 30g de cereales

1 fruta pequeña

media mañana

h.

Media taza de leche o 1 yogur o 20g de queso, jamón, atún...

40g de pan o 30g de cereales o tostadas

comida

h.

1 plato de verdura o ensalada

Escoger:

Pasta
Arroz
Patata
Guisante
Legumbre

2 cucharones sin pan

1 cucharón + 40g de pan

Sin cucharón + 80g de pan

100g de carne o 150g de pescado

1 fruta mediana

merienda

h.

1 taza de leche o 2 yogures

40g de pan o 30g de cereales o tostadas

1 fruta pequeña

cena

h.

Igual que en la comida. Variar los menús

antes de dormir

h.

Media taza de leche o 2 yogures

Aceite total /día 60 gramos (6 cucharadas soperas)

1 cucharón igual a 40g de pan

Barra de 200g

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dieta de 1750 kcal



TOMAS	Nº de intercambios	EJEMPLOS
desayuno y merienda		
Lácteos	1	1. Un vaso de leche desnatada, cereales "Corn Flakes" (30g-2l), una pieza de fruta pequeña.
Alimento hidrocarbonato	2	2. Un vaso de leche desnatada con café o infusión, galletas (4-2), aceite de oliva, una pieza de fruta .
Alimento proteico		3. Un yogur desnatado, pan (40g-2l), una cucharada de aceite de oliva, una pieza de fruta.
Fruta	1	
media mañana		
Alimento proteico o lácteo	0,5	1. Un café solo o infusión, pan (40g-2l), fiambre de pavo (30g).
Alimento hidrocarbonado	2	2. Un café con leche (100ml), un croissant (60g-2l)
comida		
Verdura	1	1. Pasta (60g-4l) con carne picada (100g), salsa de tomate y champiñones. Una pieza de fruta.
Alimento hidrocarbonado	4	2. Lentejas (55g-3l) guisadas con patatas (50g-1l). Una dorada (150g) al horno con pimientos asados (300g). Una manzana asada.
Alimento proteico	2	3. **Paella:** arroz blanco (45g-3l) con guisantes (60g-1l), pimiento, judías verdes, pollo (100g). Una pieza de fruta.
Fruta	2	4. Espinacas (300g) rehogadas con ajetes. Un filete de ternera (100g) a la plancha con patatas (100g-2l). Pan (40g-2l). Una pieza de fruta.
		5. Puré de zanahoria (100g-1l) y patata (50g-1l). Revuelto de champiñones, gambas y espárragos. Pan (40g-2l). Una pieza de fruta.
		6. Alcachofas (100g) con jamón (una loncha picada). Calamares (100g) a la plancha con patatas (100g-2l). Pan (40g-2l). Una pieza de fruta.
cena		
Verdura	1	1. Sopa de arroz (30g-2l). Una tortilla francesa con fiambre de pavo (100g), espárragos (300g). Pan (40g-2l). Una pieza de fruta.
Alimento hidrocarbonado	4	2. Sopa de fideos (30g-2l). Un filete de pavo (120g) a la plancha con champiñones. Pan (40g-2l). Una manzana asada.
Alimento proteico	2	3. Menestra de verduras (300g). Salmón (150g) a la plancha con patatas (100g-2l). Pan (40g-2l). Una pieza de fruta.
Fruta	2	4. Pisto (300g) con patata (100g-2l). Tortilla francesa con queso semigrasa* (40g). Pan (40g-2l). Una pieza de fruta.
		5. Puré de verduras (300g). Pechuga de pollo a la plancha (100g) con arroz (30g-2l) . Pan (40g-2l). Una pieza de fruta.
		6. Ensalada con pasta (30g-2l), almendras (50g), jamón York (60g), espinacas (300g). Pan (40g-2l). Una compota de manzana.
antes de dormir		
Lácteos	1	1. Un vaso de leche o 2 yogures desnatados
Grasas total /día	60 gramos (6 cucharadas soperas de aceite)	

Los intercambios de alimentos hidrocarbonados de la media mañana pueden sustituirse por fruta.
En la dieta de 1750 kcal los lácteos son desnatados.

More than 5 years have passed since the publication of this Clinical Practice Guideline, and its validity has not been reviewed

Dieta 2000 kcal



More than 5 years have passed since the publication of this Clinical Practice Guideline, and its validity has not been reviewed

tomas	LÁCTEOS *	ALIMENTOS PROTEÍCOS	VERDURAS	ALIMENTOS HIDROCARBONADOS	FRUTAS	GRASAS
desayuno	1			2	1	1
media mañana		1		3		
comida		2	1	6	2	2
merienda	1			2	1	1
cena		2	1	6	2	2
antes de dormir	1					

* Desnatados

cantidad de alimento por unidad de intercambio

lácteos

- 200 ml de leche (entera, semi, desnatada)
- 2 yogures (naturales, sabores, bio, desnatados)
- 2 Actimel líquido (0% M.G.)



alimentos proteícos

- 50g de ternera magra, buey, pollo, conejo, cordero* o cerdo
- 60g de jamón de York*, pechuga de pavo
- 75g de pescado blanco, azul, marisco
- 40g de embutido*
- 40g de queso: fresco, cremoso, seco*
- 35g de jamón serrano
- 1 huevo



verduras

- 300g de escarola, lechuga, endibias, acelgas, espinacas, setas, espárragos, pepinos, tomates, pimientos, col, berenjenas, coliflor, calabacín, champiñón
- 200g de judías verdes, nabos, puerros
- 100g de alcachofas, coles de Bruselas, zanahoria, remolacha, cebolla



alimentos hidrocarbonados

- 60g de guisantes, habas
- 50g de patatas, boniatos
- 20g de legumbres
- 20g de pan
- 20g de cereales de desayuno integrales
- 15g de tostadas, biscotes, cereales para desayuno, galletas
- 15g de arroz, sémola, harina
- 15g de pasta (fideos, macarrones, canelones)



frutas

- 150g de melón, sandía
- 100g de naranja, albaricoque, pera, mandarina, ciruelas, piña, kiwi, fresón, paraguayo
- 50g de plátano, uva, cerezas, higos, chirimoya, níspero, mango, caquis, frutos secos



grasas

- 1 cucharada de aceite de oliva, mahonesa
- 10g de mantequilla*, margarina
- 40g de aceitunas
- 30g de nata*

* Para calcular a qué cantidad de alimento (que no esté en nuestro listado) equivale un intercambio, se utiliza la siguiente fórmula: 1000 / gramos (por cada 100g de alimento) = gramos de alimento que equivale a un intercambio

More than 3 years have passed since the publication of this Spanish Practice Guideline and its validity has not been reviewed

plan de alimentación por intercambios

desayuno

h.

1 taza de leche o 2 yogures

40g de pan o 30g de cereales

1 fruta pequeña

media mañana

h.

Media taza de leche o 1 yogur o 20g de queso, jamón, atún...

60g de pan o 45g de cereales o tostadas

comida

h.

1 plato de verdura o ensalada

Escoger:

Pasta
Arroz
Patata
Guisante
Legumbre

3 cucharones sin pan

1 cucharón + 80g de pan

2 cucharones + 40g de pan

Sin cucharón + 120g de pan

100g de carne o 150g de pescado

1 fruta mediana

merienda

h.

1 taza de leche o 2 yogures

40g de pan o 30g de cereales o tostadas

1 fruta pequeña

cena

h.

Igual que en la comida. Variar los menús

antes de dormir

h.

1 taza de leche o 2 yogures

Aceite total /día 60 gramos (6 cucharadas soperas)

1 cucharón igual a 40g de pan

Barra de 200g

More than 5 years have passed since the publication of this Clinical Practice Guideline, and its validity has not been reviewed

dieta de 2000 kcal



TOMAS	Nº de intercambios	EJEMPLOS
desayuno y merienda		
Lácteos	1	1. Un vaso de leche entera con café o infusión, bizcocho (25g-2I), una pieza de fruta.
Alimento hidrocarbonato	2	2. Un vaso de leche entera con café o infusión, 4 galletas (2I), una pieza de fruta .
Alimento proteico		3. Un yogur de sabor, pan (40g-1I), una cucharada de aceite de oliva, una pieza de fruta.
Fruta	1	
media mañana		
Alimento hidrocarbonado	1	1. Una magdalena (15g-1I), jamón York (40g).
Alimento proteico o lácteo	1	2. 1 rebanada de pan de molde (20g-1I), _ latita de atún en escabeche, 1 rodaja de tomate.
comida		
Verdura	1	1. Lentejas (80g-4I) guisadas con patatas (100g-2I). Un lenguado a la plancha (150g) con champiñones. Una pieza de fruta.
Alimento hidrocarbonado	6	2. Pasta (75g-5I) con carne picada (100g), guisantes (60g-1I), salsa de tomate y champiñones. Una pieza de fruta.
Alimento proteico	2	3. **Paella:** arroz blanco (60g-4I) con guisantes (120g-2I), pimiento, judías verdes, pollo (100g). Una pieza de fruta.
Fruta	2	4. Espinacas (300g) rehogadas con ajetes. Un filete de ternera (100g) empanado (10g de pan rallado) (1I) con patatas (100g-2I). Pan (60g-3I). Una pieza de fruta.
		5. Berenjenas (300g) empanadas (10g de pan rallado) (1I). Trucha (150g) al horno con jamón (una lancha) y patatas (100g-2I). Pan (60g-3I). Una pieza de fruta.
		6. Patatas (100g-2I) guisadas con guisantes (120g-2I) y costillas (100g). Ensalada de lechuga y tomate. Pan (40g-2I). Una pieza de fruta.
cena		
Verdura	1	1. Sopa de verduras. Un huevo frito con arroz (45g-3I) y salsa de tomate. Una pieza de fruta.
Alimento hidrocarbonado	6	2. Pasta (90g-6I) con nueces (50g), queso semigraso (30g), lechuga, una manzana asada.
Alimento proteico	2	3. Menestra de verduras (300g) con guisantes (60g-1I). Sardinas (150g) a la plancha con patatas (150g-3I). Pan (40g-2I). Una pieza de fruta.
Fruta	2	4. Pisto (300g) con patata (150g-3I). Tortilla francesa con queso semigraso (40g). Pan (60g-3I). Una pieza de fruta.
		5. Ensalada con arroz (90g-6I), nueces (50g), jamón York (75g), espinacas (300g). Una compota de pera.
		6. Puré de zanahorias (100g) con patata (100g-2I). Pescado blanco (150g) al horno con arroz (45g-3I) . Pan (60g-3I). Una pieza de fruta.
antes de dormir		
Lácteos	1	1. Un vaso de leche o 2 yogures desnatados
Grasas total /día	50 gramos (5 cucharadas soperas de aceite)	

Los intercambios de alimentos hidrocarbonados de la media mañana pueden sustituirse por fruta.

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Appendix 3. Hypoglycaemic drugs

Vademecum of antidiabetic drugs and insulins

More than 5 years have passed since the publication of this Clinical Practice Guideline and its validity has not been reviewed

	Product	Brand name	Appropriate dosage (mg/day)	Adverse effects
Sulfonylureas	Chlorpropamide	Diabinese®	250-500 mg (single dose)	• Hypoglycaemia, weight increase and gastrointestinal disorders such as nauseas, vomiting, diarrhoea and constipation. • The use of chlorpropamide is not recommended due to the long duration of its effects and the higher risk of hypoglycaemia. • Glibenclamide has a higher hypoglycaemia risk than the rest of sulfonylureas. • In case of hepatic failure: avoid its use or take lower doses. Avoid the use of glimepiride. • Gliclazide and glimepiride can be useful for elderly people or for those suffering from mild-moderate renal failure due to its lower risk of severe hypoglycaemias.
	Glibenclamide	Daonil® 5 mg Euglucon® 5 mg Norglicem® 5 mg	2.5-15 mg (1 to 3 doses)	
	Gliclazide	Diamicron® 30 mg	30-120 mg (single dose)	
	Glipentide or glisentide	Staticum® 5 mg	2.5-20 mg (1 to 3 dose)	
	Glipizide	Minodiab® 5 mg	2.5-20 mg (1 to 3 doses)	
	Gliquidone	Glurenor® 30 mg	15-120 mg (1 to 3 doses)	
	Glimepiride	Amaryl® 1, 2 and 4 mg Glimepiride EFG 1, 2, 3 and 4 mg Roname® 1, 2 and 4 mg	1-4 mg (single dose)	
Fast-acting secretagogues (glinides)	Repaglinide	Novonorm® 0,5, 1 and 2 mg Prandin® 0,5, 1 and 2 mg	1.5-12 mg (3 doses)	• Weight increase and hypoglycaemias. • Hypoglycaemia incidence with repaglinide and sulfonylureas is similar, though repaglinide produces less severe hypoglycaemias in elderly people and patients who miss one meal.
	Nateglinide*	Starlix® 60, 120 and 180 mg	80-360 mg (3 doses)	
α-glucosidase inhibitors	Acarbose	Glucobay® 50 and 100 mg Glumide® 50 and 100 mg	150-300 mg (3 doses)	• Frequent gastrointestinal adverse effects, mainly flatulence.
	Miglitol	Diastabol® 50 and 100 mg Plumarol® 50 and 100 mg	150-300 mg (3 doses)	

	Product	Brand name	Appropriate dosage (mg/day)	Adverse effects
GPL-1 Analogues	Exenatide*	Byetta® 5 mcg injected solution Byetta® 10 mcg injected solution	10-20 mg (single dose)	• Nauseas, vomiting, diarrhoea, severe pancreatitis cases in post-authorisation studies.
Biguanides	Metformin	Dianben® 850 mg Metformin EFG 850 mg	850-2.550 mg (1 to 3 doses)	• Gastrointestinal adverse effects (abdominal pain, nausea and diarrhoea) which can increase due to the intake of some food and slow dosage titration. • Does not provoke hypoglycaemia nor weight increase. • No lactic acidosis increase has been detected in the general population, though there is data missing on its effects in case of renal or hepatic failure.
Glitazones	Rosiglitazona*	Avandia® 4 y 8 mg	4-8 mg (dosis única)	• Increase the risk of heart failure Do not use in patients with heart failure. • Rosiglitazone increases the risk of myocardial infarction. • Weight increase and increase of fractures in the case of women.
	Pioglitazone*	Actos® 15 and 30 mg	15-45 mg (single dose)	
Glitazonas + biguanidas	Rosiglitazona* + Metformina	Avandamet® 2 mg/500 mg Avandamet® 2 mg/1.000 mg Avandamet® 4 mg/1.000 mg	4-8 mg/2.000 mg (2 dosis)	
Glitazonas + sulfonilureas	Rosiglitazona* + glimepirida	Avaglim® 4 y 8 mg/4 mg	4-8 mg/4 mg (dosis única)	
Incretins	Sitagliptin	Januvia® 100 mg	100 mg (single dose)	• Higher risk of infection and headaches.
	Vildagliptin	Galvus® 50 mg	100 mg (1-2 doses)	
	Vildagliptin + Metformin	Eucreas® 50 mg/850 mg	100 mg/1.700-2.000 mg (2 doses)	

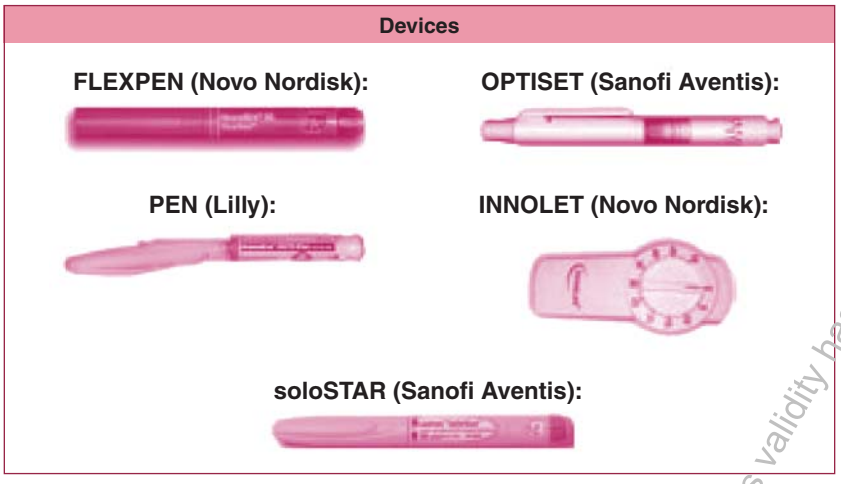
* Hospital diagnose drug.

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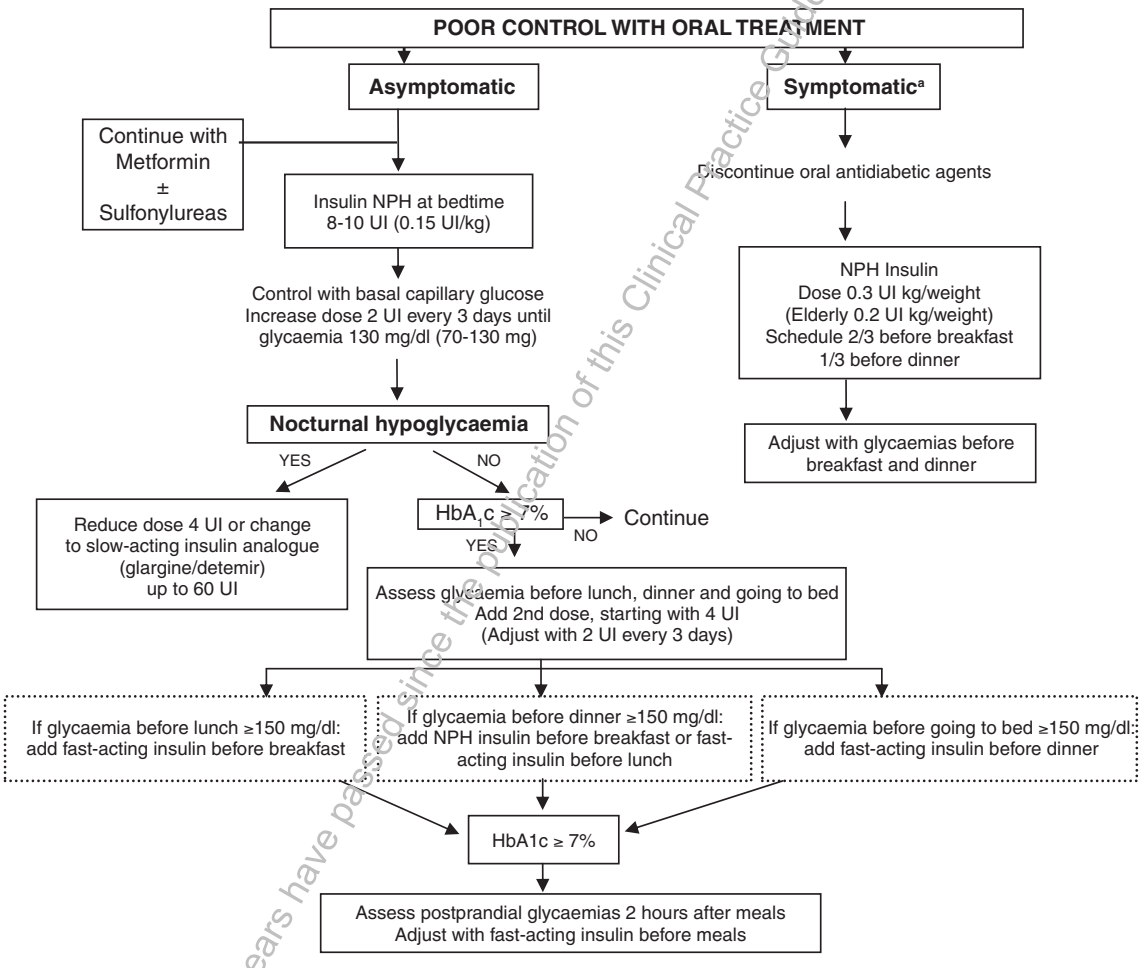
Analogues		
Action profile	**Disposable systems***	**Vial 10 ml***
FAST-ACTING INSULIN		
Insulin Lispro	Humalog©Pen (5 cartridges of 3 ml) (Lilly)	Humalog© (Lilly)
Insulin Aspart	NovoRapid© FlexPen© (5 cartridges of 3 ml) (Novo Nordisk)	
Insulin Glulisine	Apidra© Optiset (5 cartridges of 3 ml) (Sanofi Aventis) Apidra© soloStar (5 cartridges of 3 ml)	
INTERMEDIATE-ACTING INSULIN (the equivalent to NPH)	Humalog NPL Pen (5 cartridges of 3 ml) (Lilly)	
MIXES		
25/75 (Lispro/Lispro protamine)	Humalog©Mix25 Pen (5 cartridges of 3 ml) (Lilly)	
50/50 (Lispro/Lispro protamine)	Humalog©Mix50 Pen (5 cartridges of 3 ml) (Lilly)	
30/70 (Aspart/Aspart protamine)	NovoMix©30 FlexPen© (5 cartridges of 3 ml) (Novo Nordisk)	
LONG-ACTING INSULIN		
Insulin Glargine	Lantus© (5 cartridges of 3 ml) (Sanofi Aventis) Lantus© Optiset (5 cartridges of 3 ml) (Sanofi Aventis) Lantus© soloStar(5 cartridges of 3 ml)	Lantus© (Aventis)
Insulin Detemir	Levemir© FlexPen (5 cartridges of 3 ml) (Novo Nordisk) Levemir© Innolet (5 cartridges of 3 ml) (Novo Nordisk)	

Human insulins		
Action profile	**Disposable systems***	**Vial 10 ml***
FAST-ACTING INSULIN	Actrapid© Innolet© (5 pre-filled pens of 3 ml) (Novo Nordisk)	Actrapid© (Novo Nordisk) Humulin© Regular (Lilly)
INTERMEDIATE-ACTING INSULIN NPH	Insulatard© FlexPen© (5 cartridges of 3 ml) (Novo Nordisk) Humulin© NPH Pen (6 cartridges of 3 ml) (Lilly)	Insulatard© (Novo Nordisk) Humulin© NPH (Lilly)
MIXES 30/70	Mixtard© 30 Innolet© (5 pre-filled pens of 3 ml) (Novo Nordisk) Humulin© 30/70 Pen (6 cartridges of 3 ml) (Lilly)	Mixtard© 30 (Novo Nordisk) Humulin© 30/70 (Lilly)

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Beginning of insulinization



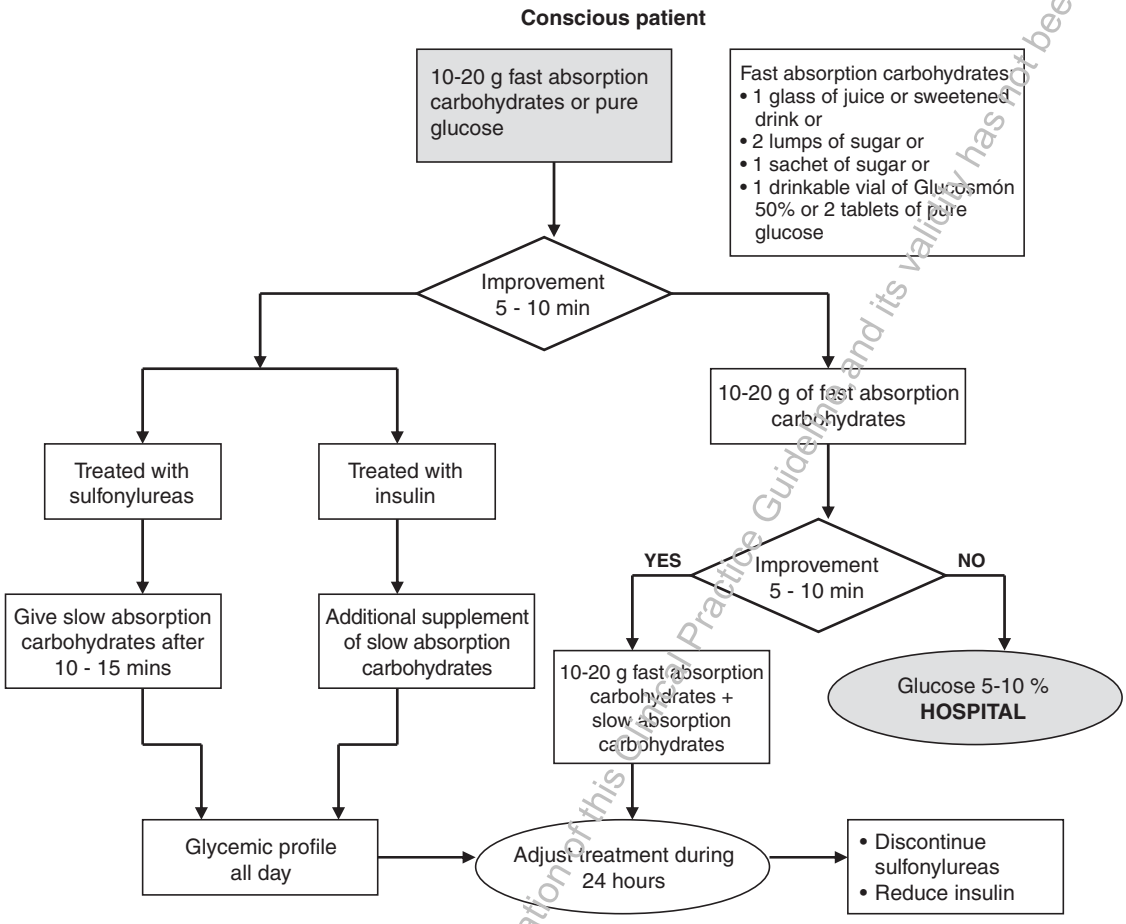
[a] Polyuria, polydipsia, ketonuria, weight loss.

The target for HbA 1c ≤7 is a guideline, as less strict aims can be considered. The aim must be individualised depending on cardiovascular risk, comorbidity, evolution time of the disease, life expectancy and the patients' preferences.

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Appendix 4. Hypoglycaemia treatment

Treatment for a conscious patient (mild/moderate)[1]

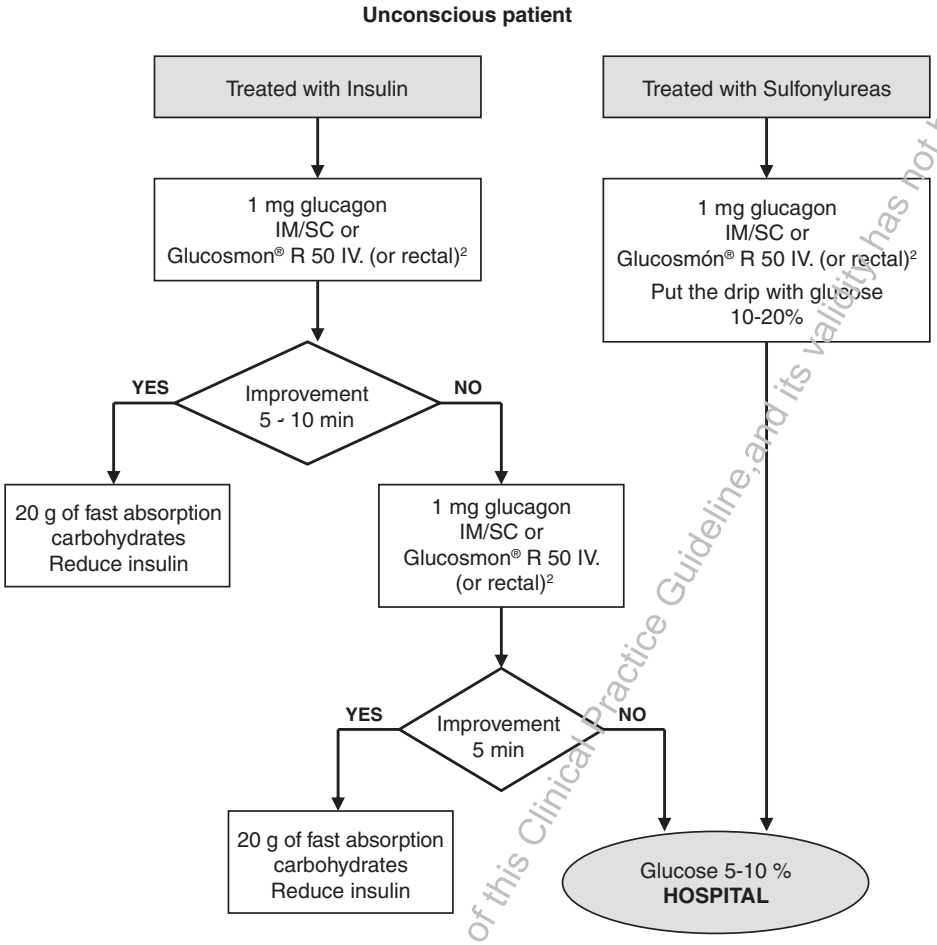


[1] Does not require aid from a third person. In any case, assess the possible cause of hypoglycaemia (omit a meal, intercurrent processes, drug interactions, dosage error, etc.).

Adapted from: Diabetes Mellitus tipo 2 en Atención Primaria. Guía de referencia rápida. Servicio Navarro de Salud-Osasunbidea. Dirección de Atención Primaria. 2006.

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Treatment for an unconscious patient (hypoglycaemia coma)[1]



[1] Under any circumstances, assess the possible cause of hypoglycaemia (omission of a meal, intercurrent processes, medicinal interactions, errors in the dosage, etc.)

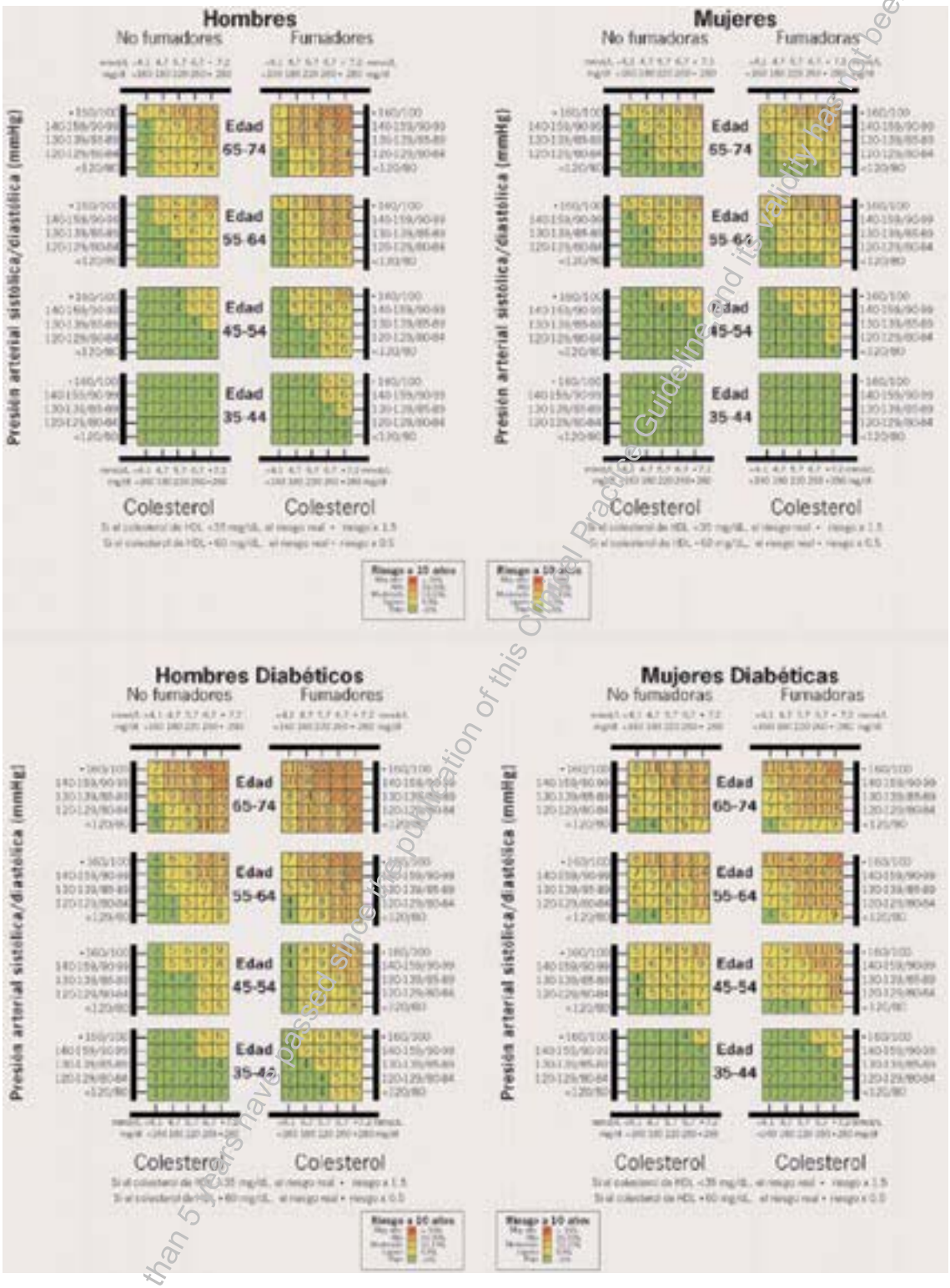
[2] When it is impossible to channel a IV vial.

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Adapted from: Diabetes Mellitus tipo 2 en Atención Primaria. Guía de referencia rápida. Servicio Navarro de Salud-Osasunbidea. Dirección de Atención Primaria. 2006.

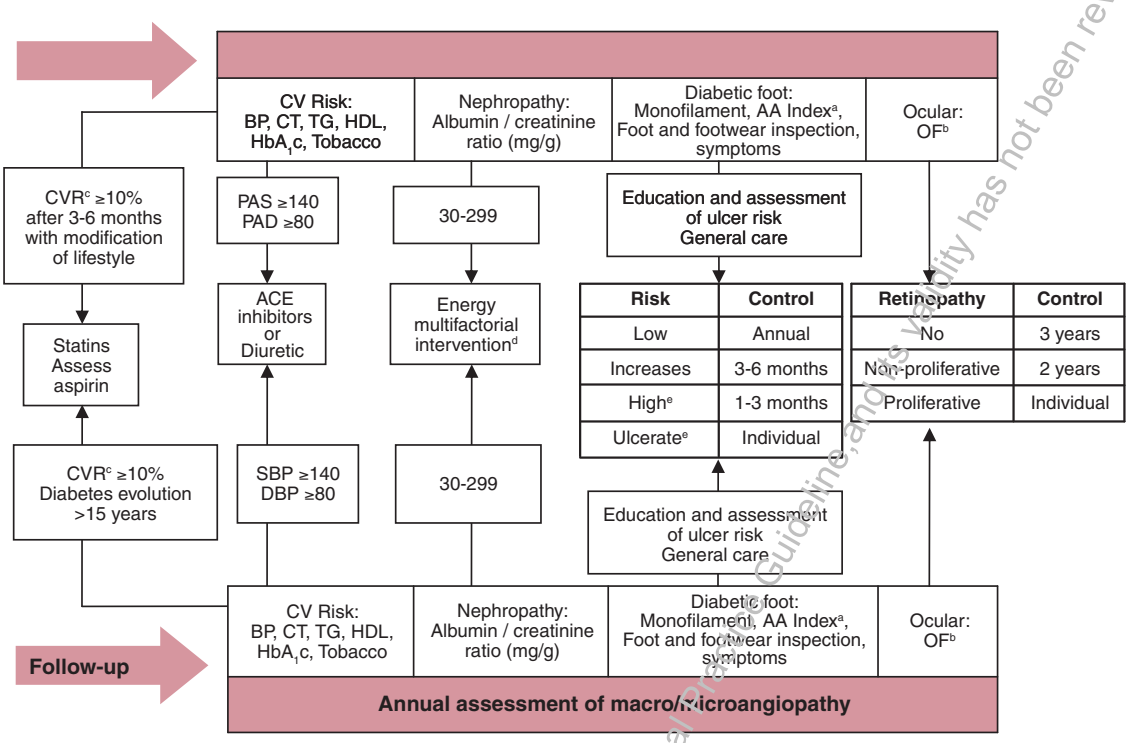
Appendix 5. Coronary risk tables: REGICOR

Coronary risk table calibrated for the Spanish population in males and females (from Marrugat J, et al. Rev Esp Cardiol. 2003; 56: 253-261)



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Appendix 6. Assessment of macro- and microangiopathy in the diagnose and follow-up of DM 2



[a] AA Index (ankle-arm): in case of abnormal physical examination or another macro/microangiopathic disorder.

[b] OF (ocular fundus): non-mydriatic camera or ophthalmologic consultation if there is no camera available.

[c] CVR (cardiovascular risk): estimate according to the REGICOR table.

[d] Diet, exercise, anti-tobacco therapy, ACE-inhibitors, aspirin, therapeutic target: SBP £130 mmHg, intensive HbA_1c and cholesterol control.

[e] Requires assessment by specialized staff or, if available, foot unit staff or chiropodist.

BP, SBP, DBP: blood pressure, systolic blood pressure, diastolic blood pressure; ; OF: ocular fundus; CT: cholesterol; TG: triglycerides.

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Appendix 7. Drugs for neuropathic pain

Doses and most frequent adverse effects of the drugs used to treat neuropathic pain (237):

Drug	Doses	Adverse effects	Observations
ANTIDEPRESSANTS			
TRICYCLICS: Amitriptyline	ID: 10-25 mg/day in a single dose at bedtime. Increase 10-25 mg each week. UD: 50-150 mg/day MD: 150 mg/day	Anticholinergic: mouth dryness constipation, urinary retention and tachycardia. Others: orthostatic hypotension, sedation, confusion, weight increase and increase in cardiac effects such as conduction blocking.	The treatment must be stopped gradually.
Duloxetine	ID: 60 mg/day in a single dose with or without meals. UD: 60 mg/day MD: 120 mg/day in divided doses	Nauseas, drowsiness, headache, dizziness.	The response must be assessed after two months. It is unlikely to see an additional response after this time has passed. The treatment must be stopped gradually.
ANTI-EPILEPTIC DRUGS			
Gabapentin	ID: 300mg /8 h. Increase 300 mg each week. UD: 1200-1400mg/day MD: 3600 mg/day	Drowsiness, mood changes, diarrhoea, ataxia, fatigue, nauseas and vertigo.	Reduce dose in case of renal failure and in elderly patients.
Pregabalin	ID: 50-150 mg/day in 2-3 doses. Increase 50- 150 mg each week. UD: 300-600 mg/day MD: 600 mg/day	Vertigo, constipation, fatigue, nauseas, sedation, weight gain, blurred vision.	Caution if used with glitazones, as the probability of peripheral oedema is increased as well as weight gain. Reduce the dose in case of renal failure and in elderly patients .
Carbamazepine	ID: 100-200 mg/day in 3-4 doses. Increase 100- 200 mg each week. UD: 600-1200 mg/day MD: 1600 mg/day	Ataxia, vertigo, diplopia or nauseas. Cases of agranulocitosis or aplastic anaemia have rarely been described.	
Opioids			
Tramadol	ID: 50 mg/day in 2 doses. Increase in 50 mg each week. UD: 50-100 mg/6-8 h MD: 600 mg/day	Nauseas, vomiting, sweat, dizziness with feeling of mouth dryness, sedation, increased convulsion risk, serotonin syndrome.	The adverse effects increase with the titration speed. The dose is to be adjusted in case of renal or hepatic failure.
Morphine	ID: 5-15 mg of fast release every 4 hours. After 7-15 days, go on to slow release. UD: 120 mg/day MD: 180 mg/day	Nauseas, vomiting, constipation, drowsiness and vertigos.	Usually, it is necessary to treat the constipation it provokes.

ID: initial dose; UD: usual dose; MD: maximum dose.

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Appendix 8. Use of monofilament

Monofilament 5.07



It assesses the sensitivity to pressure and touch, which is known as «protective sensitivity».

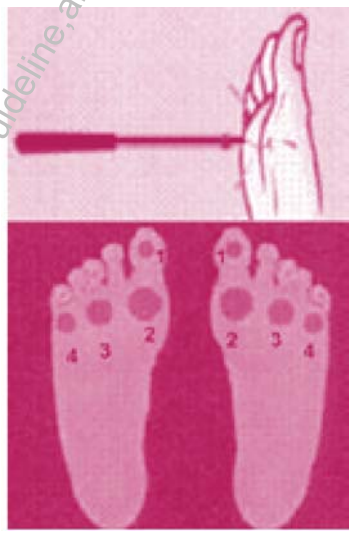
It consists of a nylon filament attached to a handle, which applies a constant 10g pressure when bent, regardless of the force which the examiner uses.

Rules to use the monofilament (MF)

- The monofilament is applied perpendicular to the patient's skin and the pressure is increased gradually until the MF is bent. It is at this stage when the assessment takes place.
- It must not be applied more than 1-2 seconds.

The screening is carried out on four plantar points in each foot: first toe (distal phalanx), base of the first, third and fifth metatarsal.

(Note: In the case of hyperkeratosis, the monofilament will be applied in the perimeter area or the screening will be repeated once the callus has been removed).



- Each of the locations will be rated 1 or 0, depending on if the patient feels the pressure or not. The total amount of these values will give the sensitivity index to the MF (from 0 to 8).
- A patient is considered sensitive only when the result is 8/8.

Cautions to be considered when using the monofilament

1. **Make sure the patient knows what to expect:** Apply the MF in a different area and which he can identify easily (upper extremities, face, etc.) so that he can get an idea of the type of sensation.
2. **During the screening:** The patient will close his eyes and will be told: "Now I am going to put this device in different points in your feet: **please let me know when you feel it and try to tell me *where* you feel it:** in which foot, in which toe, in which sole...." When the MF is applied, ***avoid*** the following question: do you feel it now? Do ask the question at some point when the monofilament is not applying any pressure.
3. Those patients with some insensitive point will have the test repeated in those same points once the first screening is finished (repeated screening in two stages). If the patient is sensitive in the second screening, this point will be considered sensitive.

In those patients who show sensitivity in all sensitive points (MF index = 8), there is no need to repeat the test.

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Appendix 9. Education of the diabetic patient and material for the patients

Diabetologic education contents

GENERAL CONSIDERATIONS
- What is diabetes?
- Risk factors related
- Types of treatment
- Control aims
- Relationship between food, weight, exercise and control

DIET
- Benefits
- Carbohydrates recommended, restricted and to be avoided
- Balanced diet
- Number of meals and schedule
- Measurements to quantify carbohydrates

TOBACCO
- Risk
- Advice to stop smoking

EXERCISE
- Appropriate exercise
- Duration and schedule
- Appropriate footwear
- Hypoglycaemia prevention
- Measures in case of hypoglycaemia
- Precautions

- Equivalence table
- Alcohol and other drinks
- Desserts and sweeteners
- Diet based on carbohydrate portions
- Diet during intercurrent disease

FEET
- Reasons for feet care
- Hygiene and daily care
- Nail care
- Appropriate footwear and socks
- Precautions
- Inquire if there is any change

ORAL DRUGS
- Trade mark and dose
- Dose schedule
- Actiwon mechanism
- Measures in case of hypoglycaemia
- Importance of adherence

SELF-MANAGEMENT
- Weight control
- Self-evaluation of the feet
- Smbg
- Advantages, types of self-analysis
- Material to be used
- Frequency, schedule
- Self-monitoring technique
- Self-monitoring record
- When to control ketonurias

HYPOGLYCAEMIAS
- Alert symptoms
- Causes
- Self-treatment
- Hypoglycaemia prevention
- Record of hypoglycaemia and its cause
- Information to relatives
- Use of glucagon

INSULIN
- Types, guideline, doses and schedule
- Administration technique
- Injection sites and rotation
- Interval between injection and intake
- Conservation of insulin
- Reuse of the material
- Measures in case of hypoglycaemia
- Importance of adherence
- Action mechanism
- Self-modification of the doses

SPECIAL SITUATIONS
- Travelling
- Comply with the schedule and treatment
- Carry supplements of carbohydrates
- Transportation of insulin
- Diabetic identification record
- Intercurrent diseases
- Assure intake of carbohydrates
- Maintain treatment
- Increase self-analyses
- Warning signs
- Celebrations

COMPLICATIONS
- Measures to prevent them
- Usefulness and frequency of examinations
- Consult in case of:
- visual disorder
- foot wounds or changes
- urinary pain
- metabolic decompensation
- thoracic pain
- intermittent claudication

Treated only with diet | Treated with oral drugs | Treated with insulin

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¿Qué es la Diabetes Tipo 2?



La diabetes es una enfermedad frecuente. De cada 100 personas, entre 6 y 10 la tienen.

La diabetes se caracteriza por un aumento de la concentración de glucosa (azúcar) en sangre (glucemia) debido a que el páncreas no produce toda la insulina que el organismo necesita y además actúa de una forma defectuosa.

La diabetes muchas veces no produce ningún síntoma que le haga sentirse mal, por lo que puede pasar desapercibida. Sin embargo, es muy importante diagnosticarla y tratarla. Si la diabetes no se controla bien, puede producir complicaciones importantes a nivel del corazón, en los pies, oculares o en el riñón.



Fetus / Accidente cerebro vascular
Retinopatía
Infarto
Insuficiencia renal
Impotencia / Incontinencia urinaria
Parestesia
Pie diabético
Insuficiencia vascular

Las causas principales de diabetes tipo 2 son la obesidad y la falta de ejercicio físico.



La mejor forma de prevenir la diabetes y de evitar sus complicaciones consiste en una alimentación sana, controlar el sobrepeso, no fumar y realizar ejercicio físico de forma regular.

Si tiene diabetes, es conveniente que se familiarice con estos términos:

Glucemia	=	Glucosa (azúcar) en sangre
Hiperglucemia	=	Glucosa en sangre en niveles superiores a la normalidad
Hipoglucemia	=	Glucosa en sangre por debajo de los niveles normales
Insulina	=	Hormona que introduce la glucosa de la sangre dentro de cada célula de nuestro organismo
Páncreas	=	Órgano donde se produce la insulina
Hidratos de carbono	=	Azúcares

¡LA GLUCOSA ALTA NO DUELE,
PERO ESTROPEA TODO EL ORGANISMO!



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EL MEJOR TRATAMIENTO DE UNA **HIPOGLUCEMIA** ES SU **PREVENCIÓN**

Seguir los horarios



Plan de alimentación



PAN, ARROZ, PASTAS Y TUBÉRCILOS

Plan de Calidad del Sistema Nacional de Salud

EUSKO JAURLARITZA
GOBIERNO VASCO

HIPOGLUCEMIA



¿Qué es Hipoglucemia?

Es un descenso del nivel de azúcar en sangre, por debajo de los límites normales (50 mg/dl).

¿Qué se siente?

Los síntomas pueden variar de una persona a otra.

Síntomas de aviso: temblor, sudor frío, palpitaciones, vista borrosa, ansiedad, hambre…



Si es más intensa: dificultad para pensar y hablar, debilidad, irritabilidad, mareos, confusión, somnolencia...





Cuando no se trata a tiempo es grave: Pérdida de conocimiento

80-110 mg/dl

60 mg/dl

¿A qué puede ser debida?



- Si ha realizado más ejercicio de lo habitual.
- Si se ha excedido en la dosis de insulina o antidiabéticos orales.



- Si se ha retrasado u olvidado alguna comida o suplemento.
- Si ha tomado alcohol o medicamentos que potencien el efecto del tratamiento.



¿Qué hacer?

Ante la duda ¡AGUA CON AZÚCAR!
Lleve siempre dos sobres de azúcar, caramelos, o fruta.



Ante los síntomas de aviso (si puede verificar con su medidor, mejor), deje/haga su actividad, y ½ vaso de zumo o refresco, o miel.

Si es más intensa, tome agua con el azúcar. Una vez haya normalizado la situación tome pan, o galletas, fruta.

* *Después de un episodio de hipoglucemia, realice controles de glucosa cada 2 horas, pues puede presentar "Hiperglucemias reactivas".*

Recuerde

Si ha perdido el conocimiento o se niega a comer. No forzar la toma de alimento o bebida.



- Llamar al equipo médico de urgencias.



- Si tiene un familiar o un amigo adiestrado de antemano, puede utilizar GLUCAGÓN.



- Cuando vuelva en sí tome zumo o similar

¿Cómo evitarlas?

Evitando las causas

- Seguir los horarios indicados.
- No dejar de comer nunca la cantidad de harinas (pasta, patatas, arroz, pan), fruta, leche que le hayan recomendado en su plan de alimentación.
- Añadir una pieza de fruta o 2-3 tostadas solo si camina más de lo habitual o hace ejercicio físico extra.

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El cuidado de los pies en la diabetes

Los pacientes diabéticos pueden tener **complicaciones en los pies** (como deformidades, úlceras o amputaciones). Esto es debido a:

- Problemas de circulación en la parte inferior de las piernas y en los pies
- Posible pérdida de sensibilidad
- Mayor riesgo de sufrir infecciones



Plan de Calidad del Sistema Nacional de Salud

EUSKO JAURLARITZA
GOBIERNO VASCO
OSASUN SAILA
DEPARTAMENTO DE SANIDAD

Cuidado de los PIES en la Diabetes



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Cuidados personales

- Inspeccione los pies todos los días. Compruebe que no haya enrojecimiento, heridas, ampollas, etc. Si tiene problemas de vista, pida a alguien que le ayude.





- Lave diariamente los pies con agua templada y jabón (5-10 min.). Al finalizar, séquelos bien, especialmente entre los dedos.



- Mantenga la piel hidratada (no dar crema entre los dedos).



- Mantenga las uñas limpias y cortas. Se deben cortar en línea recta y después del lavado, así estarán más blandas. Utilice tijeras de punta roma (sin punta), excepto si las uñas están muy duras, en este caso utilice una lima.

- Si las uñas son muy gruesas o la vista no es buena, solicite que otra persona se las corte o acuda al podólogo.





- No utilice callicidas, ni use instrumentos afilados o cuchillas para cortar los callos o durezas.

- No aplique calor o frío a sus pies (manta eléctrica, bolsa o botella de agua caliente, hielo).





- Haga uso de calzado adecuado. No utilice zapatos mal ajustados o calcetines que le opriman.

- Camine diariamente, nunca descalzo ni en casa, playa o piscina.



Ante cualquier lesión en los pies, recuerde que el mejor desinfectante es el agua y jabón.





Informe al personal sanitario de su Centro de Salud.

Recuerde



- La diabetes debe estar bien controlada.

- No prestar atención a una lesión en un pie, junto con una diabetes mal controlada, puede acarrear problemas muy graves .



- La falta de dolor no quita gravedad a las lesiones

- Aunque no note nada, su circulación y su sensibilidad pueden estar disminuidas



- Una buena higiene de los pies previene en gran parte las complicaciones

- El exceso de humedad favorece la infección y la sequedad excesiva permite que se hagan grietas

- Según pasan los años, la atención y el cuidado de los pies debe ser mayor

- No fume



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Appendix 10. Assessment proposal. Indicators

The authors of this CPG have designed some indicators in order to assess both the care provided to a DM 2 patient as well as the possible impact the implementation of this guideline could have. The aim has not been to design an in-depth and detailed assessment which implies the use of all the indicators proposed. The aim is to create a tool for clinicians and managers interested in this field, that can be useful to create a specific assessment on the care of DM 2 patients.

The indicators proposed are related to both the process (laboratory determinations, examination activities and content of the medical consultations) as well as the outcomes, subrogated or final, expected according to the control aims proposed and which are supposed to be the fulfilment of an appropriate and effective care of the type 2 diabetic patient.

Those in charge of the CPG's impact and diabetic patients' care assessment must choose the most appropriate time to which each indicator refers to.

Process indicators
• Number of patients ≥45 years with fasting blood glucose carried out in the last 3 years /Population ³ 45 years (percentage).
• Number of patients diagnosed with DM 2/population ≥ 15 years (percentage).
• Number of DM 2 patients with two HbA 1c determinations per year / DM 2 patients (percentage).
• DM 2 patients <75 years with albumin/creatinine ratio carried out in the last year / DM patients <75 years (percentage).
• DM 2 patients with feet examination carried out in the last year / DM 2 patients (percentage).
• DM 2 patients with ocular fundus carried out in the last 3 years / DM 2 patients (percentage).
• Patients with three different educational activities registered in the last year / DM 2 patients (percentage).
• DM 2 patients following an insulin treatment and with a record of self-monitoring of blood blucose / DM 2 patients following an insulin treatment (percentage).
• DM 2 patients without an insulin treatment and with an inappropriate indication of self-monitoring of blood glucose / DM 2 patients without insulin treatment.
Indicators of subrogate outcomes
• DM 2 patients with the average of the last two HbA 1c <7% / DM 2 patients (percentage).
• DM 2 patients with the average of the last two BP determinations < 140 / 80 / DM 2 patients (percentage).
• Non-smoking DM 2 patients / DM 2 patients (percentage).
• DM 2 patients treated with Metformin / DM 2 patients treated with oral anti-diabetic drugs (percentage).
• DM 2 patients registered with ulcers or amputations / DM 2 patients (percentage).
• DM 2 patients with cardiovascular disease under a treatment with statins or antiplatelet agents / DM 2 patients and cardiovascular disease.
• DM 2 patients without cardiovascular disease with coronary risk estimate according to the REGICOR equation / DM 2 patients.
• DM 2 patients without cardiovascular disease but with high coronary risk under treatment with statins / DM 2 patients without cardiovascular disease.

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Indicators of final outcomes
• Number of lower limb amputations / DM 2 patients (percentage). • Number of patients with terminal renal disease / DM 2 patients (percentage). • Number of deaths due to cardiovascular disease / DM 2 patients (percentage). • Number of patients with coronary disease / DM 2 patients (percentage). • Number of patients with cerebrovascular disease / DM 2 patients (percentage). • Number of photocoagulations and vitrectomies / DM 2 patients (percentage). • Number of admission due to hyperosmotic coma or hypoglycaemias / DM 2 patients (percentage).

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Appendix 11. Glossary and abbreviations

Glossary

Cochrane Library: Database on effectiveness created by the Cochrane Collaboration, which includes the original systematic reviews of this organization.

Randomised clinical trial: It is study where the individuals are assigned to two groups at random: one (experimental group) receives the treatment being tested and the other (comparative or control group) receives a standard treatment (or sometimes a placebo). Both groups are assessed to observe any differences in the outcomes. This is how the effectiveness of the treatment is assessed.

Cohort study: consists of the follow-up carried out to one or more cohorts of individuals which includes different levels of exposure to a risk factor and where the incidence of the disease or the condition being tested is measured.

Case-control studies: Study which identifies people with a disease (cases), for example, lung cancer, and compares them to a group without the disease (control). The relationship between one or several factors (for example, tobacco) associated with the disease is assessed by comparing the exposure frequency to this or other factors of both the cases and the controls.

Embase: European database (Dutch) created by Excerpta Medica with biomedical and pharmacological information.

Specificity: Is the amount (or percentage) of really healthy people with a negative outcome in the test. This means, the amount of real negatives.

Altered basal glycaemia: Stage used to define basal glycaemia, which is between normal glycaemia and diabetes. It is defined between the 110-125 mg/dl margins according to the WHO / IDF (between 100-125 mg/dl according to the ADA).

Focal group: It is a conversational technique to obtain information for qualitative investigation, and as such, responds to the targeted sampling criteria, flexibility and circularity characteristic of this methodology. It consists of a group debate, where the participants (between 5 and 10) present and discuss their evaluations on a topic proposed by the researcher-moderator. The debate plan is open or semi-structured and the conversation is recorded and is then transcribed for its further analysis.

Heterogeneity: See «Homogeneity».

Intermediate hyperglycaemias (pre-diabetes or pre-diabetic stages): Impaired fasting glucoseand impaired glucose tolerance are considered intermediate hyperglycaemias.

Homogeneity: Means «similarity». Studies are considered homogeneous if their results do not vary between them more than can be expected at random. Homogeneity is the opposite of heterogeneity.

Confidence interval: It is an interval in which the real magnitude of the effect (never fully known) is found, with a safety or confidence prefixed level. Frequently, the expression «95% confidence interval» is used. This means that within that interval the real value would take place in 95% of the cases.

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Impaired Glucose Tolerance (IGT): Is the stage defined by plasma glycaemia in venous blood two hours after the 75 g glucose tolerance test which is between 140 mg/dl and 200 mg/dl.

Medline: Mainly clinical database created by the American National Library of Medicine.

Meta-analysis: It is a statistical technique which introduces the outcomes of the different studies (diagnose test studies, clinical trials, cohort studies, etc.) in one single estimator, thus giving more importance to the results obtained from major studies.

NICE: Is an organisation, which belongs to the NHS (National Health Service). Its role is to provide physicians, patients and the public with as much evidence as possible, mainly through clinical guidelines.

NNT/NNH: It is a measure of the effectiveness of a treatment. It is the number of people needed to treat (NNT) with a specific treatment to produce or avoid an additional event. In the same way, the number needed to harm (NNH) is defined in order to assess the possible undesirable effects.

Odds Ratio (OR): It is a measure of the effectiveness of a treatment. If it is equal to 1, the effect of the treatment is not different from the control effect. If the OR is greater (or less) than 1, the effect of the treatment is greater (or less) than that of the control. It should be mentioned that the effect being tested can be adverse (for example, death, disability) or desirable (for example, stop smoking).

Pre-diabetes: See «intermediate hyperglycaemias».

Clinical Prediction Rule: It is a clinical tool which quantifies the individual contribution of several components of clinical history, physical examination and the laboratory outcomes or other variables on the diagnose, prognosis or the most probable response of a treatment in a specific patient.

Systematic Reviews (SR): It is a review where the evidence on a specific issue has been systematically identified, assessed and summarised according to predetermined criteria. It may or may not include the meta-analysis.

Relative Risk (RR): The quotient between the event rate in the treatment and control group. Its value follows the same interpretation as the OR.

SIGN: Multidisciplinary Scottish Agency which creates clinical practice guidelines based on evidence as well as on methodological documents on the design of these guidelines.

The terms related to methodological aspects are taken from the CASPe glossary (Critical Appraisal Skills Programme in Spain) in http://www.redcaspe.org/homecasp.asp

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Abbreviations

AA.CC	Autonomous Communities
AAI	Ankle-arm Index
ADA	American Diabetes Association
AHRQ	Agency for Healthcare Research and Quality
AHT	Arterial hypertension
ALLHAT Trial	Antihypertensive and lipid lowering treatment to prevent heart attack Trial
AMI	Acute myocardial infarction
ARB II	Angiotensin –II receptor blocker
ARR	Absolute risk reduction
ATB	Antibiotic
BMI	Body Mass Index
BP	Blood pressure
CARDS Trial	Collaborative Atorvastatin Diabetes Study
CF	Cardiac frequency
CH	Carbohydrates
CI	Confidence Interval
CPG	Clinical Practice Guideline
CPR	Clinical Prevention Rules
CV	Cardiovascular
CVR	Cardiovascular risk
DBP	Diastolic blood pressure
DM	Diabetes Mellitus
DM 2	Diabetes Mellitus type 2
DPP4	Dipeptidyl peptidase-4
DREAM Trial	Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication
ECG	Electrocardiogram
GEDAPS	Spanish study group on diabetes in primary care
GIP	Glucose-dependent insulinotropic polypeptide
GLP-1	Glucagon-like peptide 1
HbA_1c	Glycosilated haemoglobin
HDL	High-density lipoprotein
HOPE Trial	Heart Outcomes Prevention Evaluation
HOT Trial	Hypertension Optimal Treatment
HR	Hazard Ratio
IDF	International Diabetes Federation
IECA	Angiotensin-converting enzyme-inhibitor
IFG	Impaired fasting glucose

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IGT	Impaired glucose tolerance
INSIGHT Trial	Intervention as a Goal in Hypertension Treatment
IV	Intravenous
LDL	Low-density lipoprotein
LH	Likelihood ratio
LIFE Trial	Cardiovascular morbidity and mortality in the Losartan Intervention for Endpoint reduction in hypertension study
MET	Metabolic Equivalent T
MF	Monofilament
n	Number of patients
NHS	National Health System
NICE	National Institute for Clinical Excellence
NNH	Number needed to harm
NNT	Number needed to treat
NPV	Negative predictive value
ODA	Oral anti-diabetic agent
OGTT	Oral glucose tolerance test
OR	Odds Ratio
PAD	Peripheral arterial disease
PDE	Phosphodiesterase
PPV	Positive predictive value
RCT	Randomised clinical trial
RR	Relative risk
SMBG	Self-monitoring of blood glucose
SBP	Systolic blood pressure
SDU	Standard drinking unit which is equivalent to 10 g of pure alcohol
SIGN	Scottish Intercollegiate Guidelines Network
SR	Systematic Review
SSRI	Selective serotonin reuptake inhibitor
SU	Sulfonylurea
TG	Triglycerides
VLDL	Very low-density lipoprotein

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Appendix 12. Declaration of interests

Pablo Daza, Arritxu Etxeberria, Josep Franch, Sonia Gaztambide, Ignacia Idarreta, Nekane Jaio, Mikel Moreno, Rafael Rotaeche, Mª Angeles Sola, Itziar Villa y Jose Antonio Vázquez have declared absence of conflict of interest.

Maria Teresa Abellán has received funding from Almirall Lab. to attend the National Diabetes Congress as well as from Sanofi Lab. to participate in the OSIRIS study. Sara Artola has received funding from GSK, MSD, Sanofi, Novo, Novartis and Servier to attend different congresses and has received fees as lecturer from GSK, MSD, Sanofi, Novo and Lilly. **Alicia Cortázar** has received funding to attend congresses by Lilly, Novo, Nordisk and Almirall and has received fees for lectures by GLAXO y MSD. Javier Díez has received funding for congresses from MSD, Novartis, GSK and Aventis and has received fees for giving lectures from GSK, MSD, Aventis and Lilly. He has also received funding from Aventis, MSD and Lilly for the Programme ADELANTE I and II, and has received financial aid from MSD, Aventis and Novartis to participate in research programs and trials. **Patxi Ezkurra** has received funding for congresses from Novartis. **Francisco Javier García** has received funding from MSD and GSK to attend congresses as well as fees to present lectures on courses from Sanofi-Aventis and Lilly. **Mercedes Machimbarrena** has attended the FAED congress through funding from Novo and has received fees to give lectures from Novo and Aventis. **José Javier Mediavilla** has received funding from Abbott, Bayer, Bristol, Myers Squib, Boehringer Ingelheim, GSK, Lacer, MSD, Novartis, Sanofi-Aventis and Lilly to attend congresses and has received fees to give lectures in courses and conferences from Abbot, Bayer, Bristol, Myers Squib, Boehringer, Ingelheim, GSK, MSD and NovoNordisk, as well as funding from Novartis to participate in a research project. **Carmen Suárez** has received funding from MSD for a Summer School on Pubic Health, she also obtained reference material from Lilly for the SEFAP (Spanish Society of Primary Care Pharmacists) Website, funding from ESTEVE for the Aula FAP (Primary Care Pharmacists) and, from Menarini, Almirall and Janssen for the SEFAP courses. **Alfredo Yoldi** has received funding from GSK to attend congresses and from Novo and Sanofi fees to present lectures.

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Bibliography

1. Estrategia en diabetes del Sistema Nacional de Salud. Madrid: Ministry of Health and Consumer Affairs. Centro de publicaciones; 2007.
2. Grupo de estudio para la diabetes en atención primaria de salud (GEDAPS). Guía para el tratamiento de la DM 2 en la Atención. 4ª ed. 2004.
3. Arteagoitia JM, Larrañaga MI, Rodríguez JL, Fernández I, Piniés JA. Incidence, prevalence and coronary heart disease risk level in known Type 2 diabetes: a sentinel practice network study in the Basque Country, Spain. Diabetología. 2003;46(7):899-909.
4. Documento 2005 de Consenso entre varias sociedades científicas sobre pautas de manejo del paciente diabético tipo 2 en España. Avances en diabetología. 2005;21(Supl 1):1-49.
5. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabet Med. 1998;15(7):539-53.
6. World Health Organization. Definition, Diagnosis and classification of diabetes mellitus and its complications: Report of a WHO Consultation. Part1: Diagnosis and clasification of diabetes mellitus. Geneve: World Heath Organization; 1999.
7. Oliva J, Lobo F, Molina B, Monereo S. Direct health care costs of diabetic patients in Spain. Diabetes Care. 2004;27(11):2616-21.
8. Orozco-Beltran D, Gil-Guillen VF, Quirce F, Navarro-Perez J, Pineda M, Gomez-de-la-Camara A, et al. Control of diabetes and cardiovascular risk factors in patients with type 2 diabetes in primary care. The gap between guidelines and reality in Spain. Int J Clin Pract. 2007;61(6):909-15.
9. Red GEDAPS. Atención primaria y diabetes mellitus tipo 2 en España. Un programa de mejora continua de la calidad asistencial. Educación Diabetológica Profesional. 2005;15(1): 23-8.
10. Age-and sex-specific prevalences of diabetes and impaired glucose regulation in 13 European cohorts. Diabetes Care. 2003;26(1):61-9.
11. Shai I, Jiang R, Manson JE, Stampfer MJ, Willett WC, Colditz GA, et al. Ethnicity, obesity, and risk of type 2 diabetes in women: a 20-year follow-up study 17. Diabetes Care. 2006;29(7):1585-90.
12. Meigs JB, Cupples LA, Wilson PW. Parental transmission of type 2 diabetes: the Framingham Offspring Study. Diabetes. 2000;49(12):2201-7.
13. Barnett AH, Eff C, Leslie RD, Pyke DA. Diabetes in identical twins. A study of 200 pairs 50. Diabetologia. 1981;20(2):87-93.
14. Grant SF, Thorleifsson G, Reynisdottir I, Benediktsson R, Manolescu A, Sainz J, et al. Variant of transcription factor 7-like 2 (TCF7L2) gene confers risk of type 2 diabetes. Nat Genet. 2006;38(3):320-3.
15. Florez JC, Jablonski KA, Bayley N, Pollin TI, de Bakker PI, Shuldiner AR, et al. TCF7L2 polymorphisms and progression to diabetes in the Diabetes Prevention Program. N Engl J Med. 2006;355(3):241-50.

More than 6 years have passed since the publication of this Clinical Practice Guideline and it has not been reviewed

16. Ryan EA, Imes S, Liu D, McManus R, Finegood DT, Polonsky KS, et al. Defects in insulin secretion and action in women with a history of gestational diabetes. Diabetes. 1995;44(5):506-12.

17. Kim C, Newton KM, Knopp RH. Gestational diabetes and the incidence of type 2 diabetes: a systematic review. Diabetes Care. 2002;25(10):1862-8.

18. Harder T, Rodekamp E, Schellong K, Dudenhausen JW, Plagemann A. Birth weight and subsequent risk of type 2 diabetes: a meta-analysis. Am J Epidemiol. 2007;165(8):849-57.

19. Rich-Edwards JW, Colditz GA, Stampfer MJ, Willett WC, Gillman MW, Hennekens CH, et al. Birthweight and the risk for type 2 diabetes mellitus in adult women. Ann Intern Med. 1999;130(4 Pt 1):278-84.

20. Owen CG, Martin RM, Whincup PH, Smith GD, Cook DG. Does breastfeeding influence risk of type 2 diabetes in later life? A quantitative analysis of published evidence. Am J Clin Nutr. 2006;84(5):1043-54.

21. Stuebe AM, Rich-Edwards JW, Willett WC, Manson JE, Michels KB. Duration of lactation and incidence of type 2 diabetes. JAMA. 2005;294(20):2601-10.

22. Hu FB, Manson JE, Stampfer MJ, Colditz G, Liu S, Solomon CG, et al. Diet, lifestyle, and the risk of type 2 diabetes mellitus in women. N Engl J Med. 2001;345(11):790-7.

23. Chan JM, Rimm EB, Colditz GA, Stampfer MJ, Willett WC. Obesity, fat distribution, and weight gain as risk factors for clinical diabetes in men. Diabetes Care. 1994;17(9):961-9.

24. Chen KW, Boyko EJ, Bergstrom RW, Leonetti DL, Newell-Morris L, Wahl PW, et al. Earlier appearance of impaired insulin secretion than of visceral adiposity in the pathogenesis of NIDDM. 5-Year follow-up of initially nondiabetic Japanese-American men. Diabetes Care. 1995;18(6):747-53.

25. Meisinger C, Doring A, Thorand B, Heier M, Lowel H. Body fat distribution and risk of type 2 diabetes in the general population: are there differences between men and women? The MONICA/KORA Augsburg cohort study. Am J Clin Nutr. 2006;84(3):483-9.

26. van Dam RM, Rimm EB, Willett WC, Stampfer MJ, Hu FB. Dietary patterns and risk for type 2 diabetes mellitus in U.S. men. Ann Intern Med. 2002;136(3):201-9.

27. Fung TT, Schulze M, Manson JE, Willett WC, Hu FB. Dietary patterns, meat intake, and the risk of type 2 diabetes in women. Arch Intern Med. 2004;164(20):2235-40.

28. Song Y, Manson JE, Buring JE, Liu S. A prospective study of red meat consumption and type 2 diabetes in middle-aged and elderly women: the women's health study. Diabetes Care. 2004;27(9):2108-15.

29. Liu S, Choi HK, Ford E, Song Y, Klevak A, Buring JE, et al. A prospective study of dairy intake and the risk of type 2 diabetes in women. Diabetes Care. 2006;29(7):1579-84.

30. Jiang R, Manson JE, Stampfer MJ, Liu S, Willett WC, Hu FB. Nut and peanut butter consumption and risk of type 2 diabetes in women. JAMA. 2002;288(20):2554-60.

31. van Dam RM, Hu FB. Coffee consumption and risk of type 2 diabetes: a systematic review. JAMA. 2005 ;294(1):97-104.

32. van Dam RM, Willett WC, Manson JE, Hu FB. Coffee, caffeine, and risk of type 2 diabetes: a prospective cohort study in younger and middle-aged U.S. women. Diabetes Care. 2006;29(2):398-403.

More than 5 years have passed since the publication of this Clinical Practice Guideline, and its validity has not been reviewed

33. Iso H, Date C, Wakai K, Fukui M, Tamakoshi A. The relationship between green tea and total caffeine intake and risk for self-reported type 2 diabetes among Japanese adults. Ann Intern Med. 2006;144(8):554-62.

34. Schulze MB, Manson JE, Ludwig DS, Colditz GA, Stampfer MJ, Willett WC, et al. Sugar-sweetened beverages, weight gain, and incidence of type 2 diabetes in young and middle-aged women. JAMA. 2004 ;292(8):927-34.

35. Carlsson S, Hammar N, Grill V. Alcohol consumption and type 2 diabetes Meta-analysis of epidemiological studies indicates a U-shaped relationship. Diabetologia. 2005;48(6): 1051-4.

36. Howard AA, Arnsten JH, Gourevitch MN. Effect of alcohol consumption on diabetes mellitus: a systematic review. Ann Intern Med. 2004;140(3):211-9.

37. Helmrich SP, Ragland DR, Leung RW, Paffenbarger RS, Jr. Physical activity and reduced occurrence of non-insulin-dependent diabetes mellitus. N Engl J Med. 1991;325(3): 147-52.

38. Lynch J, Helmrich SP, Lakka TA, Kaplan GA, Cohen RD, Salonen R, et al. Moderately intense physical activities and high levels of cardiorespiratory fitness reduce the risk of non-insulin-dependent diabetes mellitus in middle-aged men. Arch Intern Med. 1996;156(12):1307-14.

39. Hu FB, Sigal RJ, Rich-Edwards JW, Colditz GA, Solomon CG, Willett WC, et al. Walking compared with vigorous physical activity and risk of type 2 diabetes in women: a prospective study. JAMA. 1999 ;282(15):1433-9.

40. Patja K, Jousilahti P, Hu G, Valle T, Qiao Q, Tuomilehto J. Effects of smoking, obesity and physical activity on the risk of type 2 diabetes in middle-aged Finnish men and women. J Intern Med. 2005;258(4):356-62.

41. Gambineri A, Pelusi C, Manicardi E, Vicennati V, Cacciari M, Morselli-Labate AM, et al. Glucose intolerance in a large cohort of mediterranean women with polycystic ovary syndrome: phenotype and associated factors. Diabetes. 2004;53(9):2353-8.

42. Tenenbaum A, Motro M, Fisman EZ, Leor J, Freimark D, Boyko V, et al. Functional class in patients with heart failure is associated with the development of diabetes. Am J Med. 2003;114(4):271-5.

43. Consensus development conference on antipsychotic drugs and obesity and diabetes. Diabetes Care. 2004;27(2):596-601.

44. Ramaswamy K, Masand PS, Nasrallah HA. Do certain atypical antipsychotics increase the risk of diabetes? A critical review of 17 pharmacoepidemiologic studies. Ann Clin Psychiatry. 2006;18(3):183-94.

45. Hypertension. Management of Hypertension in adults in primary care. Clinical Guideline 18. National Institute for Clinical Excellence. 2004;Clinical Guideline 18.

46. Elliott WJ, Meyer PM. Incident diabetes in clinical trials of antihypertensive drugs: a network meta-analysis. Lancet. 2007;369(9557):201-7.

47. Luna B, Feinglos MN. Drug-induced hyperglycemia. JAMA. 2001;286(16):1945-8.

48. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care. 1997;20(7):1183-97.

More than 5 years have passed since the publication of this Clinical Practice Guideline and its validity has not been reviewed

49. Brunner EJ, Shipley MJ, Witte DR, Fuller JH, Marmot MG. Relation between blood glucose and coronary mortality over 33 years in the Whitehall Study. Diabetes Care. 2006;29(1): 26-31.

50. Levitan EB, Song Y, Ford ES, Liu S. Is nondiabetic hyperglycemia a risk factor for cardiovascular disease? A meta-analysis of prospective studies. Arch Intern Med. 2004;164(19): 2147-55.

51. Sorkin JD, Muller DC, Fleg JL, Andres R. The relation of fasting and 2-h postchallenge plasma glucose concentrations to mortality: data from the Baltimore Longitudinal Study of Aging with a critical review of the literature. Diabetes Care. 2005;28(11):2626-32.

52. Will new diagnostic criteria for diabetes mellitus change phenotype of patients with diabetes? Reanalysis of European epidemiological data. DECODE Study Group on behalf of the European Diabetes Epidemiology Study Group. BMJ. 1998;317(7155):371-5.

53. Barrett-Connor E, Ferrara A. Isolated postchallenge hyperglycemia and the risk of fatal cardiovascular disease in older women and men. The Rancho Bernardo Study. Diabetes Care. 1998;21(8):1236-9.

54. Glucose tolerance and cardiovascular mortality: comparison of fasting and 2-hour diagnostic criteria. Arch Intern Med. 2001;161(3):397-405.

55. Colagiuri S, Hussain Z, Zimmet P, Cameron A, Shaw J. Screening for type 2 diabetes and impaired glucose metabolism: the Australian experience. Diabetes Care. 2004;27(2): 367-71.

56. Jimeno MJ, Molist BN, Franch NJ, Morato GJ, Ozet G, I, Pons BP. Diagnosticando la diabetes mellitus tipo 2: en atención primaria, con la glucemia basal y la hemoglobina glucosilada es suficiente. Aten Primaria. 2004;34(5):222-8.

57. Perry RC, Shankar RR, Fineberg N, McGill J, Baron AD. HbA 1c measurement improves the detection of type 2 diabetes in high-risk individuals with nondiagnostic levels of fasting plasma glucose: the Early Diabetes Intervention Program (EDIP). Diabetes Care. 2001;24(3):465-71.

58. Ko GT, Chan JC, Tsang LW, Cockram CS. Combined use of fasting plasma glucose and HbA 1c predicts the progression to diabetes in Chinese subjects. Diabetes Care. 2000;23(12): 1770-3.

59. Droumaguet C, Balkau B, Simon D, Caces E, Tichet J, Charles MA, et al. Use of HbA 1c in predicting progression to diabetes in French men and women: data from an Epidemiological Study on the Insulin Resistance Syndrome (DESIR). Diabetes Care. 2006;29(7):1619-25.

60. Consensus Committee. Consensus Statement on the Worldwide Standardization of the Hemoglobin A1C Measurement: The American Diabetes Association, European Association for the Study of Diabetes, International Federation of Clinical Chemistry and Laboratory Medicine, and the International Diabetes Federation. Diabetes Care. 2007;30(9):2399-400.

61. Screening for type 2 diabetes mellitus in adults: recommendations and rationale. Ann Intern Med. 2003;138(3):212-4.

62. Waugh N, Scotland G, McNamee P, Gillett M, Brennan A, Goyder E, et al. Screening for type 2 diabetes: literature review and economic modelling. Health Technol Assess. 2007;11(17):1-144.

63. Grupo de Prevención Cardiovascular del PAPPS. Recomendaciones preventivas cardiovasculares. Aten Primaria. 2007;39(Supl 3):15-26.

More than 5 years have passed since the publication of this Clinical Practice Guideline, and its validity has not been reviewed

64. Screening for type 2 diabetes. Diabetes Care. 2004;27 Suppl 1:S11-S14.

65. Kruijshoop M, Feskens EJM, Blaak EE, de Bruin TWA. Validation of capillary glucose measurements to detect glucose intolerance or type 2 diabetes mellitus in the general population. Clinica Chimica Acta. 2004;341(1-2):33-40.

66. Stahl M, Brandslund I, Jorgensen LG, Hyltoft PP, Borch-Johnsen K, de Fine ON. Can capillary whole blood glucose and venous plasma glucose measurements be used interchangeably in diagnosis of diabetes mellitus? Scand J Clin Lab Invest. 2002;62(2):159-66.

67. Colagiuri S, Sandbaek A, Carstensen B, Christensen J, Glumer C, Lauritzen T, et al. Comparability of venous and capillary glucose measurements in blood. Diabet Med. 2003;20(11):953-6.

68. Sandbaek A, Lauritzen T, Borch-Johnsen K, Mai K, Christiansen JS. The comparison of venous plasma glucose and whole blood capillary glucose in diagnoses of Type 2 diabetes: a population-based screening study. Diabet Med. 2005;22(9):1173-7.

69. Feig DS, Palda VA, Lipscombe L. Screening for type 2 diabetes mellitus to prevent vascular complications: updated recommendations from the Canadian Task Force on Preventive Health Care. CMAJ. 2005;172(2):177-80.

70. Santaguida PL, Balion C, Hunt D, Morrison K, Gerstein H, Raina P, et al. Diagnosis, prognosis, and treatment of impaired glucose tolerance and impaired fasting glucose. Evid Rep Technol Assess (Summ). 2005;(128):1-11.

71. Borch-Johnsen K, Colagiuri S, Balkau B, Glumer C, Carstensen B, Ramachandran A, et al. Creating a pandemic of prediabetes: the proposed new diagnostic criteria for impaired fasting glycaemia. Diabetologia. 2004;47(8):1396-402.

72. Gillies CL, Abrams KR, Lambert PC, Cooper NJ, Sutton AJ, Hsu RT, et al. Pharmacological and lifestyle interventions to prevent or delay type 2 diabetes in people with impaired glucose tolerance: systematic review and meta-analysis. BMJ. 2007;334(7588):299.

73. Norris SL, Zhang X, Avenell A, Gregg E, Schmid CH, Lau J. Long-term non-pharmacological weight loss interventions for adults with prediabetes. Cochrane Database Syst Rev. 2005;(2):CD005270.

74. Van de Laar FA, Lucassen PL, Akkermans RP, Van de Lisdonk EH, De Grauw WJ. Alpha-glucosidase inhibitors for people with impaired glucose tolerance or impaired fasting blood glucose. Cochrane Database Syst Rev. 2006;(4):CD005061.

75. Gerstein HC, Yusuf S, Bosch J, Pogue J, Sheridan P, Dinccag N, et al. Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial. Lancet. 2006;368(9541):1096-105.

76. Beletate V, El DR, Atallah A. Zinc supplementation for the prevention of type 2 diabetes mellitus. Cochrane Database Syst Rev. 2007;(1):CD005525.

77. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med. 2002;346(6):393-403.

78. Chiasson JL, Josse RG, Gomis R, Hanefeld M, Karasik A, Laakso M. Acarbose treatment and the risk of cardiovascular disease and hypertension in patients with impaired glucose tolerance: the STOP-NIDDM trial. JAMA. 2003;290(4):486-94.

79. NICE. Clinical Guideline. Management of type 2 diabetes: Management of blood glucose. London: National Institute for Clinical Excellence; 2002.

More than 5 years have passed since the publication of this Clinical Practice Guideline and its validity has not been reviewed

80. IDF Clinical Guidelines Task Force. Guía global para la DM 2. Brussels: International Diabetes Federation; 2006.

81. Anderson JW, Randles KM, Kendall CWC, Jenkins DJA. Carbohydrate and Fiber Recommendations for Individuals with Diabetes: A Quantitative Assessment and Meta-Analysis of the Evidence. J Am Coll Nutr. 2004;23(1):5-17.

82. Nield L, Moore H, Hooper L, Cruickshank J, Vyas A, Whittaker V, et al. Dietary advice for treatment of type 2 diabetes mellitus in adults. Cochrane Database Syst Rev. 2007;(3):CD004097.

83. Norris SL, Zhang X, Avenell A, Gregg E, Schmid CH, Kim C, et al. Efficacy of pharmacotherapy for weight loss in adults with type 2 diabetes mellitus: a meta-analysis. Arch Intern Med. 2004;164(13):1395-404.

84. Norris SL, Zhang X, Avenell A, Gregg E, Brown TJ, Schmid CH, et al. Long-term non-pharmacologic weight loss interventions for adults with type 2 diabetes. Cochrane Database Syst Rev. 2005;(2):CD004095.

85. Williamson DF, Thompson TJ, Thun M, Flanders D, Pamuk E, Byers T. Intentional weight loss and mortality among overweight individuals with diabetes. Diabetes Care. 2000;23(10):1499-504.

86. American Diabetes Association. Nutrition Recommendations and Interventions for Diabetes: A position statement of the American Diabetes Association. Diabetes Care. 2007;30(suppl_1):S48-S65.

87. Scheen AJ, Finer N, Hollander P, Jensen MD, Van Gaal LF. Efficacy and tolerability of rimonabant in overweight or obese patients with type 2 diabetes: a randomised controlled study. The Lancet. 2006;368(9548):1660-72.

88. Buchwald H, Avidor Y, Braunwald E, Jensen MD, Pories W, Fahrbach K, et al. Bariatric surgery: a systematic review and meta-analysis. JAMA. 2004;292(14):1724-37.

89. Soinio M, Laakso M, Lehto S, Hakala P, Rönnemaa T. Dietary Fat Predicts Coronary Heart Disease Events in Subjects With Type 2 Diabetes. Diabetes Care. 2003;26(3):619-24.

90. Krauss RM FAU, Eckel RH FAU, Howard BF, ppel LJ FAU, niels SR FAU, ckelbaum RJ FAU, et al. AHA Dietary Guidelines: revision 2000: A statement for healthcare professionals from the Nutrition Committee of the American Heart Association.

91. Garg A. High-monounsaturated-fat diets for patients with diabetes mellitus: a meta-analysis. Am J Clin Nutr. 1998;67(3):577S-582.

92. Farmer A, Montori V, Dinneen S, Clar C. Fish oil in people with type 2 diabetes mellitus. Cochrane Database Syst Rev. 2001;(3):CD003205.

93. Koppes LL, Dekker JM, Hendriks HF, Bouter LM, Heine RJ. Meta-analysis of the relationship between alcohol consumption and coronary heart disease and mortality in type 2 diabetic patients. Diabetologia. 2006;49(4):648-52.

94. The implementation of nutritional advice for people with diabetes. Diabetic Medicine. 2003;20(10):786-807.

95. Gillespie S, Kulkarni KD, Daly A. Using Carbohydrate Counting in Diabetes Clinical Practice. Journal of the American Dietetic Association. 1998;98(8):897-905.

96. Pi-Sunyer FX, Maggio CA, McCarron DA, Reusser ME, Stern JS, Haynes RB, et al. Multicenter randomized trial of a comprehensive prepared meal program in type 2 diabetes. Diabetes Care. 1999;22(2):191-7.

More than 5 years have passed since the publication of this Clinical Practice Guideline and its validity has not been reviewed

97. Thomas DE, Elliott EJ, Naughton GA. Exercise for type 2 diabetes mellitus. Cochrane Database Syst Rev. 2006;3:CD002968.

98. Sigal RJ, Kenny GP, Boule NG, Wells GA, Prud'homme D, Fortier M, et al. Effects of Aerobic Training, Resistance Training, or Both on Glycemic Control in Type 2 Diabetes: A Randomized Trial. Ann Intern Med. 2007;147(6):357-69.

99. Church TS, Cheng YJ, Earnest CP, Barlow CE, Gibbons LW, Priest EL, et al. Exercise capacity and body composition as predictors of mortality among men with diabetes. Diabetes Care. 2004;27(1):83-8.

100. Hu FB, Stampfer MJ, Solomon C, Liu S, Colditz GA, Speizer FE, et al. Physical activity and risk for cardiovascular events in diabetic women. Ann Intern Med. 2001;134(2):96-105.

101. Wei M, Gibbons LW, Kampert JB, Nichaman MZ, Blair SN. Low cardiorespiratory fitness and physical inactivity as predictors of mortality in men with type 2 diabetes. Ann Intern Med. 2000;132(8):605-11.

102. Sundstrom J, Riserus U, Byberg L, Zethelius B, Lithell H, Lind L. Clinical value of the metabolic syndrome for long term prediction of total and cardiovascular mortality: prospective, population based cohort study. BMJ. 2006;332(7546):878-82.

103. Tanasescu M, Leitzmann MF, Rimm EB, Hu FB. Physical activity in relation to cardiovascular disease and total mortality among men with type 2 diabetes. Circulation. 2003;107(19):2435-9.

104. Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ. 2000;321(7258):405-12.

105. Selvin E, Marinopoulos S, Berkenblit G, Rami T, Brancati FL, Powe NR, et al. Meta-analysis: glycosylated hemoglobin and cardiovascular disease in diabetes mellitus. Ann Intern Med. 2004;141(6):421-31.

106. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. Lancet. 1998;352(9131):837-53.

107. Qaseem A, Vijan S, Snow V, Cross JT, Weiss KB, Owens DK, et al. Glycemic Control and Type 2 Diabetes Mellitus: The Optimal Hemoglobin A1c Targets. A Guidance Statement from the American College of Physicians. Ann Intern Med. 2007;147(6):417-22.

108. Gaede P, Vedel P, Larsen N, Jensen GV, Parving HH, Pedersen O. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. N Engl J Med. 2003;348(5):383-93.

109. Action to Control Cardiovascular Risk in Diabetes (ACCORD) Trial. ACCORD Blood Sugar Treatment Strategy Announcement, February 6, 2008. Available at: http://www.nhlbi.nih.gov/health/prof/heart/other/accord/ [Accessed in February 2008].

110. Winocour PH. Effective diabetes care: a need for realistic targets. BMJ. 2002;324(7353):1577-80.

111. Bolen S, Feldman L, Vassy J, Wilson L, Yeh HC, Marinopoulos S, et al. Systematic Review: Comparative Effectiveness and Safety of Oral Medications for Type 2 Diabetes Mellitus. Ann Intern Med. 2007;147(6):386-99.

More than 5 years have passed since the publication of this Clinical Practice Guideline and its validity has not been reviewed

112. Inzucchi SE. Oral antihyperglycemic therapy for type 2 diabetes: scientific review. JAMA. 2002;287(3):360-72.

113. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. Lancet. 1998;352(9131):854-65.

114. Donnelly LA, Doney AS, Hattersley AT, Morris AD, Pearson ER. The effect of obesity on glycaemic response to metformin or sulphonylureas in Type 2 diabetes. Diabet Med. 2006;23(2):128-33.

115. Ong CR, Molyneaux LM, Constantino MI, Twigg SM, Yue DK. Long-term efficacy of metformin therapy in nonobese individuals with type 2 diabetes. Diabetes Care. 2006;29(11):2361-4.

116. Garber AJ, Duncan TG, Goodman AM, Mills DJ, Rohlf JL. Efficacy of metformin in type II diabetes: results of a double-blind, placebo-controlled, dose-response trial. Am J Med. 1997;103(6):491-7.

117. Saenz CA, Fernandez E, I, Mataix SA, Ausejo SM, Roque M, Moher D. Metformina para la diabetes mellitus tipo 2. Revisión sistemática y metaanálisis. Aten Primaria. 2005;36(4):183-91.

118. Salpeter S, Greyber E, Pasternak G, Salpeter E. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus. Cochrane Database Syst Rev. 2006;(1):CD002967.

119. Amori RE, Lau J, Pittas AG. Efficacy and Safety of Incretin Therapy in Type 2 Diabetes: Systematic Review and Meta-analysis. JAMA. 2007;298(2):194-206.

120. Goday Arno A, Franch Nadal J, Mata Cases M. Criterios de control y pautas de tratamiento combinado en la DM 2. Update 2004. Medicina Clínica. 2004;123(5):187-97.

121. 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.

122. Van de Laar FA, Lucassen PL, Akkermans RP, Van de Lisdonk EH, Rutten GE, van WC. Alpha-glucosidase inhibitors for patients with type 2 diabetes: results from a Cochrane systematic review and meta-analysis. Diabetes Care. 2005;28(1):154-63.

123. Holman RR, Cull CA, Turner RC. A randomized double-blind trial of acarbose in type 2 diabetes shows improved glycemic control over 3 years (U.K. Prospective Diabetes Study 44). Diabetes Care. 1999;22(6):960-4.

124. Richter B, Bandeira-Echtler E, Bergerhoff K, Clar C, Ebrahim SH. Pioglitazone for type 2 diabetes mellitus. Cochrane Database Syst Rev. 2006;(4):CD006060.

125. Richter B, Bandeira-Echtler E, Bergerhoff K, Clar C, Ebrahim S. Rosiglitazone for type 2 diabetes mellitus. Cochrane Database Syst Rev. 2007;(3):CD006063.

126. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. N Engl J Med. 2007;356(24):2457-71.

127. Singh S, Loke YK, Furberg CD. Thiazolidinediones and Heart Failure: A teleoanalysis. Diabetes Care. 2007;30(8):2148-53.

128. Singh S, Loke YK, Furberg CD. Long-term Risk of Cardiovascular Events With Rosiglitazone: A Meta-analysis. JAMA. 2007;298(10):1189-95.

More than 5 years have passed since the publication of this Clinical Practice Guideline, and its validity has not been reviewed

129. Lincoff AM, Wolski K, Nicholls SJ, Nissen SE. Pioglitazone and risk of cardiovascular events in patients with type 2 diabetes mellitus: a meta-analysis of randomized trials. JAMA. 2007;298(10):1180-8.

130. 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 randomised controlled trial. Lancet. 2005;366(9493):1279-89.

131. Isley WL. Pioglitazone did not reduce a composite endpoint of macrovascular complications and increased risk for heart failure in type 2 diabetes with macrovascular disease. ACP J Club. 2006;144(2):34.

132. Riesgo cardiaco asociado a rosiglitazona. Comunicación de la AEMPS sobre datos recientemente publicados. Nota informativa 2007/08 de la AEMPS Agencia Española de Medicamentos y Productos Sanitarios. Available at http://www.agemed. es/actividad/alertas/usoHumano/seguridad/rosiglitazona-mayo07.htm; [Acceso septiembre 2007].

133. Kahn SE, Haffner SM, Heise MA, Herman WH, Holman RR, Jones NP, et al. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. N Engl J Med. 2006;355(23):2427-43.

134. Safety Alerts for Drugs, Biologics, Devices, and Dietary Supplements. Available at: http:// www fda gov/medwatch/safety/2007/Actosmar0807 pdf [Acceso julio 2007].

135. Rosiglitazona y pioglitazona: incremento de riesgo de fracturas en mujeres 738. Nota informativa 2007/05 de la AEMPS Agencia Española de Medicamentos y Productos Sanitarios. Available at: http://www.agemed.es/actividad/alertas/usoHumano/seguridad/rosiglitazona.htm [accessed in 2007].

136. UKPDS 28: a randomized trial of efficacy of early addition of metformin in sulfonylurea-treated type 2 diabetes. U.K. Prospective Diabetes Study Group. Diabetes Care. 1998;21(1):87-92.

137. Derosa G, Gaddi AV, Piccinni MN, Salvadeo S, Ciccarelli L, Fogari E, et al. Differential effect of glimepiride and rosiglitazone on metabolic control of type 2 diabetic patients treated with metformin: a randomized, double-blind, clinical trial. Diabetes Obes Metab. 2006;8(2):197-205.

138. Garber A, Klein E, Bruce S, Sankoh S, Mohideen P. Metformin-glibenclamide versus metformin plus rosiglitazone in patients with type 2 diabetes inadequately controlled on metformin monotherapy. Diabetes Obes Metab. 2006;8(2):156-63.

139. Dailey GE, III, 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(4):223-9.

140. Roberts VL, Stewart J, Issa M, Lake B, Melis R. Triple therapy with glimepiride in patients with type 2 diabetes mellitus inadequately controlled by metformin and a thiazolidinedione: results of a 30-week, randomized, double-blind, placebo-controlled, parallel-group study. Clin Ther. 2005;27(10):1535-47.

141. Ko GT, Tsang PC, Wai HP, Kan EC, Chan HC. Rosiglitazone versus bedtime insulin in the treatment of patients with conventional oral antidiabetic drug failure: a 1-year randomized clinical trial. Adv Ther. 2006;23(5):799-808.

More than 2 years have passed since the publication of this Clinical Practice Guideline and its validity has not been reviewed

142. Schwartz S, Sievers R, Strange P, Lyness WH, Hollander P. Insulin 70/30 mix plus metformin versus triple oral therapy in the treatment of type 2 diabetes after failure of two oral drugs: efficacy, safety, and cost analysis. Diabetes Care. 2003;26(8):2238-43.

143. Rosenstock J, Sugimoto D, Strange P, Stewart JA, Soltes-Rak E, Dailey G. Triple therapy in type 2 diabetes: insulin glargine or rosiglitazone added to combination therapy of sulfonylurea plus metformin in insulin-naive patients. Diabetes Care. 2006;29(3):554-9.

144. Goudswaard AN, Furlong NJ, Rutten GE, Stolk RP, Valk GD. Insulin monotherapy versus combinations of insulin with oral hypoglycaemic agents in patients with type 2 diabetes mellitus. Cochrane Database Syst Rev. 2004;(4):CD003418.

145. Goudswaard AN, Stolk RP, Zuithoff P, de Valk HW, Rutten GE. Starting insulin in type 2 diabetes: continue oral hypoglycemic agents? A randomized trial in primary care. J Fam Pract. 2004;53(5):393-9.

146. Douek IF, Allen SE, Ewings P, Gale EA, Bingley PJ. Continuing metformin when starting insulin in patients with Type 2 diabetes: a double-blind randomized placebo-controlled trial. Diabet Med. 2005;22(5):634-40.

147. Kvapil M, Swatko A, Hilberg C, Shestakova M. Biphasic insulin aspart 30 plus metformin: an effective combination in type 2 diabetes. Diabetes Obes Metab. 2006;8(1):39-48.

148. Janka HU, Plewe G, Riddle MC, Kliebe-Frisch C, Schweitzer MA, Yki-Jarvinen H. Comparison of basal insulin added to oral agents versus twice-daily premixed insulin as initial insulin therapy for type 2 diabetes. Diabetes Care. 2005;28(2):254-9.

149. Banerjee S, Tran K, Li H, et al. Short-acting insulin analogues for diabetes mellitus: meta-analysisi of clinical outcomes and assessment of cost-effectiveness [Technology Report no 87]. Ottawa: Canadian Agency for Drugs and Technologies in Heath; 2007.

150. Siebenhofer A, Plank J, Berghold A, Jeitler K, Horvath K, Narath M, et al. Short acting insulin analogues versus regular human insulin in patients with diabetes mellitus. Cochrane Database Syst Rev. 2006;(2):CD003287.

151. Horvath K, Jeitler K, Berghold A, Ebrahim SH, Gratzer TW, Plank J, et al. Longacting insulin analogues versus NPH insulin (human isophane insulin) for type 2 diabetes mellitus. Cochrane Database Syst Rev. 2007;(2):CD005613.

152. Rosenstock J, Dailey G, Massi-Benedetti M, Fritsche A, Lin Z, Salzman A. Reduced hypoglycemia risk with insulin glargine: a meta-analysis comparing insulin glargine with human NPH insulin in type 2 diabetes. Diabetes Care. 2005;28(4):950-5.

153. Warren E, Weatherley-Jones E, Chilcott J, Beverley C. Systematic review and economic evaluation of a long-acting insulin analogue, insulin glargine. Health Technol Assess. 2004;8(45):iii, 1-iii,57.

154. [DRAFT] Long-acting insulin analogues for the treatment of diabetes mellitus: meta-analyses of clinical outcomes. Update of CADTH Technology Report No. 92. Ottawa: Canadian Agency for Drugs and Technologies in Heath; 2007.

155. Hu G, Jousilahti P, Qiao Q, Peltonen M, Katoh S, Tuomilehto J. The gender-specific impact of diabetes and myocardial infarction at baseline and during follow-up on mortality from all causes and coronary heart disease. J Am Coll Cardiol. 2005;45(9):1413-8.

156. Juutilainen A, Kortelainen S, Lehto S, Ronnemaa T, Pyorala K, Laakso M. Gender difference in the impact of type 2 diabetes on coronary heart disease risk. Diabetes Care. 2004;27(12):2898-904.

More than 5 years have passed since the publication of this Clinical practice Guideline, and its validity has not been reviewed

157. Natarajan S, Liao Y, Cao G, Lipsitz SR, McGee DL. Sex differences in risk for coronary heart disease mortality associated with diabetes and established coronary heart disease. Arch Intern Med. 2003;163(14):1735-40.

158. Whiteley L, Padmanabhan S, Hole D, Isles C. Should diabetes be considered a coronary heart disease risk equivalent?: results from 25 years of follow-up in the Renfrew and Paisley survey. Diabetes Care. 2005;28(7):1588-93.

159. Vaccaro O, Eberly LE, Neaton JD, Yang L, Riccardi G, Stamler J. Impact of diabetes and previous myocardial infarction on long-term survival: 25-year mortality follow-up of primary screenees of the Multiple Risk Factor Intervention Trial. Arch Intern Med. 2004;164(13):1438-43.

160. Wannamethee SG, Shaper AG, Lennon L. Cardiovascular disease incidence and mortality in older men with diabetes and in men with coronary heart disease. Heart. 2004;90(12):1398-403.

161. Becker A, Bos G, de VF, Kostense PJ, Dekker JM, Nijpels G, et al. Cardiovascular events in type 2 diabetes: comparison with nondiabetic individuals without and with prior cardiovascular disease. 10-year follow-up of the Hoorn Study. Eur Heart J. 2003;24(15):1406-13.

162. Cho E, Rimm EB, Stampfer MJ, Willett WC, Hu FB. The impact of diabetes mellitus and prior myocardial infarction on mortality from all causes and from coronary heart disease in men. J Am Coll Cardiol. 2002;40(5):954-60.

163. Eberly LE, Cohen JD, Prineas R, Yang L. Impact of incident diabetes and incident nonfatal cardiovascular disease on 18-year mortality: the multiple risk factor intervention trial experience. Diabetes Care. 2003;26(3):848-54.

164. Haffner SM, Lehto S, Ronnemaa T, Pyorala K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. N Engl J Med. 1998;339(4):229-34.

165. Evans JM, Wang J, Morris AD. Comparison of cardiovascular risk between patients with type 2 diabetes and those who had had a myocardial infarction: cross sectional and cohort studies. BMJ. 2002;324(7343):939-42.

166. Lee CD, Folsom AR, Pankow JS, Brancati FL. Cardiovascular events in diabetic and nondiabetic adults with or without history of myocardial infarction. Circulation. 2004;109(7):855-60.

167. Lotufo PA, Gaziano JM, Chae CU, Ajani UA, Moreno-John G, Buring JE, et al. Diabetes and all-cause and coronary heart disease mortality among US male physicians. Arch Intern Med. 2001;161(2):242-7.

168. Hu FB, Stampfer MJ, Solomon CG, Liu S, Willett WC, Speizer FE, et al. The impact of diabetes mellitus on mortality from all causes and coronary heart disease in women: 20 years of follow-up. Arch Intern Med. 2001;161(14):1717-23.

169. Hackam DG, Tan MK, Honos GN, Leiter LA, Langer A, Goodman SG. How does the prognosis of diabetes compare with that of established vascular disease? Insights from the Canadian Vascular Protection (VP) Registry. Am Heart J. 2004;148(6):1028-33.

170. McGin T, Guyatt G. Diagnosis. Clinical prediction Rules. In: American Medical Association, editor. User's Guides to the Medical Literature. A manual for evidence-based clinical practice. 2002.

More than 5 years have passed since the publication of this Clinical Practice Guideline and its validity has not been reviewed

171. Marrugat J, D'Agostino R, Sullivan L, Elosua R, Wilson P, Ordovas J, et al. An adaptation of the Framingham coronary heart disease risk function to European Mediterranean areas. J Epidemiol Community Health. 2003;57(8):634-8.

172. Marrugat J, Solanas P, D'Agostino R, Sullivan L, Ordovas J, Cordon F, et al. Estimación del riesgo coronario en Espana mediante la ecuación de Framingham calibrada. Rev Esp Cardiol. 2003;56(3):253-61.

173. Marrugat J, Subirana I, Comin E, Cabezas C, Vila J, Elosua R, et al. Validity of an adaptation of the Framingham cardiovascular risk function: the VERIFICA Study 811. J Epidemiol Community Health. 2007;61(1):40-7.

174. Stevens RJ, Kothari V, Adler AI, Stratton IM. The UKPDS risk engine: a model for the risk of coronary heart disease in Type II diabetes (UKPDS 56). Clin Sci. 2001;101(6):671-9.

175. Jimeno Mollet J, Molist Brunet N, Franch Nadal J, Serrano Borraz V, Serrano Barragán L, Gracia Giménez R. Variabilidad en la estimación del riesgo coronario en la diabetes mellitus tipo 2. Atención Primaria. 2005;35(1):30-6.

176. Hernáez R, Choque L, Giménez M, Costa A, Márquez JI, Conget I. Estimación del riesgo coronario en pacientes con diabetes mellitus tipo 2. ¿Escalas de población general o escalas específicas? Revista Española de Cardiología. 2004;57(6):573-80.

177. Faglia E, Manuela M, Antonella Q, Michela G, Vincenzo C, Maurizio C, et al. Risk reduction of cardiac events by screening of unknown asymptomatic coronary artery disease in subjects with type 2 diabetes mellitus at high cardiovascular risk: an open-label randomized pilot study. Am Heart J. 2005;149(2):e1-e6.

178. Hayden M, Pignone M, Phillips C, Mulrow C. Aspirin for the primary prevention of cardiovascular events: a summary of the evidence for the U.S. Preventive Services Task Force. Ann Intern Med. 2002;136(2):161-72.

179. Hansson L, Zanchetti A, Carruthers SG, Dahlof B, Elmfeldt D, Julius S, et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. Lancet. 1998;351(9118):1755-62.

180. Sacco M, Pellegrini F, Roncaglioni MC, Avanzini F, Tognoni G, Nicolucci A. Primary prevention of cardiovascular events with low-dose aspirin and vitamin E in type 2 diabetic patients: results of the Primary Prevention Project (PPP) trial. Diabetes Care. 2003;26(12):3264-72.

181. Sanmuganathan PS, Ghahramani P, Jackson PR, Wallis EJ, Ramsay LE. Aspirin for primary prevention of coronary heart disease: safety and absolute benefit related to coronary risk derived from meta-analysis of randomised trials. Heart. 2001;85(3):265-71.

182. Risk estimation and the prevention of cardiovascular disease. A national clinical guideline. Edinburgh: Scottish Intercollegiate Guidelines NetworK; 2007.

183. Aspirin effects on mortality and morbidity in patients with diabetes mellitus. Early Treatment Diabetic Retinopathy Study report 14. ETDRS Investigators. JAMA. 1992;268(10): 1292-300.

184. Hennekens CH. Update on aspirin in the treatment and prevention of cardiovascular disease. Am J Manag Care. 2002;8(22 Suppl):S691-S700.

More than 5 years have passed since the publication of this Clinical Practice Guideline and it's validity has not been reviewed

185. de GG. Low-dose aspirin and vitamin E in people at cardiovascular risk: a randomised trial in general practice. Collaborative Group of the Primary Prevention Project. Lancet. 2001;357(9250):89-95.

186. Ridker PM, Cook NR, Lee IM, Gordon D, Gaziano JM, Manson JE, et al. A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. N Engl J Med. 2005;352(13):1293-304.

187. Vijan S, Hayward RA. Pharmacologic lipid-lowering therapy in type 2 diabetes mellitus: background paper for the American College of Physicians. Ann Intern Med. 2004;140(8):650-8.

188. Costa J, Borges M, David C, Vaz CA. Efficacy of lipid lowering drug treatment for diabetic and non-diabetic patients: meta-analysis of randomised controlled trials. BMJ. 2006;332(7550):1115-24.

189. Allemann S, Diem P, Egger M, Christ ER, Stettler C. Fibrates in the prevention of cardiovascular disease in patients with type 2 diabetes mellitus: meta-analysis of randomised controlled trials. Curr Med Res Opin. 2006;22(3):617-23.

190. Colhoun HM, Betteridge DJ, Durrington PN, Hitman GA, Neil HA, Livingstone SJ, et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. Lancet. 2004;364(9435):685-96.

191. Knopp RH, d'Emden M, Smilde JG, Pocock SJ. Efficacy and safety of atorvastatin in the prevention of cardiovascular end points in subjects with type 2 diabetes: the Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in non-insulin-dependent diabetes mellitus (ASPEN). Diabetes Care. 2006;29(7):1478-85.

192. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. The Lancet. 2005;366(9500):1849-61.

193. Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet. 2005;366(9493):1267-78.

194. Law M, Rudnicka AR. Statin safety: a systematic review. Am J Cardiol. 2006;97(8A):52C-60C.

195. Pfeffer MA, Keech A, Sacks FM, Cobbe SM, Tonkin A, Byington RP, et al. Safety and tolerability of pravastatin in long-term clinical trials: prospective Pravastatin Pooling (PPP) Project. Circulation. 2002;105(20):2341-6.

196. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. UK Prospective Diabetes Study Group. BMJ. 1998;317(7160):703-13.

197. Schrier RW, Estacio RO, Esler A, Mehler P. Effects of aggressive blood pressure control in normotensive type 2 diabetic patients on albuminuria, retinopathy and strokes. Kidney Int. 2002;61(3):1086-97.

198. Turnbull F, Neal B, Algert C, Chalmers J, Chapman N, Cutler J, et al. Effects of different blood pressure-lowering regimens on major cardiovascular events in individuals with and without diabetes mellitus: results of prospectively designed overviews of randomized trials. Arch Intern Med. 2005;165(12):1410-9.

More than 5 years have passed since the publication of this Clinical Practice Guideline, and its validity has not been reviewed

199. Vijan S. Hypertension in diabetes. In: BMJ Publishing Group, editor. Clinical Evidence. 2006. p. 1-12.

200. Llisterri Caro JL, Rodriguez Roca GC, onso Moreno FJ, Lou AS, vison Garrote JA, Santos Rodriguez JA, et al. Control de la presión arterial en la población hipertensa española atendida en atención primaria. Estudio PRESCAP 2002. Med Clin (Barc). 2004;122(5):165-71.

201. Whelton PK, Barzilay J, Cushman WC, Davis BR, Iiamathi E, Kostis JB, et al. Clinical outcomes in antihypertensive treatment of type 2 diabetes, impaired fasting glucose concentration, and normoglycemia: Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). Arch Intern Med. 2005;165(12):1401-9.

202. Tatti P, Pahor M, Byington RP, Di Mauro P, Guarisco R, Strollo G, et al. Outcome results of the Fosinopril Versus Amlodipine Cardiovascular Events Randomized Trial (FACET) in patients with hypertension and NIDDM. Diabetes Care. 1998;21(4):597-603.

203. Estacio RO, Jeffers BW, Hiatt WR, Biggerstaff SL, Gifford N, Schrier RW. The effect of nisoldipine as compared with enalapril on cardiovascular outcomes in patients with non-insulin-dependent diabetes and hypertension. New England Journal of Medicine. 1998;338(10):645-52.

204. Mancia G, Brown M, Castaigne A, de LP, Palmer CR, Rosenthal T, et al. Outcomes with nifedipine GITS or Co-amilozide in hypertensive diabetics and nondiabetics in Intervention as a Goal in Hypertension (INSIGHT). Hypertension. 2003;41(3):431-6.

205. Grossman E, Messerli FH. Are calcium antagonists beneficial in diabetic patients with hypertension? Am J Med. 2004;116(1):44-9.

206. Lindholm LH, Ibsen H, Dahlof B, Devereux RB, Beevers G, de Faire U, et al. Cardiovascular morbidity and mortality in patients with diabetes in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. Lancet. 2002;359(9311):1004-10.

207. Wiysonge CS, Bradley H, Mayosi BM, Maroney R, Mbewu A, Opie LH, et al. Beta-blockers for hypertension. Cochrane Database Syst Rev. 2007;(1):CD002003.

208. ONTARGET Investigators, Yusuf S, Teo KK, Pogue J, Dyal L, Copland Schumacher H, Dagenais G, Sleight P, Anderson C. Telmisartan, ramipril, or both in patients at high risk for vascular events. N engl J Med. 2008;358(15):1547-59.

209. Patel A, MacMahon S, Chalmers J, et al. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. Lancet. 2007;370:829-40.

210. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. Heart Outcomes Prevention Evaluation Study Investigators. Lancet. 2000;355(9200):253-9.

211. Adler AI, Stevens RJ, Manley SE, Bilous RW, Cull CA, Holman RR, et al. Development and progression of nephropathy in type 2 diabetes: the United Kingdom Prospective Diabetes Study (UKPDS 64). Kidney International. 2003;63(1):225-32.

212. Strippoli GF, Craig M, Craig JC. Antihypertensive agents for preventing diabetic kidney disease. Cochrane Database Syst Rev. 2005;(4):CD004136.

213. Casas JP, Chua W, Loukogeorgakis S, Vallance P, Smeeth L, Hingorani AD, et al. Effect of inhibitors of the renin-angiotensin system and other antihypertensive drugs on renal outcomes: systematic review and meta-analysis. The Lancet. 366(9502):2026-33.

More than 5 years have passed since the publication of this Clinical Practice Guideline and its validity has not been reviewed

214. Rahman M, Pressel S, Davis BR, Nwachuku C, Wright JT, Jr., Whelton PK, et al. Renal outcomes in high-risk hypertensive patients treated with an angiotensin-converting enzyme inhibitor or a calcium channel blocker vs a diuretic: a report from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). Archives of Internal Medicine. 2005;165(8):936-46.

215. NICE. Clinical Guideline. Management of type 2 diabetes:Retinopathy,screening and early management. London: National Institute for Clinical Excellence; 2002.

216. Harper CA, Livingston PM, Wood C, Jin C, Lee SJ, Keeffe JE, et al. Screening for diabetic retinopathy using a non-mydriatic retinal camera in rural Victoria. Aust N Z J Ophthalmol. 1998;26(2):117-21.

217. Lin DY, Blumenkranz MS, Brothers RJ, Grosvenor DM. The sensitivity and specificity of single-field nonmydriatic monochromatic digital fundus photography with remote image interpretation for diabetic retinopathy screening: a comparison with ophthalmoscopy and standardized mydriatic color photography. Am J Ophthalmol. 2002;134(2):204-13.

218. Hernáez-Ortega MC, Soto-Pedre E, Vázquez JA, Gutiérrez MA, Asúa J. Estudio de la eficiencia de una cámara de retina no-midriática en el diagnóstico de retinopatía diabética. Rev Clin Esp. 1998;198(4):194-9.

219. Younis N, Broadbent DM, Vora JP, Harding SP. Incidence of sight-threatening retinopathy in patients with type 2 diabetes in the Liverpool Diabetic Eye Study: a cohort study. Lancet. 2003;361(9353):195-200.

220. Vazquez JA, Hernaez-Ortega MC, Miguel N, Soto F. Incidencia de retinopatía diabética a partir de un programa de despistaje en cámara no midriática empleado en pacientes diabéticos de la Comunidad Autónoma del País Vasco (CAPV). Investigación comisionada. Report nº Osteba D-06-03. Vitoria-Gasteiz: Health Department. Basque Government; 2003.

221. National Institute for Clinical Excellence. Clinical Guideline F. Management of type 2 diabetes. Renal disease-prevention and early management. London: National Institute for Clinical Excellence; 2002.

222. Newman DJ, Mattock MB, Dawnay AB, Kerry S, McGuire A, Yaqoob M, et al. Systematic review on urine albumin testing for early detection of diabetic complications. Health Technol Assess. 2005;9(30):iii-163.

223. Strippoli GF, Bonifati C, Craig M, Navaneethan SD, Craig JC. Angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists for preventing the progression of diabetic kidney disease. Cochrane Database Syst Rev. 2006;(4):CD006257.

224. Parving HH, Lehnert H, Brochner-Mortensen J, Gomis R, Andersen S, Arner P, et al. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. New England Journal of Medicine. 2001;345(12):870-8.

225. Brenner BM, Cooper ME, de ZD, Keane WF, Mitch WE, Parving HH, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med. 2001;345(12):861-9.

226. Lewis EJ, Hunsicker LG, Clarke WR, Berl T, Pohl MA, Lewis JB, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. New England Journal of Medicine. 2001;345(12):851-60.

More than 5 years have passed since the publication of this Clinical Practice Guideline and its validity has not been reviewed

227. Jennings DL, Kalus JS, Coleman CI, Manierski C, Yee J. Combination therapy with an ACE inhibitor and an angiotensin receptor blocker for diabetic nephropathy: a meta-analysis. Diabet Med. 2007;24(5):486-93.

228. Adriaensen H, Plaghki L, Mathieu C, Joffroy A, Vissers K. Critical review of oral drug treatments for diabetic neuropathic pain-clinical outcomes based on efficacy and safety data from placebo-controlled and direct comparative studies. Diabetes Metab Res Rev. 2005;21(3):231-40.

229. Wong Mc, Chung JWY, Wong TKS. Effects of treatments for symptoms of painful diabetic neuropathy: systematic review. BMJ. 2007;335(7610):87.

230. Wiffen PJ, McQuay HJ, Edwards JE, Moore RA. Gabapentin for acute and chronic pain. Cochrane Database Syst Rev. 2005;(3):CD005452.

231. Wiffen PJ, McQuay HJ, Moore RA. Carbamazepine for acute and chronic pain. Cochrane Database Syst Rev. 2005;(3):CD005451.

232. Hollingshead J, Duhmke RM, Cornblath DR. Tramadol for neuropathic pain. Cochrane Database Syst Rev. 2006;3:CD003726.

233. Eisenberg E, McNicol ED, Carr DB. Efficacy and safety of opioid agonists in the treatment of neuropathic pain of nonmalignant origin: systematic review and meta-analysis of randomized controlled trials. JAMA. 2005;293(24):3043-52.

234. Jose VM, Bhansali A, Hota D, Pandhi P. Randomized, double-blind study comparing the efficacy and safety of lamotrigine and amitriptyline in painful diabetic neuropathy. Diabet Med. 2007;24(4):377-83.

235. Raskin J, Smith TR, Wong K, Pritchett YL, D'Souza DN, Iyengar S, et al. Duloxetine versus routine care in the long-term management of diabetic peripheral neuropathic pain. J Palliat Med. 2006;9(1):29-40.

236. Gilron I, Bailey JM, Tu D, Holden RR, Weaver DF, Houlden RL. Morphine, gabapentin, or their combination for neuropathic pain. N Engl J Med. 2005;352(13):1324-34.

237. Actualización en el tratamiento del dolor neuropático. Infac Vol 15; Nº 3. Available at: http://www osanet euskadi.net 238. Canadian Diabetes Association. Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada. Can J Diabetes; 2003. Report No.: 27.

239. Vardi M, Nini A. Phosphodiesterase inhibitors for erectile dysfunction in patients with diabetes mellitus. Cochrane Database Syst Rev. 2007;(1): CD002187.

240. Apomorphine for erectile dysfunction. Available at http://www jr2 ox ac uk/bandolier/booth/SexHlth/Apo html [Acceso agosto 2007].

241. Gontero P, D'Antonio R, Pretti G, Fontana F, Panella M, Kocjancic E, et al. Clinical efficacy of Apomorphine SL in erectile dysfunction of diabetic men. Int J Impot Res. 2004;17(1):80-5.

242. Tharyan P, Gopalakrishanan G. Erectile dysfunction. Clin Evid. 2006;(15):1227-51.

243. Von Keitz AT, Stroberg P, Bukofzer S, Mallard N, Hibberd M. A European multicentre study to evaluate the tolerability of apomorphine sublingual administered in a forced dose-escalation regimen in patients with erectile dysfunction. BJU Int. 2002;89(4):409-15.

244. Melnik T, Soares B, Nasselo A. Psychosocial interventions for erectile dysfunction. Cochrane Database Syst Rev. 2007;(3):CD004825.

More than 5 years have passed since the publication of this Clinical Practice Guideline, and its validity has not been reviewed

245. NZGG. Management of type 2 diabetes. New Zealand Guidelines Group; 2003.

246. NICE. Clinical Guideline. Management of type 2 diabetes: Prevention and management of foot problems. London: National Institute for Clinical Excellence; 2003.

247. Singh N, Armstrong DG, Lipsky BA. Preventing foot ulcers in patients with diabetes. JAMA. 2005;293(2):217-28.

248. Mayfield JAM, Sugarman JRM. The Use of the Semmes-Weinstein Monofilament and Other Threshold Tests for Preventing Foot Ulceration and Amputation in Persons with Diabetes. Journal of Family Practice. 2000;49(11):S17-S29.

249. Khan NA, Rahim SA, Anand SS, Simel DL, Panju A. Does the clinical examination predict lower extremity peripheral arterial disease? JAMA. 2006;295(5):536-46.

250. McCabe CJ, Stevenson RC, Dolan AM. Evaluation of a diabetic foot screening and protection programme. Diabet Med. 1998;15(1):80-4.

251. Donohoe ME, Fletton JA, Hook A, Powell R, Robinson I, Stead JW, et al. Improving foot care for people with diabetes mellitus--a randomized controlled trial of an integrated care approach. Diabet Med. 2000;17(8):581-7.

252. Lavery LA, Wunderlich RP, Tredwell JL. Disease management for the diabetic foot: effectiveness of a diabetic foot prevention program to reduce amputations and hospitalizations. Diabetes Res Clin Pract. 2005;70(1):31-7.

253. Anichini R, Zecchini F, Cerretini I, Meucci G, Fusilli D, Alviggi L, et al. Improvement of diabetic foot care after the Implementation of the International Consensus on the Diabetic Foot (ICDF): results of a 5-year prospective study. Diabetes Res Clin Pract. 2007;75(2): 153-8.

254. Valk GD, Kriegsman DM, Assendelft WJ. Patient education for preventing diabetic foot ulceration. Cochrane Database Syst Rev. 2005;(1):CD001488.

255. Reiber GE, Smith DG, Wallace C, Sullivan K, Hayes S, Vath C, et al. Effect of therapeutic footwear on foot reulceration in patients with diabetes: a randomized controlled trial. JAMA. 2002;287(19):2552-8.

256. Busch K, Chantelau E. Effectiveness of a new brand of stock 'diabetic' shoes to protect against diabetic foot ulcer relapse. A prospective cohort study. Diabet Med. 2003;20(8): 665-9.

257. Shilipak M. Diabetic nephropaty. Clin Evidence. 2006;15:1-15.

258. Spencer S. Pressure relieving interventions for preventing and treating diabetic foot ulcers. Cochrane Database Syst Rev. 2000;(3):CD002302.

259. Nelson EA, O'Meara S, Craig D, Iglesias C, Golder S, Dalton J, et al. A series of systematic reviews to inform a decision analysis for sampling and treating infected diabetic foot ulcers. Health Technol Assess. 2006;10(12):iii-x, 1.

260. PRODIGY Guidance. Diabetes Type 1 and 2 - foot disease . http://www cks library nhs uk/diabetes_foot_disease [Acceso Junio 2007]

261. Smith J. Debridement of diabetic foot ulcers. Cochrane Database Syst Rev. 2002;(4): CD003556.

262. Bergin SM, Wraight P. Silver based wound dressings and topical agents for treating diabetic foot ulcers. Cochrane Database Syst Rev. 2006;(1):CD005082.

More than 5 years have passed since the publication of this Clinical Practice Guideline and its validity has not been reviewed

263. Bouza C, Munoz A, Amate JM. Efficacy of modern dressings in the treatment of leg ulcers: a systematic review. Wound Repair Regen. 2005;13(3):218-29.

264. The NHS Health Technology Assessment Programme. Randomised controlled trial of the use of three dressing regimens in the management of chronic ulcers of the foot in diabetes (proyect in progress). http://www hta ac uk/project/1357 asp [Acceso junio 2007].

265. Shilipak M. Diabetic nephropathy. In: BMJ Publishing Group, editor. Clinical Evidence. London: 2006. p. 1-15.

266. Armstrong DG, Nguyen HC, Lavery LA, van Schie CH, Boulton AJ, Harkless LB. Off-loading the diabetic foot wound: a randomized clinical trial. Diabetes Care. 2001;24(6):1019-22.

267. Caravaggi C, Faglia E, De GR, Mantero M, Quarantiello A, Sommariva E, et al. Effectiveness and safety of a nonremovable fiberglass off-bearing cast versus a therapeutic shoe in the treatment of neuropathic foot ulcers: a randomized study. Diabetes Care. 2000;23(12):1746-51.

268. Katz IA, Harlan A, Miranda-Palma B, Prieto-Sanchez L, Armstrong DG, Bowker JH, et al. A randomized trial of two irremovable off-loading devices in the management of plantar neuropathic diabetic foot ulcers. Diabetes Care. 2005;28(3):555-9.

269. Zimny S, Meyer MF, Schatz H, Pfohl M. Applied felted foam for plantar pressure relief is an efficient therapy in neuropathic diabetic foot ulcers. Exp Clin Endocrinol Diabetes. 2002;110(7):325-8.

270. Cruciani M, Lipsky BA, Mengoli C, de LF. Are granulocyte colony-stimulating factors beneficial in treating diabetic foot infections?: A meta-analysis. Diabetes Care. 2005;28(2):454-60.

271. NICE. Guidance on the use of patient-education models for diabetes. Technology appraisal 60. London: National Institute for Clinical Excellence; 2003.

272. Loveman E, Cave C, Green C, Royle P, Dunn N, Waugh N. The clinical and cost-effectiveness of patient education models for diabetes: a systematic review and economic evaluation. Health Technol Assess. 2003;7(22):iii, 1-iii190.

273. Gary TL, Genkinger JM, Guallar E, Peyrot M, Brancati FL. Meta-analysis of randomized educational and behavioral interventions in type 2 diabetes. Diabetes Educ. 2003;29(3): 488-501.

274. Ellis SE, Speroff T, Dittus RS, Brown A, Pichert JW, Elasy TA. Diabetes patient education: a meta-analysis and meta-regression. Patient Educ Couns. 2004;52(1):97-105.

275. van Dam HA, van der HF, van den BB, Ryckman R, Crebolder H. Provider-patient interaction in diabetes care: effects on patient self-care and outcomes. A systematic review. Patient Educ Couns. 2003;51(1):17-28.

276. Montori VM. Review: interventions focusing on patient behaviors in provider-patient interactions improve diabetes outcomes. ACP J Club. 2004;140(2):51.

277. Norris SL, Engelgau MM, Narayan KM. Effectiveness of self-management training in type 2 diabetes: a systematic review of randomized controlled trials. Diabetes Care. 2001;24(3):561-87.

278. Chodosh J, Morton SC, Mojica W, Maglione M, Suttorp MJ, Hilton L, et al. Meta-analysis: chronic disease self-management programs for older adults. Ann Intern Med. 2005;143(6):427-38.

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279. Norris SL, Nichols PJ, Caspersen CJ, Glasgow RE, Engelgau MM, Jack L, et al. Increasing diabetes self-management education in community settings. A systematic review. Am J Prev Med. 2002;22(4 Suppl):39-66.

280. Deakin T, McShane CE, Cade JE, Williams RD. Group based training for self-management strategies in people with type 2 diabetes mellitus. Cochrane Database Syst Rev. 2005;(2):CD003417.

281. Dalmau Llorca MR, Garcia BG, Aguilar MC, Palau GA. Educación grupal frente a individual en pacientes diabéticos tipo 2. Aten Primaria. 2003;32(1):36-41.

282. Karter AJ, Ackerson LM, Darbinian JA, D'Agostino RB, Jr., Ferrara A, Liu J, et al. Self-monitoring of blood glucose levels and glycemic control: the Northern California Kaiser Permanente Diabetes registry. Am J Med. 2001;111(1):1-9.

283. Nathan DM, McKitrick C, Larkin M, Schaffran R, Singer DE. Glycemic control in diabetes mellitus: have changes in therapy made a difference? Am J Med. 1996;100(2):157-63.

284. Welschen LM, Bloemendal E, Nijpels G, Dekker JM, Heine RJ, Stalman WA, et al. Self-monitoring of blood glucose in patients with type 2 diabetes who are not using insulin. Cochrane Database Syst Rev. 2005;(2):CD005060.

285. Home glucose monitoring makes little difference in type 2 diabetes. J Fam Pract. 2005;54(11):936.

286. Sarol JN, Jr., Nicodemus NA, Jr., Tan KM, Grava MB. Self-monitoring of blood glucose as part of a multi-component therapy among non-insulin-requiring type 2 diabetes patients: a meta-analysis (1966-2004). Curr Med Res Opin. 2005;21(2):173-84.

287. Farmer A, Wade A, Goyder E, Yudkin P, French D, Craven A, et al. Impact of self monitoring of blood glucose in the management of patients with non-insulin treated diabetes: open parallel group randomised trial. BMJ. 2007;335(7611):132.

288. Oria-Pino A, Montero-Pérez FJ, Luna-Morales S, del Campo-Vazquez P, Sánchez-Guijo P. Efectividad y eficacia del autoanálisis de la glucemia capilar en pacientes con DM 2. Med Clin (Barc). 2006;126(19):728-35.

289. O'Kane MJ, Bunting B, Copeland M, Coates VE; on behalf of the ESMON group. Efficacy of self monitoring of blood glucose in patients with newly type 2 diabetes (ESMON study): randomised controlled trial. BMJ. 2008 Apr 17. [Epub ahead of print].

290. Griffin S, Kinmonth AL. Diabetes care: the effectiveness of systems for routine surveillance for people with diabetes. Cochrane Database Syst Rev. 2000;(2): CD000541.

291. Renders CM, Valk GD, Griffin S, Wagner EH, Eijk JT, Assendelft WJ. Interventions to improve the management of diabetes mellitus in primary care, outpatient and community settings. Cochrane Database Syst Rev. 2001;(1):CD001481.

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