Inhibidores de DPP- 4 y Guías de Práctica Clínica: ¿Un amor (im)posible?

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Medical Management of Hyperglycemia in Type 2 Diabetes: A Consensus Algorithm for the Initiation and Adjustment of Therapy

A consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes

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Diabetes Care 32:193–203,

The epidemic of type 2 diabetes and the recognition that achieving specific glycemic goals can substantially reduce morbidity have made the effective treatment of hyperglycemia a top priority (1–3). While the management of hyperglycemia, the hallmark metabolic abnormality associated with type 2 diabetes, has historically taken center stage in the treatment of diabetes, therapies directed at other coincident features, such as dyslipidemia, hypertension, hypercoagulability, obesity, and insulin resistance, have also been a major focus of research and therapy. Maintaining glycemic levels as close to the nondiabetic range as possible has been demonstrated to have a powerful beneficial effect on diabetes-specific microvascular complications, including retinopathy, nephropathy, and neuropathy, in the setting of type 1 diabetes (4,5); in type 2 diabetes, more intensive treatment strategies have likewise been demonstrated to reduce microvascular complications (6–8). Intensive glycemic management resulting in lower A1C levels has also been shown to have a beneficial effect on cardiovascular disease (CVD) complications in type 1 diabetes (9,10); however, current studies have failed to demonstrate a beneficial effect of intensive diabetes therapy on CVD in type 2 diabetes (11–13).

The development of new classes of blood glucose–lowering medications to supplement the older therapies, such as lifestyle-directed interventions, insulin, sulfonylureas, and metformin, has increased the number of treatment options available for type 2 diabetes. Whether used alone or in combination with other blood glucose–lowering interventions, the increased number of choices available to practitioners and patients has heightened uncertainty regarding the most appropriate means of treating this widespread disease (14). Although numerous reviews on the management of type 2 diabetes have been published in recent years (15–17), practitioners are often left without a clear pathway of therapy to follow. We developed the following consensus approach to the management of hyperglycemia in the nonpregnant adult to help guide health care providers in choosing the most appropriate interventions for their patients with type 2 diabetes.

Process

The guidelines and algorithm that follow are derived from two sources. One source is the clinical trials that address the effectiveness and safety of the different modalities of therapy. Here, the writing group reviewed a wide variety of studies related to the use of drugs as monotherapy or in combination to lower glycemia. Unfortunately, the paucity of high-quality evidence in the form of well-controlled clinical trials that directly compare different diabetes treatment regimens remains a major impediment to recommending one class of drugs, or a particular combination of therapies, over another.

The second source of material that informed our recommendations was clinical judgement, that is, our collective knowledge and clinical experience, which takes into account benefits, risks, and costs in the treatment of diabetes. As in all clinical decision making, an evidence-based review of

From the [1]Diabetes Center, Massachusetts General Hospital, Boston, Massachusetts; the [2]University of North Carolina School of Medicine, Chapel Hill, North Carolina; the [3]Clinical Center for Research Excellence, Charles R. Drew University, Los Angeles, California; the [4]Department of Internal Medicine, University of Pisa, Pisa, Italy; the [5]Diabetes Trials Unit, Oxford Centre for Diabetes, Endocrinology and Metabolism, Oxford University, Oxford, U.K.; the [6]Department of Internal Medicine and Yale Center for Clinical Investigation, Yale University School of Medicine, New Haven, Connecticut; and the [7]Samuel Lunenfeld Research Institute, Mount Sinai Hospital, University of Toronto, Toronto, Ontario, Canada.
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An American Diabetes Association consensus statement represents the authors' collective analysis, evaluation, and opinion at the time of publication and does not represent official association opinion.
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Índice

- ¿Cómo interpretar las GPC?
- Inhibidores DPP-4: ¿qué dicen las GPC?
- ¿Cuál sería el perfil del paciente candidato a tratamiento con inhibidores DPP-4?

Índice

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MEDICINA BASADA EN LA EXPERIE[illegible]A

MEDICINA BASADA EN [illegible]EVIDENCIA

¡Evidentemente no exime del BUEN JUICIO CLÍNICO!

Consensos
GPC
Algoritmos

¿AUTOMATISMO CLÍNICO BASADO EN LA EVIDENCIA?

Type 2 Diabetes Guidelines

Basadas en la opinión de expertos	ADA/EASD algorithm 2009 ACE/AACE Diabetes Road Map 2009
Basadas en el consenso	Canadian Diabetes Association 2008
Basadas en la evidencia	National Institute for Clinical Excellence 2009

Sistema de gradación de la evidencia (ADA)

A	- Ensayos clínicos bien diseñados - Metanálisis de calidad
B	- Estudios de cohortes - Metanálisis de cohortes - Estudios caso-control
C	- Ensayos clínicos con fallos metodológicos
D	- Estudios observacionales - Serie de casos
E	- Opinión de expertos

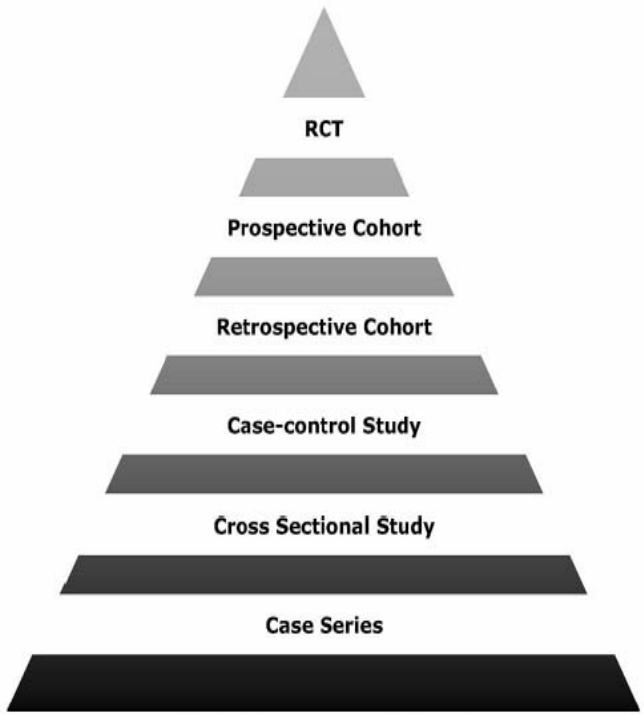
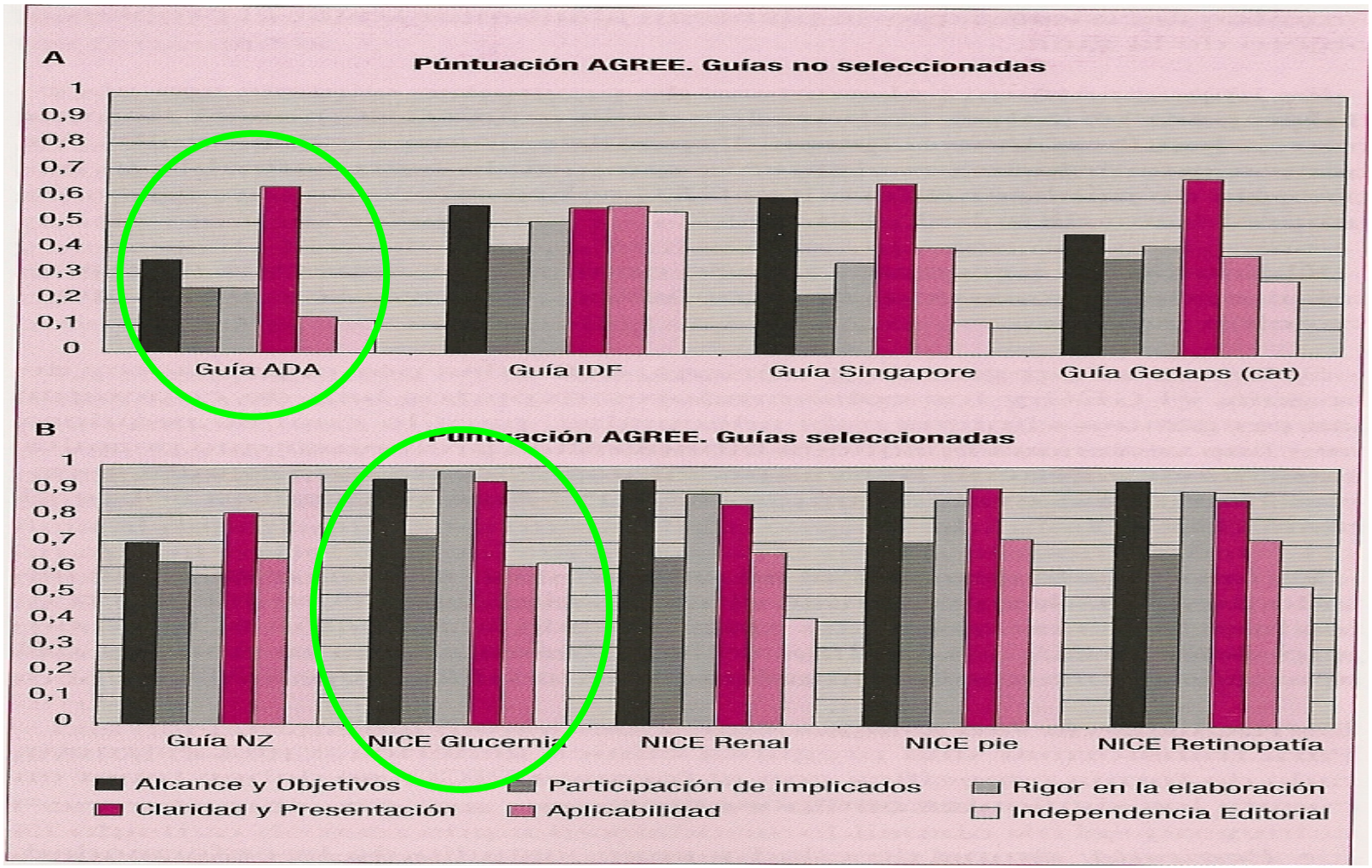


Figure. The pyramid of evidence.

Limitaciones de los consensos

- Revisiones no sistemáticas
- Alta subjetividad
- Sesgo del experto

¿medicina basada en la eMinencia?



[1] The AGREE collaboration. AGREE instrument Spanish versión. Disponible en: http://www.agreecollaboration.org/pdf/es.pdf

Terapia individualizada de la DM2

- **PACIENTE:**
  - edad
  - factores psicosociales
  - comorbilidad (peso, ECV previa)
  - esperanza de vida
  - intereses y expectativas

- **DIABETES:**
  - tiempo de evolución de la DM2
  - HbA1c basal
  - objetivos de control glucémico

- **TRATAMIENTO:**
  - sencillez
  - potenciales efectos adversos
  - costes

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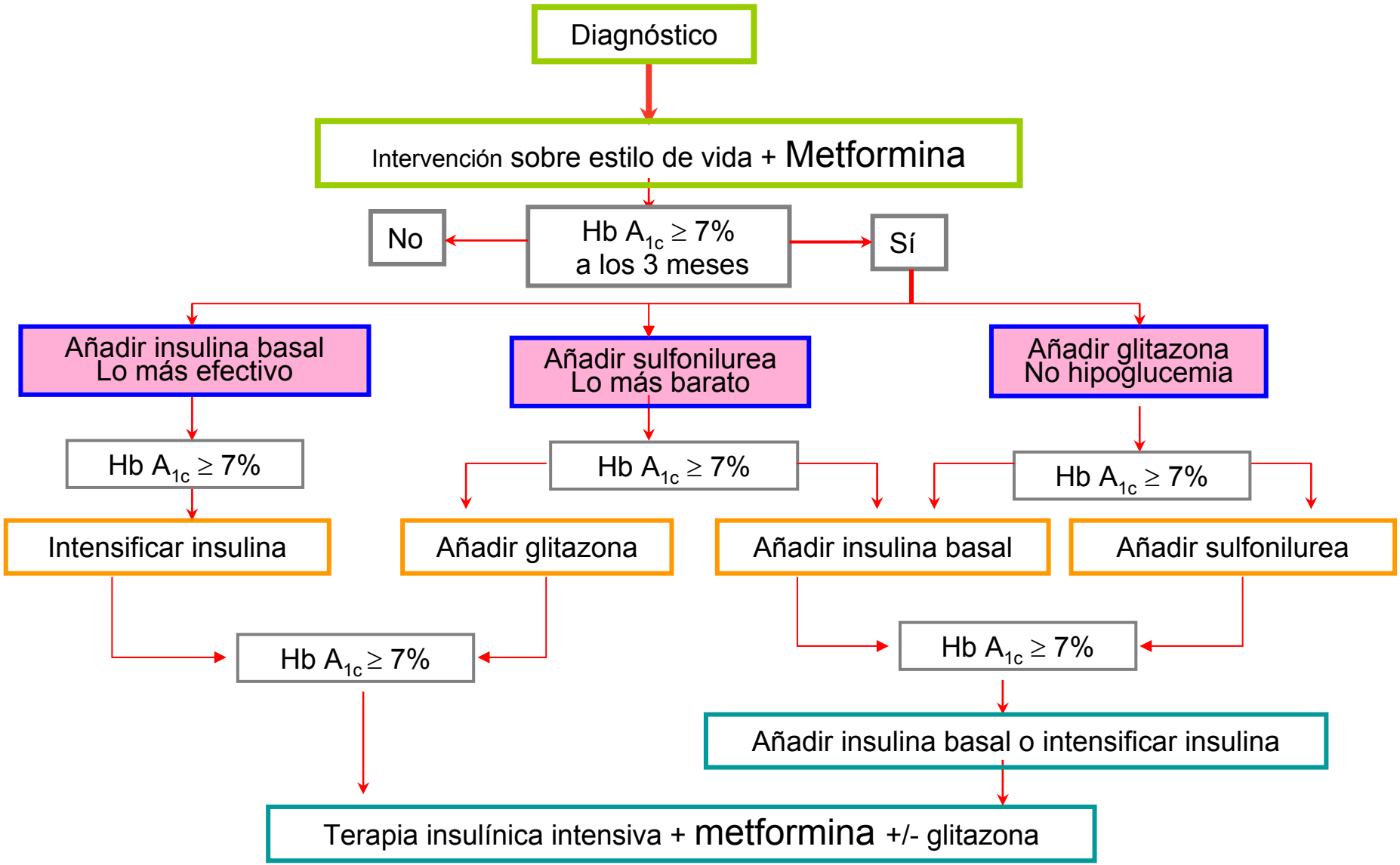
Consensos

1. American Diabetes Association (ADA)
   - 2008-2009
2. Canadian Diabetes Association
   - 2008
3. National Institute for Health and Clinical Excellence
   - (NICE) 2008-2009
4. AACE - ACE
   - 2009

Algoritmo de tratamiento DMT2 - 2008



American Diabetes Association.
Cure • Care • Commitment®

EASD
European
Association for the
Study of Diabetes

2009

Reviews/Commentaries/ADA Statements

CONSENSUS STATEMENT

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An American Diabetes Association consensus statement represents the authors' collective analysis, evaluation, and opinion at the time of publication and does not represent official association opinion.

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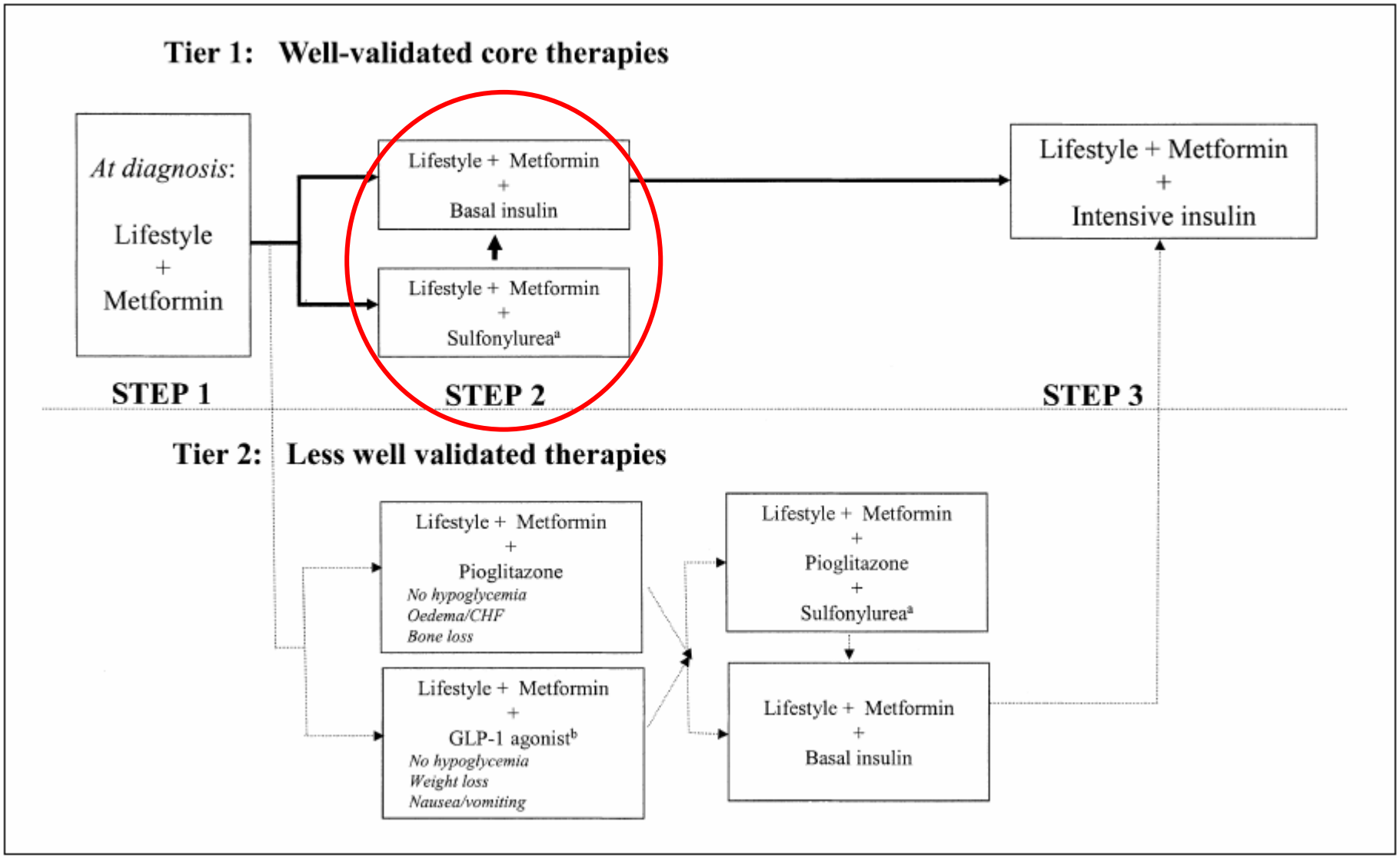
"El consenso representa la opinión, evaluación y análisis colectivo de los autores en el momento de la publicación, y no la opinión oficial de la asociación"

Algoritmo de tratamiento DMT2 - 2009



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Nathan DM et al. Diabetes Care 2009; 32:193–203.

AACE/ACE Diabetes Algorithm *For Glycemic Control*

A1C Goal ≤ 6.5%*

LIFESTYLE MODIFICATION

A1C 6.5 – 7.5%**

Monotherapy

MET | TZD [2] | DPP4 [1] | AGI [3]

2 - 3 Mos***

Dual Therapy

MET	+	GLP-1 or DPP4 [1]
		TZD [2]
		Glinide or SU [5]
TZD	+	GLP-1 or DPP4 [1]
MET	+	Colesevelam
		AGI [3]

2 - 3 Mos***

Triple Therapy

MET + GLP-1 or DPP4 [1]	+	TZD [2]
		Glinide or SU [4,7]

2 - 3 Mos***

INSULIN ± Other Agent(s) [6]

A1C 7.6 – 9.0%

Dual Therapy [8]

MET	+	GLP-1 or DPP4 [1,10] or TZD [2]
		SU or Glinide [4,5]

2 - 3 Mos***

Triple Therapy [9]

MET	+	GLP-1 or DPP4 [1]	+ TZD [2]
		GLP-1 or DPP4 [1]	+ SU [7]
		TZD [2]	

2 - 3 Mos***

INSULIN ± Other Agent(s) [6]

A1C > 9.0%

Drug Name | Under Treatment

Symptoms | No Symptoms

INSULIN ± Other Agent(s) [6]

MET	+	GLP-1 or DPP4 [1]	± SU [7]
		TZD [2]	
		GLP-1 or DPP4 [1]	± TZD [2]

INSULIN ± Other Agent(s) [6]

AACE/ACE Algorithm for Glycemic Control Subcommittee

Co-chairpersons:
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Zachary T. Bloomgarden, MD, FACE
James A. Davidson, MD, FACP, MACE
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Edward S. Horton, MD, FACE
Harold Lebovitz, MD, FACE
Philip Levy, M.D., MACE
Rita S. Mayfield, MD, FACP, FACE
Stanley S. Schwartz, MD, FACE

1 May not be appropriate for all patients
2 For patients with diabetes and A1C <6.5%, pharmacologic Rx may be considered
3 If A1C goal not achieved safely
4 DPP4 if ↑ PPG and ↑ FPG or GLP-1 if ↑↑ PPG
5 TZD if metabolic syndrome and/or nonalcoholic fatty liver disease (NAFLD)
6 AGI if ↑ PPG
7 Glinide if ↑ PPG or SU if ↑ FPG
8 Consider secretagogue monotherapy
9 a) Discontinue insulin secretagogue with multidose insulin
b) Can use preprandial bolus with prandial insulin
10 Decrease secretagogue by 50% when added to GLP-1 or DPP-4
11 If A1C <8.5%, combination Rx with agents that cause hypoglycemia should be used with caution
12 If A1C >8.5%, in patients on Dual Therapy, insulin should be considered
13 GLP-1 not approved for initial combination Rx

ALGORITMO CANADIAN DIABETES ASSOCIATION 2008

ESTILOS de VIDA

Intervenciones sobre estilos de vida (dieta y actividad física)

- HbA1c<9% → **Metformina**
- HbA1c>9% → **Fármacos sin esperar efecto estilos de vida**
  - **Metformina + otros F**
  - **Insulina**
- Hiperglucemia sintomática y descompensación metabólica → **Insulina ± Metformina**

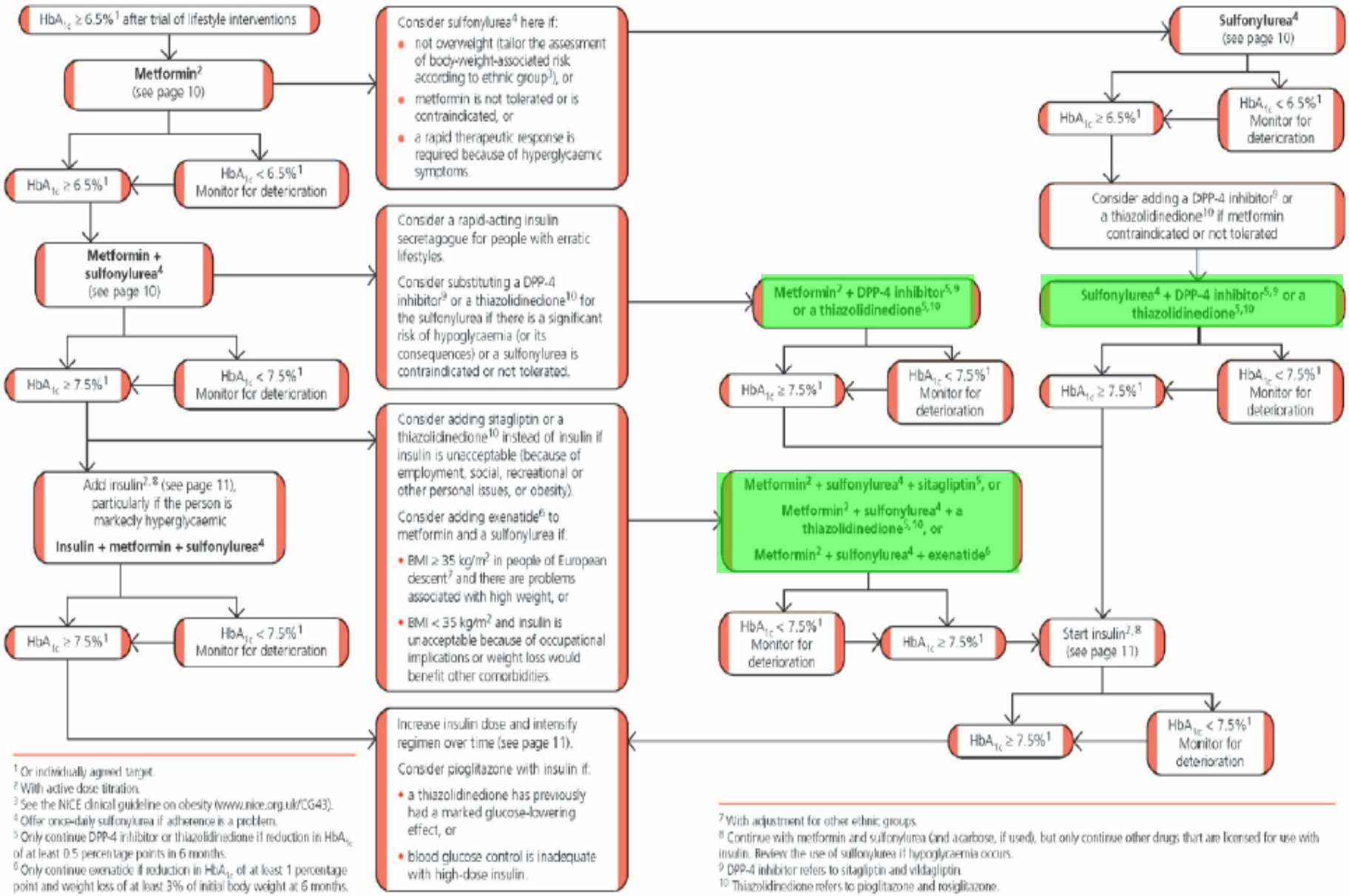
Si no se alcanza objetivo → Añadir otro fármaco según ventajas e inconvenientes

Familia	HbA1c	Hipos	Ventajas	Inconvenientes
Glitazona	↓↓	Rara	Monoterapia persistente	Necesita 6-12 semanas para máx efecto Aumento de peso Edema, I.Cardiaca, fracturas en mujeres
Inhib Alfaglucos	↓	Rara	Control glucemia postprandial Peso neutral	Efectos gastrointestinal
Inhib DPP4	↓ o ↓↓	Rara	Control glucemia postprandial Peso neutral	Nuevo (seguridad desconocida)
Insulina	↓↓↓	Si	No tope de dosis Pautas flexibles	Ganancia peso
Meglitinida	↓ o ↓↓	Sí	Control glucemia postprandial	Requiere 2-3 dosis
Sulfonilurea	↓↓	Sí	Las nuevas menos hipoglucemias	Ganancia peso
Perdida peso	↓	No	Pérdida peso	Efectos gastrointest inal (Orlistat) Aumento frec cardiaca (sibutramina)

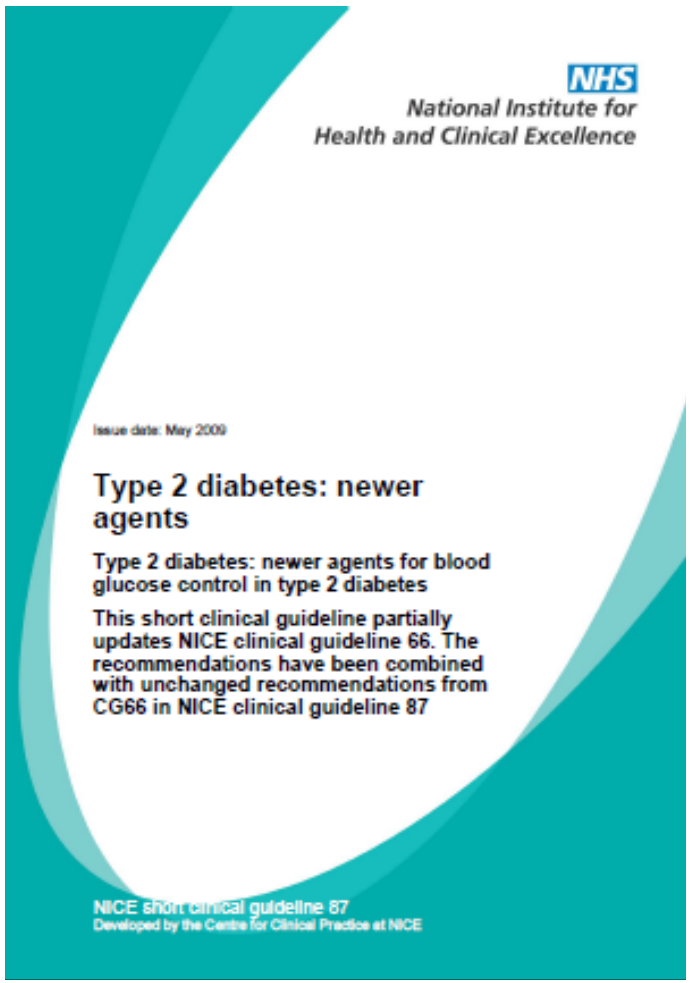
- Añadir otro F de diferente clase
- Añadir insulina basal bedtime a los FO
- Intensificar la dosis de insulina

1.2 Care pathway

Blood-glucose-lowering therapy



[1] Or individually agreed target.
[2] With active dose titration.
[3] See the NICE clinical guideline on obesity (www.nice.org.uk/CG43).
[4] Offer once-daily sulfonylurea if adherence is a problem.
[5] Only continue DPP-4 inhibitor or thiazolidinedione if reduction in HbA_{1c} of at least 0.5 percentage points in 6 months.
[6] Only continue exenatide if reduction in HbA_{1c} of at least 1 percentage point and weight loss of at least 3% of initial body weight at 6 months.
[7] With adjustment for other ethnic groups.
[8] Continue with metformin and sulfonylurea (and acarbose, if used), but only continue other drugs that are licensed for use with insulin. Review the use of sulfonylurea if hypoglycaemia occurs.
[9] DPP-4 inhibitor refers to sitagliptin and vildagliptin.
[10] Thiazolidinedione refers to pioglitazone and rosiglitazone.



1 Summary

1.1 List of all recommendations[1]

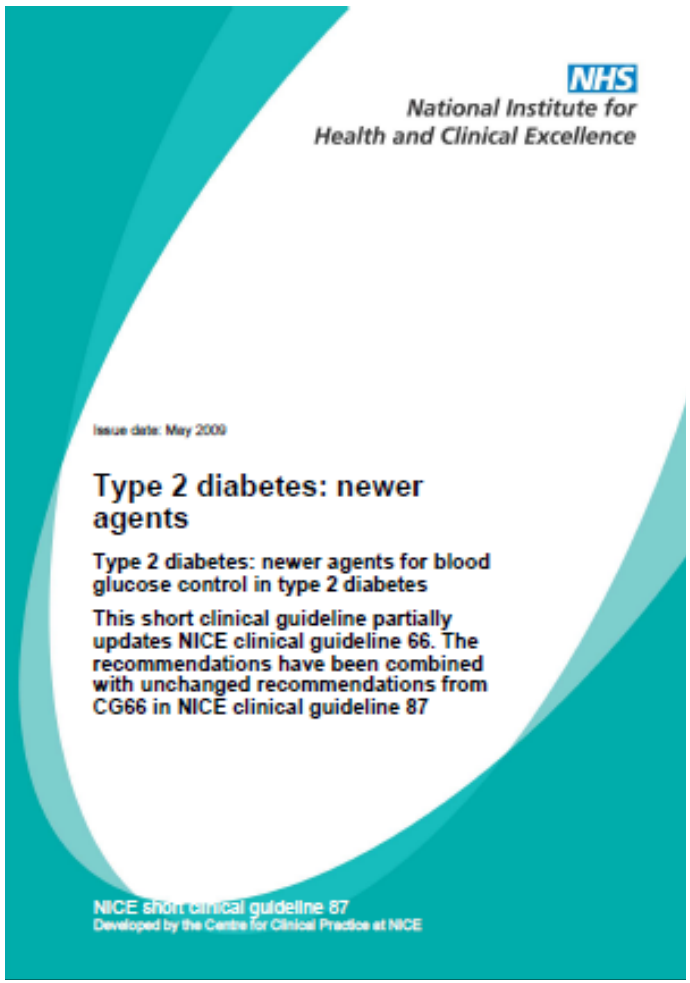
DPP-4 inhibitors (sitagliptin, vildagliptin)

1.1.1 Consider adding a DPP-4 inhibitor (sitagliptin, vildagliptin) instead of a sulfonylurea as second-line therapy to first-line metformin when control of blood glucose remains or becomes inadequate (HbA_{1c} ≥ 6.5%, or other higher level agreed with the individual) if:

- the person is at significant risk of hypoglycaemia or its consequences (for example, older people and people in certain jobs [for example, those working at heights or with heavy machinery] or people in certain social circumstances [for example, those living alone]), or
- the person does not tolerate a sulfonylurea or a sulfonylurea is contraindicated.

1.1.2 Consider adding a DPP-4 inhibitor (sitagliptin, vildagliptin) as second-line therapy to first-line sulfonylurea monotherapy when control of blood glucose remains or becomes inadequate (HbA_{1c} ≥ 6.5%, or other higher level agreed with the individual) if:

- the person does not tolerate metformin, or metformin is contraindicated.



1.1.3 Consider adding sitagliptin[2] as third-line therapy to first-line metformin and a second-line sulfonylurea when control of blood glucose remains or becomes inadequate ($HbA_{1c} \geq 7.5\%$ or other higher level agreed with the individual) and insulin is unacceptable or inappropriate[3].

1.1.4 Only continue DPP-4 inhibitor therapy (sitagliptin, vildagliptin) if the person has had a beneficial metabolic response (a reduction of at least 0.5 percentage points in HbA_{1c} in 6 months).

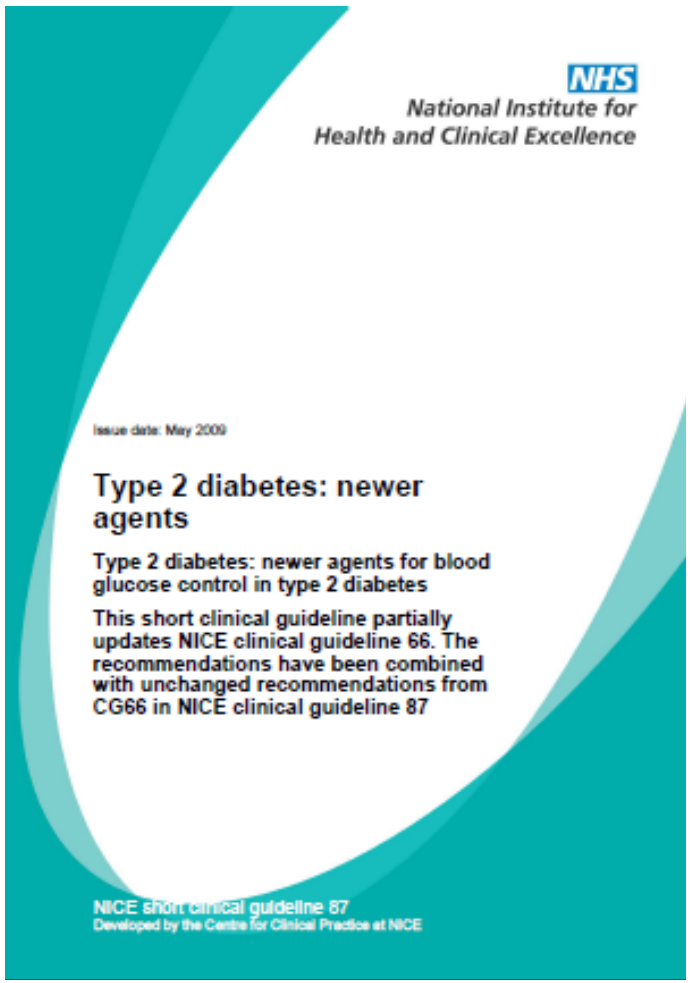
1.1.5 Discuss the potential benefits and risks of treatment with a DPP-4 inhibitor (sitagliptin, vildagliptin) with the person to enable them to make an informed decision.

A DPP-4 inhibitor (sitagliptin, vildagliptin) may be preferable to a thiazolidinedione (pioglitazone, rosiglitazone) if:

- further weight gain would cause or exacerbate significant problems associated with a high body weight, or
- a thiazolidinedione (pioglitazone, rosiglitazone) is contraindicated, or
- the person has previously had a poor response to, or did not tolerate, a thiazolidinedione (pioglitazone, rosiglitazone).

There may be some people for whom either a DPP-4 inhibitor (sitagliptin, vildagliptin) or a thiazolidinedione (pioglitazone, rosiglitazone) may be suitable and, in this case, the choice of treatment should be based on patient preference.

2.6 Cost effectiveness



The GDG considered that the DPP-4 inhibitors were cost-effective options for use in dual therapy (that is in combination with either metformin or a sulfonylurea). There was no evidence on clinical and cost-effectiveness grounds that would suggest there are any significant differences between the DPP-4 inhibitors. The GDG considered that these drugs were likely to be highly cost-effective alternatives to relevant comparators. The GDG also believed that sitagliptin is a suitable option in triple-therapy regimens specifically if insulin use is considered inappropriate or is unacceptable to the person with diabetes.

Inhibidores DPP-4 y GPC

GPC	1º escalón	2º escalón	3º escalón
ADA-EASD			
NICE			
CDA			
AACE/ACE			

recomendado

no recomendado

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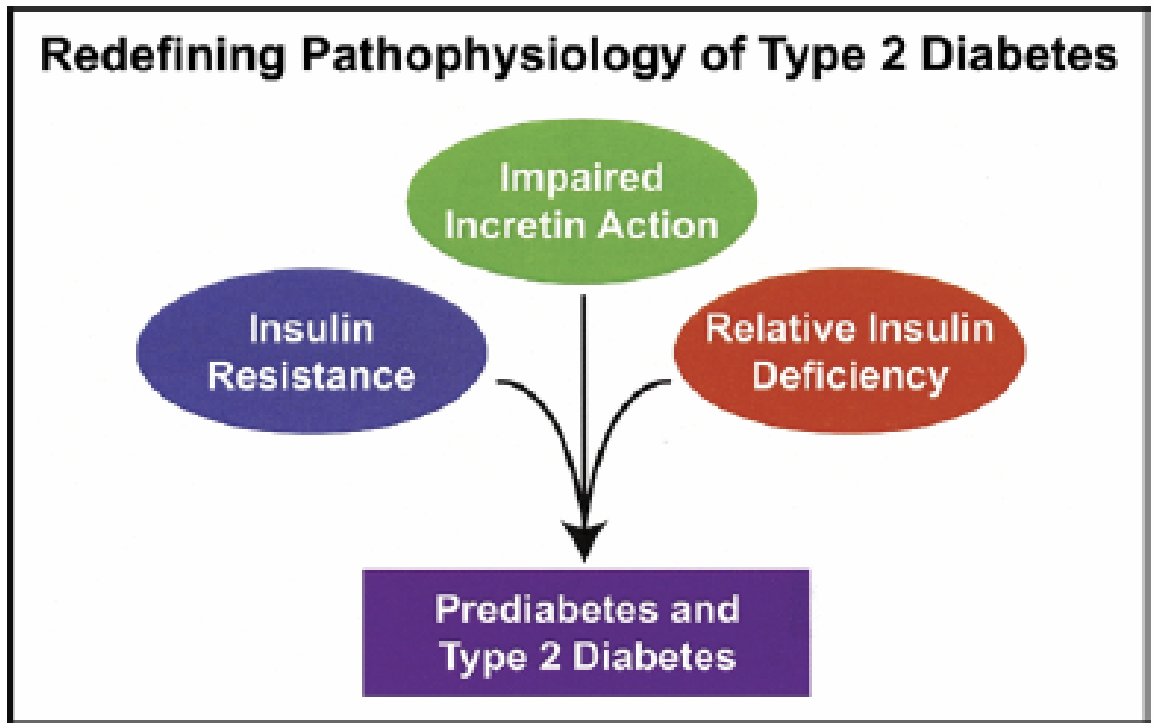
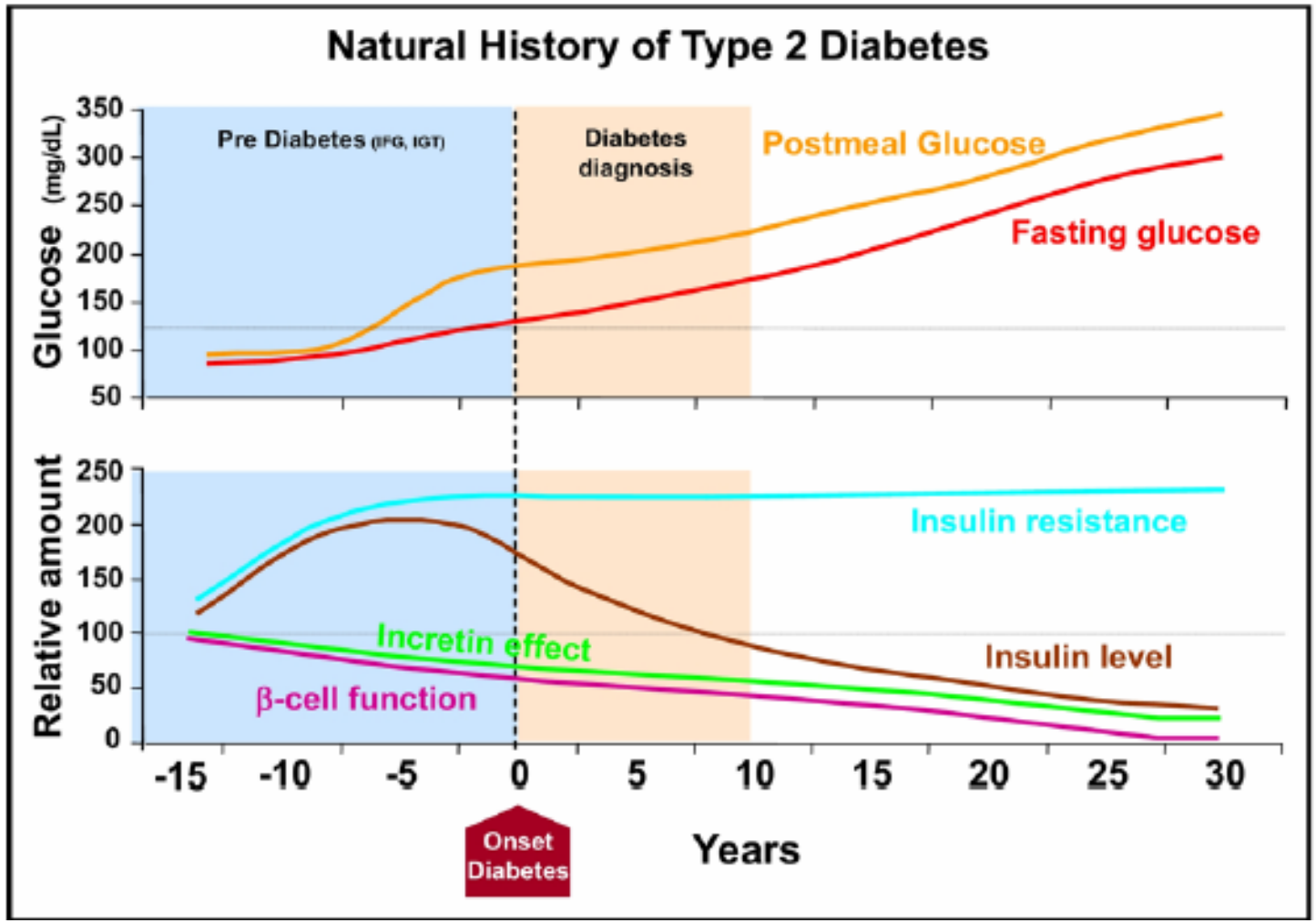
¿Qué aporta los Inhibidores DPP-4 sobre otros tratamientos?

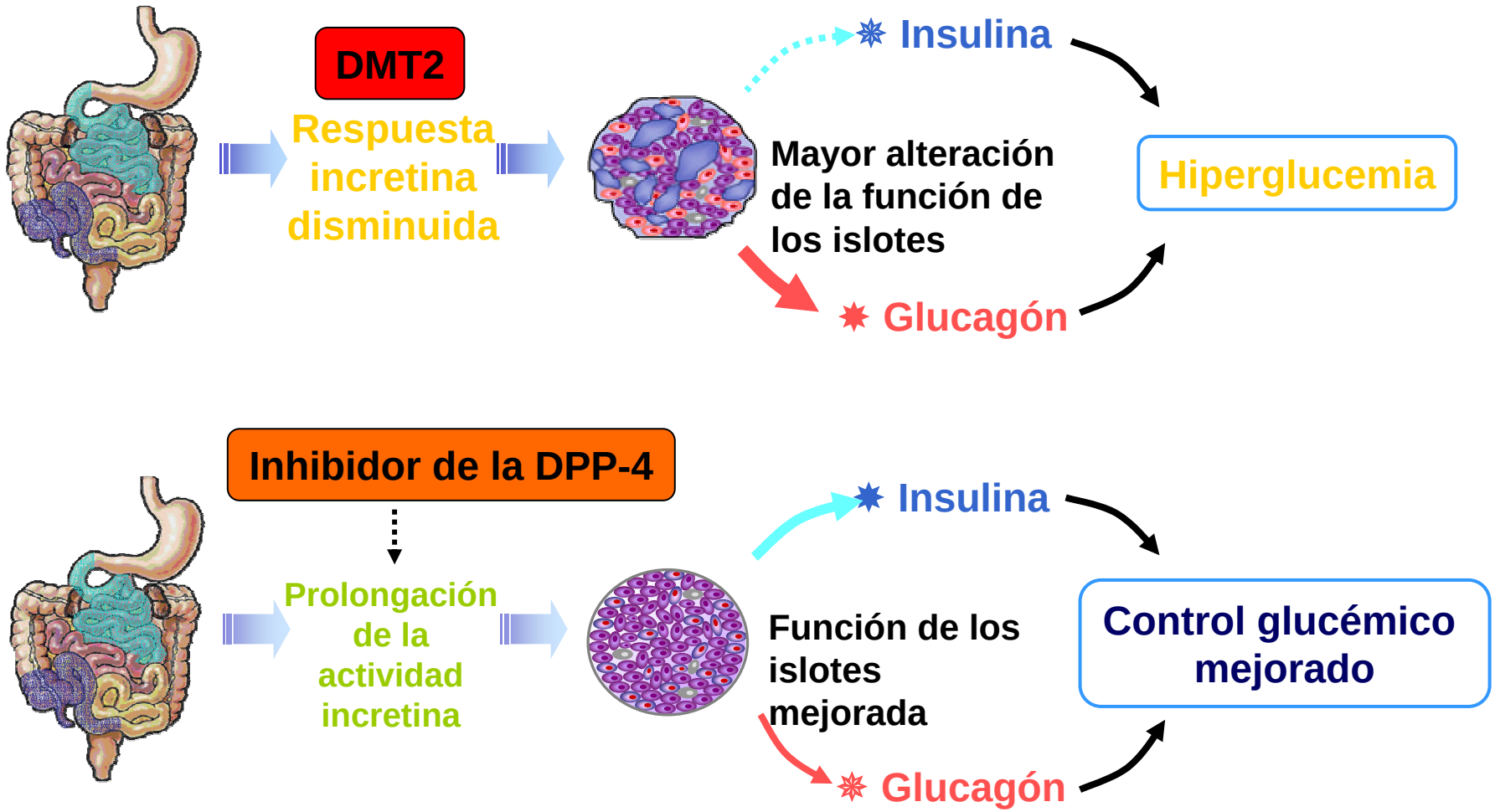
- **Enfoque fisiopatológico de la DMT2**
- **No hipoglucemias**
- **No ganancia de peso**
- **Buena tolerancia**
- Preservación de la función beta ?
- Protección cardiovascular ?


Redefining Pathophysiology of Type 2 Diabetes
Impaired Incretin Action
Insulin Resistance
Relative Insulin Deficiency
Prediabetes and Type 2 Diabetes



The American Journal of Medicine, Vol 122, No 6A, June 2009

El bloqueo de la DPP-4 puede mejorar la actividad incretina y corregir la relación insulina: glucagón en la DMT2



DPP-4=dipeptidil peptidasa-4; T2DM=diabetes mellitus tipo 2

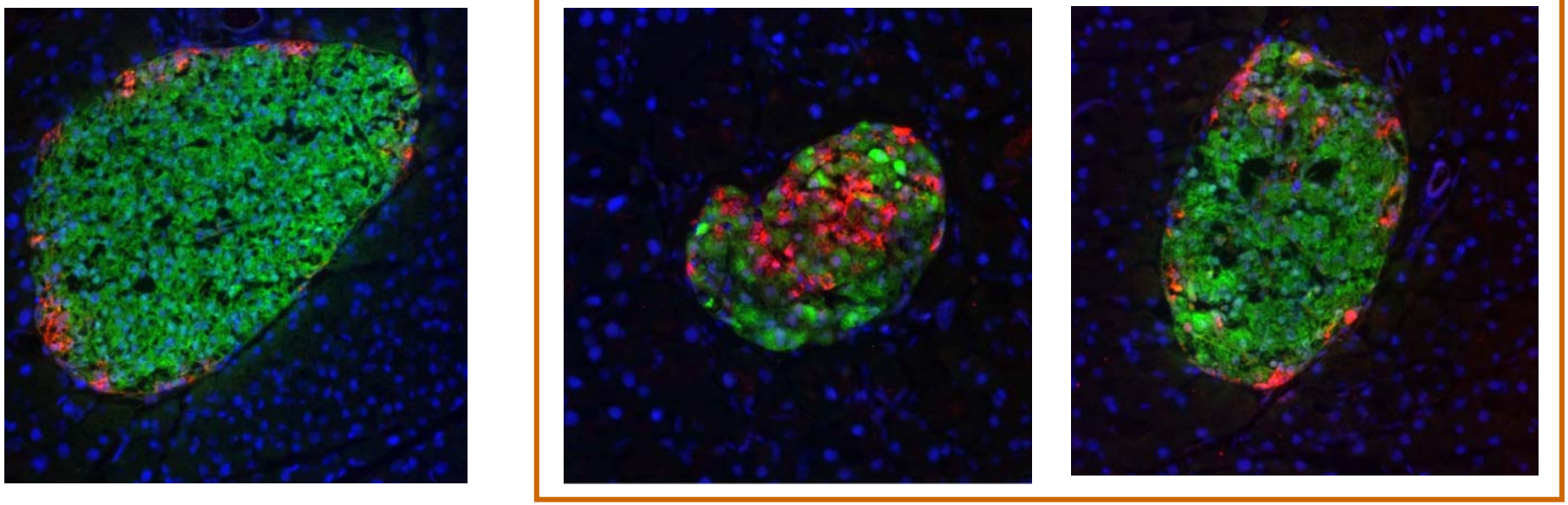
Adaptado de Unger RH. *Metabolism.* 1974; 23: 581–593. Ahrén B. *Curr Enzyme Inhib.* 2005; 1: 65–73.

Restoration of Pancreatic Islet Beta Cells by Restoring GLP-1 Levels

Lean control mice

Diabetic mice

Diabetic mice + DPP-4 Inhibitor



Green: Insulin-producing β-cell
Red: Glucagon-producing α-cell

Diabetic mice received 10 weeks of treatment with MK-0431 analog.
DPP-4 = Dipeptidyl peptidase-4

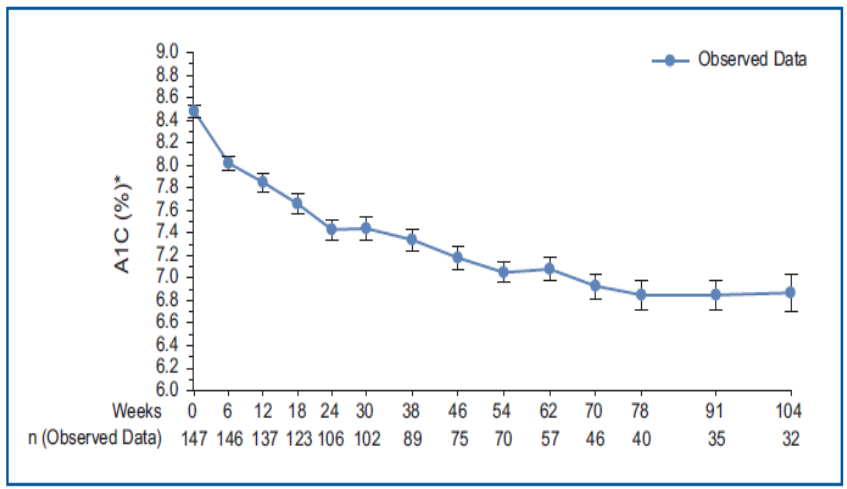
Adapted from Zhang BB et al. Poster presentation at the 64th Scientific Session of the ADA, Orlando, Florida, USA, June 2004.

Long-term Efficacy with Sitagliptin as Monotherapy or Add-on Therapy to Metformin: Improvement in Glycemic Control over 2 Years in Patients with Type 2 Diabetes

Debora Williams-Herman, Thomas Seck, Gregory Golm, Hongwei Wang, Jeremy Johnson, Keith D. Kaufman, Barry J. Goldstein

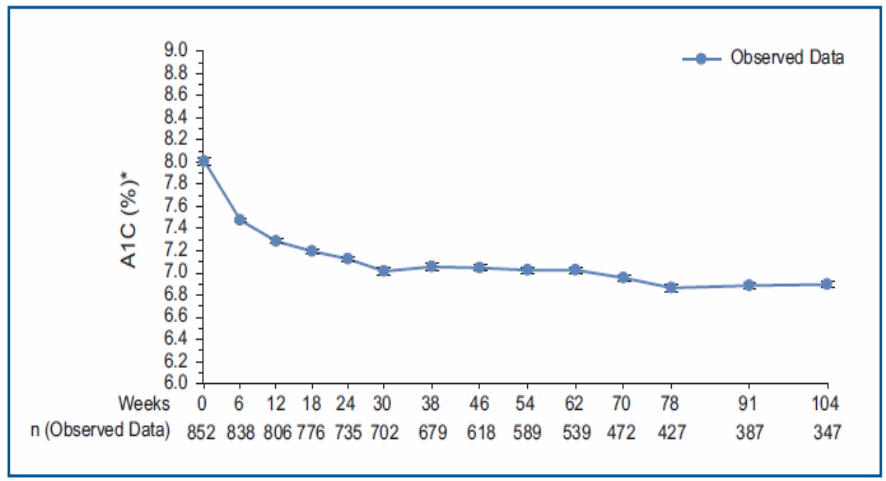
Rahway, NJ, United States

Sitagliptin monotherapy: A1C over time



*LS mean ± SE

Sitagliptin added-on to metformin: A1C over time



*LS mean ± SE

American Diabetes Association
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New Orleans, LA

Inhibición de DPP-4: mejora los factores de riesgo cardiovascular
LÍPIDOS

- Vildagliptina mejora el perfil lipídico (CT -2.7%, LDL -2.1%, HDL +3.8%) (TG -0.6% ns) (Nathwani A. ADA, 2006)
- Reducción de los niveles de triglicéridos postprandiales y los quilomicrones con vildagliptina durante 4 semanas (Matikainen et al, *Diabetologia* 2006)
- Sitagliptina asociada a metformina mejora significativamente el perfil lipídico frente a placebo a 24 semanas (CT -2.8%, TG -16.9%, HDL +2%) (LDL -0.8% ns) (Charbonell et al, *Diabetes Care* 2006)

Inhibición de DPP-4: mejora los factores de riesgo cardiovascular
PRESIÓN ARTERIAL

- Reducción de presión arterial (PAS/PAD -4.1 / -2.7 mmHg) con vildagliptina en monoterapia y en terapia combinada a las 24 semanas (Nathwani et al, ADA 2006, 474-P).
- Vildagliptina reduce la presión arterial sistólica y diastólica en pacientes DMT2 hipertensos (combinación de estudios fase III , n=536) PAS/PAD -8.3/-4.5 mmHg; $p<0.001$ (Bosi et al; ADA 2007, 521-P)
- Sitagliptina reduce la presión arterial ambulatoria en pacientes no diabéticos con hipertensión leve a moderada PAS -2.2 mmHg, PAD -1.6; PAM 24-h -1.6 mmHg; $p<0.05$ (Mistry et al; J Clin Pharmacol 2008)

Rationale and Design of The Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS)

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The purpose of TECOS is to evaluate the potential impact of sitagliptin, a dipeptidyl peptidase-4 inhibitor, on cardiovascular outcomes and clinical safety in a multinational, randomized, double-blind, placebo-controlled trial.

TECOS is a pragmatic, academically run trial that will recruit approximately 14,000 patients with type 2 diabetes who are ≥50 years old, have documented cardiovascular disease, and who have an HbA_{1c} ≥6.5% and ≤8% on stable doses of any one or two of three oral antihyperglycemic agents (metformin, sulfonylurea, pioglitazone). A minimum of 2000 patients will be on metformin monotherapy and 2000 patients on pioglitazone (alone or in combination). Randomization will be 1:1 to the addition of double-blind sitagliptin (100 mg/day) or matching placebo to a patient's existing diabetes care regimen in a usual care setting, with the aim of achieving glycemic equipoise in the two groups. Patients with moderate, but not severe, renal insufficiency can be included but will be given reduced doses of sitagliptin. Patient accrual, which began in December 2008, will take 2 years in around 30 countries. The primary end point will be the time to the first occurrence of a composite cardiovascular outcome (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke or hospitalization for unstable angina). Cardiovascular events will be adjudicated by an independent committee, blinded to study therapy. In this noninferiority trial, 1300 confirmed primary end points are needed to provide 90% power to yield the upper limit of the adjusted 95% CI for a hazard ratio <1.20 at a one-sided α level of 0.025. Follow-up will be four monthly in the first year, then twice yearly for a minimum of 4 years or until 1300 primary end points have occurred.

Inhibidores DPP-4

FORTALEZAS	DEBILIDADES
• **No hipoglucemias**	• **Faltan estudios a largo plazo:** - durabilidad control glucémico - efectos CV - seguridad
• **Efecto ponderal neutro**	
• **Buena adherencia:** vía oral (1-2 dosis/día) buena tolerancia	• **Precio**
• **Restaura efecto incretina**	
• **Preserva función beta ?** • **Cardioprotección ?**	

Inhibidores DPP-4
¿Cuándo? ¿A quién?

Paciente ideal	A evitar
• **Diabetes tipo 2 no muy evolucionada** • **Pacientes con sobrepeso / obesidad** • **Pacientes en riesgo de hipoglucemia** • hipoglucemias previas (asintomáticas) • trabajos de riesgo (alturas, maquinaria, conductores) • sociales (ancianos, monoparentales, Ramadán) • alto riesgo CV	• **I. renal moderada – grave** • **Hepatopatía** (vildagliptina) • **Embarazo y lactancia** • **Descompensaciones agudas**

Predicción

- Los I-DPP-4 ofrecen una novedosa aproximación al tratamiento de la DT2 y ...
- Los veremos como terapia validada en los próximos algoritmos de la ADA-EASD