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The T2D is a complex and heterogeneous disease, with multiple variables that might influence on its treatment. For example, it can appear in a wide range of ages, the evolution time is very variable, the patients usually have overweight or obesity, but they can also have a normal weight, concomitant diseases can occur that contraindicate the use of certain antihyperglycemics, the tolerance of the drugs is individual, etc. On the other hand, its prevalence is alarmingly high, with a constant growth during the last years. It seems that it will not stop at least during the next decade, with an estimate of more than 300 million patients with T2D worldwide. Only these two last characteristics explain the reason of the deluge of consensus and guidelines published recently about the treatment of T2D. Its heterogeneity might make us doubt about which is the best therapeutic option for a certain patient, and its high prevalence make the health/governmental authorities take an active part with the intention of avoiding a pharmaceutical bulky invoice. Moreover, at present we count with more than 30 antihyperglycemic agents corresponding to nine different therapeutic groups (biguanides, alpha glucosidase inhibitors, sulphonylureas, glinides, glitazones, dipeptidyl peptidase-4 inhibitors [DPP-4], glucagon-like peptide-1 analogues [GLP-1], basal insulin and fast acting insulin), which need to find their place at the therapeutic scheme of the T2D.

During 2008, we have attended to the almost simultaneous publication of an important number of consensus and guidelines about the treatment of T2D that though addressed to a same objective; differ in the way of achieving it. Of all of them, perhaps the most known one is the consensus of the American Diabetes Association-European Association for the Study of Diabetes (ADA-EASD), published at the end of 2008, and which caused certain controversy within the scientific community. However, there are other guidelines and consensus that have also come out during the same year and that deserve our attention. Therefore, the characteristics of the already mentioned consensus ADA-ESAD and the National Institute for Clinical Excellence (NICE) are detailed below as well as the consensus of the Canadian Diabetes Association (CDA) the guidelines of the Ministry of Health (MH) of Spain and the Diabetes in Primary Care Study Group (GEDAPS). In order to compare them, we shall discuss about the first, second and third stage of the treatment.
Therapeutic objective

The glycosylated hemoglobin (HbA1c) determines the therapeutic objective. Practically, all of them base themselves in their therapeutic actions in achieving a HbA1c lower than 7%. Only the NICE looks for HbA1c lower than 6.5% initially, passing onto an objective of HbA1c <7.5% once the biotherapy fails. The comparisons among the recommendations of the different consensus and guidelines according to the different therapeutic stages are summarized in Table 1.

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<th>Table 1. Comparison of the guidelines and consensuses according to the different therapeutic stages for the T2D</th>
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Therapeutic objective

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Special characteristics of the analyzed consensus and guidelines

In the ADA-EASD consensus, it is advised against the glibenclamide due to the high incidence of hypoglycemias it entails, the sulphonylureas are suspended when starting the treatment with basal insulin, and the rest of the treatments are included in a second level of lower scientific evidence. The pioglitazone is placed in this level, but not the rosiglitazone due to its potential cardiovascular risk, and also the exenatide. The consensus includes the DPP-4 inhibitors in “other treatments” as well as the alpha-glucosidase inhibitors, the glinides and the pramlintide, due to its lower or equivalent hypoglycemic power, its scarce experience and its high cost.

The NICE consensus advises to use sulphonylureas as treatment starting in case of normal weight or high glycemies, and the possibility of treatment with exenatide is included in the third stage if the body mass index (BMI) is >35 kg/m² and if there are psychological repercussions arisen from obesity. In case of considering the treatment with glitazones, the pioglitazone is recommended. The treatment with DPP-4 inhibitors is not considered either with insulin detemir, which shall be analyzed in a specific document that will come out in the next months.

Importance is given to the control of the post-prandial glycemia in the Canadian consensus and it is explained which are the specific drugs that can control it. The rosiglitazone is not excluded because it is considered that there are no clear evidences about the implication in a higher cardiovascular risk. The GLP-1 agonists are not included, without specifying the reason, nor are the sulphonylureas suspended when starting the basal insulin.

The possibility of sulphonylureas are considered in the MH guideline as starting of the treatment in case of normal weight; the treatment with glitazones is recommended only as a second option in case of intolerance / contraindication to other drugs, and the use of pioglitazone is recommended. In case of intolerance to the metformin in the first stage, the sulphonylureas are recommended and pioglitazone in the second stage. Neither the GLP-1 nor the DPP-4 inhibitors are included, due to the lack of data about its safety at long term.

Finally, the GEDAPS Network does not recommend to suspend the sulphonylureas when starting the basal insulin, it does not include
the insulin in the second stage or incorporate the GLP-1 agonists. These two last aspects are being evaluated again, with a high probability to be included in the next guideline update.

This analysis might conclude with the following phrase: “same problem, different consensus”. The main discrepancies would turn around the administration or not of metformin as from the diagnosis, how to act when the first therapeutic option fails (some authors recommend to add sulphonylureas and others to choose the drug according to the characteristics of the patient) and what to do in the third therapeutic stage (third drug versus adding insulin). As regards to the common weaknesses, we could mention that all the consensuses recommend starting in the same way, without taking into account the initial HbA1c, except for the Canadian consensus, which categorizes according to the HbA1c level (<9 or >9%). There are not either many specifications about what to do if metformin is contraindicated or it is not tolerated, as it does not seem logical from a physiopathology point of view to restart to the sulphonylureas directly. It has not been studied in depth about the differences that exist among the different sulphonylureas that we might choose if they are indicated, except for the recommendation of avoiding glibenclamide. Finally, everything is based in the HbA1c. However, we know that when we get closer to the therapeutic objective, for example with HbA1c <7.3%, the postprandial control becomes more important, which has to be taken into account when choosing a drug or the other. It is not known with accuracy if other parameters (HOMA-R, HOMA-B, C-peptide, glycemic variability, etc.) might be useful when taking the decision, though all this can be history if finally the investigation in pharmacokinetics allows us to choose the treatments à la carte.

In conclusion, it is evident that up to date there are different strategies with the objective of achieving the best glycemic control of the patient with T2D, which might probably reflect the own heterogeneity of such disease. Perhaps this datum is the one that offers more cohesion to the treatment individualization, as regards to the different characteristics of the patients (weight, evolution time, age, HbA1c, etc.). One of the most important current limitations of the treatment algorithms for the T2D is the shortage of well-designed randomized and controlled studies, which compare the different strategies of treatment, particularly the different combinations of drugs among them. In view of all this, the starting of head-to-head studies of the different therapeutic options might be very useful, as well as others addressed to assess the effects on the cardiovascular risk factors, that determine the first causes of mortality of most the patients with T2D.

As a personal opinion, the central objective when issuing any therapeutic consensus has to be the patient, and other factors (financing, etc.) should not constitute the main argument for it. Moreover, we should not forget that most of the health expenses caused by the diabetes arise from the chronic complications. An adequate and early treatment of this disease might prevent the onset of many of them, though it might not be necessary (or yes?) to reach the proposal of Dr. DeFronzo (metformin, pioglitazone and exenatide since the diagnosis of T2D).

Declaration of potential conflict of interests
F.J. Escalada San Martín states that there are no conflicts of interest as regards to the content of this article.

References
Abstract
Type 1 diabetes (T1D) is a chronic immune-mediated disease, characterised by a selective loss of insulin-producing β-cells in the pancreatic islets. Susceptibility is determined by interactions of multiple genes with unknown environmental factors. Around 50% of the genetic risk of the disease is explained by HLA, although other genes with a smaller effect are also involved. Most of the known risk genes for T1D play a role in immunity, mostly through T-cell regulation (CTLA4, PTPN22, IL-2RA) and cytokine production or modulation (VDR, SUMO4). The insulin gene (INS) represents an exception to this, and is probably the only gene specifically associated with T1D and not with other autoimmune diseases. Ongoing genome-wide association studies are providing evidence of multiple known and previously unknown risk genes. New analytical tools are continuously being developed to handle the vast amounts of data produced, as well as to account for multiple comparisons and assess combined effects such as gene-gene and gene-environment interactions. In this review, we will give an overview of the most important genes identified to date, analyse the genetic evidence supporting them as T1D susceptibility genes and discuss the mechanisms mediating their contribution to the pathogenesis of the disease.

Keywords: autoimmune, insulin-dependent, family risk, prediction.

Introduction
Type 1 diabetes (T1D) is one of the most common chronic diseases in childhood, with an incidence ranging from 0.1 to 64/100,000 per year (China vs Finland) and increasing in most of the countries where it has been studied DIAMOND and EURODIAB.1-3 In Spain, according to most studies, the incidence per 100,000 inhabitants and year ranges between 9.5 and 16.4 for children diagnosed before the age of 15.6-13 An exception to these are represented by recent results from Castilla-Leon, showing an incidence of 22/100,000/yr,14 from Ciudad Real (26/100,000/yr)15 and data from the Canary Islands. The latter region has the highest rate of childhood T1D ever reported in Spain, with the most recent incidence (32/100,000/yr on the island of La Palma) approaching that of some Northern European countries.16,17 In addition, some studies show an increasing trend in the incidence of T1D in Spain,12,16 whereas others do not.6

Type 1A diabetes (T1D) is a complex, multifactorial disease, which leads to the autoimmune destruction of pancreatic, insulin-producing, β-cells. Its ultimate cause is unknown, but both environmental and genetic factors have proved to play a role in its development. The present review will focus on the latter. Although only 10-12% of patients with T1D have a family history of the disease at diagnosis, with longer follow-up the frequency increases to up to 25%.18 In addition, having a first degree relative with the disease increases the risk from 2.5 to more than 100 times, depending on who the affected family member is (table 1).

The most established genetic locus contributing to T1D and many other autoimmune diseases is the major histocompatibility complex (MHC), which includes the genes encoding the human leukocyte antigen gene (HLA), crucial in antigen presentation. In addition, several other genes have been established as contributing to the development of the disease, although to a smaller extent than HLA. More than 20 different loci have been proposed to account for the genetic risk of T1D (figure 1), but only a minority had been confirmed until very recently. At
present, we are witnessing an «explosion» of risk genes, thanks to the availability of new genotyping technologies and bioinformatic tools.

**Recent development in genetic research**

The genotyping and analytical tools made available in recent years have profoundly changed the way we understand genetics research. Genotyping methods have allowed for several hundreds of thousands genetic variations to be studied, as opposed to only a few at a time with previous technology. This fact has also changed the strategy of studies, moving from directed, hypothesis-based search for candidate genes to non hypothesis-based, unbiased whole genome association studies which complement the former. Sample sizes have increased from a few hundreds to many thousands of patients. In complex diseases like diabetes, this increase in sample size is crucial if we aim to identify genes with moderate effects on disease risk. In that sense, we have moved from competition to collaboration between research groups and large networks and consortia have been established: the Type 1 Diabetes Genetics Consortium (T1DGC), the Wellcome Trust Case Control Consortium (WTCCC) and The Genetics Association Information Network (GAIN).

Finally, new analytical tools have had to be developed in order to tackle the vast amounts of information delivered by high through-put genotyping technologies. Both linkage and association studies become more complex with increasing number of genes being simultaneously included. The risk of false positive results has to be accounted for, interaction analyses are necessary to elucidate combined genetic effects, and new tools for analysis are in continuous development.19-21

**Most established risk genes**

**Major histocompatibility complex**

The genetic region encoding the human MHC, HLA, also designated as IDDM1, is by far the most solidly estab-
lished risk locus for T1D.\textsuperscript{22-24} It is located on the short arm of chromosome 6 (6p21.3), a dense region of highly polymorphic genes extending for 3.5 Mb. The classical class I HLA loci (telomeric) comprise HLA-A, -B, and -C, and class II (centromeric) comprise HLA-DR (DRA, DRB), -DQ (DQA, DQB) and -DP (DPA, DPB). The class III HLA region (located between class I and class II) includes the complement genes C2, C4, Bf, heat shock proteins genes (\textit{HSP70}), tumour necrosis factor genes (\textit{TNF}), 21-hydroxylase (21-OH) and others (figure 2).

HLA accounts for up to 50\% of the genetic risk,\textsuperscript{25} with major effects attributed to certain DR and DQ genes. However, due to high linkage disequilibrium in the region (DR and DQ alleles tend to be inherited together) it is difficult to determine those responsible for the risk. Indeed, associations of HLA alleles with T1D should be considered haplotype specific rather than allele specific. A recent meta-analysis of 38 studies confirmed that haplotypes comprised of DRB1*0401, *0402 or *0405 and DQB1*0301 (DR4-DQ8) were associated with the highest risk of T1D, followed by DRB1*0301 DQB1*0200 (DR3-DQ2) and DRB1*0404 DQB1*0302. The highest risk of T1D is given by the combination of DR3 and DR4 in one genotype. The “neutral” category of haplotypes includes DRB1*0800 DQB1*0402, DRB1*0901 DQB1*0303 (DR9) and DRB1*0100 DQB1*0501 (DR1) and the most protective includes DRB1*1400 DQB1*0503 and DRB1*1500 DQB1*0602 (DR2).\textsuperscript{26} Results from the T1DGC expand these haplotypes to include DQA1, as well as DRB1 and DQB1\textsuperscript{27} (table 2). Their results also indicate that the risk associated with certain HLA haplotypes can be influenced by the genotypic context, as exemplified by the high risk conferred by the trans-complementing DQ heterodimer encoded by the DQA*0501 allele on DR3 and the DQB1*0302 on some DR4 haplotypes.\textsuperscript{27}

In Spain, unlike in other European populations, DR3 seems to confer a higher risk of T1D than DR4 according to most,\textsuperscript{28,29} albeit not all of the studies.\textsuperscript{7} These findings may be due to the particularly high-risk haplotypes associated with DR3 in Spain.\textsuperscript{28,30}

Although DR and DQ alleles confer most of the genetic risk for T1D, class I alleles and maybe other loci within the MHC region are also important in the development of the disease. Further genotyping of class I alleles in
carriers of high-risk class II HLA haplotypes has given further insight into this matter. Siblings of patients with T1D, identical for their DR3/DR4-DQ8 genotypes, who share both HLA haplotypes (defined by HLA A and B, too) with the proband, have a 55% risk of developing T1D by the age of 12 (vs 5% of those sharing 1 or no haplotype). Furthermore, the remarkably conserved HLA A1-B8-DR3 haplotype seems to reduce the risk conferred by DR3-DQ2. Several other reports support an effect of HLA class I genes on disease susceptibility, in particular the HLA-A*2401, *0101 and *0302 and HLA-B*39 alleles. A highly conserved haplotype (B18 AH 18.2), particularly prevalent in the Spanish population, modulates the risk conferred by the DR3-DQ2 alleles. In fact, markers included in the HLA class III region (BAT-2*2 and TNFa2bI) have been found to predict risk in carriers of DR3-DQ2, although it is uncertain whether this effect persists after accounting for class I genes. In addition, a recent report from the T1DGC MCH fine-mapping project identifies additional risk single-nucleotide polymorphisms (SNPs) in the vicinity of HLA-G, COL11A2 and RING1. Other genes within the MHC region that have been reported to be associated with T1D include MIC-A and ITP3, but the results have not been replicated when LD with other class I and class II genes has been taken into account.

Finally, a new locus telomeric to MHC (UBD/MAS1L) has shown to predict development of type 1 diabetes independently of class I and class II genes. Replication in other populations, as well as functional studies of the candidate genes should provide information about their role in the pathogenesis of the disease.

Non-MHC genes

Although HLA is responsible for up to 50% of the genetic risk of T1D, other genes are involved, too, albeit with a weaker effect (odds ratios in the 1.15-1.3 range). Most of these genes play important roles in immunity and many are not specific to T1D, but also influence risk for other autoimmune diseases (table 3).

**INS**

The insulin gene (INS), located on chromosome 11p15.5 (IDDM2), is expressed in β-cells and in the human thymus, an expression site likely to be involved in immune tolerance. Two recent studies confirmed that insulin is a major and primary target for autoreactive T-cells both in humans with T1D and in NOD mice. The susceptibility locus IDDM2 maps to a minisatellite composed of a variable number of tandem repeat (VNTR) polymorphism situated 0.5 kb upstream of INS, in the promoter region of the gene. In Caucasians, the main classes of VNTR region minisatellites are named VNTR I (26-63 repeating units) and VNTR III (140-210 units) alleles, where the former is associated with the highest risk of T1D. Although the precise function of the VNTR is still uncertain, the feature of the promoter region of INS may influence the binding of the AIRE transcription factor. The latter regulates the expression of self antigens and controls the thymic expression of insulin and the deletion of autoreactive T-cells during negative selection. The development of immune tolerance to insulin may be reduced through reduction of insulin transcription in thymic medullary epithelial cells. Indeed, the level of insulin expression in the human thymus correlates with the VNTR polymorphism, which in turn correlates with diabetes susceptibility. Recent studies of the INS locus showed that the SNPs -2221MspI, -23 HphI (A/T) and +1140 (A/C) confer the highest susceptibility to T1D. Because of their strong linkage disequilibrium with the VNTR, these polymorphism can even be used as markers of the latter.

**CTLA4**

The cytotoxic T lymphocyte antigen-4 (CTLA4) plays an important role in immune response regulation and is strongly associated with autoimmune diseases.
CD28 homologue is mapped to the genetic region of the human IDDM12 locus on chromosome 2q31.60 Its exclusive expression on activated CD4+ and CD8+ T-cells carrying CD2861 in mice seems to be controlled by the Foxp3 gene.62-64 CTLA4 appears to attenuate immune responses by several mechanisms. As a negative regulator of T-cell activation, CTLA4 inhibits T-cell co-stimulation through intercellular interaction, competing for CD28 ligands (CD80/CD86) that are expressed on the surface of antigen presenting cells (APCs). Unlike CD28, which contributes to T-cell activation and maintenance of T-cell response (two signal hypothesis),65,66 CTLA4 restricts the initiation and progression of T-cell immunity.67-69 It also inhibits T-cell activation by different intracellular signalling pathways,70,71 mediates apoptosis of activated human T lymphocytes in an antigen-restricted way72,73 and has an effect on the suppressive activity of regulatory T-cells (Tregs).74-76 The latter are important for maintenance of self-tolerance and immune homeostasis in the absence of exogenous antigens (Ag) and for control of Ag-specific responses.77 Specific deficiency of CTLA4 in Tregs in knock-out mice impairs suppressive function of Tregs and results in spontaneous development of systemic lymphoproliferation and fatal T-cell-mediated autoimmune disease with multiorgan lymphocytic infiltration and tissue destruction.58,80,81

The T1D-associated CTLA4 haplotype contains several polymorphisms in tight linkage disequilibrium (LD), any one of which or a combination thereof could determine the functional effect. The SNP +6230G>A (CT60) rs706778 (A/G), rs3118470 (G/T), ss52580101, rs11594656 is associated with splicing or altered levels of steady state CTLA4 mRNA.59,60 However, recent results82,83 deny the effect of this SNP on modulation of steady-state mRNA of any known CTLA4 isoform but do not rule out its potential role in the development of T1D. Promoter polymorphisms -319C>T and -1661A>G (the latter in Moroccan and Indian population) possibly contribute to T1D through transcriptional effects on expression,84,85 and SNP +49A>G on exon 1 of CTLA486 causes a change in the signal peptide, resulting in less CTLA4 at the cell surface. This explains the reduced inhibitory function of CTLA4 reported in individuals with the +49G allele and is associated with reduced control of T-cell proliferation.87,88 Both the CD28 and CTLA4 pathways are targets for current immunomodulatory therapies.89
PTPN22

Similar to CTLA4, PTPN22 (protein tyrosine phosphatase non-receptor type 22) is a diabetes susceptibility locus that is shared by several autoimmune diseases.80-81 It is located on chromosome 1p13 and encodes a lymphoid protein tyrosine kinase (Lyp). Lyp is expressed in lymphoid T-cells, where it modulates the activation of protein kinases involved in early T-cell receptor (TCR) mediated signalling events,92 acting as a negative regulator of TCR signalling.92-94 The Arg620Trp (1858C/T) SNP in PTPN22 appears to promote autoimmunity in multiple ways, though there is only limited data regarding the mechanism by which variations in this gene contribute to the pathogenesis of T1D and how they affect immune function in humans. The Arg620Trp variant has been reported to be associated with the development of insulin autoantibodies (in contrast to GAD and IA-2 antibody levels, which were not significantly influenced by this polymorphism) and an accelerated progression of the autoimmune process in T1D.95 According to two studies,93,96 the Arg620Trp variant causes a gain-of-inhibitory function that leads to enhanced suppression of TCR signal transduction, a profound defect in T-cell responsiveness to antigen stimulation and decreased interleukin 2 (IL-2) secretion in T-cells. IL-2 is mainly produced by activated T-cells, promoting their proliferation and expansion.97 Homozygosity for the Arg620Trp variant is associated with reduced CD4+T-cell and B-cell activation and a shift in the memory T- and B-cell populations to an increase in circulating memory T-cells and fewer and less effective memory B-cells.94,96 Lower T-cell signalling may allow the escape of self-reactive T-cells from thymic deletion and lead to impaired self tolerance and reduced Treg development,96,98 and cause autoimmunity.57 There have been attempts to assess whether the SNPArg620Trp is the sole T1D susceptibility variant in PTPN22 and, although it seems to be the major risk variant for T1D in this chromosomal region in European populations, the possibility still remains that a yet unidentified variant could have a role in susceptibility to the disease.99-101

IL-2RA

A polymorphism in interleukin-2 receptor (IL-2RA), located on chromosome 10p15-p14,102 has recently shown an association with risk of T1D. IL-2RA encodes the α-chain of the high-affinity heterodimeric IL-2 cytokine receptor (CD25), highly expressed by activated Tregs.103,104 Genetic evidence also suggests a crucial role for IL-2 in T1D.102,103 Located on chromosome 4q27, IL-2 plays a critical role in programming T-cells for activation-induced cell death and interferes with immune regulation.95 IL-2 or IL-2RA knock-out mice completely lack Tregs and suffer from a lymphoproliferative syndrome and spontaneous autoimmune disease.105 The association of IL-2 and IL-2RA to T1D is probably due to reduced proliferation of a variety of lymphocytes, including Tregs, whose depletion and altered function directly contribute to T1D pathogenesis.106 Still, the precise role by which IL-2RA/IL-2 are involved in T1D susceptibility needs to be evaluated.

VDR

Epidemiological studies show differences in T1D incidence which are associated with geographical latitude and sun exposure107 and vitamin D intake before108 and during infancy109-112 seems to protect against the disease. In vitro, vitamin D suppresses the antigen-presenting capacity of T-cells and dendritic cells.111 In fact, down-regulation of MHC class II molecules and adhesion molecules114 and inhibition of IL-12 is seen after treatment with vitamin D or its analogues.115-119 The relationship between Vitamin D and autoimmune diseases has been thoroughly reviewed elsewhere.120,121

Vitamin D actions are mediated by the highly polymorphic vitamin D receptor115 which is encoded by VDR, located on 12q12-14.122 The FokI polymorphism in exon 2 leads to a shorter and more active form of VDR protein, and displays a different distribution (P 0.0049) in subjects with T1D and controls.112 However, genetic studies are somewhat contradictory, with some showing an association between VDR variations and T1D,122-131 whereas others do not.132-134 Population heterogeneity and differences in exposure to ultraviolet radiation may account for these differences. A recent meta-analysis of 16 studies in 19 regions showed an interaction with ambient winter ultraviolet radiation and association between certain VDR alleles and T1D.135 This study supports the role of vitamin D in the development of T1D, though further studies combining genetic data and information on exposure to ultraviolet radiation and vitamin D status should further clarify this matter.

SUMO4

The association of the small ubiquitin-like modifier (SUMO) gene, SUMO4, located in the IDDM5 locus on chromosome 6q25, has been confirmed in Asian populations despite controversial observations in Caucasians. A single amino acid substitution (163A>G, Met163Val) at an
evolutionarily conserved residue of SUMO4 enhances NFκB transcriptional activity and IL-12B expression and is associated with increased risk for T1D.\textsuperscript{136,137}

**Other genes and regions**

Interferon induced with helicase C domain 1 gene (IFIH1), involved in anti-viral response, is the most plausible risk gene for T1D in a linkage disequilibrium block on chromosome 2q24 (IDDM19),\textsuperscript{138-140} though its association with other autoimmune diseases, like Graves’ disease\textsuperscript{141,142} and multiple sclerosis,\textsuperscript{143} is controversial.

A number of other associations with type 1 diabetes have been identified and replicated for SNPs in two regions on chromosome 12, 12q24 near C12orf30 and 12q13 near erythroblastic leukemia viral oncogene homolog 3 (ERBB3), a region on 16p11 near C-type lectin domain family 16, member A (CLEC16A/KIAA0350), a region on 18p11 near protein tyrosine phosphatase, nonreceptor type 2 (PTPN2), a region on 2q12-22 encoding interleukin 1 receptor 1 and a region on 21q22.3 in the ubiquitin associated and SH3 domain containing, A (UBASH3A, STS/TULA family) locus.\textsuperscript{22,112,144-148} Many other chromosomal regions are likely to be discovered during ongoing analysis of the data obtained from the WTCCC, T1DGC and GAIN consortia. Detailed and updated information about T1D associated loci can be found in T1DBase (www.t1dbase.org).

**Additional candidate genes**

A different approach to identifying new genes involved in T1D consists of trying to replicate results found in closely related diseases, such as T2D, autoimmune diabetes presenting as part of a syndrome and other autoimmune diseases.

Several attempts have been made at associating T2D genes to T1D, but most have been negative.\textsuperscript{149,150} Patients with autoimmune diabetes diagnosed after the age of 35 and with a clinical presentation more close to T2D (LADA) are an exception. These patients have features of both type 1 and type 2 diabetes, clinically as well as genetically.\textsuperscript{151-153}

Autoimmune diabetes is also a minor component of severe monogenic syndromes such as APS-I or IPEX. APS1 (autoimmune polyglandular syndrome type 1) or autoimmune polyendocrinopathy candidiasis ectodermal dystrophy (APECED)\textsuperscript{154-156} is a recessive disease caused by mutations of the AIRE gene,\textsuperscript{157} located on 21q22,\textsuperscript{158} which encodes a transcription factor with an important role in promoting tolerance and preventing autoimmunity.\textsuperscript{159-161} Children with the IPEX syndrome (immune dysregulation, polyendocrinopathy, enteropathy, X-linked), also termed the XPID syndrome (X-linked polyendocrinopathy, immune dysfunction and diarrhoea), present with severe multiorgan autoimmunity (including diabetes) and lymphoproliferation which may lead to death in the first 2 years of life,\textsuperscript{162} caused by regulatory T-cell failure due to mutations in FOXP3, located on Xq11.23-Xq13.3.\textsuperscript{163-165}

**Perspectives**

At present, the clinically useful application of genetics in type 1 diabetes is limited to identifying monogenic forms of diabetes where an atypical clinical presentation of T1D (eg: in the first 6 months of life, with a strong family history of diabetes or as part of a distinct syndrome) suggests a monogenic etiology of the disease and where treatments other than insulin may be considered. In addition, identification of individuals at a high risk of developing T1D may be of clinical interest in the future, if interventions that are presently being tested in clinical trials\textsuperscript{166-168} prove to be safe and effective.

HLA genotyping is a complex process, due to the highly polymorphic nature of the genetic region. Taking advantage of the high linkage disequilibrium in the HLA region, high-risk HLA can be detected by simply analysing a few SNPs\textsuperscript{169} and thus, high-risk individuals, candidates for intervention, could be easily identified. The already established markers of disease plus the discovery of additional ones may allow further definition in risk assessment. Nevertheless, for the time being, genetic counselling to families of patients with T1D cannot be accompanied by preventive measures.

**Conclusions**

T1D is a complex autoimmune disease with a proved genetic background. Most (around 50%) of its genetic risk is accounted for by class I and class II HLA haplotypes, although other genes with a smaller effect are also involved. Most of the known risk genes for T1D play a role in immunity, mostly through T-cell regulation (CTLA4,
Practical considerations

- Genetics can improve risk prediction in type 1 diabetes.
- HLA haplotypes can explain the main part of genetic risk in type 1 diabetes.
- Due to the lack of efficient intervention protocols/measures, routine genotyping of type 1 diabetes patients and relatives is not recommended at present.

PTPN22, IL-2RA) and cytokine production or modulation (VDR, SUMO4). The insulin gene (INS) represents and exception to this, and is probably the only gene specifically associated with T1D and not with other autoimmune diseases.

Ongoing genome-wide association studies are providing evidence of multiple known and previously unknown risk genes. New analytical tools are continuously being developed to handle the vast amounts of data produced, as well as to account for multiple comparisons and assess combined effects such as gene-gene and gene-environment interactions.

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References


Blood pressure targets in various clinical situations
in diabetic patients

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Abstract
The objective of this paper is to review the evidence that supports the recommendations of the Clinical Practice Guidelines on arterial hypertension and diabetes mellitus with regard to blood pressure control targets. Nearly all the Guidelines currently state, with certain nuances, that the targets are to achieve and maintain a systolic blood pressure of <130 mmHg and a diastolic blood pressure of <80 mmHg. Apart from certain exceptions —diabetic nephropathy with proteinuria greater than 1 g/24 hours is the only one— those targets do not vary according to the presence of other pathologies associated with diabetes. The review of the clinical trials makes it possible to conclude that blood pressure lowering is, without a doubt, beneficial. Nevertheless, even in the conditions of the clinical trials, which are very far removed from the practical reality of Primary Health Care, a substantial percentage of patients do not achieve the control targets recommended in the guidelines; this is especially true in the case of systolic blood pressure, despite the use of combinations of two or more antihypertensive drugs.

Keywords: diabetes mellitus, hypertension, control.

Introduction
From the vascular point of view, the diabetic patient with blood hypertension (BHT) ages earlier. The co-existence of BHT and T2D speeds up the progression of the atherosclerosis and at the same time the onset of macrovascular complications (heart disease, brain vascular disease and peripheral arteriopathy) but also the microangiopathies (nephropathy, retinopathy and neuropathy). Therefore, the clinical practice guidelines (CPG) about the BHT consider the hypertensive and diabetic patient as a person at high cardiovascular risk (CVR).  

On the other hand, the blood pressure (BP), both in a population context and regarding to the CVR, is a con-
tinuous variable, so the limits in order to determine the BHT diagnosis are arbitrary. The epidemiologic studies prove that values of BP >115/75 mmHg are associated to an increase in the incidence of cardiovascular events (CV) and mortality in diabetic subjects. In this sense, the CPG of the European Societies of BHT and Cardiology of 2007,¹ and the American Diabetes Association (ADA) in its document of 2009,² consider lower levels of BP (≥130/80 mmHg, compared to the recommendations of ≥140/90 mmHg, in general) to determine the diagnosis of BHT and recommend the starting of an hypertensive treatment.

Therefore, the treatment of the diabetic patient as regards to the BP has certain characteristics that differentiate it from other clinical situations. As previously mentioned, the CPG recommend to start the antihypertensive treatment earlier and from the lowest possible levels of BP. Moreover, and according to what has been mentioned, the tensional control objectives recommended in the CPG¹⁻⁴ are stricter in diabetic patients than in other hypertensive patients without diabetes. The most agreed proposal is to achieve and maintain values of BP <130/80 mmHg, compared with the general target of BP <140/90 mmHg.

Benefits of the hypertensive treatment in diabetes

There are several clinical studies performed in diabetic patients that have proved important benefits of the antihypertensive treatment, in terms of CV complications reduction.⁵⁻¹² Most of the specified studies have included hypertensive patients, though in the ABCD⁵ (Appropriate Blood Pressure Control in Diabetes) and the ADVANCE¹³ (Action in Diabetes and Vascular disease: preterAx and diamicron-MR Controlled Evaluation) a considerable percentage of the patients show normal blood pressure.

Several studies have evaluated specifically, the benefits of the different strategies with antihypertensive drugs on the progression of the diabetic nephropathy, as it is the case of the RENAAL¹⁴ (Reduction of Endpoints in NIDDM with the AI Antagonist Losartan), BENEDICT¹⁵ (BErgamo NEphrologic Diabetes Complications Trial), IRMA-²¹⁶ (Irbesartan in patients with type 2 diabetes and MicroAlbuminuria) and IDNT¹⁷ (Irbesartan Diabetic Nephropathy Trial). The control objectives in several of these studies¹⁶,¹⁷ were values of BP <135/85 mmHg, even lower in the case of the BENEDICT study (<120/80 mmHg), in spite of the fact that the mean values were of 139/80 mmHg during this study.

As regards to the heart disease, the sub-study in diabetic patients of the INVEST¹⁸ study (INternational VErapamil SR-trandolapril study), performed in subjects with ischemic cardiopathy history, used an algorithm based on reaching BP levels of <130/85 mmHg, that have been achieved in more than 40% of the patients. However, a tendency to a higher number of events could be observed with BP values of <110/60 mmHg.

In all these trials, as in most of the trials, about the BHT, the benefits of the treatment are due mostly to the reduction per se of the BP, which has been achieved in most of the cases with the use of the combination of two or more antihypertensive drugs.¹⁹ In the case of the diabetes, up to the third part of the patients shall need three or more antihypertensive drugs. Therefore, the combination therapy is the rule and the use of fixed combinations is recommendable in order to facilitate the therapeutic compliance.

Clinical practice guidelines and control objectives of the blood pressure in diabetic patients

Some of the mentioned studies, as the ABCD,⁵ or the HOT⁶ (Hypertension Optimal Treatment) and the UKPDS⁷ (United Kingdom Prospective Diabetes Study), have been designed with the objective to prove if a stricter control of the BP entailed major benefits and in fact this was proved indeed. Precisely, these trials are the best possible evidence to determine the current recommendations about the control of the pressure values in diabetic patients. However, in the UKPDS the mean final BP was of 144/82 mmHg in the “intensive control” group (target BP <150/85 mmHg) and 154/87 mmHg in the control group (target BP <180/105 mmHg).

In more recent trials, as ADVANCE¹³ and STENO-²,²⁰ the reduction of the BP that has been achieved with the treatment was considerable and close to the target values of the CPG. In the ADVANCE trial, the initial values of BP were 145/81 mmHg and 137/75 mmHg at the end of the study in the group assigned to the active treatment. In the Steno-2 study, 51% of the patients assigned
to the intensive intervention group reached systolic arterial pressure (SAP) of <130 mmHg at the end of the trial, while 72% could maintain a diastolic arterial pressure (DAP) of <80 mmHg. However, after a follow-up of more than 13 years, the mean values of the BP were of 140/74 mmHg in the intensive treatment group. Therefore, even in the conditions of the clinical trials, the BP targets dated in the CGP, especially the systolic component, related to an increase in the arterial rigidity are not easy to achieve. An excellent review of Mancia and Grassi stated the difficulties to achieve pressure control objectives in general and in diabetic patients, especially in the SAP. The figure 1 depicts the BP values at the starting and end of a long series of clinical trials. If a considerable number of trials reach the DAP targets of <80-85 mmHg, the same does not happen with the SAP <130-135 mmHg.

Up to 2003, there have been considerable differences among the CPG on the BHT control targets in the diabetic patients. At present there is a generalized agreement in considering that the objectives are to achieve and maintain SAP and DAP values of <130 and <80 mmHg respectively, with certain nuances on the recommendation level. Table 1 sums up the control objectives, in different clinical situations, in some of the reviewed CPG. Thus, for the ADA and the Canadian Diabetes Association, the SAP target of <130 mmHg is level C recommendation and DAP <80 mmHg is level B, while the Canadian Guideline of BHT considers the control target of the DAP of <80 mmHg as level A and SAP <130 mmHg as level C. The CPG of the European Societies of BHT and Cardiology reflect these same targets. But, surprisingly, their authors consider that the criterion of SAP of <130 mmHg are not only wrongly documented but besides it is difficult to achieve. A recent work proved that trying to achieve the SAP objectives <130 mmHg, which in this study was reached in a third part of the patients, suggests that more than half of the patients reduces the values of DAP less than 70 mmHg; this situation might increase the CV risk in elder patients or patients with heart disease. Some CPG, as the National Institute for Clinical Excellence (NICE), with a more realistic approach, state some “audit” objectives in the region of 140/80

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Figure 1. Effects of the antihypertensive treatment on the systolic arterial pressure (SAP) and diastolic arterial pressure (DAP), in hypertensive patients with diabetes in several trials. The discontinued lines correspond to the guidelines targets (BP <130/80 mmHg at present, the BP targets <135/85 mmHg) are also depicted. B: values of basal BP; T: values of BP during the treatment. Taken from Mancia and Grassi.
The always expected and influencing American CPG of the Joint National Committee (JNC), has not been updated since 2003.24

The most differentiated clinical situation in the CPG as regards to the DM, is the diabetic nephropathy, which with levels of proteinuria >1 g/day sets out stricter control objectives (BP <125/75 mmHg). The evidences that support this recommendation are scarce and extrapolated of studies performed with different populations. The AASK25 (African American Study of Kidney Disease and Hypertension), conducted in Afro-American hypertensive patients with hypertensive nephropathy (nephroangiosclerosis) compared the effect of two control objectives of mean BP (“usual” of 102-107 mmHg and “stricter” ≤92 mmHg) on the reduction of the glomerular filtration, as main variable. No relevant differences were observed at the end of the study between both strategies.

Which is the reality as regards to the blood pressure control in diabetes?
In different studies performed in Spain in the primary care field, an improvement in the BHT control level is observed. The study Controlpres,26 of 2003, showed a percentage of 38%. And the PRESCAP,27 of 2006, exceeded the 40%. However, in this last study, the control rate in diabetic hypertensive patients, with the criterion of BP <130/80 mmHg was very low (approximately of 15%). In the study DISEHTAC II28 (Diagnosis and Monitoring of Hypertension in Catalonia) the level of the BHT control was of 32.4%, while in the diabetic patients with a BP target of <130/85 mmHg, the control values were in the region of 10.9%. Therefore, the recommendations of the CPG, at least in primary care, are difficult to comply. This important gap among the CPG recommendations and the real control level of the risk factors might be a consequence of the therapeutic inertia.29 The distrusts in the acceptance of the GPC objectives are recognized as one of the causes of certain conservative attitude when intensifying the BHT treatment. However, there is a wide improvement margin, seen positively.

Conclusions
There is wide evidence among the benefits of the BP reduction in diabetic patients. As regards to the BP control targets, the most agreed proposal is to achieve and main-

| Table 1. Control targets of blood pressure (mmHg) in several CPG on BHT and diabetes |
|--------------------------------|--------------------|--------------------|--------------------|--------------------|
| General                         | <140/90      | <140/90      | <140/90      | <140/90 |
| Elderly patients                | <140/90      | <140/90      | <140/90      | <140/90 |
| Diabetic patients               | <130/80      | <130/80      | <130/80      | <130/80 |
| Renal disorder                  | <130/80      | <125/75      | <130/80      | <130/80 |
| Non diabetic nephropathy with proteinuria >1 g/day | <125/75 | |
| Ictus or heart disease          | <130/80      | |
| Audit targets                   | <140/90      | |

BHT: blood hypertension; CPG: clinical practice guidelines.

Practical considerations
- The co-existence of blood hypertension and diabetes mellitus speeds up the progression of the atherosclerosis and with it the onset of micro vascular and macro vascular complications.
- There is wide evidence that shows that the control of the blood pressure in diabetic patients entails the cardiovascular risk benefits. In diabetes, the most agreed proposal is to achieve and maintain blood pressure values of <130/80 mmHg, compared with the general target of <140/90 mmHg.
- Up to the third part of the patients shall need three or more drugs for the control of the blood pressure, suggesting that many patients shall need a combined therapy.
tain values of <130/80 mmHg, which are difficult to achieve in the clinical practice in spite of using combinations of three or more hypertensive drugs.

Declaration of potential conflicts of interests
M. de la Figuera states that there are no conflicts of interests as regards to the content of this article.

References
Seminars on diabetes

Treatment algorithm of high blood pressure in type 2 diabetes

Algoritmo de tratamiento de la hipertensión arterial en la diabetes mellitus tipo 2

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Abstract
Type 2 diabetes mellitus and arterial hypertension are common entities closely related by multiple etiopathogenic mechanisms that become apparent usually associated in clinical practice. This association implies a high cardiovascular risk. Therefore specific blood pressure targets have been established for patients with diabetes. Furthermore, arterial hypertension in this context has differential features from general population resulting in an important risk factor which needs to be treated with maximal priority. After confirming the diagnosis, lifestyle changes must be undertaken to improve the global metabolic profile. Several drugs will usually be required in order to achieve optimal blood pressure control in type 2 diabetes. Current evidence supports a tight control of blood pressure in patients with diabetes, because cardiovascular risk reduction is higher in this population, being considered even a more cost-effective therapy than achieving tight glucose control.

Keywords: arterial hypertension, type 2 diabetes, cardiovascular risk, antihypertensive drugs.

Introduction
The treatment of the blood pressure (BP) in diabetic patients has a great relevance due to the high cardiovascular risk (CVR) that they present and to the early development of meta diabetic complications. The probabilities of showing a cardiovascular disease increase exponentially, when blood hypertension (BHT) co-exists, which is responsible for the 85% of such risk in T2D. The risk of showing a cardiovascular event is double in diabetic patients compared to the general population, and doubles or triples when the patient is diabetic and hypertensive, especially if nephropathy is present. These patients are benefited more than the rest of the hypertensive population from the reduction of the BP values. Since the high prevalence of T2D worldwide, which will increase in the future decades according to the epidemiologic models, in our daily practice we usually find ourselves exposed...
to suffer cardiovascular diseases. These diseases comprise ictus, myocardial infarction and peripheral arteriopathy. Moreover, it has been proved that both entities are closely related, as the hypertensive patients have the double of risk of showing some degree of intolerance to the glucose than the non-diabetic patients. At the same time, the persons with T2D show BHT more frequently than the rest of the population.

From what has been exposed in the previous paragraph it can be supposed that the possibilities that the diabetic patients show cardiovascular events might be limited if we insist definitely in the associated risk factors. In this article, we will investigate the best way to treat the BHT in the population with T2D according to the objectives established by the competent authorities. At the same time, we will develop an algorithm that will facilitate the choice of the most adequate drugs in each case. The interest in this clinical situation should be a priority, considering the scarce data obtained as regards to the early diagnosis and the intensive treatment of the BHT in the T2D, according to the values from several studies performed in Spain. A wide population with moderate-high CVR does not receive an optimized treatment in spite of the available resources. This stresses the importance of an adequate BP control in patients with T2D. We will deepen into this subject along these lines.

Etiopathogenic relation between BHT and T2D

The genetic predisposition to suffer BHT and T2D jointly has been described on a polygenic heritance basis, but a concrete alteration and clearly contributing factor has not been stated, unlike what happens with more rare causes of BHT. Several mechanisms have been proposed that both conditions interrelate:

• Expansion of intravascular volume by insulin stimulus on the reabsorption of sodium in the renal proximal tubules.
• Alterations on the vasodilatation by the increase of the vascular walls rigidity, which is manifested by an anomalous response to the local nitric oxide administration. It has been placed in the context of the protein glycosylation of the vascular matrix.
• Over-stimulation of the renin-angiotensin-aldosterone axis with an increase of the insulin resistance and the reabsorption of sodium and water.
• Activation of the sympathetic nervous system and higher resulting insulin resistance.
• Increase of intracellular calcium.
• Reabsorption of the filtered glucose excess.

As it is evident, the mechanisms of the production of BHT in this population are multiple, what makes the BP values control complicated and requires more than one drug in several occasions. Usually, to act on only one factor will be insufficient, and we should resort to combinations that might block the different etiopathogenic processes.

Diagnosis of BHT

The establishment of a definite diagnosis of BHT shall be based in the information obtained in different BP mechanisms, and shall be performed during each patient’s visit. In order to confirm the diagnosis, the abnormally high values of the BP have to be determined during at least two different occasions, separated in a month between them as minimum. The technique of BP self-determination shall be correct, with the patient at rest during 5 minutes, placing the pressure cuff near the heart, and having taken the indicated hypertensive medication, if this is the case. Moreover, it is useful to perform measurements in sedation, decubitus and bipedestation if a possible disautonomy is suspected.

In certain occasions, it will be difficult to rule out the “white coat BHT” and determine a diagnosis with certainty if we count exclusively with the values obtained in the specialized care consultation. We might use the information that the self-measurement provides us as regards to the blood pressure and, even, to the outpatient blood pressure monitoring.

Peculiarities of the BHT in T2D

The BHT of the diabetic patients has some differential characteristics regarding to the non-diabetic hypertensive population. It is usual to find higher BP values in diabetic patients up to 70 years of age, in the context of the early arteriosclerosis that these patients suffer. These differences tend to disappear in more advanced ages. Another characteristic factor is the higher difference between the systolic BP and the diastolic BP, known as pulse pressure. This phenomenon increases with the age and is associated to a higher CVR than the simultaneous
increase of both values.\textsuperscript{11} It is also frequent to find an isolated systolic BHT, caused by the excessive rigidity of the arteries that hinders from expanding in response to the ventricular ejection. It is considered an independent risk factor by cardiovascular death, hypertrophy of left ventricle and microalbuminuria.\textsuperscript{8,12} It can be observed the pattern known as dipper, with a scarce or null reduction of BP during the night (reduction under 10% as regards to the day values).\textsuperscript{1}

Whatever has been mentioned previously only ratifies the high CVR of these patients, what makes the BP control a key factor to prevent the onset of complications both macrovascular and microvascular. In fact, it has been determined that the relation risk / benefit is more favorable for the pressure control than for the glycemic control.\textsuperscript{13,14}

**Treatment algorithm of BHT in T2D (figure 1)**

**Blood pressure objectives**

Considering the results obtained in several clinical studies, the international organisms have established the value of 130/80 mmHg as objective for diabetic patients.\textsuperscript{9,12} Lower BP objectives have been studied as well, as a diastolic BP lower than 60 mmHg, without demonstration of relevant benefits in the reduction of CVR.\textsuperscript{2} In another section of this seminar the BP objectives will be dealt with in depth in several clinical situations.

It has to be pointed out the proved fact that the cardiovascular benefit is only obtained while the BP values are maintained under the mentioned limits. In the diabetic population, unlike it happens with the glycemic control, there is no “bequeathed effect” when the strict pressure control is abandoned.\textsuperscript{15} Therefore, the follow-up of the BP should not be overlooked and it should be a constant practice in the follow-up of the patient with T2D and BHT.

**Non-pharmacological treatment**

The change of lifestyle is accepted as initial therapy before starting a treatment with drugs in diabetic patients with BP up to 139/89 mmHg if there are no other associated CVR factors, microalbuminuria or lesion of target organs.\textsuperscript{3} During three months, the patient shall modify the lifestyle in order to: a) reduce his weight, as obesity usually occurs in the same clinical context than the BHT and the T2D, b) improve the lipid profile that is characterized by cholesterol particles bond to low density lipoproteins more atherogenic, low values of cholesterol bound to high density lipoproteins and high triglycerides, and c) increase the insulin sensitivity. It is recommended to perform moderate-intense physical exercise almost every day of the week, though with certain precaution in patients with ischemic cardiopathy suspicion, to whom a previous ergometry shall be performed before starting the exercise. Of course, the patients should be encouraged to abandon the tobacco habit, which is a CVR known factor. The consumption of salt plays a relevant role in this group of patients, due to the already mentioned increase of the renal absorption of sodium and the intravascular volume that is produced in the T2D. The reduction of the salt intake is more useful in these patients than in the population in general, especially in elder patients who show a higher sensitivity to the volume expansion.\textsuperscript{1,2}

**Pharmacological treatment**

At present, we count with a wide range of antihypertensive drugs based on different action mechanisms that might be useful in diabetic patients with BHT.
The renin-angiotensin-aldosterone system blockers (RAASB) are considered as first choice, which comprise the angiotensin-converting enzyme inhibitors (ACEI) and the angiotensin II receptor antagonists type I (ARA II). It has previously been mentioned about the hyperactivity of this axis in the group of hypertensive diabetic patients, being the inhibition under study during the last years. These drugs have proved to be able to achieve an adequate BHT control, but they have a relevant renal protection effect in T2D than any other pharmacological group, taking into account that they revert the microalbuminuria, stop the progression of the microalbuminuria and prevent the progression of the renal disorder.16,17 Moreover, in some studies its use has been associated to a lower incidence of DM in prediabetic subjects and to a lower rate of ischemic cardiopathy and heart disorder in the diabetic population.1,18,19 The most frequent side effect of the ACEI is the dry cough, as consequence of the bradicin in accumulation. A follow-up should be performed on the renal function in order to rule out its worsening or the onset of hyperpotassemia, especially in patients with previous nephropathy and bilateral stenosis of the renal artery or unilateral in monorenals.

When the pressure control is not sufficient by means of the RAASB, the association of drugs that insist in the volume expansion has to be considered. The thiazides play an important role here, as the hydrochlorothiazide in low doses, of 6.25-12.5 mg. These drugs are considered as effective as the ACEI or the calcium antagonists to reduce the CVR. The reduction in the incidence of heart disorder in patients who receive this medication has been considered as an added benefit.20 In case of advanced renal failure, loop diuretics should be used as the thiazides loose their efficacy. The most usual adverse effect is the hypopotassium that might compensate the effect on the potassium of the ACEI or ARA II when used concomitantly. On the other hand, some data indicate that these drugs favor the onset of T2D as regards to other treatments, which has to be assessed in each clinical context.2

The commercialized drug within the RAASB is the aliskiren, which the renal protector effect in diabetic patients seems to go beyond the mere reduction of the pressure values and is additive to the ACEI.27

There are two groups within the calcium antagonists: the dihydropyridine (DHP) and the non dihydropyridine (non-DHP). The first ones have a predominant peripheral vasodilation effect while the second ones are mainly cronotropes and negative inotropes. At first a renal protector effect has been described for the non-DHP group but the recent commercialization of DHP of new generation DHP have demonstrated to have a higher clinical efficiency with lower onset of edemas, its most frequent adverse effect.21,22 As they lack of a negative metabolic profile, taking into account its antihypertensive potential, the calcium antagonists are an important group for the treatment of the BHT.2

The beta blockers have a good antihypertensive effect and the experience in its handling is wide. They can be cardioselective or not, which has raised a certain interest.
as regards to the disappearance of adrenergic symptoms during the hypoglycemia. It is a relevant datum in the diabetic patients, especially in those who receive insulin therapy. They are associated to a negative metabolic profile taking into account the increase of the triglycerides and early evolution of T2D. However, they are a first option in the ischemic cardiopathy and improve the clinical evolution of heart failure.\textsuperscript{23}

The alpha-blockers are another group of antihypertensive drugs to resort to. In spite of the hypotensor effect, they have certain side effects. One of them is the “phenomenon of the first administration”, a sudden reduction of the BP that takes place at the beginning of the therapy, therefore they should be administered preferably before the patient goes to sleep. Most worrying is the higher incidence of heart failure described in some studies, which limited its use.\textsuperscript{24} They are a good resource in patients who show prostatic hypertrophy.

In a last stage we can consider the antihypertensive drugs of central action, as clonidine or hidralazine. They might play a role in diabetic patients with BHT of difficult control and on which the antihypertensive drugs of other pharmacological groups have failed.\textsuperscript{8,10}

In not a few occasions we would need to use combinations to control the BHT in T2D. They can be indicated initially when the values of BP are over the objective and it will be usual to resort to them at some moment of the evolution of the disease.\textsuperscript{1,7} Combinations of fixed doses of several antihypertensive drugs have been commercialized, as ACEI or ARA II with thiazides or calcium antagonists, which increase their antihypertensive strength, and at the same time reduce the incidence of side effects. The numbers of patients who show edemas and ionic disorders have been reduced and the clinical efficiency is preserved.

**Conclusions**

The treatment of the BHT in patients with T2D is a key factor but complicated and in most of the occasions this treatment will need several drugs to achieve the determined BP. We can start the treatment with only one drug

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### Table 2. Antihypertensive drugs commercialized in Spain\textsuperscript{26}

<table>
<thead>
<tr>
<th>Diuretics</th>
<th>Beta-blockers</th>
<th>RAASB</th>
<th>Calcium antagonists</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiazides</td>
<td>Loop CS Non-CS</td>
<td>ACEI ARA II DHP</td>
<td>Non-DHP Alpha-blockers</td>
<td></td>
</tr>
<tr>
<td>Chlorotaldon</td>
<td>Furosemide</td>
<td>Atenolol Benazepril Carvedilol Candesartan</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydrochlorothiazide</td>
<td>Piretanide</td>
<td>Bisoprolol Captopril Eprosartan</td>
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<td></td>
</tr>
<tr>
<td>Indapamide</td>
<td>Torasemide</td>
<td>Carotolol</td>
<td>Amlodipin Bamilodipin</td>
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</tr>
<tr>
<td>Xipamide</td>
<td></td>
<td></td>
<td>Furosemide</td>
<td></td>
</tr>
</tbody>
</table>

ACEI: angiotensin-converting enzyme inhibitors; ARA II: angiotensin II receptor antagonists type 1; CS: cardioselective; DHP: dihydropyridine; non-CS: non-cardioselective; non-DHP: non-dihydropyridine; o.r.: oral route; RAASB: renin-angiotensin-aldosterone system blockers.

### Table 3. Special indications of antihypertensive drugs

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAASB</td>
<td>Diabetic nephropathy</td>
</tr>
<tr>
<td>Thiazides</td>
<td>Heart failure</td>
</tr>
<tr>
<td>Loop diuretics</td>
<td>Renal failure</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>Ischemic cardiopathy</td>
</tr>
<tr>
<td>Alpha-blockers</td>
<td>Prostatic hyperplasia</td>
</tr>
</tbody>
</table>

RAASB: renin-angiotensin-aldosterone system blockers.
or with combinations if the CVR is high. The most useful drugs in this clinical context are the RAASB, followed by the thiazides. The ACEI and ARA II bring about an improvement of the cardiovascular disease beyond the simple reduction of the BP. However, we should consider the addition of other drugs if the control is insufficient, without leaving aside the possible additional benefits or the adverse effects of each family of antihypertensive drugs for each patient in a customized manner.

Declarations of potential conflict of interests
P. Pedrianes and P.L. de Pablos state that there is no conflict of interests in the issuance of this article.

References
Introduction

The renin and the renin-angiotensin-aldosterone system (RAAS) have an undeniable relevance in the pathogenesis of the cardiovascular disease (CV), and during the last years it has advanced considerably as regards to the knowledge of the vascular atherosclerosis disease due to the development of drugs that block the RAAS in some way. Though we have evidences of the existence of renin since more than 100 years,1 the scientific interest for this molecule started in 1934, when Goldblatt published...

his first paper about renal ischemia in rats and its relation with the blood hypertension (BHT). The first direct renin inhibitors (DRI) for clinical investigation have been developed approximately 50 years ago, though it has been during the last five years when evidences have been collected thanks to a high number of clinical trials, until the approval of the aliskiren by the Food and Drug Administration (FDA) in March 2007 and the European Medicines Agency (EMEA) in August 2007, as the first oral DRI for the treatment of the BHT.

Since aliskiren constitutes the first drug of the first new class of antihypertensive introduced in more than one decade, the development and the pharmacology of this molecule count with wide and detailed revisions in the scientific literature. It seems considerable to think that the rennin is a very appropriate objective when blocking the RAAS, taking into account that it corresponds with the first step in the system regulation. The first trials to achieve an inhibition of the renin were based on the use of antibodies against the renin, peptide analogues of the precursors of the renin and peptides based on the molecular structure of the statins. The development of the molecular disposition and the determination of the crystallographic structure of the active site of the renin have contributed essentially in the identification of the renin inhibitors. The distinctive drug of this new class of non-peptide drugs is the aliskiren, an oral active hypertensive, with a high affinity for the renin, which confers a high selectivity for this enzyme.

There is no doubt that the RAAS constitutes a fundamental therapeutic objective when achieving a reduction of the morbimortality associated to the progression of the atherosclerosis disease and, therefore, of the CV and renal disease, for being one of the main pathogenic agents that cause the development of organic damage and a risk increase of CV events onset. There is an increasing number of evidences that endorse the antihypertensive efficacy of aliskiren, both in monotherapy and in pharmacological combination which offer results of good tolerability and a good safety profile. We have revised in this article the characteristics that distinguish aliskiren as antihypertensive, evaluating the potential advantages of the RAAS blocking by means of this new pharmacology class and determining the prevention capacity as regards to the development of organic damages through the results of the most recent clinical trials, though there are important ongoing studies about morbidity and mortality. It is expected that the results shall be useful to reply to a great number of questions.

Need of new antihypertensive therapies
The RAAS is one of the most important pharmacology objectives when treating the hypertensive patient. The angiotensin-converting enzyme inhibitors (ACEIs) and the angiotensin II receptor antagonists (ARA II) have a moderate effective antihypertensive effect that achieves the prevention of complications arisen from the CV disease evolution associated to the insufficient control of the CV risk factors, with a scarce number of side effects associated to its use. Likewise, the antagonists of the aldosterone are a coadjuvant therapy with high effectiveness at situations of wild BHT of different causes. However, the morbidity and mortality associated to the CV disease are still very high, therefore the approach on the need of another class of drugs that add some clinical benefit by means of a different approach of RAAS inhibition is very justified.

A great number of basic investigation studies suggest that the drugs that inhibit the RAAS should provide a cytoprotector benefit in the target organ tissues, achieving a higher organic protection compared to the rest of the antihypertensive drugs, with similar reductions of blood pressure (BP). However, the studies about clinical results in relation to the possible independent added benefits of the BP with ACEI or ARA II have offered contradictory results on some occasions, in part because these drugs do not achieve a complete inhibition of the RAAS. The DRI might provide a higher organ protection through a more complete inhibition.

Comparison of aliskiren with the rest of the RAAS inhibitor drugs
The inhibition of the angiotensin II (Ang II) and the cessation of the production of cytokines that stimulate the cellular growth, free radicals, mediators of inflammation and tissue fibrosis that dependent on the Ang II, are some of the mechanisms that contribute to the clinical benefit determined by the renin-angiotensin-aldosterone blocker system (RAAS) in the CV and renal therapeutic. However, the heterogeneous methods of RAAS suppression present relevant differences at a biochemical level. The DRI favors the increase of the circulating and intrarenal renin level when interrupting the renin-angiotensin II
negative feedback as the ACEI and the ARA II. However, the catalytic activity of the renin molecules inhibits completely during day with the use of the DRIs, inducing a very low plasma level of Ang I and II. On the contrary, the enzymatic activity of the renin that is generated by a kidney that has received ACEI or ARA II is kept active, resulting in a high circulating level of Ang I and a lower level of Ang II. These differences in the release of renin might counteract the pharmacological inhibition of SAAR at the end of the ACEI or ARA II dose interval. Considering its high renin affinity, its inhibitory strength, its slow dissociation from the binding site to the active site of the renin and its pharmacological half-life, aliskiren should inhibit each of the renin molecules released to blood flow or the kidney. In this way, the DRIs might offer an additional protection compared to the rest of the RAAS inhibitors when interfering with the high renin and pro-renin catalytic activity, once these molecules have bound to the receptor.19

The discovery of the pro-renin receptor and the recent advances in the knowledge of its functions are changing the concept and understanding of the RAAS at present. The observation that the pro-renin molecule is activated from the biological point of view when binding to its receptor has a special interest considering the recent data that relate this molecule with the microvascular pathology development in the diabetic patient.20 However, a great amount of information about this matter has been unknown during some time. One of the questions that should be solved is if aliskiren inhibits the renin and pro-renin enzymatic activity once they get bound to the receptor of the latter. If the DRIs get to inhibit these recently discovered actions of the renin and the pro-renin, they can have a therapeutic advantage on the ACEI and the ARA II. Another relevant question is if the DRIs alter the activation of the intracellular routes, not mediated by the Ang II, induced by binding to the pro-renin receptor, as there are no clear data on this regard up to date. Another difference with the rest of the drugs that achieve the RAAS blocking is that aliskiren induces a stronger vasodilatation response in healthy subjects who have received a diet low in sodium compared to the ACEI.21 The clinical implications arisen of these data might be relevant regarding to the capacity of organ protection under circumstances in which the generation of intrarenal Ang II has activation routes depending or not of the converting enzyme, as in patients with diabetic nephropathy or in patients with a high salt intake, in which it is expected a higher benefit in the inhibition of the renin in the renal tissue.22

**Update of the clinical evidences provided by aliskiren**

The treatment with ACEI and ARA II is accompanied by benefits in morbimortality in patients throughout the CB continuum.23 However, there is an extensive discussion whether the RAAS inhibition offers a higher CV protection compared to other antihypertensive therapies for most of the patients.24 Among the reasons put forward to explain the possible causes for which there is no consensus among the results of the published clinical trials, it can be observed the insufficient reduction of BP among the groups and the use of inadequate doses, entailing an incomplete system inhibition.

Since its introduction in the 90s, the ARA II have arisen a great clinical expectation given the promising results on the protection of the target organs that set out higher than those offered by the ACEI, as they eliminated the release effect of the Ang II, which was observed as positive when promoting the receptors activity that increase the release of nitric acid, therefore other protector mechanisms of the blood vessel start. However, there is an increase in the CV mortality in the population that has to set out the possibility of finding improvements in the therapeutic. Aliskiren provides a new opportunity to prove if a higher inhibition of RAAS shall be translated into a higher organic protection regardless of the effect on the BP compared to the ACEI and the ARA II.

A main question that should be solved is to observe if in case of a determined reduction of BP, similar for all the pharmacological classes, there would be a higher organ protection with aliskiren, or which would be the response when adding DRI to the patient who already takes one of the other drugs. Oparil et al. have published recently a double-blind study that included 1,797 patients with level 1 and 2 BHT who have been randomized to receive aliskiren, valsartan, a combination of both or placebo during 8 weeks.25 The combination of aliskiren and valsartan in the maximum recommended doses (300 and 320 mg/day, respectively) offered a higher reduction of the BP values, both in the clinics and in the outpatient 24 hours monitoring, compared to each drug in single therapy.
In the dose in which it has been commercialized, in other words, 150 and 300 mg, aliskiren has proved an adequate tolerability with a profile of adverse effects similar to placebo, very close as the one we know about the ARA II. It does not cause cough as it does not inhibit the metabolism of bradicinines. It has a remarkable affinity characteristic for the renin at a renal level, therefore it also seems logical to think in promising renal protection effects. In this sense, both the ACEI and the ARA II have proved to be superior to the rest of the antihypertensive drugs that do not block the RAAS when improving the renal prognosis. The superiority of the ACEI is endorsed, both in diabetic and non-diabetic patients, by its capacity of slowing down the chronic renal disease progression, while the ARA II have proved to prevent, return and delay the nephropathy in hypertensive patients with T2D.

Though it seems clear that the ACEI and the ARA II achieve a slowing down of the proteinuric nephropathy, it does not seem so evident that they might prevent the development of the advanced renal disease, though they delay the replacing renal treatment starting approximately 6-8 months. The most recent data on the usefulness of the combination of both RAAS inhibitors in patients at high risk have suggested that it does not offer a CV benefit superior than any other of them in monotherapies. Therefore, the therapeutic strategy based on aliskiren should reply to the matter about if it could be superior regarding to the prevention and regression of the organic lesion, in delaying the onset of CV events and, mainly, in improving the mortality associated to the CV disease. There are preclinical data related to the organic protection associated to the treatment with aliskiren that should be confirmed in the ongoing clinical trials at present.

As other endocrine systems, the RAAS has a capacity of controlled auto-regulation through a system of inhibition by negative feedback. The stimulation of the AT₁ receptor by the Ang II suppresses the renin release. When blocking the action of the Ang II on its receptor, the ARA II interferes in the feedback circuit and stimulates the production of renin. When valsartan is indicated in monotherapy, the plasma renin activity (PRA) is increased, while if it is combined with aliskiren, the PRA is reduced (table 1). If the activation PRA compensatory action really limits the effectiveness of the suppressor drugs of the AT₁ drugs, it can be understood that the concomitant administration with a DRI shall achieve a more complete suppression of the system and a better organ protection related to the ARA II in monotherapy.

When assessing concrete data about the organic protection in patients at high risk treated with aliskiren, it has to be taken into account a program of clinical studies ongoing at present whose objective is the evaluation of aliskiren all through the CV continuum. The first data that are being published are from two studies in patients at high risk of CV. The AVOID (Aliskiren in Evaluation of Proteinuria in Diabetes) is a 24 week multicenter, randomized, double-blind study which included 599 hypertensive patients with T2D and proteinuria and who received losartan during 12-14 previous weeks in optimum doses to achieve the BP objective and diabetes values. Aliskiren was added after these 12 weeks (150 mg) or placebo, and 12 weeks later the dose of aliskiren was increased up to 300 mg during 12 more weeks. The objective of this study was to determine if the concomitant treatment reduces effectively the albumin urinary excretion, compared to a treatment with losartan in doses that
had already demonstrated to be renal protectors. The results of the study evidenced that adding aliskiren to the usual therapy achieved a reduction of the proteinuria in an addition of 20% (p ≤0.0009) compared to placebo in this type of patients with controlled BP. Moreover, 24.7% of the patients to whom aliskiren was added reached an equal or higher than 50% reduction in the proteinuria as from the basal level, compared to the 12.5% of the patients who received placebo (p= 0.0002). The tolerability of aliskiren taking was similar to placebo. The authors conclude that adding aliskiren to this population of patients at high risk offered a protection of the renal function.

In the target organ lesion, the data corresponding to the study ALLAY (Aliskiren in Left Ventricular Assessment of Hypertrophy) have proved a similar reduction in the antihypertensive standard therapy in hypertensive patients with overweight and left ventricular hypertrophy diagnosis (LVH). In the study ALOFT (Aliskiren Observation of Heart Failure Treatment), 302 patients have been randomized with class II-IV heart failure of the New York Heart Administration (NYHA) with BHT history and a plasmatic concentration of BNP (brain natriuretic peptide) higher than 100 pg/mL and who received stable treatment with ACEI and beta-blockers, to take into comparison to those who received placebo, in which there was an increase of 762 ± 6.123 pg/mL (p= 0.0106) of the final value of NT-proBNP as indicator that the group that received added aliskiren reduced the mean value of NT-proBNP to 244 ± 2.025 pg/mL (p= 0.0106) with good tolerability. No clinical alterations have been observed in the rest of the biochemical parameters.

Conclusions
We can conclude that the DRIs, which representative is aliskiren, are consolidated as a new pharmacological class with action mechanisms exerted through a new form of RAAS suppression, and what we know at present about the RAAS inhibition causes an increase of the plasmatic renin activity. Therefore, it is necessary to know more data in relation to the response of the renin-pro-renin bond with its receptor and the possible vascular damage, as well as the potential improvement of the actions mediated by such binding and the inhibition by aliskiren. Both in monotherapy and in combination, the high effectiveness and tolerability of aliskiren has been demonstrated. Finally, there are data about the organ protection in patients at high cardiovascular risk.

Practical considerations

- Aliskiren is the first drug that is a direct inhibitor of the renin administered by oral route.
- Unlike the ACEI or the ARA II, that do not achieve a complete inhibition of the renin-angiotensin-aldosterone system, the direct inhibitors of the renin seem to provide a higher organ protection through a more complete inhibition.
- Aliskiren is effective both in monotherapy and in combination with other drugs. Additionally, data are appearing about the benefits of this drug regarding to organ protection in patients with high cardiovascular risk.

Declaration of potential conflict of interests
J.A. García-Donaire and L.M. Ruilope Urioste state that there are no conflicts of interests as regards to the content of this article.

References
Abstract

Objectives: To evaluate quality of life (QoL) characteristics and outcomes in subjects with T1D with and without non-severe (NSH)/severe hypoglycaemia (SH) as a main indication for CSII. Patients and methods: Two groups of T1D subjects were selected from candidates to CSII following the criteria of the Catalan National Health Service. Twenty-one subjects (aged 34.6±7.5 years; 13 women) in whom CSII was started because of recurrent NSH and SH were included (H Group). They were compared to 18 T1D subjects (aged 32.3±10.1 years; 14 women) in whom CSII was initiated because of non-optimal control without repeated NSH/SH (NH group). General characteristics, metabolic control and QoL/health state (DQoL/SF-12 questionnaires) were evaluated (baseline/after 12-months).

Results: In the H group, the number of NSH/week diminished from 5.01±1.56 (baseline) to 2.76±1.09 after 12 months (p <0.001). SH diminished from 1.24±0.62 per subject year (baseline) to 0.12±0.21 (12 months, p <0.001). There were no differences in A1c (6.9±1.3 vs 6.5±0.8%; NH and H) after 12-months of CSII. The H group scored better in DQoL-impact of treatment subscale at baseline (45.7±7.0 vs 33.7±7.3; p <0.001, NH and H). QoL improved similarly after 12 months in both groups, but the difference in DQoL-impact of treatment (41.5±8.5 vs 31.0±5.8; p <0.001) was maintained. Conclusions: CSII improves QoL independently of its main indication. Subjects who initiate CSII because of repeated hypoglycaemic episodes display a different QoL perception than those without this indication when starting this therapy. Although this finding does not preclude favorable results, probably it has to be considered in order to encourage patients to start this modality of treatment.

Keywords: quality of life, type 1 diabetes, CSII, repeated hypoglycaemia.

Introduction

Continuous subcutaneous insulin infusion (CSII) represents an alternative to a conventional intensive insulin therapy with multiple daily injections (MDI) when it is unable to achieve the major metabolic goals of diabetes treatment: HbA1c within desirable levels without an unacceptable incidence of hypoglycaemia.1-3 Up to now, CSII has demonstrated beneficial effects in reducing the number of episodes of severe hypoglycaemia, as well as, diminishing HbA1c depending on the meta-analysis.4-6 However, data and information on the relative benefits of this type of treatment in terms of quality of life and health perception is still scarce particularly when comparing data obtained in subgroups of subjects with type 1 diabetes (T1D) with different indications for CSII treatment.7

Frequent, unpredictable and repeated non-severe and severe hypoglycaemia is one of the main indications for health service or health insurance-funded CSII. The aim of our study was to evaluate quality of life perception characteristics and outcomes in subjects with T1D with and without non-severe (NSH)/severe hypoglycaemia (SH) as a main indication for starting CSII.

Patients and methods

We included twenty-one subjects with T1D (aged 34.6±7.5 years; 13 women, T1D duration 16.2±6.6 years,
A1c 6.7±1.1%) in whom CSII was started because of recurrent hypoglycaemic episodes (more than 4 NSH episodes/week -last 8 weeks- and more than 2 SH during the last 2 years) in spite of MDI treatment supported by optimised education (H group). They were compared to a group of 18 T1D subjects (aged 32.3±10.1 years; 14 women, T1D duration 16.2±8.9 years; A1c 8.2±1.2%) in whom CSII treatment was initiated because of non-optimal glycaemic control (intensive insulin therapy with MDI had been unable to maintain A1c levels <7.5% without disabling hypoglycaemia) without repeated NSH/SH (NH group). These two groups of subjects were selected from candidates in whom the initiation of CSII treatment was proposed following the criteria for reimbursement of the Catalan National Health Service authorities. In groups (H and NH groups), general characteristics, metabolic control (HbA1c; Menarini Diagnostici, Firenze, Italy, normal range 3.5-5.5%) and data concerning quality of life and health state perception (Diabetes Quality of Life questionnaire; DQoL, SF-12 health survey questionnaire) were evaluated at baseline and after 12-months of initiating CSII therapy. DQoL questionnaire scores evaluate different aspects including: satisfaction with treatment, impact of treatment, worries about social and vocational issues and worries about diabetes-related issues (higher scores relate to deterioration in QoL).3 NSH events were defined as symptoms or signs associated with hypoglycaemia experienced by the patient and self-treated without the need of assistance from a third party or a blood glucose measurement of <3.3 mmol/l. SH events were defined as those associated with neuroglycopenia severe enough to require treatment from a third party and they were collected during the previous two years. All the subjects included in our study received our specific therapeutic education programme for patients beginning CSII. Patients were instructed on glucose goals and self-monitoring glucose control when necessary.

All patients were using pumps with pre-programmable variable basal rates. In H Group 12 subjects used insulin lispro (Humalog, Eli Lilly and Company, Indianapolis, IN, USA) and 9 used insulin aspart (Novorapid, Novo Nordisk A/S, Bagsvaerd, Denmark). In NH Group, 11 patients used insulin lispro and 7 used insulin aspart. Pumps, infusions sets, insulin, finger test strips and capillary glucose meters were provided to all the patients and were funded by the National Health Service. The Ethical Committee of Hospital Clínic i Universitari approved the study and all subjects gave informed written consent.

Results are presented as mean±SD. Comparisons between were performed using a paired or unpaired Student’s t-test as required. A p value <0.05 was considered statistically significant. All statistical calculations were performed with the Statistical Package for Social Science (SPSS, v 14.0) for personal computers.

Results
At baseline, no differences were observed between the groups with respect to age, gender and T1D duration. As expected, A1c (8.2 vs 6.7%, p <0.01) and insulin dose before CSII (0.83±0.27 vs 0.64±0.14 UI/kg, p <0.01) were lower in H group. In the H group, the mean number of episodes of NSH per week diminished from 5.01±1.56 at baseline to 2.76±1.09 after 12 months, respectively (p <0.001). When the number of SH episodes were analyzed they diminished from 1.24±0.62 per subject year at baseline to 0.12±0.21 at the end of the follow-up (p <0.001). Likewise, there were no differences with respect to A1c values (6.9±1.3 vs 6.5±0.8%; NH and H groups, respectively) after 12-months of CSII. Regarding QoL outcomes, the H group scored better in DQoL-impact of treatment subscale at baseline (45.7±7.0 vs 33.7±7.3; p <0.001, NH and H groups) and this was nearly the case in the QoL-social/vocational worrying subscale (15.7±3.8 vs 13.2±3.7; p= 0.055, NH and H groups) (figure 1A). We did not observe differences in the scores obtained from the SF-12 health survey questionnaire neither at baseline nor at the end of the follow-up. In spite of the fact that all the items evaluated in QoL questionnaires improved similarly after 12 months in both groups of subjects (table 1), the difference in DQoL-impact of treatment subscale (41.5±8.5 vs 31.0±5.8; p <0.001, NH and H groups) was maintained (figure 1B).

Discussion
In addition to the expected clinical and metabolic differences at baseline, subjects in whom CSII was indicated mainly because of repeated hypoglycaemia had different QoL perception than those without this indication for starting CSII. However, CSII improves QoL in both groups after 12 months of follow-up.

Our study confirms that the use of CSIII has a positive impact on quality of life outcomes evaluated, with the exception of the SF-12 health survey questionnaire.9,10 A
very recent case-control study regimens suggest that the quality of life improvement is derived from greater lifestyle flexibility, less fear of hypoglycaemia, and higher treatment satisfaction, when CSII is compared with either glargine-based or NPH-based MDI regimens.\textsuperscript{11}

Intensive insulin therapy significantly reduces the risk of micro and macrovascular complications in subjects with T1D and represents the standard treatment from the onset of the disease. However, this sort of therapy is unfailingly associated with 3 to 4-fold risk of hypoglycaemia including severe episodes, precluding in some cases this type of therapy. Hypoglycaemia is one of the most troubling problems in the management of T1D. The presence of hypoglycaemia produces a “vicious circle” of repeated hypoglycaemia, the appearance of hypoglycaemic unawareness, together causing a predisposition to severe episodes. Because hypoglycaemia is one of the most feared and disabling complication of diabetes treatment, it is surprising that patients with such a problem scored very low on the Diabetes Quality of Life (DQoL) Questionnaires.

### Table 1. Quality of life outcomes/scores at baseline and after 12 months of follow-up

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>12 months</th>
<th>p</th>
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<tr>
<td><strong>DQoL Satisfaction</strong></td>
<td></td>
<td></td>
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<tr>
<td>H Group</td>
<td>36.1±9.1</td>
<td>32.5±5.5</td>
<td>&lt;0.05</td>
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<tr>
<td>NH Group</td>
<td>37.9±9.0</td>
<td>30.0±6.4</td>
<td>&lt;0.01</td>
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<tr>
<td><strong>DQoL Impact of treatment</strong></td>
<td></td>
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<tr>
<td>H Group</td>
<td>33.7±7.3</td>
<td>31.0±3.8</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>NH Group</td>
<td>45.7±7.0</td>
<td>41.4±4.5</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td><strong>DQoL Social/vocational worrying</strong></td>
<td></td>
<td></td>
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<tr>
<td>H Group</td>
<td>13.2±3.7</td>
<td>11.6±1.8</td>
<td>=0.06</td>
</tr>
<tr>
<td>NH Group</td>
<td>15.7±3.8</td>
<td>12.4±1.5</td>
<td>=0.06</td>
</tr>
<tr>
<td><strong>DQoL Diabetes-related issues worrying</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H Group</td>
<td>10.1±2.5</td>
<td>8.7±1.9</td>
<td>=0.07</td>
</tr>
<tr>
<td>NH Group</td>
<td>9.3±2.8</td>
<td>8.6±2.0</td>
<td>=0.08</td>
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</table>

DQoL: Diabetes Quality of Life. CSII: continuous subcutaneous insulin infusion.

### Figure 1

Results of the Diabetes Quality of Life Questionnaires (DQoL) in both groups of subjects with T1D. A) Baseline. B) After 12-months of starting CSII. *p <0.001. DT: diabetes
better in some aspects of quality of life measurements than subjects without it (impact of treatment and social/vocational worrying). In our study this finding remained stable at the end of the 12-month follow-up. However, our results are in agreement with previous studies demonstrating that the concern about hypoglycaemia is underscored in subjects with T1D when compared to their cohabitants. The possible contributors to this underestimation of the problem are multiple and they were not directly addressed in our study. In our opinion, the massive and disproportionate importance that professionals of diabetes management have given to hyperglycaemia and its consequences for decades in comparison with the attention paid to hypoglycaemia could be partly responsible. Fortunately, as well as in the group of subjects in which hypoglycaemia was not the indication for initiating CSII, the improvement in quality of life evaluation was also observed in the group of subjects who initiated CSII because of repeated non-severe and severe hypoglycaemia.

Conclusions

In summary, independently if the main indication for starting CSII includes or not repeated hypoglycaemia, this therapy improves QoL. Subjects who initiate CSII mainly because of repeated hypoglycaemic episodes display a different QoL perception at baseline than those without this indication when starting this type of therapy. Although this finding does not preclude favorable results at short-term, probably it has to be considered in order to encourage patients to start this modality of treatment, as well as, when evaluating QoL results.

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I. Conget and I. Levy have received speaker’s fees from Medtronic and Roche in the past 5 years.

Bibliografía

Teleophthalmology as screening method for diabetic retinopathy

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Abstract
The aim of this study was to evaluate the suitability of teleophthalmology as a method for screening of diabetic retinopathy. It was designed as a transversal and observational study using the retinal fundus images of 520 patients that were studied during the first six months of 2006. This sample comes from a group of patients that are integrated in the Program of digital retinal screening. This screening program was established by the Integral Plan of Diabetes in Andalusia in 2005. It was evaluated the quality of images, the pick-up rate of the illness, the accuracy and the efficiency of the method. In 90% of the patients, the images possessed quality to be evaluated. The pick-up rate of the illness was 2.1. Agreement between existence or absence of diabetic retinopathy was analyzed by using unweighted kappa and its results equal 1. In conclusion, the results obtained in the study provide evidence for the reliability of telemedicine as a screening method for diabetic retinopathy.

Keywords: diabetic retinopathy, screening, teleophthalmology, technology, digital image.

Introduction
Diabetic retinopathy (DR) is a microangiopathy complication of diabetes mellitus (DM) with high social, medical and economical impact, being the second cause of blindness in Spain and the first cause on blindness during labor life.¹,² DR is a disease that fulfils the criteria for screening, since it is asymptomatic during initial stages of the process and an effective treatment to halt progression of the disease is available.¹,³ Screening of DR is accomplished by fundus examination, and the gold standard for the procedure are stereoscopic retinographies of 7 fields and 30 degrees (14 pictures) and ophthalmoscopy with contact and non contact lenses. Fundus examination should be performed at least once a year.³ However, data collected in United States indicate that 50% of diabetic population do not undergo periodical examinations and 60% of patients that need laser therapy do not receive it.⁴ Therefore, attendance to eye clinics seems not to be a suitable approach for DR screening. Further problems should also be considered, such as the time required for examination (35-40 min) and the need for eye doctor to perform the examination. These features, and the need to carry out the examination on a yearly basis,¹ determine that screening of DR with these techniques cannot be performed by an average eye unit.¹,⁵

The above referred situation and the perspectives for a 72% increase in the prevalence of DM for the year 2026 with regard to the year 2003, has aroused the search for alternative screening methods.² Among the options currently available, teleophthalmology represents a first choice alternative to the traditional methods for DR diagnosis.²,⁴ Screening by teleophthalmology is accomplished by visualization at the computer screen of retinography taken at distance in time and space. This option displays a set of features that makes it suitable for screening in a public health system: first, it reaches required standards of sensibility and specificity.²,⁶ Second, the time needed for evaluation of images is 5 minutes on average and third, it allows to store files of images that can be transferred in a minimal time. The Integral Plan for Diabetes in Andalusia aims at decreasing morbidity and mortality related to this disease and one of the programs addresses the improvement of the approach to chronic complications such as DR. Among the lines of action established to decrease the number of blindness caused by
diabetes, the early detection in order to get a diagnosis in stages that respond to treatment. Consequently, teleophthalmology was established as screening method.

The aim of our study is to evaluate teleophthalmology as a screening procedure for DR by means of the data collected over the first 6 months of the program in 2006.

Methods
In this survey, 1,734 type 2 diabetic patients with no previous history of DR entered the screening program summarized in figure 1. Patient selection is carried out by PCPs and nurse personnel. Retinographs from 3 retinal fields for each eye are carried out by nurse personnel at the PC centre. In case of poor quality of images, a drop of tropicamide is instilled and the procedure is repeated. First screen of images is performed by PCP at the PC centre. Images considered containing signs compatible with DR or any other retinopathy are sent to the ophthalmology service of the reference hospital. Poor quality images and images arousing doubts to the PCP were also sent to the reference ophthalmology service. In this second screen, patients with no DR are filtered again and decision is made concerning the need to be studied in the clinic.

Digital images were obtained in 11 Health Centres at the north district of the province of Seville with a non midriatic fundoscopic camera (Topcon, TCR NW-100). Images were stored in JPEG files 140 kb size on average. Images are sent to a central server and then sent to San Lazaro reference’s hospital. Telematic process is by the intranet of the sanitary network of Andalusia. The quality of the images received at the reference hospital was evaluated. Criteria to classify images as non-evaluable were blurred temporary arcades and/or more than 1/3 of the image field with no sharpness (with the exception of DR signs in the sharp areas of the image). Prevalence, stage according to 2003 Global Diabetic Retinopathy Project Group7 and detection rate of DR was also studied. In order to determine the exactitude and the degree of self concordance for DR diagnosis between the certainty method and teleophthalmology, comparisons between the results obtained by the same ophthalmologist were made with kappa statistics. Clinical examination of the retina with indirect ophthalmoscope and biomicroscopy of central retina with 78 dioptres lens were used as certainty method.
Results
The age of the patients was 67.4±10 years, and 64.7 were female. Ninety percent of the images transferred from PC were of enough quality to be evaluated. The prevalence of DR was 38%. From this percentage, it was inferred that the rate of detection of the disease or pick-up rate was 2.1 (Figure 2). Figure 3 shows the distribution according to the gravity of DR. About 70.9% of 520 patients whose images were derived displayed lesions of mild grade, 19.3% showed lesions of moderate grade and 3.2% showed lesions of severe grade. In addition, macular edema was detected in 19.9% of diagnosed patients.

With respect to the 52% of patients whose images were no considered compatible with the diagnosis of DR (figure 2) both non pathological and pathological signs were detected. Non pathological findings were drusen (21.7%) and chorioretinal atrophy (8.1%). Both findings constitute the principal cause of doubts and wrong diagnosis by PCP. On the other hand, among pathological findings, wet age-related macular degeneration was detected in 4% of cases and vein occlusion in 2% of cases. Statistical comparison performed with kappa statistics to determine the exactitude and the degree of interpersonal concordance in the diagnosis of DR by means of the certainty method and the teleophthalmology method, gave a result of 1. That is, a complete agreement was evidenced.

Figure 4 shows that 1,750 patients were evaluated by teleophthalmology. Seventy percent (1,230 patients) were cleared. The remaining 30% showed suspected images that were sent to the eye doctor. Twelve percent were cleared by the eye doctor and 17% (304 out 1,750) required direct examination in office for having images compatible with retinopathy (diabetic or not) or for having poor quality images.

Discussion
The aim of our study was to evaluate the suitability of teleophthalmology as screening method for DR. Results speaks in favour of this method for several reasons: first, the fact that only 10% of the images did not have enough quality to be informed leads us to infer that the diabetic population can be screened with this method. Second, the degree of interpersonal concordance in diagnosis of DR (kappa= 1) proves that digital imaging of the fundus obtained by fun-
Endoscopic camera and transmitted by internet is valid to perform a correct diagnosis of DR. Both conclusions agree well with the results reported in other studies.\textsuperscript{2,5}\n
Finally, if we consider the percentage of patients filtered by PCP (70\%) and the percentage filtered by ophthalmologists (42\% of patients transferred from PC, figure 4), one can conclude that this method results in a substantial decrease in the workload that the program generates to the ophthalmology service. In addition, the implementation of the program has allowed a faster access to supplementary tests and treatments in patients that need it. In terms of economics, according to the fares published in BOJA, the cost of PC office is 52 € and the cost of ophthalmology office is 145 €. It is clear that screening of patients at the PC results in a substantial saving. Teleophthalmology seems to be a reliable, effective and efficient method that can be applied to diabetic population.

In summary, although this method presents some limitations such as the detection of macular edema\textsuperscript{2,5} and will no replace direct ophthalmologic examination, it features qualities that make it the most suitable method for DR screening in health public systems.

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\textbf{Potential conflicts of interest}  
The authors are not aware of any conflicts of interest related to the subject of the review.

\textbf{References}  
Male aged 83 with T2D of 16 years evolution, who showed a good general condition and an HbA1c of 8.6%.

Personal history
The patient received the diagnosis of non-proliferative retinopathy and cataracts, undergoing surgery in the left eye. Moreover, he shows mild distal polyneuropathy, incipient nephropathy without renal failure, hypertension, hyperuricemia and mixed hyperlipemia, as well as non-autoimmune primary hypothyroidism. He undergoes treatment with metformin (2,550 mg/day) glimepiride (4 mg/day) and insulin glargine in morning doses of 22 IU, atorvastatin (20 mg/day), irbesartan (300 mg/day), hydrochlorothiazide (25 mg/day), levotiroxin (125 μg/day) and acetylsaliclic acid (AAS) (100 mg/day). He never smoked and drank only moderately. He was a professor in his active life. He is very worried because he is losing weight. The fasting glycemia during the last controls was not reduced below 180 mg/dL.

Data corresponding to the last revision
Weight 75 kg, height 169 cm, blood pressure (BP) 138/92 mmHg, abdominal waist 92 cm. The cardiac auscultation reveals pure and rhythmic tones. Abdominal megalies and signs of peripheral vascular failure or edema cannot be observed. There is a reduction of the peripheral vibration and thermal sensitivity, higher in the right foot, as well as of patellar and Achilles reflex. In the differed analytics, the following results appear: creatinine of 1.3 mg/dL, basal glycemia 223 mg/dL, HbA1c 8.6%, uric acid 7.6 mg/dL, total cholesterol 203 mg/dL, triglycerides 148 mg/dL, HDL cholesterol (c-HDL) 47 mg/dL, and microalbuminuria 58 μg/mL. There are no other pathological biochemical determinations, including the thyroid hormones. As regards to the patient’s outpatient control, he undergoes 2 glycemic profiles of 3 preprandial points once a week and BP measurement.

Which modifications would you do to this patient’s hypoglycemi treatment?
Altogether, he is a patient of advanced age, with an apparent good life quality, but with limited life expectation (83 years) and with a treatment based on a long acting insulin analogue in doses that, though they are recommended in elderly persons (0.3 U/kg), they might be possibly insufficient. The glycemic control is not adequate (HbA1c; 8.6%) and he shows an insulin deficiency sign as the loss of weight.
The glycemic control objectives in an elder patient have to be identical a priori to those of an adult person. However, the balance among the intensification risks of the hypoglycemicant treatment—higher than those of a younger patient—and the benefits—lower than those of the younger persons—should be assessed in detail. The main risks that shall be considered are basically two: the risk of suffering hypoglycemias secondary to the hypoglycemiant drugs and the pharmacological interactions inherent to every patient treated with polypharmacy, as this case. On the contrary, the potential benefits in a person of advanced age are comprised mainly in relation to an adequate metabolic control—and there are evidences in this patient of not having achieved it—and, in a lower extent, though not underestimated, to the prevention of the microvascular complications (retinopathy, nephropathy and neuropathy) or to avoid its progression if they are already present, as it happens in this patient.

In this special case, the hypoglycemia risk is low, as the patient does not refer any previous hypoglycemia events and the baseline glycemias are sufficiently high so as to suppose that he has no risk of suffering them, except if they are due to frequent diet transgressions. As regards to the second risk—the pharmacology interaction—the possibility of this patient is high when receiving treatment with seven drugs besides the insulin. Therefore, to add more medication to what he is already taking should be assessed carefully, especially the balance between the hypothetical benefit, which is supported by the previous evidence, and the possible inherent risk to any treatment.

A relevant datum in this case is the recent loss of weight, which is a concern reason for the patient and for the physician, as this indicates us about the probable insulin deficiency in spite of being already treated with insulin. We have to consider that this is a patient with a body mass index (BMI) value close to the normal weight (26) and without abdominal obesity (abdominal circumference of 92 cm). These two values (BMI and normal waist perimeter) oblige us to think that the main etiopathogenic factor of the inadequate glycemic control is the insulin deficiency, surely much more important than the resistance to the insulin. In view of all this, and considering the lack of data, the optimal alternative for this patient should be to set out an intensification of the insulin therapy (figure 1).1

In relation to the therapy with oral drugs, we should consider that the patient is already being treated with two of them, metformin and glimepiride, with different action mechanisms. To add another drug taking into account the scarce expected benefits of a third drug, the polypharmacy already received and the expectation of life of this patient, is not an adequate alternative.

As regards to the use of the current hypoglycemicant drugs, metformin might still be used since the glomerular filtration estimated by means of the brief MDRD formula of this patient is of 56 mL/min/1.73 m². With the glomerular filtration is lower than 30 mL/min, the risk of lactic acidosis compels us to withdraw it. As regards to the glimepiride, we should consider that, together with the glicazide, the sulphonylureas are preferable in this elder person because they have a lower risk of hypoglycemia than glibenclamide and are safe in cases of renal failure which is a frequent situation in the patient of advanced age. In spite of the fact that the indicated dose of glimepiride (4 mg) is low, the increase of the dose should not be an effective alternative to reduce the glycosylated hemoglobin, because as it is secretagogue drug it would difficult the improvement the pancreatic reserve. On the contrary, this might worsen mostly due to the exhaustion of the beta cell.

In view of the above, the most adequate in this patient would be to intensify the insulin therapy and, at the same time, to assess the suspension of the treatment with glimepiride keeping the metformin (with a light reduction of doses) if the glomerular filtration is higher than 30 mL/min.

Would you do any changes in the treatment of the rest of the morbidities?
As regards to the cardiovascular disease, it is evident that this is a patient with two cardiovascular risk factors (CVRF) besides the diabetes, as the dyslipidemia and the blood hypertension (BHT). This is a patient who receives at present a treatment for both factors and with a lipid profile and BP values as minimum acceptable, therefore we should analyze if it is justified to intensify the treatment of one or the other.

Treatment of the dyslipidemia
At present, we do not count with controlled clinical trials (CCT) in primary prevention of cardiovascular disease in diabetic patients older than 75 years of age. Many studies of primary prevention have analyzed sub-
groups of patients with diabetes, but the only trial designed specifically is the study CARDS, that will be useful for us as reference. In this clinical trial the patients with cLDL <160 mg/dL and some CVRF (similar case as the one of our patient, though there is no information of the initial cLDL) have been treated with 10 mg of atorvastatin versus placebo, proving a relative reduction of 37% of cardiovascular events in the patients treated with the drug after 4 years. However, we should do several considerations, as that the scope of the analyzed age was of 60-75 years, therefore any recommendation in older ages shall be an extrapolation of the results in younger ages. In second place, all the patients were treated with 10 mg of atorvastatin and our patient is already receiving the double (20 mg) of the dose used in the trial. Therefore, our recommendation would be conservative. The cHDL and the triglycerides are controlled. The cLDL shows a value lower than 130 mg/dL (estimating the LDL as from the analytical data, this result in 126 mg/dL). Taking into account that: 1) there are no studies with patients of this age; 2) the patient does not have any ischemic cardiopathy history, and 3) is receiving already a stand/high doses of statins (20 mg of atorvastatin) it does not seem adequate to increase the dose that the patient is already receiving or add a fibrate.

**Treatment of the blood hypertension**

As regards to the BHT, we shall take into account that, like we have indicated for the hyperlipidemia, we do not
count with ECC in advanced ages (the scope of age in the UKPDS was of 40 to 65 years) that have given reply to this matter. Though most of the entities (ADA) recommend values of BP <130/80 mmHg in all the diabetic patients, in those with renal or retinal affection (NICE) this recommendation has an E evidence level (recommendation of experts), without ECC that endorse such values. An approach based on the evidence and without taking the age into account (the studies are performed in patients under 65 years of age) supports the systolic arterial pressure (SAP) <140 mmHg (UKPDS) and diastolic (DAP) <80 mmHg (HOT), always taking into account that these values are well tolerated by the patient (absence of dizziness or cephalic instability), especially if the patient is of advanced age. No signs of orthostatic hypotension are evidenced in this specific patient, therefore we could intensify the treatment to achieve a main reduction of the DAP (92 mmHg) and secondarily of the SAP (138 mmHg), as this one could be considered more adequate. Given that the patient is receiving a treatment with angiotensin II receptor inhibitors as the irbesartan at full doses (300 mg) (protector of the nephropathy) together with a diuretic --also at high doses: 25 mg of hydrochlorothiazide-- it would be recommendable to add a non-dihydropyridine calcium antagonist, as the amlodipine.

As regards to the use of AAS as primary prevention of the cardiovascular disease, though the clinical guidelines they continue recommending its use, the last EEC are conclusive considering the scarce reduction of the risk in diabetic patients. In spite of the fact that in both studies patients older than 60 years of age are included, in the Ogawa study older patients (up to 85 years of age) have been included. Therefore, and taking into account that we are facing a case of primary prevention, we should withdraw the AAS.

**Which is the number of glycemic and pressure controls you consider appropriate for the patient to undergo?**

Initially, we set out an increase of the dose of basal insulin. Determinations should be done on morning capillary glycemia while we increase the dose of insulin, until achieving that the basal glycemia is acceptable and the hemoglobin lower than 7%. If we achieve an acceptable basal glycemia, but the glycosylated hemoglobin is still >7%, we should set out an intensification of the insulin therapy through the bolus basal method that consists of adding one or several fast insulin supplements to the ba-
sal insulin (ADA-EASD consensus). This guideline needs the performance of preprandial glycemic profile with 3 determinations (breakfast, lunch and dinner), until achieving preprandial glycemias lower than 130 mg/dL. Once we reached adequate preprandial glycemias, we will determine again the glycosylated hemoglobin. If it is higher than 7% we should perform pre and postprandial glycemia profiles (6 per day) in order to detect the moment of the day when the hyperglycemia is produced (figure 2).

Would you do any complementary test?
As complementary emergency test, the determination of ketonuria/ketonemia should be done in first place to assess the level of insulin deficiency to explain the recent loss of weight. Finally, and though there are no signs of peripheral arteriopathy, it is indicated to determine the ankle-arm index (AAI) in order to detect the silent peripheral arteriopathy, as this is a patient of advanced age, with CVRF and microvascular complications, all of them risk factors for suffering a silent peripheral arteriopathy.

Declaration of potential conflict of interest
X. Mundet Tuduri stated that there is no conflict of interests as regards to this paper.

References
The chronic complications in diabetes mellitus type 2 (T2D) which influence in terms of public health are well-known by everyone. Likewise, since the publication of the results of the UKPDS and DCCT\textsuperscript{1,2} studies, we know that the reduction of the glycemic values in patients with T2D diminishes the risk of complications, primarily microvascular events. Starting from this data, different international organizations have put together clinical guidelines for the initial therapeutic management of T2D\textsuperscript{3-5} and have defined as therapeutic objective values of glycosylated hemoglobin (HbA\textsubscript{1c}) around a 6.5\% (NICE and IDF) or a 7\% (ADA and EASD).

In the global treatment diagram of patients with T2D and the control of cardiovascular risk factors, we have been able to improve certain aspects as time goes by, as the lipid or tensional profile, although in the glycemic control it has not been possible.\textsuperscript{6} This has been demonstrated in the rates of patients which exceed the desirable levels of HbA\textsubscript{1c}, of 63\% and 69\% in the United States and in Europe respectively.\textsuperscript{7,8} This fact is based, among other factors, to the progressive aspect of the pathology,\textsuperscript{9} in which a continuous damage of the function of the beta cell is observed, which entails the need to intensify the therapy to keep the target values of HbA\textsubscript{1c}. Such physiopathologic process has its clinic correlate in which it has been denominated as a “secondary decision”,\textsuperscript{10,11} in other words, the need to add a second drug to keep the HbA\textsubscript{1c} levels to <7\% or to reach values of 8\% maintaining the monotherapy treatment.

Different studies have showed that none of the strategies used at the beginning of the monotherapy treatment succeed to keep an optimum control at medium-long term. A meta-analysis showed clearly a medium fall in the HbA\textsubscript{1c} of 1\% with pioglitazone, of 1.2\% with rosiglitazone, of 1.1\% with metformin, of 1.5\% with sulfonylureas, of 0.5\% with nateglinide, and of 0.8\% with asacarbose.\textsuperscript{12} If we pay attention to the proportion of lack of effectiveness in a medium-long term, the glibenclamide was incapable of keeping the level of HbA\textsubscript{1c} below a 7\%, in 53 and 71\% of the patients at 3 and 6 years respectively.\textsuperscript{13} In this same study, metformin was not able to keep the HbA\textsubscript{1c} below the 7\% in 56 and 66\% of the patients at 3 and 6 years respectively. Another study,\textsuperscript{14} showed that between the 10 and 15\% of the patients showed a secondary decision in only 36 months with metformin as first election for the monotherapy treatment. Such variation in the failure of the control showed an inverse relation in the fall of the HbA\textsubscript{1c} reached during the first year of treatment.

Before the difficulty of being able to reach the desired glycemic control and its consequences in relation to the development of a microangiopathy—as is suggested in the UKPDS study, in which significant clinical differences were found among the patients which kept medium levels HbA\textsubscript{1c}, of after 6 years of 6.6 vs. 7.4\%—, the recom-
Recommendations of the classical treatment establish the suitability to increase the dose of the drugs or continue with the scale of drug combination, although not as much in the course of action. In that way particular criterions when choosing one or another medication appear in function of the medical experience, the secondary effects, the patients tolerability, the ability of being able to follow the therapeutic indications, the economical concern and the none glycemic effects of the drugs.

**Do we have arguments to defend that the early use of medication combinations could increase the effectiveness of the treatment of T2D?**

The early combined use of glibenclamide/metformin or nateglinide/metformin has shown to be much more effective than the use of any of them in monotherapy. Equally useful, and with better rates of secondary effects that the use of metformin in maximum doses, the combination of a thiazolidinedione with sub-maximal doses of metformin, looking for the synergy among drugs with different action mechanisms.

The use of drugs based on incretin action show certain additional advantages to those of the glycemic control, as the positive effect on the weight and the improvement of the cardiovascular risk factors. Nowadays it is unknown if the phenomenon’s of cytoprotection of the beta cell, clearly demonstrated in animal models, can be reproducible in human beings. If this would be the case, then this type of therapy should be introduced in combination with insulin-sensitizing agents at the moment of the diagnosis, with the desire of modifying the natural course of T2D.

At a lack of clinical essays that guarantee the effectiveness of an intensive strategy of early pharmacological combination, the use of mathematic simulation methods seems to foresee benefits in the prevention of chronic complications by means of an intensive combined treatment. However, this proposal of combined therapy, complementary and intensive shall be varied when taken into practice, in light of the data recently provided by the studies ACCORD, ADVANCE, and VADT. In this sense, it seems advisable to individualize the degree and speed of intensification in the treatment of HbA1c, in terms of a decrease, probably in function of the degree of concomitant macro vascular pathology and the profile of cardiovascular drugs used, including the effect of weight gain. On the other hand, the economical aspects as well as the different drug combinations should be taken into account. Along these lines, a cost-effectiveness study recently published shows that each year the evolution of T2D implies an extra expense per patient of 75 dollars if it is adjusted by demographic factors and comorbidity, although it is highlighted that only the implantation of therapeutic intensification means an extra expense of 52 dollars per year. Our predisposition of incorporating an intensive medical treatment with early pharmacological combinations could eminently increase the cost of such treatment modality, what maybe could cause a cost-effectiveness immediate negative valuation. But in our opinion, an intensive therapy cautiously set up with an individualized valuation shall demonstrate at a long term, more years of life and of a better quality for our patients.

Using a sports comparison, we could compare T2D with a long distance running, in which to be able to aspire to the victory in the patients with T2D it is indispensible to maintain since the diagnosis an intensive and continuous treatment rhythm (but individualized in function, above all in the cardiovascular characteristics), that in this case is the minimization of the possible chronic complications. Thereby, we mediate for the use of an early pharmacological combined therapy to be able to keep a good metabolic control at long term. In this sense, we think that, just like the use of metformin has been protocolized since the diagnosis, before the impossibility of maintaining a good glycemic adjustment with lifestyle modifications, it shall be advised in an early manner the use of pharmacological combinations according to the patients’ profile.

**Declaration of potential conflict of interests**

A.J. Blanco and M. Puig Domingo state that there are no conflicts of interest as regards to the content of this article.

**References**

Current issues

Benefits of glycemic control in type 2 diabetes.
New certainties and old doubts*

Beneficios del control glucémico en la diabetes tipo 2.
Certezas e incertidumbres derivadas de los últimos estudios

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Abstract
There are strong evidences about the microvascular benefits of intensive glycemic control, but the impact of glycemic control and antidiabetic therapy on cardiovascular morbimortality in type 2 diabetes is still a matter of intense debate. Recently, the results of several landmark clinical studies (STENO-2, ACCORD, ADVANCE, UKPDS to 10 years, VADT) have been published, that can contribute decisively to modify our clinical practice. The key messages are two: a) cardiovascular prevention in type 2 diabetes requires an integral approach to all risk factors, and b) glycemic targets should be individualized. Achieving an HbA1c <7% is still a desirable and safe target for most patients. However, young patients with recent-diagnosed type 2 diabetes may benefit for a more strict glycemic control (HbA1c <6.5%), if this can be achieved safely, to reduce long-term cardiovascular morbidity. By contrast, in patients with limited life expectancy, a history of severe hypoglycemia, significant morbidity or advanced atherosclerotic disease, it is reasonable to consider more conservative objectives.

Keywords: type 2 diabetes, cardiovascular complications, glycemic control.

Introduction
Solid evidence exists for over more than one decade, which demonstrates that the improvement of the glycemic control reduces microvascular complications (retinopathy, nephropathy, and diabetic neuropathy), with independence of the type of diabetes treated and of the hypoglycemic agent used (insulin or oral antidiabetics).1-3 The intensive glycemic control in type 1 diabetes mellitus (T1D) also reduces the cardiovascular (CV) morbimortality at long term. In the DCCT-EDIC study, the group treated during the intervention stage with intensive insulin therapy showed less vascular complications after 17 years of follow up (relative reduction risk [RRR] of 42%; p= 0.02), in spite of that in the observational stage of the study the differences of HbA1c disappeared among the groups with intensive and convention-
al insulin therapy (effect of “hyperglycemic memory” or “of inheritance”). Nevertheless, the impact of the glycemic control and the antidiabetic therapy in the CV morbimortality of type 2 diabetes mellitus (T2D) continues to be object of an intense debate.

**Importance of a strict glycemic control in cardiovascular morbimortality in T2D**

Until now, no controlled clinical study has demonstrated that the intensive glycemic control reduces the CV complications of T2D. The potential CV benefit of the glycemic control is sustained by observational studies and in a meta-analysis, which concluded that in patients with T2D an increase of 1% of the HbA1c is related with a relative risk (RR) of cardiovascular disease of 1.18 (confidence interval: 1.10-1.26).

In the UKPDS study, the development of micro complications was extremely linked to the glycemic control (linear correlation with levels of HbA1c, with a RRR of 25% in 10 years in the groups of intensive therapy in relation with the control group), but the relation between the HbA1c and the acute myocardial infarction (AMI) was lesser (RRR of 16%). Only the overweight patients (≥20% of the ideal weight) treated with metformin showed a significant reduction of AMI (RRR of 39%; p= 0.01) and of total mortality (RRR of 36%; p= 0.01). It is remarkable, that in well controlled diabetic patients (HbA1c <6%), the AMI incidence was 2-3 times higher than that of microvascular damage, which explains the importance of other risk factors (RF), included the dysglycemia in non diabetic range, in atherosclerosis pathogenesis.

The ten years post-intervention observational follow-up of the UKPDS study, recently published, concludes that the intensive glycemic control in patients with T2D of recent diagnosis (as was the case of the patients included in this study) contributes with, besides confirmation of microvascular benefit, with a long term CV benefit, reducing both the coronary risk as the global mortality, in spite of that from the beginning of the first year post-intervention the differences of HbA1c disappeared among the groups, something similar to what was observed in the T1D (DCCT-EDIC study). Until now, the strategies of CV prevention highlighted the importance of the tensional and lipid control. As from this study, the importance of a glycemic control shall be added, at least in T2D from the beginning of the CV disease. The UKPDS recruited a relative young population (with a mean of 53 years of age) starting with T2D, and mainly without associated important comorbidity, for that reason results should not be generalized to other people (elders, diabetic patients with associated CV disease). In the last months various studies have been published which analyze the impact of diverse interventions about the CV risk in patients with high risk T2D.

The observational extension of the STENO-2 study, shows that, in patients with T2D and microalbuminuria a multifactorial intervention about the different RF (glycemic control associated with angiotensin-converting enzyme inhibitors, acetylsalicylic acid [AAS], statins and modification of the life style) reduces the CV mortality almost in 60% during a period of 13 years, regardless of the glycemic control objective (HbA1c <6.5%) it was reached in 20% of the patients. These results reinforce the idea that, in patients with T2D, the vascular protector effect of the glycemic intensive control can be lesser than other interventions relating to arterial blood pressure or to hypercholesterolemia. We shall remember, that in the UKPDS, the arterial pressure control generated major reductions of meta-diabetic complications than the glycemic control, both microvascular as, specially macrovasculars, with a significant reduction of the number of cerebrovascular accidents and of congestive heart failure, as well as a greater reduction of mortality associated with diabetes.

In February 2008, the National Heart, Lung and Blood Institute (NHLBI)-North American National Institutes of Health (NIH) communicated the premature suspension of the 3.5 years (17 months before the foreseen) of the study group ACCORD (Action to Control Cardiovascular Risk in Diabetes), which objective was to reach a strict glycemic control of (HbA1c <6%), when a temporary analysis of security found an excess of global mortality (22%) in relation to the glycemic conventional control (HbA1c between 7 and 7.9%). The ACCORD seems to bring into question the convenience of offering as an alternative the ultra intensive glycemic control, with objectives of HbA1c inferior to the ones recommended in the actual guidelines, at least in the type 2 diabetic populations with high CV risk, as the one included in this clinical trial: patients with a mean age of 62 years, with fully-developed diabetes (mean of 10 years) and history of CV disease or subclinical and or multiple risk factors.
Simultaneously, the results of the ADVANCE study were reported (Action in Diabetes and Vascular Disease-Preterax and Diamicron Modified Release Controlled Evaluation)\textsuperscript{13} which, in a similar population to the one of ACCORD, conclude that the intensive treatment of diabetes during a medium follow-up of 5 years reduces the microvascular complications (above all nephropathy) but not the macrovasculars. In distinction from the ACCORD, in the ADVANCE a mortality increase was not registered in the group under intensive therapy, despite that the levels of HbA\textsubscript{1c} reached were similar in both studies (of 6.4 versus 7.5% in the ACCORD, and the 6.5 versus 7.3 in the ADVANCE, with intensive and conventional therapy, respectively).

Waiting for the secondary analysis, different explanations have been postulated about the greater mortality related with the strict glycemic control observed in the ACCORD study. Among them, the greater incidence of hypoglycemias (symptomatic and asymptomatic), the marked gain weight in some patients, the fast decrease of the HbA\textsubscript{1c} (at the beginning of the study it was greater in ACCORD than in ADVANCE, from 8.1 versus 7.2%), or the possible medical interactions in relation with the polypharmacy or the intensive insulin therapy. It must be pointed out that the greater mortality does not seem associated to any specific medication or to a drug combination, and particularly it is not related with the use of rosiglitazone, a relevant issue, due to the recent controversy about the CV security of rosiglitazone\textsuperscript{14}.

Finally, some of the results of the VADT (Veterans Af faire Diabetes Trial) have been known, performed in a population (almost exclusively male) of patients with poorly controlled T2D (basal HbA\textsubscript{1c} of 9.4%). After 5 years of follow-up, and after having carried out an intensive treatment of the rest of the RF in all the population of the study, the intensive antidiabetic treatment to reach a HbA\textsubscript{1c} of 6.9% did not contribute cardiovascular benefits on mortality or in the microvascular complications in relation to the conventional antidiabetic treatment (final HbA\textsubscript{1c} of 8.4%). In this study, the events of hypoglycemia, the presence of previous cardiovascular disease, the age, the amount of HbA\textsubscript{1c}, and the low cholesterol levels linked to high density lipoprotein were predictor factors of a greater CV risk with intensive therapy.\textsuperscript{15} The principal differential characteristics of the studies ACCORD, ADVANCE and VADT, appear summarized in table 1.

We shall highlight that the results in these three studies are not relevant in T2D patients of low risk (young, without associated CRF or CV, and with T2D of short evolution). As a matter of fact, the analysis of the ACCORD subgroups suggests that the strict glycemic control could be beneficial from the CV point of view in subjects without previous CV disease or with a HbA\textsubscript{1c} <8%. Likewise, the VADT post hoc analysis found a CV advantage in the antidiabetic intensive treatment in patients with less than 12 years of evolution, as well as those whom showed low concentrations of coronary and aortic calcium.

**Consequence of the antidiabetic treatment in the cardiovascular risk**

The CV diseases are responsible of more than 70% of the deaths in the T2D population.\textsuperscript{16} Therefore, the impact of the antidiabetic treatment in the CV risk is of maximum relevance. All the consensus, in function of the results of UKPDS, recommends to administer metformin as an initial therapy of election in T2D. However, in the UKPDS it was only demonstrated a reduction of CV risk (mainly of ictus) in a reduced subgroup (n= 324) of obese patients treated with metformin in monotherapy. This protective effect disappeared when the metformin was combined with sulfonylureas. In fact, the association of metformin with sulfonylureas was related with an increase in the CV mortality, although this deleterious effect could be supposed to a selection bias since we are talking about older patients (mean age superior in 5 years), more obese, with a highly developed diabetes and worse controlled.\textsuperscript{17}

A recent metanalysis concludes that the combination of metformin and sulfonylureas, in comparison with the diet or the monotherapy with metformin or with sulfonylureas, increases the CV events, but does not increase mortality.\textsuperscript{18} It has been suggested that due to the CV benefits of metformin in relation to sulfonylureas in the UKPDS an similar glycemic control was obtained, metformin can contribute to a CV benefit added to its antidiabetic effectiveness, maybe related with the pleiotropic and insulin sensitizers. The association of sulfonylureas could balance these benefits through diverse mechanisms, such as hypoglycemias, weight gain, or loss of myocardial ischemic preconditioning. The observational extension of UKPDS\textsuperscript{8} shows that the macrovascular benefits of the metformin last for a long time in patients with T2D.
### Table 1. Differential characteristics of the ACCORD, ADVANCE and VADT studies

<table>
<thead>
<tr>
<th></th>
<th>ACCORD 10,251</th>
<th>ADVANCE 11,140</th>
<th>VADT 1,791</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>10,251</td>
<td>11,140</td>
<td>1,791</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>62</td>
<td>66</td>
<td>60</td>
</tr>
<tr>
<td>Length of the diabetes (years)</td>
<td>10</td>
<td>8</td>
<td>11.5</td>
</tr>
<tr>
<td>Percentage of males (%)</td>
<td>39</td>
<td>42</td>
<td>97</td>
</tr>
<tr>
<td>Patients insulinized at the beginning of the study (%)</td>
<td>35</td>
<td>1.5</td>
<td>52</td>
</tr>
<tr>
<td>Previous CVD (%)</td>
<td>35</td>
<td>32</td>
<td>40</td>
</tr>
<tr>
<td>CV risk quotient</td>
<td>0.90</td>
<td>0.94</td>
<td>0.87</td>
</tr>
<tr>
<td>Follow-up length (years)</td>
<td>3.5</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>BMI mean at the beginning of the study (kg/m²)</td>
<td>32</td>
<td>28</td>
<td>31</td>
</tr>
<tr>
<td>Weight gain at the end of the study (kg) (I vs C)</td>
<td>3.5 vs 0.4</td>
<td>–0.1 vs –1</td>
<td>7.8 vs 3.4</td>
</tr>
<tr>
<td>Weight gain &gt;10 kg at the end of the study (%)</td>
<td>28</td>
<td>14</td>
<td>–</td>
</tr>
<tr>
<td>Basal HbA₁c (%)</td>
<td>8.1</td>
<td>7.2</td>
<td>9.4</td>
</tr>
<tr>
<td>Final HbA₁c (I vs C)</td>
<td>6.4 vs 7.5%</td>
<td>6.5 vs 7.3%</td>
<td>6.9 vs 8.4%</td>
</tr>
<tr>
<td>HbA₁c reduction in the group of intensive therapy during the first year (%)</td>
<td>1.7</td>
<td>0.6</td>
<td>1.5</td>
</tr>
<tr>
<td>Systolic arterial pressure/diastolic mean at the end of the study (mmHg) (I vs C)</td>
<td>126/67 vs 127/68</td>
<td>134/74 vs 138/74</td>
<td>125/68 vs 126/69</td>
</tr>
<tr>
<td>Smokers at the end of the study (%)</td>
<td>10</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Severe hypoglycemia’s (I vs C)</td>
<td>16.2 vs 5.1%</td>
<td>2.7 vs 1.5%</td>
<td>21 vs 10%</td>
</tr>
<tr>
<td>Polypharmacy (3-5 OAD plus insulin) (%)</td>
<td>62</td>
<td>17</td>
<td>–</td>
</tr>
<tr>
<td>Patients treated with statins* (I vs C)</td>
<td>88 vs 88%</td>
<td>46 vs 48%</td>
<td>85 vs 83%</td>
</tr>
<tr>
<td>Patients treated with AAS* (I vs C)</td>
<td>76 vs 76%</td>
<td>57 vs 55%</td>
<td>88 vs 86%</td>
</tr>
<tr>
<td>Patients treated with secretagogues* (I vs C)</td>
<td>87 vs 74%</td>
<td>93 vs 62%</td>
<td>–</td>
</tr>
<tr>
<td>Patients treated with metformin* (I vs C)</td>
<td>95 vs 87%</td>
<td>74 vs 67%</td>
<td>–</td>
</tr>
<tr>
<td>Patients treated with glitazones* (I vs C)</td>
<td>91 vs 58%</td>
<td>17 vs 11%</td>
<td>53 vs 42%</td>
</tr>
<tr>
<td>Patients treated with insulin* (I vs C)</td>
<td>77 vs 55%</td>
<td>40 vs 24%</td>
<td>89 vs 74%</td>
</tr>
<tr>
<td>Principal variable</td>
<td>CV death Non mortal AMI Non mortal ACVA</td>
<td>Microvascular events (retinopathy, nephropathy) and macrovascular (death, AMI, ACVA)</td>
<td>CV death Non mortal AMI Non mortal ACVA Hospitalization because of congestive heart failure Revascularization</td>
</tr>
<tr>
<td>HR for the principal variable (CI of 95%)</td>
<td>0.90% (0.78-1.04)</td>
<td>0.90% (0.82-0.98)</td>
<td>0.88% (0.74-1.05)</td>
</tr>
<tr>
<td>HR for the mortality (CI of 95%)</td>
<td>1.22% (1.01-1.46)</td>
<td>0.93% (0.83-1.06)</td>
<td>1.07% (0.81-1.42)</td>
</tr>
</tbody>
</table>

*Patients treated at the end of the study. AAS: acetylsalicylic acid; ACVA: acute cerebrovascular accident; AMI: acute myocardial infarction; C: group on conventional therapy; CI: confidence interval; CHF: congestive heart failure; CV: cardiovascular; CVD: cardiovascular disease; HR: hazard ratio; I: group on intensive therapy; OAD: oral antidiabetics.
In experimental and preclinical studies multiple vasoprotective effects of the glitazones have been demonstrated: it improves the endothelial function, inhibition of inflammatory and procoagulant processes and antiproliferative and antioxidants effects. In animal studies, the glitazones delay the progression of atherosclerosis. In human beings, they improve the lipidic profile, they are modestly hypotensive, reduce the microalbuminuria and the C-reactive protein, they reduce the arterial rigidity and delay the progression of the carotid atheromatosis. These effects are independent of the hypoglycemic effect, and they are also produced on non diabetic subjects. The glitazones reduce more than 60% of the coronary restenosis in type 2 diabetic patients subdued to revascularization. In the PROActive study it was found that the treatment with pioglitazone in type 2 diabetic patients with CV disease reduce the incidence of vascular death, AMI or non lethal ictus a 2.1% in 3 years (RRR of 16%). The controversy about the security of rosiglitazone in CV patients will be clear after the publication of the definitive results of the RECORD and BARI-2 studies. Until now, the temporary analysis of RECORD as well as the security analysis of the DREAM and ADAPT studies, have not found any increase of CV morbidity or mortality, with the exception of a greater incidence of heart failure, a class effect of the glitazones. Therefore, the glitazones are secure drugs if used adequately, with a favorable relation of risk-benefit. They are contraindicated in patients with heart failure. In the case of rosiglitazone, the European Medicament Agency recommends not to use it in patients with symptomatic ischemic cardiopathy or with peripheral arterial disease.

To date, we lack of studies that analyze the impact of the new agents (incretin-mimetics, DPP-IV inhibitors) in the CV morbidity and mortality.

Conclusions
The improvement of the glycemic control in the diabetic patient is the most important objective. The strict glycemic control reduces and delays the microvascular complications, independently of the type of diabetes and the antidiabetic treatment used. The intensive insulin therapy also reduces at long term the CV morbidity and mortality in T1D. Until now, no antidiabetic therapy has demonstrated in a conclusive manner CV benefits in T2D. However, a multifactorial intervention about the glycemia and other RF diminishes in a significant way the CV morbidity and mortality in the patients with type 2 diabetes.

The current consensus suggests an intensive and proactive approach of diabetes, with HbA1c objectives less than 7 or 6.5% in most of the cases. The paradigm “while the glycemia is lower the benefit is greater” can be questioned after the ACCORD results, since reducing the glycemia below the valid recommendations (until normoglycemic levels, with a HbA1c ≤6%) it seems to increase the mortality in patients with T2D of advanced middle aged with high vascular risk. In selected subjects (with a long life expectancy, scarce comorbidity and low risk of hypoglycemias) an objective of HbA1c ≥6%.

At last, the T2D is a heterogeneous syndrome. The evidence points out more towards an individualized treatment in the patients with T2D. Therefore, the future of the antidiabetic therapy shall tend towards individualization of the objectives and of the treatments in function of the phenotypic and genotypic characteristics in the patients. Although certain studies, such as ACCORD, the ADVANCE and VADT, give results which apparently are contradictory and paradoxical, they do not give a definitive answer to the issue about the glycemic control or the CV risk, but definitely they have helped in a determining manner how to improve our knowledge about it. In summary, these works suggest that, in comparison with the control of other risk factors, the CV benefit of the intensive glycemic control is discrete and at long term. As it happens with the microvascular complications, it seems that the glycemic control is more important to prevent the macrovascular complications before they appear, while their impact is minor or null in patients with more advanced atherosclerosis.

Waiting for new communications that shed a new light about the subject, with the current evidence we could summarize the following conclusions:
• The contribution of the glycemic control at a short term in CV morbidity and mortality seems low. The additive impact or other associated RF (high blood pressure, dyslipidemia, hypercoagulability) in the macrovascular disease is greater at short term than the glycemia.
• The reduction of the CV risk in T2D requires, therefore, a multifactorial approach. The priority subject is not only to reduce the glycemic control objectives but also to reach an integral control of the RF, as it is recommended in the actual consensus (something that is
obtained in our environment in less than 10% of the patients with type 2 diabetes).\textsuperscript{43}

- We shall tend towards an individualization of the anti-diabetic strategies and objectives. In most of the patients, for a CV prevention objective, it will be reasonable and safe to have an HbA\textsubscript{1c} <7%. While in some subgroups of type 2 diabetic patients (young, with beginning of diabetes, without previous CV disease) it would be appropriate to bring up more strict objectives, this proposal could be associated to a greater mortality in T2D patients with CV high risk or with diabetes of long evolution.\textsuperscript{45}

\textbf{Declaration of potential conflict of interests}

R. Gómez Huelgas has done clinical trials and other investigation studies with Bayer, Novo Nordisk, and Sanofi-Aventis. He has also received fees for conferences from Lilly, GlaxoSmithKline, Merck Sharp & Dohme, Novartis, Novo Nordisk and Sanofi-Aventis.

\textbf{References}


LIST OF ERRATA

In the article “Importance of the therapeutic compliance in diabetes mellitus” (Av. Diabetol. 2009; 25:55-61) of M. Jansà and M. Vidal the following note should have been included:

*This article forms part of the review done by request of the Associació Catalana de Diabetis (ACD) “La diabetes avui: adherència als tractaments de les malalties cròniques. El cas de la diabetis” (M. Jansà i Morató), available at http://www.acdiabetis.org/d_avui/docs/adherencia_tractaments.pdf

In page number 55, in line number 5 of the abstract, where it says “The treatment of diabetes with one chronic disease” should have said “The treatment of diabetes as a chronic disease”.

In page number 57, in the section “Methods to analyze the therapeutic compliance”, in the lines 8 and 9, where it says “The partially methodic conduct is very frequent” it should have said “The partially adherent conduct is very frequent”.

Last in line number 14 of the same page, where it says “A clear example of intentional compliance” it should have said “A clear example of non compliance”.
The main objective of the gestational diabetes (GD) treatment is to achieve concentrations of glycemia close to normal, with the intention of reducing at maximum the maternal-fetus complications risk. The mothers with previous GD have a higher risk at long term of developing a T2D,1 and rarely, T1D. As regards to the descendants, it has a higher tendency to obesity, to the abnormal tolerability to carbohydrates and/or to T2D in adolescence or in the adult age. The macrosomia, defined as weight at birth equal or higher than the percentile 90 (taking into account the sex and the gestational age), is still the main obstetric complication of the woman with GD. The macrosomia risk in women with T1D ranges between 48.8 and 62.5%,2-4 while in the GD it is approximately of 20-30%.5 The GD is a risk factor for the de-

**Introduction**

**Abstract**

Gestational diabetes mellitus is associated with maternal and fetal complications, including macrosomia as the most frequent influencing to a great extent the high rate of caesarean in this population. The main objective in the treatment of gestational diabetes mellitus is to reach glycemic concentrations close to normal. Blood glucose monitoring in pregnant displaying gestational diabetes has demonstrated to reduce associated risks. For this reason, self-monitoring of blood glucose is a fundamental tool and thereby therapeutic education in diabetes is irreplaceable in its instruction. Glycemic targets before and after meals have been reviewed in the most recent guidelines and included in this article, as well as our recommendations about frequency of self-monitoring under different circumstances. The new glucometers incorporate memory for a number of data that can be analyzed with specific software. New technologies, like continuous glucose monitoring systems, can add valuable information in the management of gestational diabetes mellitus and can complement the information obtained by means of self-monitoring of blood glucose.

**Keywords:** gestational diabetes mellitus, self-monitoring of blood glucose, therapeutic education, continuous glucose monitoring systems, ketone monitoring.

**Keywords:**

gestational diabetes mellitus, self-monitoring of blood glucose, therapeutic education, continuous glucose monitoring systems, ketone monitoring.

**Resumen**

La diabetes gestacional se asocia con complicaciones materno-fetales, de las cuales la macrosomía es la más frecuente y condiciona, en gran medida, la alta tasa de cesáreas en esta población. El objetivo principal en el tratamiento de la diabetes gestacional es alcanzar concentraciones de glucemia próximas a la normalidad. La monito-rización de la glucemia capilar ha demostrado reducir los riesgos que esta entidad conlleva. Por tanto, la automonitorización de la glucemia capilar es una herramienta terapéutica fundamental, y, por ello, la educación terapéutica es insustituible en su instrucción. Los objetivos glucémicos antes y después de las comidas se han revisado en las guías terapéuticas más recientes y se han incluido en este artículo, así como nuestras recomendaciones en cuanto a la frecuencia de automonitorización en distintas circunstancias. Las nuevas tecnologías, como los sistemas de monitorización continua de glucosa, pueden aportar una información muy valiosa en el seguimiento de la diabetes gestacional y pueden complementar la información obtenida mediante la AMGC.

**Palabras clave:** diabetes gestacional, automonitorización de la glucemia capilar, educación terapéutica, sistemas de monitorización continua de glucosa, medición de cuerpos cetónicos.

**Keywords:**

diabetes gestacional, automonitorización de la glucemia capilar, educación terapéutica, sistemas de monitorización continua de glucosa, medición de cuerpos cetónicos.
Development of complications, both in the mother and in her descendant. The urinary and vaginal infections stand out among the mother complications during pregnancy, as well as polyhydramnios, the hypertension, the prematurity and the increase of caesarean section probability. As complications for the neonate, besides the macrosomia that conditions many of the following, the intracranial hemorrhage or the shoulder dystocia, obstetric traumatisms (brachial paralysis), fetal immaturity (that can be manifested as respiratory distress syndrome, or metabolic impairments, as the neonatal hypoglycemia or the jaundice have been described.

The observational studies performed demonstrate that there is a clear correlation among the glucose postprandial levels and the macrosomia risk, especially during the second and third quarter of the pregnancy.6,7 The incorporation of the glycemia postprandial monitoring to the educative programs proved to reach reductions of weight at birth.7,8 Likewise, it is important to avoid the excess of treatment, as mean glycemies lower than 87 mg/dL are related to a higher incidence of the intrauterine growth restriction (IUGR).9

The capillary glycemia monitoring during pregnancy allows that the pregnant woman and the therapeutic team knowing the level of the metabolic control and thus be able to carry out modifications in the treatment, with the objective of achieving the values recommended in the international conferences about GD (table 1).10

**Table 1. Control objectives of the capillary blood glucose self-monitoring according to the recommendations of the Fifth International Workshop-Conference on Gestational Diabetes Mellitus (2007)**10

- Basal glycemia <95 mg/dL
- Postprandial glycemia 1 h <140 mg/dL
- Postprandial glycemia 2 h <120 mg/dL

**Table 2. Contents of the therapeutic education program in gestational diabetes**

<table>
<thead>
<tr>
<th>Basic knowledge about the physiopathology of the gestational diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>• To know the risk and the complications that might arise during the delivery:</td>
</tr>
<tr>
<td>– To inform about the possibility that the newborn requires the admission at the neonates unit for control</td>
</tr>
<tr>
<td>– Role of the nutritional therapy, the excess of weight and the physical exercise</td>
</tr>
<tr>
<td>– The importance of the glycemic control during the gestation and the delivery</td>
</tr>
<tr>
<td>– To train the patient on the performance of complete daily glycemic profiles, in order to observe the daily glycemia fluctuations</td>
</tr>
<tr>
<td>– To ensure that the patient carries out a correct technique of the samples collection and that she uses the glucometer correctly</td>
</tr>
<tr>
<td>– To understand correctly the obtained results and carry out the timely changes, if necessary</td>
</tr>
<tr>
<td>– Hypoglycemiant treatment (in case the patient needs it), to understand the signs and symptoms of the hypoglycemia and how to correct them</td>
</tr>
</tbody>
</table>

The capillary glycemia monitoring during pregnancy allows that the pregnant woman and the therapeutic team knowing the level of the metabolic control and thus be able to carry out modifications in the treatment, with the objective of achieving the values recommended in the international conferences about GD (table 1).10

**Therapeutic education program**

The objectives of the therapeutic education program will be addressed to train women with GD for: a) the training in the capillary blood glucose self-monitoring (CB-GSM); b) the knowledge of the objective values according to the determination moment, pre-prandial or post-prandial (table 1), and c) the adequate application of the therapy, only with diet and physical exercise, or to implement also insulin in order to achieve the control objectives. In order to achieve these, we should develop a structured educative program including essential contents (table 2).

**Capillary blood glucose self-monitoring**

The women with GD should learn to use the glucometer for the determination of the capillary glycemia (figure 1). We should insist in the importance to achieve an optimal control in order to reduce in this way the fetal macrosomia risk and other complications during the birth and at long term. According to the current recommendations, we shall consider an adequate glycemic control as a preprandial glycemia of <95 mg/dL, <140 mg/dL one hour after the meals and <120 mg/dL two hours after the meals.10

Most of the clinical guidelines about GD do not need the number and the moment for the performance of the CBGSM11 The most recent version of the care diabetes and pregnancy guideline of the GEDE (Diabetes and Pregnancy Spanish Group)12 stating: “it is recommended
Therapeutic education in diabetes


the practice of preprandial capillary glycemia controls and especially postprandial controls, as well as ketonurias, for the adjustment of quantity and the adequate distribution of the carbohydrates. The recommendations of the Fifth International Workshop-Conference on Gestational Diabetes Mellitus in 2007, recognize that the daily CBGSM is preferable for the detection of glycemia levels that require an intensification of the treatment. This consensus emphasizes that some physicians recommend reducing the frequency of self-analysis when the metabolic control is satisfactory. However, it considers that there are not sufficient scientific data to perform an explicit recommendation on this regard.

In a woman with GD and insulin treatment, the recommendations of the CBGSM are similar to the valid recommendations for the pregestational diabetes and include to perform a daily control of the pre-prandial and postprandial glycemia and, a dawn control (2-3:00) with variable frequency (weekly...). During short terms in which an intensification or treatment change is being assessed, it might be convenient to determine the pre-prandial or postprandial daily profiles. In customized cases with an optimal control of the treatment by means of lifestyle measures, the profiles might be reduced, always including postprandial values.

The adequate moment in which the postprandial glycemic control has to be performed is a controversial aspect. It is not clearly determined if has to be after 60 or 120 minutes of the intake. Some authors recommend using the value obtained one hour after the intake. Others have demonstrated that there are no differences if they are registered one or two hours after such intake. In our clinical practice, we recommend to do it one hour after the intake, though the moment can always be adapted (1-2 h after) to the patient’s needs.

The current glucometers allow storing in their memory several results of CBGSM and there are software programs that analyze them graphically and numerically. Its use is recommendable in these cases as this allows a more complete assessment of the great number of data provided by each patient, in whom the therapeutic decisions are made with stricter control targets than the ones used in other situations. The use in the daily clinic of these capillary glycemia data download has been expressly recommended by the Fifth International Workshop-Conference on Gestational Diabetes Mellitus of 2007.

Monitoring value with glycosylated hemoglobin

The determination of the glycosylated hemoglobin (HbA₁c) is not a good indicator of the glycemic control during the second and third quarter of the pregnancy in this type of patients. In this period, the HbA₁c tends to be reduced physiologically, and therefore its reduction does not imply necessarily a control improvement. Notwithstanding, the GEDE group recommends its determination each 4-8 weeks.

Continuous glucose monitoring system

On occasions, we find macrosomic newborns though during the gestation follow-up the glycemic control has apparently been acceptable. The use of continuous glucose monitoring system (CGMS) allows knowing that these patients show hyperglycemic peaks that are not detected with the CBGSM.

The CGMS are minimally invasive systems that assess the subcutaneous glycemia values each 1-10 minutes during long periods (between 12 and more than 75 h) (figure 2). Considering the system, there are two reading possibilities: retrospective, mainly used as diagnosis tool, and reading systems in real time, that are also useful as educative and therapeutic tool. It is a good educa-
tive tool as it allows knowing visually the consequences that certain factors exert on the glycemia, as the diet, the exercise and the insulin treatment (figure 3).

The continuous record of the interstitial glycemia indicates that the higher number of patients with GD need insulin treatment, compared to the information obtained by means of the CBGSM. The CGMS allow the follow-up of the woman with GD to the therapeutic team and modify the treatment, if necessary. Its use provides information about postprandial fluctuations and unnoticed hypoglycemias that are not recorded with the CBGSM.16-20

Measurement of the ketonuria and/or capillary ketonemia

The determination of ketonic bodies in urine has been recommended in case of serious hyperglycemia, loss of weight during pregnancy and other possible signs of “ketosis malnutrition”.10 The determination of the ketonemia by means of capillary puncture can improve the precision of the measurement as regards to the ketonuria. However, there is no data that prove the reduction of risks associated to the GD by the use of these techniques.

Prevention program after delivery

The presence of hyperglycemia is frequent in the immediate post-delivery of women with GD. It is recommendable to carry out some fasting determinations and/or randomly before discharge in order to assess this aspect. In the post-delivery visit (6-8 weeks), an oral glucose overload (OGO) should be done (75 g) for the reclassification.10-12 The basal glycemia is not valid for this target, since its reduced sensitivity in the detection of impairments of the persistent glucose metabolism. Then, it the performance of another OGO is recommended after one year and each 3 years, besides an annual basal glycemia.10

The patients who have showed a GD should be included in a customized post-delivery program of physical activ-

Conclusions
The GD is associated to mother-fetus complications. The most recent scientific data are still confirming the link between the glycemic control during the pregnancy and these complications. The clinical guidelines have coincided in requesting a more and stricter metabolic control between the glycemic control during the pregnancy and the insulin resistance, and avoid hyperglycemia (corticoids, etc.) when possible. The patient should be informed about the symptoms associated to the hyperglycemia to request a medical care when they detect them, and they have to take into account to follow these preventive measures, especially if they are thinking about a new gestation.21

Declaration of potential conflict of interests
E. Cortés García, R.M. Ortiz Sánchez and F. Gómez Peralta state that there is no conflict of interests as regards to the content of this article.

References
**Case report**

Male aged 47 with chronic infection (HIV) since 1995 after sexual route transmission, under antiretroviral treatment since 1997. At present, he undergoes a concomitant regime of lopinivir-ritonavir and abacavir-lamivudine. In 1999, secondary diabetes was diagnosed to the antiretroviral treatment with irregular metabolic control in spite of the administration of two doses of basal insulin (determin insulin 1.02 IU/kg/day) and a sensitizer to the insulin action (metformin 1.700 mg/day). The last HbA1c control was of 8.2%. During the last 8 months, he developed generalized lipodystrophy, with predominant affectation of the subcutaneous fat of the face (malar lipoatrophy, figures 1 and 2).

**Comment**

The lipodystrophic syndromes make up a heterogeneous group of congenital and acquired disorders. The most frequent one is the lipodystrophy associated to the infection by HIV, characterized by atrophy of the peripheral adipose tissue, especially in limbs and face, back-cervical region and abdomen.1 The most important risk factors associated to its onset are the antiretroviral drugs and the infection itself by HIV.2,3 The treatment with protease inhibitors lead frequently to the development of insulin resistance, intolerance to the carbohydrates and diabetes.4 The use of insulin sensitizers as the thiazolidindiones or the metformin contribute to the reduction of the insulin resistance and the reduction of the lipoatrophy and the accumulation of fat in the abdomen.5

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**References**