Posicionamiento, monitorización y uso racional de los nuevos antidiabéticos para la Diabetes Mellitus tipo 2

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Conflicto de intereses

- He recibido honorarios por participar como ponente en charlas, cursos y congresos patrocinados por la industria farmacéutica.

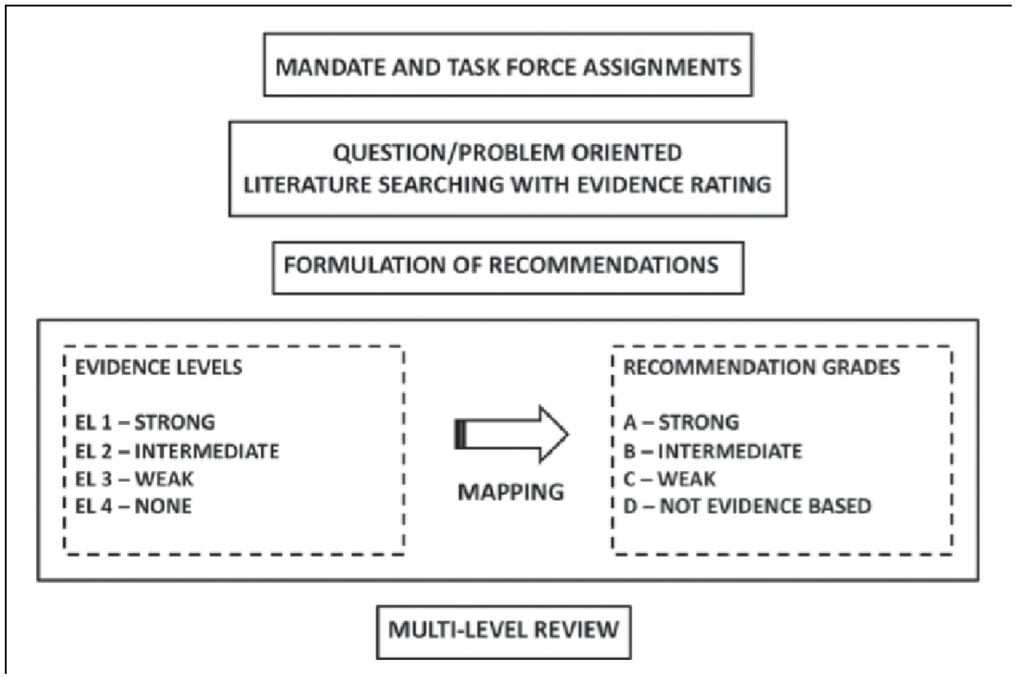

Table 1
2010 American Association of Clinical Endocrinologists Protocol for Production of Clinical Practice Guidelines—Step I: Evidence Rating[a]

Numerical descriptor (evidence level)[b]	Semantic descriptor (reference methodology)
1	Meta-analysis of randomized controlled trials (MRCT)
1	Randomized controlled trials (RCT)
2	Meta-analysis of nonrandomized prospective or case-controlled trials (MNRCT)
2	Nonrandomized controlled trial (NRCT)
2	Prospective cohort study (PCS)
2	Retrospective case-control study (RCCS)
3	Cross-sectional study (CSS)
3	Surveillance study (registries, surveys, epidemiologic study, retrospective chart review, mathematical modeling of database) (SS)
3	Consecutive case series (CCS)
3	Single case reports (SCR)
4	No evidence (theory, opinion, consensus, review, or preclinical study) (NE)

[a] Adapted from (1): *Endocr Pract.* 2010;16:270-283.
[b] 1, strong evidence; 2, intermediate evidence; 3, weak evidence; and 4, no evidence.

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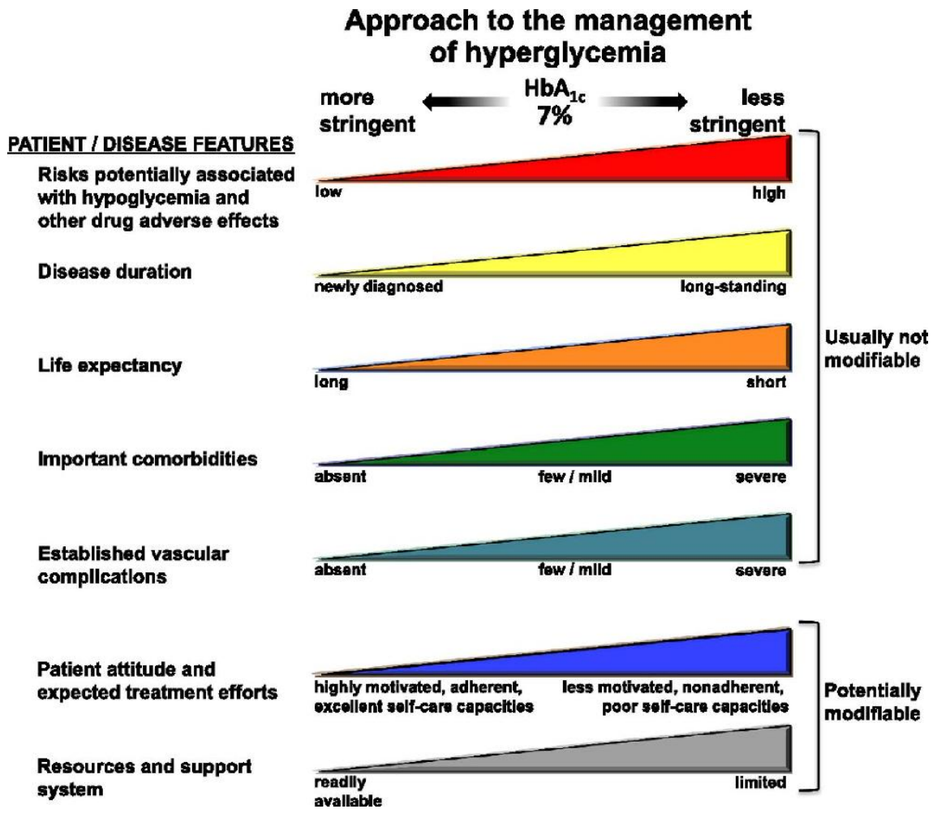
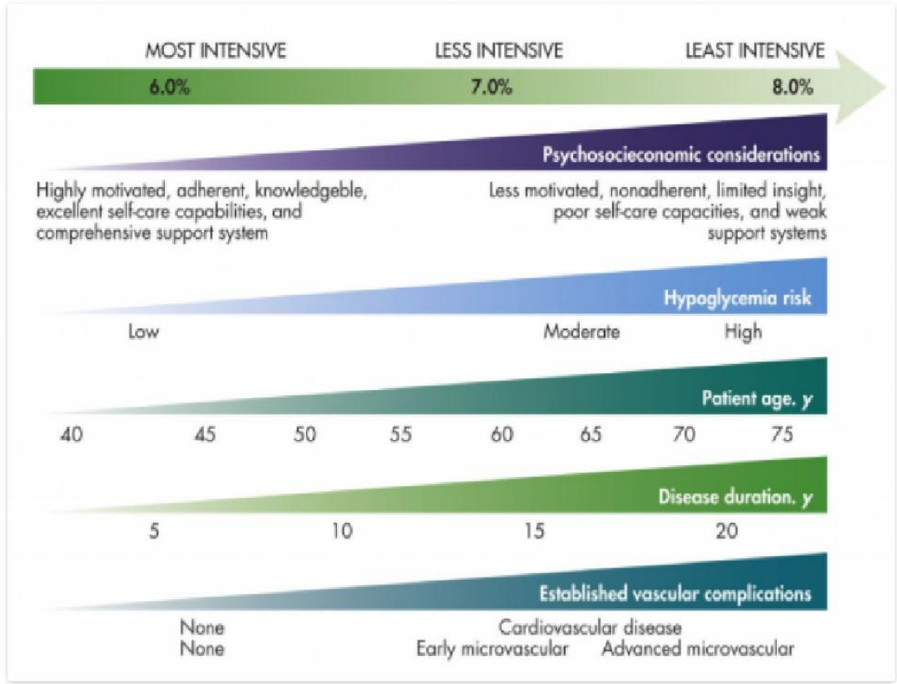
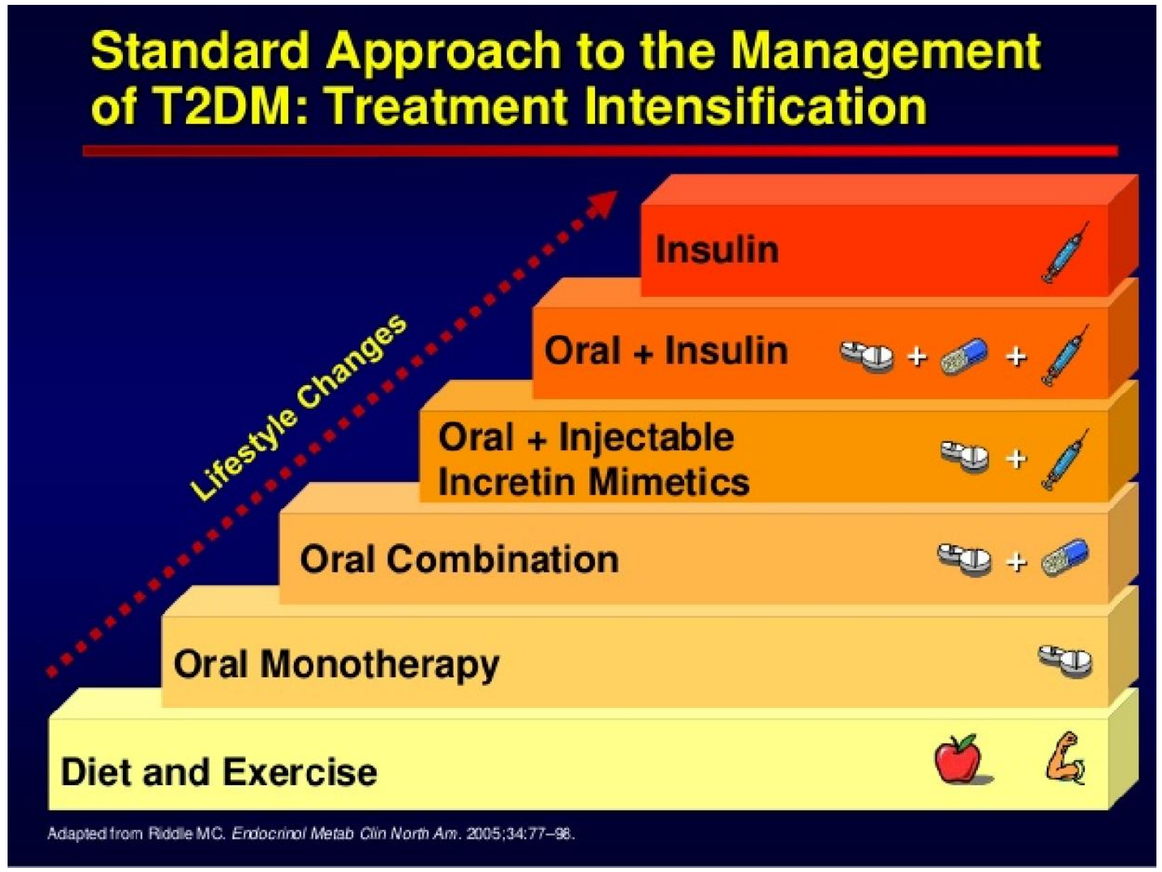


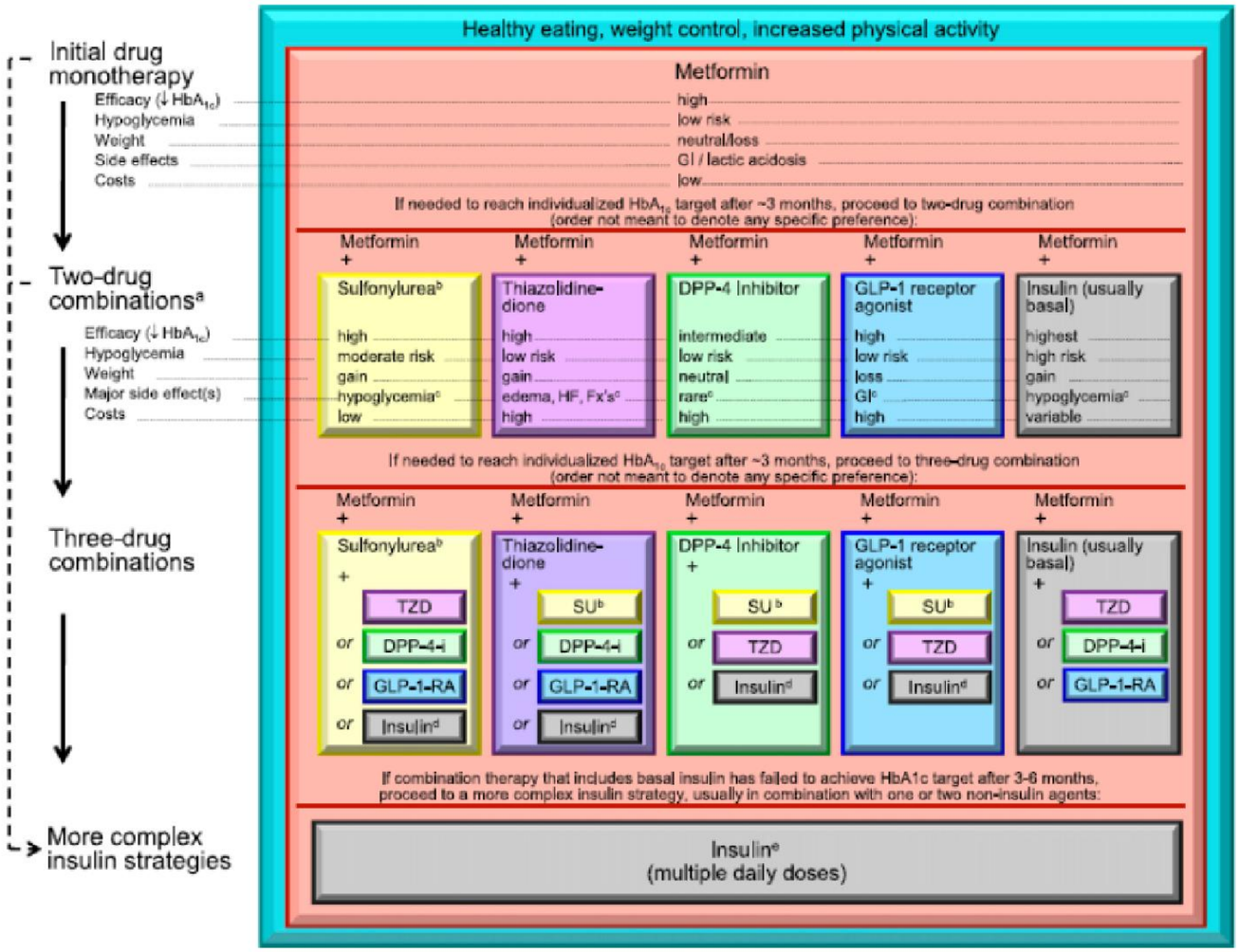
Diabetes Care 2012 Jun; 35(6): 1364-1379



http://www.accurateinsulin.org/for-doctors/deciding-whether-to-transition-your-patient-to-mealtime-insulin/



- A patient-centered approach should be used to guide the choice of pharmacologic agents. Considerations include efficacy, hypoglycemia risk, history of atherosclerotic cardiovascular disease, impact on weight, potential side effects, renal effects, delivery method (oral versus subcutaneous), cost, and patient preferences. E


Initial drug monotherapy
Efficacy (↓ HbA1c)
Hypoglycemia
Weight
Side effects
Costs
Two-drug combinations[a]
Efficacy (↓ HbA1c)
Hypoglycemia
Weight
Major side effect(s)
Costs
Three-drug combinations
More complex insulin strategies
Healthy eating, weight control, increased physical activity
Metformin
high
low risk
neutral/loss
GI / lactic acidosis
low
If needed to reach individualized HbA1c target after ~3 months, proceed to two-drug combination (order not meant to denote any specific preference):
Metformin + Sulfonylurea[b]
high
moderate risk
gain
hypoglycemia[c]
low
Metformin + Thiazolidine-dione
high
low risk
gain
edema, HF, Fx's[c]
high
Metformin + DPP-4 Inhibitor
intermediate
low risk
neutral
rare[c]
high
Metformin + GLP-1 receptor agonist
high
low risk
loss
GI[c]
high
Metformin + Insulin (usually basal)
highest
high risk
gain
hypoglycemia[c]
variable
If needed to reach individualized HbA1c target after ~3 months, proceed to three-drug combination (order not meant to denote any specific preference):
Metformin + Sulfonylurea[b] + TZD or DPP-4-i or GLP-1-RA or Insulin[d]
Metformin + Thiazolidine-dione + SU[b] or DPP-4-i or GLP-1-RA or Insulin[d]
Metformin + DPP-4 Inhibitor + SU[b] or TZD or Insulin[d]
Metformin + GLP-1 receptor agonist + SU[b] or TZD or Insulin[d]
Metformin + Insulin (usually basal) + TZD or DPP-4-i or GLP-1-RA
If combination therapy that includes basal insulin has failed to achieve HbA1c target after 3-6 months, proceed to a more complex insulin strategy, usually in combination with one or two non-insulin agents:
Insulin[e] (multiple daily doses)

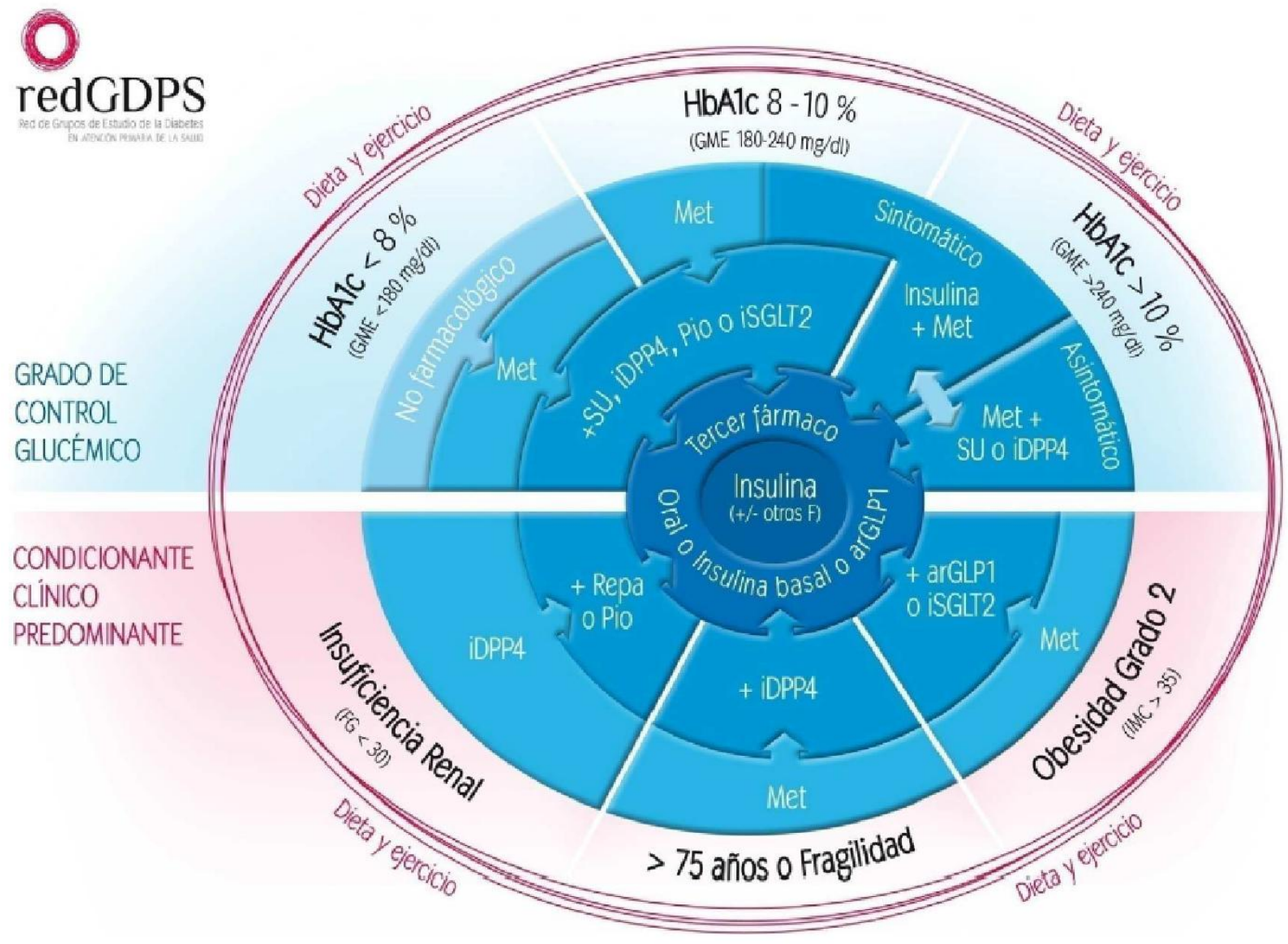
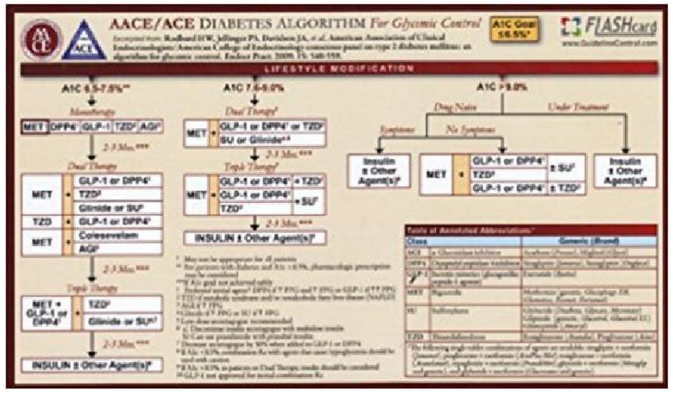


Figura 3 Individualización del tratamiento según la RedGDPS 2014.



AACE/ACE Guidelines

AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY – CLINICAL PRACTICE GUIDELINES FOR DEVELOPING A DIABETES MELLITUS COMPREHENSIVE CARE PLAN – 2015

Yehuda Handelsman, MD, FACP, FACE, FNLA[1]; Zachary T. Bloomgarden, MD, MACE[2];

665. **McGwin G Jr, Sims RV, Pulley L, Roseman JM.** Diabetes and automobile crashes in the elderly. A population-based case-control study. *Diabetes Care*. 1999;22:220-227. [EL 2; RCCS]

666. **Koepsell TD, Wolf ME, McCloskey L, et al.** Medical conditions and motor vehicle collision injuries in older adults. *J Am Geriatr Soc*. 1994;42:695-700. [EL 2; RCCS]

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668. **Liu SC, Tu YK, Chien MN, Chien KL.** Effect of anti-diabetic agents added to metformin on glycaemic control, hypoglycaemia and weight change in patients with type 2 diabetes: a network meta-analysis. *Diabetes Obes Metab*. 2012;14:810-820. [EL 1; MRCT]

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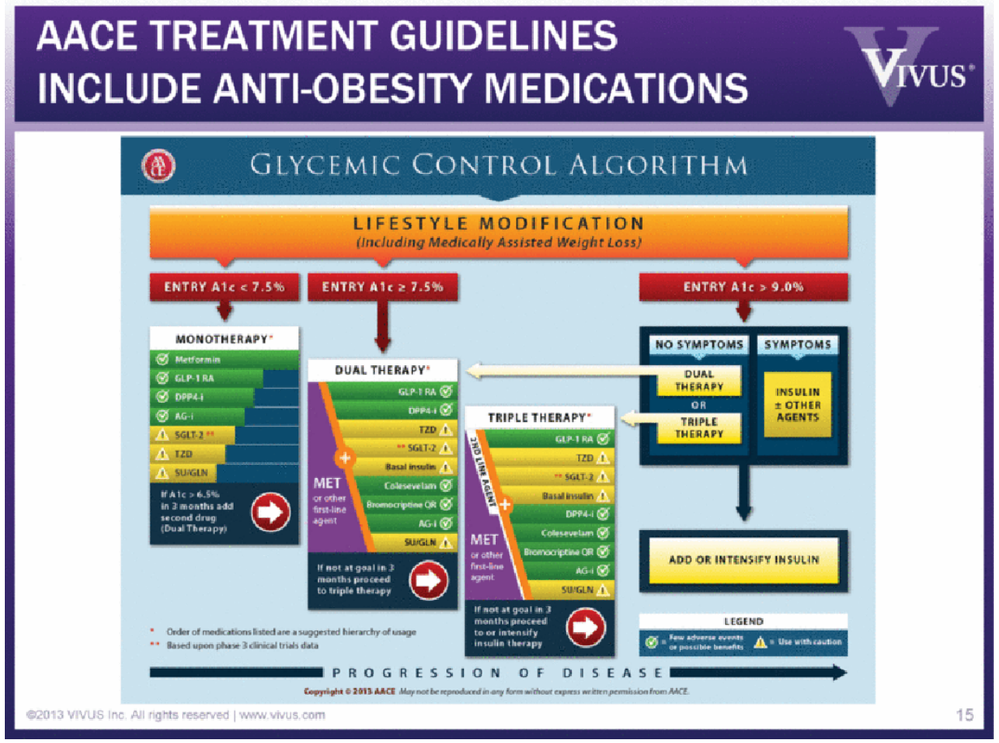
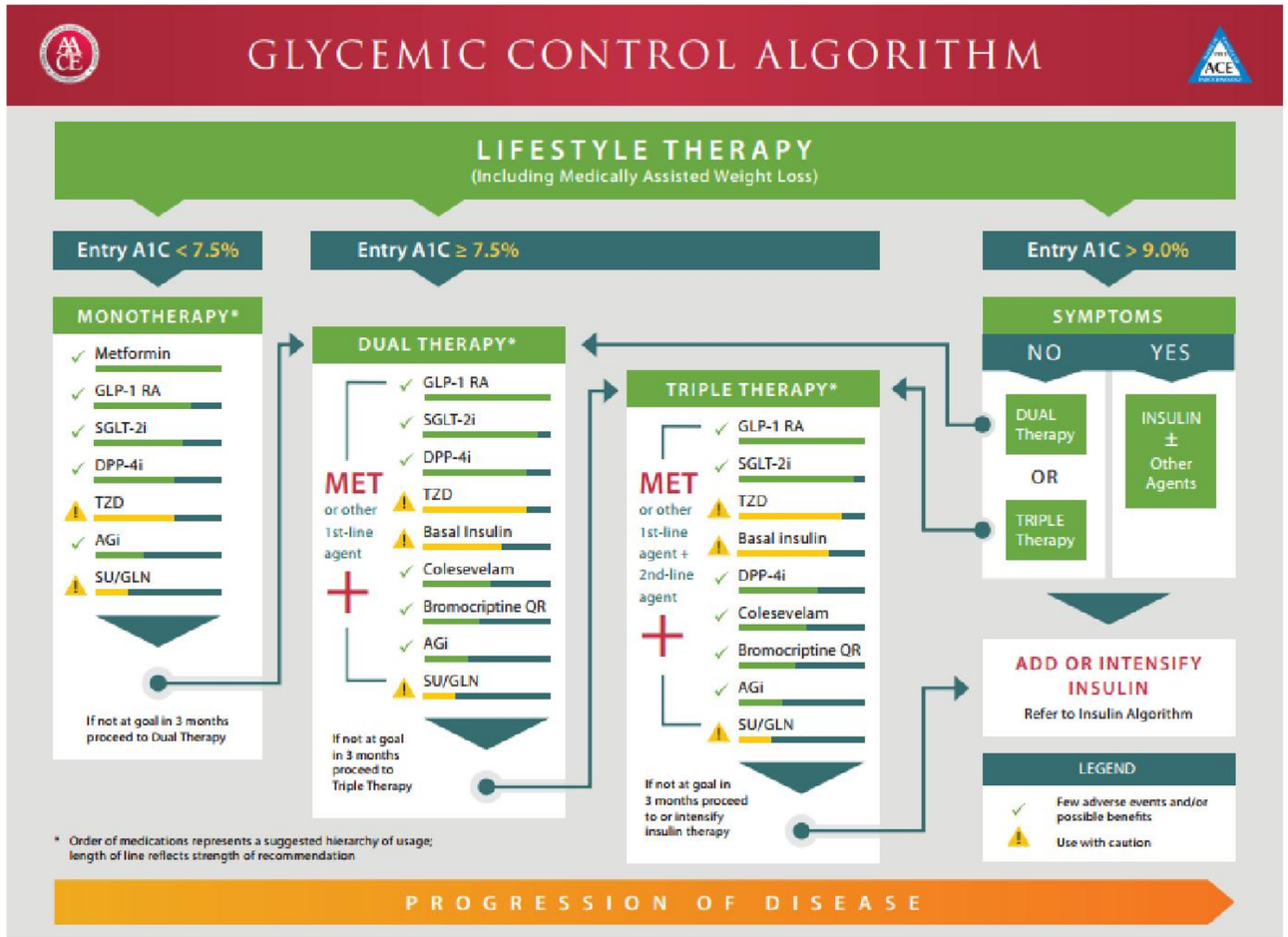
671. **Borgia P, Forastiere F, Rapiti E, et al.** Mortality among taxi drivers in Rome: a cohort study. *Am J Ind Med*. 1994;25:507-517. [EL 3; SS]





AACE/ACE COMPREHENSIVE TYPE 2 DIABETES MANAGEMENT ALGORITHM 2017 – Link And Excerpts

Posted on December 12, 2017

PROFILES OF ANTIDIABETIC MEDICATIONS

	MET	GLP-1 RA	SGLT-2i	DPP-4i	AGi	TZD (moderate dose)	SU / GLN	COLSVL	BCR-QR	INSULIN	PRAML
HYPO	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Moderate/Severe / Mild	Neutral	Neutral	Moderate to Severe	Neutral
WEIGHT	Slight Loss	Loss	Loss	Neutral	Neutral	Gain	Gain	Neutral	Neutral	Gain	Loss
RENAL / GU	Contrain-dicated if eGFR < 30 mL/min/1.73 m²	Exenatide Not Indicated CrCl < 30 Possible Benefit of Liraglutide	Not Indicated for eGFR < 45 mL/min/1.73 m² Genital Mycotic Infections Possible Benefit of Empagliflozin	Dose Adjustment Necessary (Except Linagliptin) Effective in Reducing Albuminuria	Neutral	Neutral	More Hypo Risk	Neutral	Neutral	More Hypo Risk	Neutral
GI Sx	Moderate	Moderate	Neutral	Neutral	Moderate	Neutral	Neutral	Mild	Moderate	Neutral	Moderate
CHF	Neutral	Possible Benefit of Liraglutide	Possible Benefit of Empagliflozin	Possible Risk for Saxagliptin and Alogliptin	Neutral	Moderate	More CHF Risk	Neutral	Neutral	More CHF Risk	Neutral
CARDIAC* ASCVD		Possible CV Benefit	Possible CV Benefit	Neutral		May Reduce Stroke Risk	?	Benefit	Safe	Neutral	
BONE	Neutral	Neutral	Canagliflozin Warning	Neutral	Neutral	Moderate Fracture Risk	Neutral	Neutral	Neutral	Neutral	Neutral
KETOACIDOSIS	Neutral	Neutral	DKA Occurring in T2D in Various Stress Settings	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral

Few adverse events or possible benefits | Use with caution | Likelihood of adverse effects | ? Uncertain effect | * FDA indication to prevent CVD death in diabetes plus prior CVD events

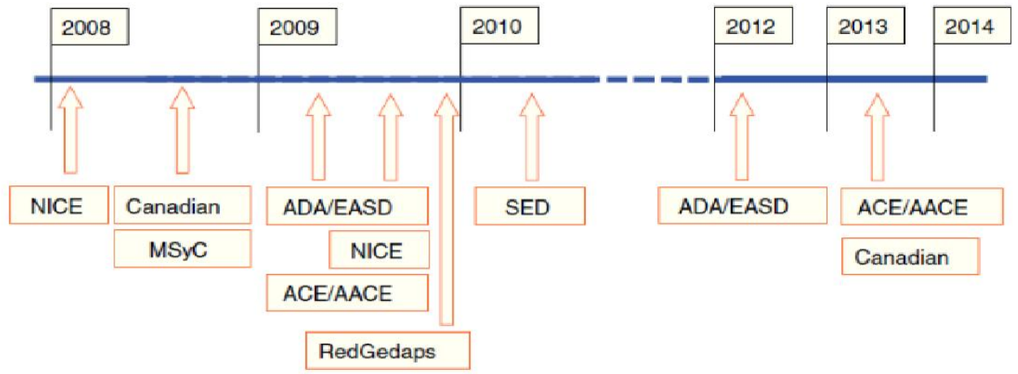


Figura 1 Orden cronológico de publicación de las principales GPC en DM2.

Tabla 1 Niveles terapéuticos según las diferentes GPC en DM2

	ADA-EASD 2012	NICE 2008	CDA 2013	MSC 2008	Red-GDPS 2010	AACE/ACE 2013
Primer escalón	E de vida+ MET	E de vida[a]	E de vida[b]	E de vida[a]	E de vida[a]	E de vida[c]
Segundo escalón	E de vida+ MET+ Otros AD (SU, GLI,DPP-4, GLP-1), o MET+ INS basal	E de vida+ MET+ SU	E de vida+ MET+ Otros según HbA1c MET+ INS basal	E de vida+ MET+ SU MET+ INS NPH	E de vida+ MET + otros AD	E de vida+ Otros AD (doble terapia) ISN+otros AD
Tercer escalón terapéutico	Metformina+ 2 fármacos (triple terapia con o sin INS)	MET+SU+ INS basal MET+ SU+ GLI	Metformin+otros AD o ISN basal	MET+ SU +INS NPH	MET+ SU+ otro AD o ISN	Otros AD (triple terapia) INS+otros

AD: antidiabético no insulínico; MET: metformina; SU: sulfonilurea, GLI: glitazona; DPP4 inhib DPP-4; GLP-1 análogo; GLP-1, INS insulina.
[a] Añadir metformina a los 3 meses si fracasan los estilos de vida (HbA1C > 7).
[b] Añadir metformina si HbA1c < 9%, y si > 9% añadir otros fármacos.
[c] Añadir otros farmacos si HbA1c > 6.5%.

Fármacos para el tratamiento en DM tipo 2

(comercializados en España)
Pablo Pérez Solís @soysolisu 2016

Fuentes:
American Association of Clinical Endocrinologists (AACE), American Diabetes Association (ADA), National Institute for Health and Care Excellence (NICE), Canadian Diabetes Association (CDA)

Fármaco	↓A1C	kg		Hipo glucemias	Otras consideraciones Efectos adversos (EA)	$
Inhibidor α-glucosidasa (acarbosa)	↓	=	Hasta FG 30	✔	EA gastrointestinales (GI) ✔ Mejora **control postprandrial**	$$
Inhibidores DPP-4 (gliptinas)	↓↓	=	½ dosis si FG<50, hasta FG 15 (salvo **linagliptina**)	✔	EA cutáneos, ¿pancreatitis?, ¿↑ingresos ICC? Evitar vilda≈ si ↑PFH ✔ **control postprandial**, tolerancia	$$$
Agonistas GLP-1 Inyección sc diaria o semanal	↓↓(↓)	↓	Hasta FG 30	✔	EA GI, pancreatitis (raro) ✔ ↓ligero LDL, TG y TA (efecto en morbimort. CV desconocido), **control postprandial**	$$$$
Sulfonilureas (gliclazida, glimepirida)	↓↓	↑	Hasta FG 30-45, gliclazida Resto en FG>60	✖	EA Evitar en insuficiencia hepática grave ✔ ↓**riesgo microvascular** (UKPDS) Glimepirida/gliclazida: menos hipoglucemias	$
Meglitinidas (repaglinida)	↓↓	↑	No precisa ajuste	✖	EA Evitar en insuficiencia hepática grave ✔ **control postprandial**; flexibilidad de dosis	$$
Tiazolidinedionas (pioglitazona) (↓**RI**)	↓(↓)	↑	No precisa ajuste si FG >30	✔	EA edema, ICC, fracturas, cáncer de vejiga (raro), evitar en ↑PFH (pero útil si h. graso) ✔ ↓TG/↑HDL; ↓hígado graso ¿↓eventos CV?	$$
Metformina (↓**RI**)	↓↓	=/↓	Con precaución y ajuste, hasta FG 30-45	✔	EA gastrointestinales, ↓B12, ↓dosis si ↑PFH; acidosis láctica (raro) ✔ ↓**eventos cardiovasculares** si sobrepeso	$
Insulina Inyección sc	↓↓↓	↑ (=tratamiento combinado)	Hasta estadío 5 (FG<15),puede precisar ajuste	✖	✔ gran eficacia, régimen flexible, ↓**riesgo microvascular** (UKPDS)	variable
Inhibidores SGLT2	↓↓	↓	No aprobado iniciar con FG <60	✔	EA infección G-U, ↓volumen, cetoacidosis, ↓masa ósea (canagliflozina) ✔ ↓TA, ↓**mort/event CV si ECV previa** (empa≈)	$$$

(↓**RI**: reduce la resistencia a insulina)

MIPROPIOLIO

blog ordenacosas sobre salud

Type 2 diabetes in adults: management

NICE guideline
Published: 2 December 2015
nice.org.uk/guidance/ng28

- Offer standard-release metformin as the initial drug treatment for adults with type 2 diabetes. [new 2015]

- In adults with type 2 diabetes, if metformin is contraindicated or not tolerated, consider initial drug treatment[1] with:
  - a dipeptidyl peptidase-4 (DPP-4) inhibitor **or**
  - pioglitazone[2] **or**
  - a sulfonylurea. [new 2015]

NICE National Institute for Health and Care Excellence

Algorithm for blood glucose lowering therapy in adults with type 2 diabetes

- Reinforce advice on diet, lifestyle and adherence to drug treatment.
- Agree an individualised HbA1c target based on: the person's needs and circumstances including preferences, comorbidities, risks from polypharmacy and tight blood glucose control and ability to achieve longer-term risk-reduction benefits. Where appropriate, support the person to aim for the HbA1c levels in the algorithm. Measure HbA1c levels at 3/6 monthly intervals, as appropriate. If the person achieves an HbA1c target lower than target with no hypoglycaemia, encourage them to maintain it. Be aware that there are other possible reasons for a low HbA1c level.
- Base choice of drug treatment on: effectiveness, safety (see MHRA guidance), tolerability, the person's individual clinical circumstances, preferences and needs, available licensed indications or combinations, and cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost).
- Do not routinely offer self-monitoring of blood glucose levels unless the person is on insulin, on oral medication that may increase their risk of hypoglycaemia while driving or operating machinery, is pregnant or planning to become pregnant or if there is evidence of hypoglycaemic episodes.

If the person is symptomatically hyperglycaemic, consider insulin or an SU. Review treatment when blood glucose control has been achieved.

ADULT WITH TYPE 2 DIABETES WHO CAN TAKE METFORMIN

If HbA1c rises to 48 mmol/mol (6.5%) on lifestyle interventions:
- Offer standard-release metformin
- Support the person to aim for an HbA1c level of 48 mmol/mol (6.5%)

If standard-release metformin is not tolerated, consider a trial of modified-release metformin

FIRST INTENSIFICATION
If HbA1c rises to 58 mmol/mol (7.5%):
- Consider dual therapy with:
  - metformin and a DPP-4i
  - metformin and pioglitazone[a]
  - metformin and an SU
  - *metformin and an SGLT-2i*[b]
- Support the person to aim for an HbA1c level of 53 mmol/mol (7.0%)

If triple therapy is not effective, not tolerated or contraindicated, consider combination therapy with metformin, an SU and a GLP-1 mimetic[c] for adults with type 2 diabetes who:
- have a BMI of 35 kg/m^2 or higher (adjust accordingly for people from black, Asian and other minority ethnic groups) and specific psychological or other medical problems associated with obesity or
- have a BMI lower than 35 kg/m^2, and for whom insulin therapy would have significant occupational implications, or weight loss would benefit other significant obesity-related comorbidities

SECOND INTENSIFICATION
If HbA1c rises to 58 mmol/mol (7.5%):
- Consider:
  - triple therapy with:
    - metformin, a DPP-4i and an SU
    - metformin, pioglitazone[a] and an SU
    - *metformin, pioglitazone[a] or an SU, and an SGLT-2i*[b]
  - insulin-based treatment
- Support the person to aim for an HbA1c level of 53 mmol/mol (7.0%)

METFORMIN CONTRAINDICATED OR NOT TOLERATED

If HbA1c rises to 48 mmol/mol (6.5%) on lifestyle interventions:
- Consider one of the following[d]:
  - a DPP-4i, pioglitazone[a] or an SU
  - an SGLT-2i[b] instead of a DPP-4i if an SU or pioglitazone[a] is not appropriate
- Support the person to aim for an HbA1c level of 48 mmol/mol (6.5%) for people on a DPP-4i, SGLT-2i or pioglitazone **or** 53 mmol/mol (7.0%) for people on an SU

FIRST INTENSIFICATION
If HbA1c rises to 58 mmol/mol (7.5%):
- Consider dual therapy[e] with:
  - a DPP-4i and pioglitazone[a]
  - a DPP-4i and an SU
  - pioglitazone[a] and an SU
- Support the person to aim for an HbA1c level of 53 mmol/mol (7.0%)

SECOND INTENSIFICATION
If HbA1c rises to 58 mmol/mol (7.5%):
- Consider insulin-based treatment
- Support the person to aim for an HbA1c level of 53 mmol/mol (7.0%)

Insulin-based treatment

- When starting insulin, use a structured programme and continue metformin for people without contraindications or intolerance. Review the continued need for other blood glucose lowering therapies[f].
- Offer NPH insulin once or twice daily according to need.
- Consider starting both NPH and short-acting insulin either separately or as pre-mixed (biphasic) human insulin (particularly if HbA1c is 75 mmol/mol (9.0%) or higher).
- Consider, as an alternative to NPH insulin, using insulin detemir or glargine[g] if the person: needs assistance to inject insulin, lifestyle is restricted by recurrent symptomatic hypoglycaemic episodes or would otherwise need twice-daily NPH insulin in combination with oral blood glucose lowering drugs.
- Consider pre-mixed (biphasic) preparations that include short-acting insulin analogues, rather than pre-mixed (biphasic) preparations that include short-acting human insulin preparations, if: the person prefers injecting insulin immediately before a meal, hypoglycaemia is a problem or blood glucose levels rise markedly after meals.
- Only offer a GLP-1 mimetic[c] in combination with insulin with specialist care advice and ongoing support from a consultant-led multidisciplinary team[h].
- Monitor people on insulin for the need to change the regimen.
- *An SGLT-2i in combination with insulin with or without other antidiabetic drugs is an option*[b].

Abbreviations: DPP-4i Dipeptidyl peptidase-4 inhibitor, GLP-1 Glucagon-like peptide-1, SGLT-2i Sodium–glucose cotransporter 2 inhibitors, SU Sulfonylurea. Recommendations that cover DPP-4 inhibitors, GLP-1 mimetics and sulfonylureas refer to these groups of drugs at a class level.

a. When prescribing pioglitazone, exercise particular caution if the person is at high risk of the adverse effects of the drug. Pioglitazone is associated with an increased risk of heart failure, bladder cancer and bone fracture. Known risk factors for these conditions, including increased age, should be carefully evaluated before treatment: see the manufacturers' summaries of product characteristics for details. Medicines and Healthcare products Regulatory Agency (MHRA) guidance (2011) advises that 'prescribers should review the safety and efficacy of pioglitazone in individuals after 3–6 months of treatment to ensure that only patients who are deriving benefit continue to be treated'.

b. See NICE technology appraisal guidance 288 & 418, 315 and 336 on dapagliflozin, canagliflozin and empagliflozin, respectively. All three SGLT-2 inhibitors are recommended as options in dual therapy regimens with metformin under certain conditions, as options in triple therapy regimens and in combination with insulin. All three are also options as monotherapies in adults in whom metformin is contraindicated or not tolerated. Serious and life-threatening cases of diabetic ketoacidosis have been reported in people taking SGLT-2 inhibitors (canagliflozin, dapagliflozin or empagliflozin) or shortly after stopping the SGLT-2 inhibitor. MHRA guidance (2015) advises testing for raised ketones in people with symptoms of diabetic ketoacidosis, even if plasma glucose levels are near normal.

c. Only continue GLP-1 mimetic therapy if the person has a beneficial metabolic response (a reduction of HbA1c by at least 11 mmol/mol [1.0%] and a weight loss of at least 3% of initial body weight in 6 months).

d. Be aware that, if metformin is contraindicated or not tolerated, repaglinide is both clinically effective and cost effective in adults with type 2 diabetes. However, discuss with any person for whom repaglinide is being considered, that there is no licensed non-metformin-based combination containing repaglinide that can be offered at first intensification.

e. Be aware that the drugs in dual therapy should be introduced in a stepwise manner, checking for tolerability and effectiveness of each drug.

f. MHRA guidance (2011) notes that cases of cardiac failure have been reported when pioglitazone was used in combination with insulin, especially in patients with risk factors for the development of cardiac failure. It advises that if the combination is used, people should be observed for signs and symptoms of heart failure, weight gain, and oedema. Pioglitazone should be discontinued if any deterioration in cardiac status occurs.

g. The recommendations in this guideline also apply to any current and future biosimilar product(s) of insulin glargine that have an appropriate Marketing Authorisation that allows the use of the biosimilar(s) in the same indication.

h. A consultant-led multidisciplinary team may include a wide range of staff based in primary, secondary and community care.

'Type 2 diabetes in adults: management', NICE guideline NG28. Published December 2015, last updated April 2017.

2.- Algoritmo de selección de antidiabéticos no insulínicos.

Modificaciones estilos de vida: dieta y ejercicio.

MONOTERAPIA

1ª elección	**MET**	(1)
2ª elección	**gliclazida** (alternativa repaglinida)	(2)
3ª elección	**PIO / iDPP4** (sitagliptina)	(3) (4) (5)

1ª INTENSIFICACIÓN
(añadir 2º antidiabético oral)

1ª elección	**MET + gliclazida** (alternativa repaglinida)	(2)
2ª elección	**MET + PIO / iDPP4** (sitagliptina)	(3) (4)
3ª elección	**MET + ISGLT2**	(5)

2ª INTENSIFICACIÓN
(alternativa a insulinización)

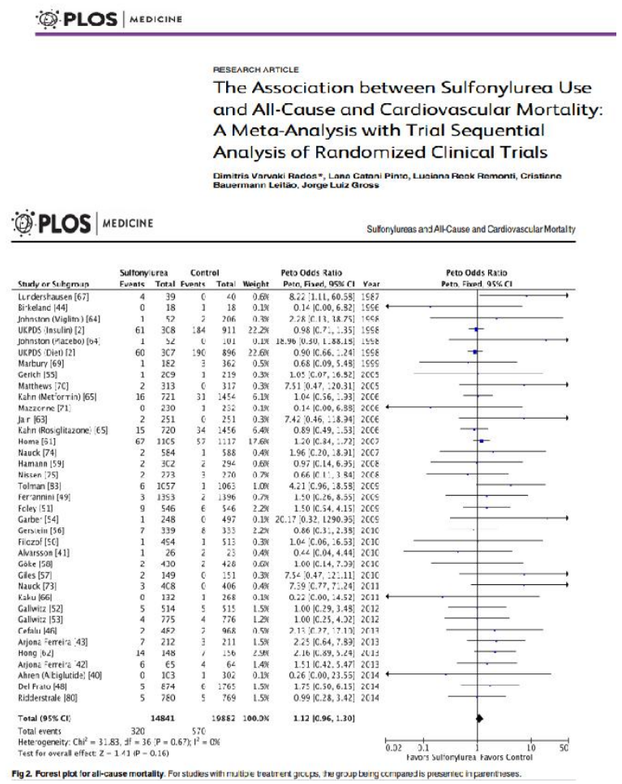
1ª elección	**MET + gliclazida + PIO / iDPP4 / iSGLT2**	(3) (4) (5)
2ª elección	**MET + gliclazida + aGLP-1**	(6)

Metformina

- Presenta problemas de tolerancia gastrointestinal.
- No interrumpir su uso, incluso con insulina, si no hay contraindicaciones y la tolerancia es buena.
- Su uso a largo plazo se asocia a déficit de vit B_{12}. Medir niveles en presencia de macrocitosis o neuropatía.
- IRC:
  - No debe iniciarse un tratamiento con un eGFR < 45 mL/min/1.73 $m^{2.}$
  - Puede mantenerse, si está siendo útil, hasta un eGFR de 30 ml/min/1.73 m^2 .
  - No debe usarse en pacientes con un eGFR < 30 mL/min/1.73 $m^{2.}$

Sulfonilureas

- Amplia experiencia de uso.
- Potencia hipoglucemiante (mientras haya reserva insulínica propia).
- Reduce complicaciones microvasculares (UKPDS).
- Gliclazida es la SU de elección:
  - Menos hipoglucemias dentro de este grupo terapeútico.
  - Menor ganancia de peso.
  - Menos efectos extrapancreáticos.
- En caso de FG < 30 mg/ml o ingestas irregulares, alternativa repaglinida.
- Ocasionan aumento de peso en una población en la que deberíamos evitar esta circunstancia.
- Se asocian a hipoglucemia.
- La recomendación de uso se basa, en buena parte, en su costo.



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RESEARCH ARTICLE

The Association between Sulfonylurea Use and All-Cause and Cardiovascular Mortality: A Meta-Analysis with Trial Sequential Analysis of Randomized Clinical Trials

Dimitris Vardas Rados*, Lane Catoni Pinto, Luciana Reck Remonti, Cristiane Bauermann Leitão, Jorge Luiz Gross

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Sulfonylureas and All-Cause and Cardiovascular Mortality

Study or Subgroup	Sulfonylurea Events	Total	Control Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI	Year	Peto Odds Ratio Peto, Fixed, 95% CI
Lurdershausen [67]	4	39	0	40	0.6%	8.22 [1.11, 60.58]	1987	
Birkeland [44]	0	18	1	18	0.1%	0.14 [0.00, 6.82]	1996	
Johnston (Vigilis) [64]	1	52	2	206	0.3%	2.28 [0.11, 18.75]	1998	
UKPDS (Insulin) [2]	61	308	184	911	22.2%	0.98 [0.7[illegible], 1.35]	1998	
Johnston (Placebo) [64]	1	52	0	101	0.1%	18.99 [0.90, 1.88.15]	1998	
UKPDS (Diet) [2]	60	367	190	896	22.6%	0.90 [0.66, 1.24]	1998	
Marbury [69]	1	182	3	362	0.5%	0.68 [0.09, 5.48]	1999	
Gerich [55]	1	209	1	219	0.3%	1.05 [0.07, 16.82]	2005	
Matthews [70]	2	313	0	312	0.3%	7.51 [0.47, 120.31]	2005	
Kahn (Metformin) [65]	16	721	33	1454	6.1%	1.04 [0.56, 1.93]	2006	
Mazzone [71]	0	230	1	252	0.1%	0.14 [0.00, 6.88]	2006	
Jar [63]	2	251	0	251	0.3%	7.42 [0.46, 118.94]	2006	
Kahn (Rosiglitazone) [65]	15	720	34	1456	6.4%	0.89 [0.49, 1.63]	2006	
Home [61]	67	1305	57	1137	17.6%	1.20 [0.84, 1.72]	2007	
Nauck [74]	2	584	1	588	0.4%	1.96 [0.20, 18.91]	2007	
Hamann [59]	2	302	2	294	0.6%	0.97 [0.14, 6.95]	2008	
Nissen [75]	2	273	3	270	0.7%	0.66 [0.11, 3.84]	2008	
Tolman [83]	6	1057	1	1063	1.0%	4.21 [0.96, 18.53]	2009	
Ferrannini [69]	3	1353	2	1396	0.7%	1.50 [0.26, 8.55]	2009	
Foley [51]	9	546	6	546	2.2%	1.50 [0.54, 4.15]	2009	
Garber [54]	1	248	0	497	0.1%	20.17 [0.32, 1290.95]	2009	
Gerstein [56]	7	339	8	333	2.2%	0.86 [0.31, 2.38]	2010	
Filozof [50]	1	454	1	511	0.3%	1.04 [0.06, 16.53]	2010	
Alvarsson [41]	1	26	2	23	0.4%	0.44 [0.04, 4.44]	2010	
Göke [58]	2	430	2	428	0.6%	1.00 [0.14, 7.09]	2010	
Giles [57]	2	149	0	151	0.3%	7.54 [0.47, 121.11]	2010	
Nauck [73]	3	408	0	406	0.4%	7.59 [0.77, 71.24]	2011	
Kaku [66]	0	132	1	268	0.1%	0.22 [0.00, 14.52]	2011	
Gallwitz [52]	5	514	5	515	1.5%	1.00 [0.29, 3.48]	2012	
Gallwitz [53]	4	775	4	776	1.2%	1.00 [0.25, 4.02]	2012	
Cefalu [46]	2	482	2	968	0.5%	2.13 [0.27, 17.13]	2013	
Arjona Ferreira [43]	7	212	3	211	1.5%	2.25 [0.64, 7.83]	2013	
Hong [62]	14	148	7	156	2.9%	2.16 [0.89, 5.24]	2013	
Arjona Ferreira [42]	6	65	4	64	1.4%	1.51 [0.42, 5.47]	2013	
Ahren (Albiglutide) [40]	0	103	1	302	0.1%	0.26 [0.00, 23.55]	2014	
Del Prato [48]	5	874	0	1765	1.5%	1.75 [0.50, 6.15]	2014	
Ridderstrale [80]	5	780	5	769	1.5%	0.99 [0.28, 3.42]	2014	
Total (95% CI)		**14841**		**19882**	**100.0%**	**1.12 [0.96, 1.30]**		
Total events	320		570					

Heterogeneity: $Chi^2 = 31.83$, $df = 36$ ($P = 0.67$); $I^2 = 0\%$
Test for overall effect: $Z = 1.43$ ($P = 0.16$)

0.02 0.1 1 10 50
Favors Sulfonylurea Favors Control

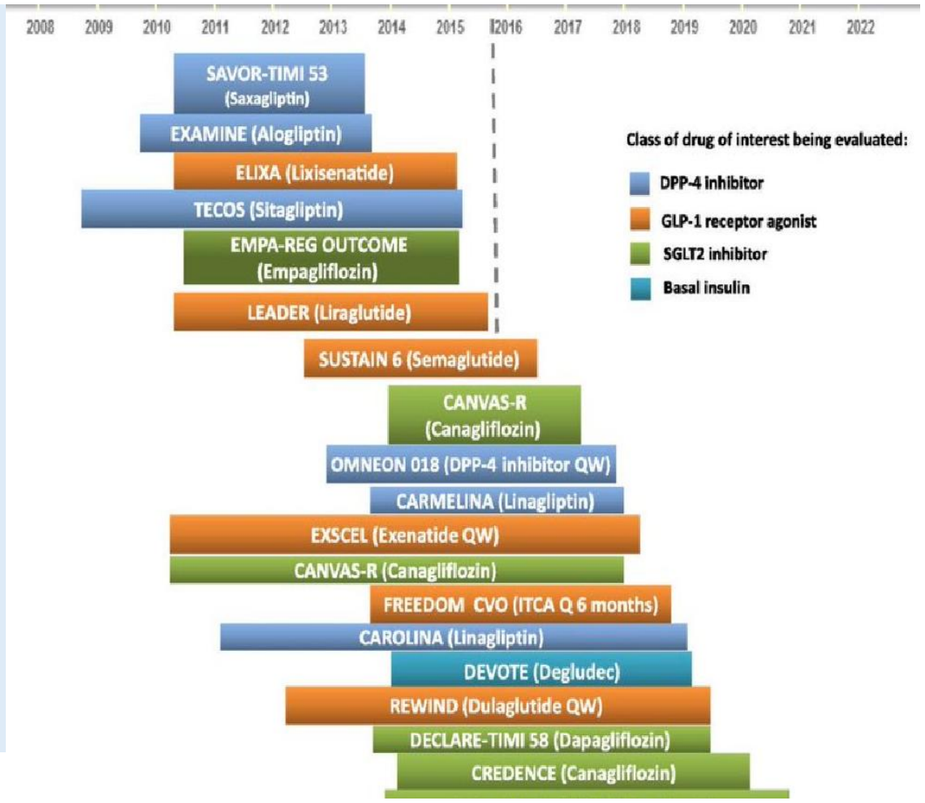
Fig 2. Forest plot for all-cause mortality. For studies with multiple treatment groups, the group being compared is presented in parentheses.

2005;26:1485-1489. [EL 2; PCS]

522. **Boucai L, Southern WN, Zonszein J.** Hypoglycemia-associated mortality is not drug-associated but linked to comorbidities. *Am J Med.* 2011;124:1028-1035. [EL 3; SS]

Glitazonas

- Las culpables del cambio en las reglas del juego: Los estudios de seguridad cardiovascular.
- Contraindicaciones:
  - Insuficiencia cardíaca.
  - Deterioro en la función hepática.
  - Cáncer de vejiga y/o hematuria macroscópica en estudio.
  - Insulinopenia (riesgo de cetoacidosis diabética).
  - *Edemas.*
  - *Aumento de peso*



Inhibidores DPP-4

- Preferible a PIO si el aumento de peso es un problema.
- Recomendado en el paciente geriátrico con fragilidad.
- La sitagliptina es el iDPP4 con mayor experiencia de uso, incluido en la GFT del SESCAM y sin que su uso añada riesgos a los pacientes con alto riesgo cardiovascular.
- Ajustar dosis a la insuficiencia renal, reduce el coste.

Treatment of Elderly Patients With Type 2 Diabetes Mellitus: A Systematic Review of the Benefits and Risks of Dipeptidyl Peptidase-4 Inhibitors

Sherwyn L. Schwartz, MD

Cetero Research, San Antonio, Texas; Founder and Director, Diabetes & Glandular Disease Clinic, PA, San Antonio, Texas

Table 1. Abstracts on Diabetes Studies With DPP-4 Inhibitors

	TECOS	SAVOR-TIMI	EXAMINE	CARMELINA
MEDICATION	**Sitagliptin**	**Saxagliptin**	**Alogliptin**	**Linagliptin**
# OF PATIENTS	14,671	16,492	5,380	8,300
HISTORY	DM2, established CVD	DM2, established CVD or multiple risk factors for CVD	DM2, recent acute coronary syndrome event	DM2, high risk for CV events, BMI ≤45
STUDY DESIGN	Multi-center, randomized, double-blind, open-label	Multi-center, randomized, double-blind, placebo-controlled	Multi-center, randomized, double-blind	Multi-center, randomized, double-blind, parallel assignment
PRIMARY OUTCOME	**4-point MACE:** CV death, nonfatal MI, nonfatal stroke, hospitalization for unstable angin, Noninferiority and superiority design	**3-point MACE**: CV death, nonfatal MI, nonfatal ischemic stroke. Superiority and noninferiority design	**3-point MACE:** CV death, nonfatal acute MI, nonfatal stroke. Noninferiority design	**4-point MACE:** CV death, nonfatal MI, nonfatal stroke, hospitalization for unstable angina
RESULTS	Primary outcome: Sitagliptin 11.4%, Placebo 11.6%, Hazard ratio: 0.98 (95% CI: 0.88 to 1.09), p<0.001. Secondary Outcome: Heart failure hospitalization, Sitagliptin 2.8%, Placebo 2.8%, Hazard ratio: 1.00 (95% CI: 0.83-1.20), p=0.98	Primary outcome: Saxagliptin 7.3%, Placebo 7.2%, Hazard ratio: 1.0 (95% CI: 0.89-1.12), p=0.99. Secondary outcome, Heart failure hoospitalization: Saxagliptin 3.5%, Placebo 2.8%, Hazard ratio: 1.27 (95% CI: 1.07-1.51), p=0.007	Primary Outcome: Alogliptin 11.3%, Placebo 11.8%, Hazard ratio: 0.96 (95% CI: <1.16), p=0.32. Post hoc analysis: Alogliptin 3.1%, Placebo 2.9%, Hazard ratio: 1.07 (95% CI: 0.79-1.46), p=0.66	Ongoing
ADDITIONAL BENEFITS/RISKS	At 4 months, HbA1C .4 percentage points lower in sitagliptin group vs placebo group; sitagliptin group less like to start long-term insulin therapy	Glycemic control was lower in saxagliptin group compared to placebo	NT-pro-BNP concentrations decreased significantly and similar in the 2 groups. Post-hoc analysis for hospitalization for heart failure	

Glucosúricos

- Vigilar infecciones urinarias y genitales.
- En fases iniciales de la enfermedad hay alternativas con mayor experiencia de uso (hipotensión, amputaciones, cetoacidosis).

Table 1. SGLT-2 inhibitors approved for the treatment of T2DM

Agent	Year Approved	Starting Dose	Required Renal Function
Canagliflozin	2013	100 mg QD	eGFR ≥45 mL/min/1.73 m²
Dapagliflozin	2014	5 mg QD	eGFR ≥60 mL/min/1.73 m²
Empagliflozin	2014	10 mg QD	eGFR ≥45 mL/min/1.73 m²

Table 2. Cardiovascular outcome trials with SGLT-2 inhibitors*

	EMPA-REG OUTCOME	CANVAS	DECLARE-TIMI 58
ClinicalTrials.gov	NCT01131676	NCT01032629	NCT01730534
Interventions (randomization)	Empagliflozin/placebo (2:1)	Canagliflozin/placebo (2:1)	Dapagliflozin/placebo (1:1)
Enrollment	7020	4411	17,276
Key inclusion criteria	Established vascular complications, HbA1c 7.0%–10.0%, age ≥18 years	Established vascular complications (age ≥30 years) or ≥2 CV risk factors (age >50 years), HbA1c 7.0%–10.5%	High risk for CV events, T2DM, age ≥40 years
Primary end point	CV death, nonfatal MI, nonfatal stroke	CV death, nonfatal MI, nonfatal stroke	CV death, nonfatal MI, nonfatal stroke
Estimated reporting	2015	2017	2019

HbA1c: glycosylated hemoglobin A1c; CV: cardiovascular; T2DM: type 2 diabetes mellitus; MI: myocardial infarction.
*Adapted from Inzucchi et al.[6]

SGLT-2 Inhibitors for Type 2 Diabetes: Renal and Urinary Issues. Renal & Urology News. December 14, 2015

Análogos de la GLP-1

- Prescripción por endocrinología.
- Alternativa a la insulinización
  - Triple terapia con ADO ineficaz, no se tolera o contraindicada.
  - Existen problemas médicos asociados con la obesidad.
- Discontinuar si a los 6 meses no se cumplen objetivos.
  - ↓ Peso >3%
  - ↓ HbA1c >1%

Table 1. Trials With GLP-1 Therapeutics

	ELIXA	*LEADER*	*SUSTAIN-6*	*EXSCEL*	*LYDIA*
MEDICATION	Lixisenatide	Liraglutide	Semaglutide	Exenatide	Liraglutide
# PATIENTS	6,068	9,340	2,735	14,000	90
HISTORY	T2D, acute coronary event within 180 days prior to randomization	T2D, high risk CVD	T2D, high risk CVD	T2D, with prior CV events and/or with or w/o known CV risks	T2D, Obese
STUDY DESIGN	Multi-center, randomized, double-blind, placebo-controlled; Non-inferiority **Superiority**	Multi-center, double-blind, placebo-controlled; Non-inferiority **Superiority**	Multi-center, double-blind, placebo-controlled; Non-inferiority **Superiority**	Phase 3/4 multi-center, randomized, double-blind, placebo-controlled, parallel-group	Prospective, randomized, open label, blind endppoint
PRIMARY OUTCOME	**4-point MACE:** CV death, nonfatal MI, nonfatal stroke, hospitalization for unstable angina (coronary revascularization)	**3-point MACE:** CV death, nonfatal MI, nonfatal stroke	**3-point MACE: CV death, nonfatal MI,** nonfatal **stroke**	**3-point MACE:** CV death, nonfatal MI, nonfatal stroke	Diastolic Fruntion (HF-NEF)
RESULTS	Lixisenatide Group: 13.4% Placebo Group: 13.2% HR 1.02; 95% CI 0.89–1.17 P<0.001 for non-inferiority P=0.81 for superiority	Liraglutide Group: 13.0% Placebo group: 14.9% HR 0.87; 95% CI 0.78-0.97 P<0.001 for non-inferiority P=0.01 for superiority	Semaglutide Group: 6.6% Placebo Group: 8.9% HR 0.74; 95% CI, 0.58 to 0.95 P<0.001 for noninferiority	Ongoing	Completed June 2016
ADDITIONAL BENEFITS/RISKS		Reduction in all-cause mortality in Rx group (8.2% vs. 9.6% in placebo group; HR 0.85; 95% CI 0.74-0.97; P=0.02)	Increased risk of retinopathy in semaglutide group		Younger Popn (Ages 18-50) 28 weeks duration

Summary of New CVOTs in Diabetes

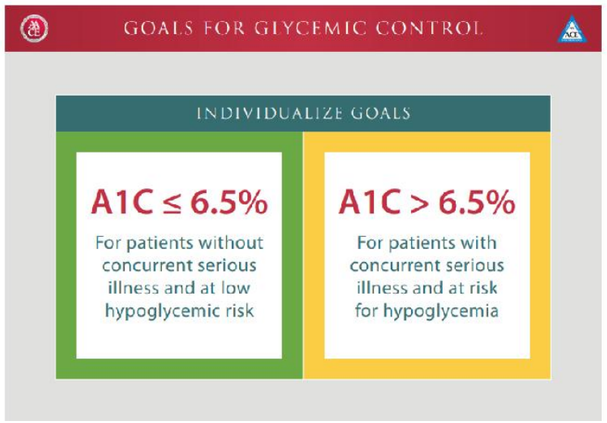
	Study	Composite MACE*	CV Death	MI	Stroke	Any Death	HHF
DPP-4i	SAVOR-TIMI53 (saxagliptin)	⇔	⇔	⇔	⇔	⇔	↑
	EXAMINE (alogliptin)	⇔	⇔	⇔	⇔	⇔	⇔
	TECOS (sitagliptin)	⇔	⇔	⇔	⇔	⇔	⇔
SGLT-2i	EMPA-REG OUTCOME (empagliflozin)	↓	↓	⇔	⇔	↓	↓
GLP-1	ELIXA (lixisenatide)	⇔	⇔	⇔	⇔	⇔	⇔
	LEADER (liraglutide)	↓	↓	⇔**	⇔	↓	⇔
	SUSTAIN-6 (semaglutide)	↓	⇔	⇔	↓ (non-fatal)	⇔	⇔

CVOT: Cardiovascular outcome trial
MACE: Major adverse cardiovascular event
HHF: hospitalization for heart failure

*all studies use 3-point MACE of CV death, MI, and stroke except TECOS and ELIXA which adds hospitalization for unstable angina.

⇔ ** p=0.05 for individual components of fatal, nonfatal, and silent MI; p=0.046 for composite of fatal, nonfatal, and silent MI

El-Masry M,
Cardiovascular safety of anti-diabetic drugs. Cardiovascular Outcome Trials (CVOTs) in Diabetes. Medscape.
Published on May 6, 2017



- In patients with type 2 diabetes and established atherosclerotic cardiovascular disease, antihyperglycemic therapy should begin with lifestyle management and metformin and subsequently incorporate an agent proven to reduce major adverse cardiovascular events and cardiovascular mortality (currently empagliflozin and liraglutide), after considering drug-specific and patient factors (**Table 8.1**). **A***

8. Pharmacologic Approaches to Glycemic Treatment: *Standards of Medical Care in Diabetes—2018*

American Diabetes Association

Diabetes Care 2018;41(Suppl. 1):S73–S85 | https://doi.org/10.2337/dc18-S008

Table 8.1—Drug-specific and patient factors to consider when selecting antihyperglycemic treatment in adults with type 2 diabetes

	Efficacy*	Hypoglycemia	Weight Change	CV Effects		Cost	CrCl/SCr	Renal Effects		Additional Considerations
				ASCVD	CHF			Progression of CKD	Dosing/Use considerations	
Metformin	High	No	Neutral (Potential for modest loss)	Potential benefit	Neutral	Low	Oral	Neutral	• Contraindicated with eGFR <30	• Gastrointestinal side effects common (diarrhea, nausea) • Potential for B12 deficiency
SGLT-2 inhibitors	Intermediate	No	Loss	Benefit: canagliflozin, empagliflozin†	Benefit: canagliflozin, empagliflozin	High	Oral	Benefit: canagliflozin, empagliflozin	• Canagliflozin: not recommended with eGFR <45 • Empagliflozin: not recommended with eGFR <45; contraindicated with eGFR <30 • Empagliflozin: contraindicated with eGFR <30	• FDA Black Box: Risk of amputation (canagliflozin) • Risk of bone fractures (canagliflozin) • DKA risk ↑ (especially rare in T2DM) • Genitourinary infections • Risk of volume depletion, hypotension • ↑LDL cholesterol
GLP-1 RAs	High	No	Loss	Neutral: dulaglutide, injectable extended-release Benefit: liraglutide†	Neutral	High	SQ	Benefit: liraglutide	• Exenatide not indicated with eGFR <30 • Use exenatide caution with eGFR <50 • Increased risk of side effects in patients with renal impairment	• FDA Black Box: Risk of thyroid C-cell tumors (liraglutide, dulaglutide, exenatide extended-release) • Gastrointestinal side effects common (nausea, vomiting, diarrhea) • Injection site reactions • Acute pancreatitis risk
DPP-4 inhibitors	Intermediate	No	Neutral	Neutral	Potential risk: saxagliptin, alogliptin	High	Oral	Neutral	• Renal dose adjustment required; can be used in renal impairment	• Potential risk of acute pancreatitis • Joint pain
Thiazolidinediones	High	No	Gain	Potential benefit: pioglitazone	Increased Risk	Low	Oral	Neutral	• No dose adjustment required • Rosiglitazone not recommended in renal impairment due to potential for fluid retention	• FDA Black Box: Congestive heart failure (pioglitazone, rosiglitazone) • Fluid retention (edema), heart failure • Benefit in NASH • Risk of bone fractures • Bladder cancer (pioglitazone) • ↑HDL cholesterol (rosiglitazone)
Sulfonylureas (2nd Generation)	High	Yes	Gain	Neutral	Neutral	Low	Oral	Neutral	• Glyburide not recommended • Glipizide & glimepiride: Initiate conservatively in renal hypoglycemia	• FDA Special Warning on increased risk of cardiovascular mortality based on studies of another sulfonylurea (tolbutamide)
Insulin: Human Insulin	Highest	Yes	Gain	Neutral	Neutral	Low	SQ	Neutral	• Lowest insulin doses required with a decrease in eGFR; titrate per clinical response	• Injection site reactions • Higher risk of hypoglycemia with human insulin (NPH or premixed formulations) vs. analogs
Insulin: Analogs						High	SQ			

*See ref. 31 for description of efficacy. †FDA approved for CVD benefit. CVD, cardiovascular disease; DKA, diabetic ketoacidosis; DKD, diabetic kidney disease; NASH, nonalcoholic steatohepatitis; RAs, receptor agonists; SQ, subcutaneous; T2DM, type 2 diabetes.

care.diabetesjournals.org

Antihyperglycemic Therapy in Adults with Type 2 Diabetes

At diagnosis, initiate lifestyle management, set A1C target, and initiate pharmacologic therapy based on A1C:

- A1C is less than 9%, **consider Monotherapy.**
- A1C is greater than or equal to 9%, **consider Dual Therapy.**
- A1C is greater than or equal to 10%, blood glucose is greater than or equal to 300 mg/dL, or patient is markedly symptomatic, **consider Combination Injectable Therapy** (See Figure 8.2).

Monotherapy — Lifestyle Management + Metformin

Initiate metformin therapy if no contraindications* (See Table 8.1)

A1C at target after 3 months of monotherapy?
- **Yes:** - Monitor A1C every 3–6 months
- **No:** - Assess medication-taking behavior
  - Consider Dual Therapy

Dual Therapy — Lifestyle Management + Metformin + Additional Agent

ASCVD?
- **Yes:** - Add agent proven to reduce major adverse cardiovascular events and/or cardiovascular mortality (see recommendations with * on p. S75 and **Table 8.1**)
- **No:** - Add second agent after consideration of drug-specific effects and patient factors (See Table 8.1)

A1C at target after 3 months of dual therapy?
- **Yes:** - Monitor A1C every 3–6 months
- **No:** - Assess medication-taking behavior
  - Consider Triple Therapy

Triple Therapy — Lifestyle Management + Metformin + Two Additional Agents

Add third agent based on drug-specific effects and patient factors# (See Table 8.1)

A1C at target after 3 months of triple therapy?
- **Yes:** - Monitor A1C every 3–6 months
- **No:** - Assess medication-taking behavior
  - Consider Combination Injectable Therapy (See Figure 8.2)

3.-Algoritmo de selección de antidiabéticos en pacientes insulinizados.

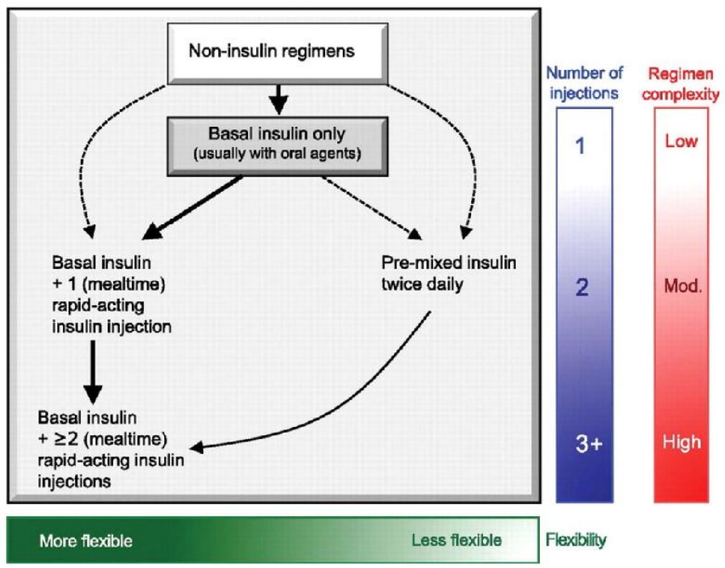
Tratamiento con antidiabéticos orales

INSULINIZACIÓN

1ª elección	**insulina basal + MET**	(1)
2ª elección	**insulina basal + MET + 2º antidiabético oral**	(2)

TERAPIA DE COMBINACIÓN PARENTERAL
(si existe mal control)

1ª elección	**cambio de régimen de insulinización**	(3)
2ª elección	**insulina + aGLP-1**	(4)



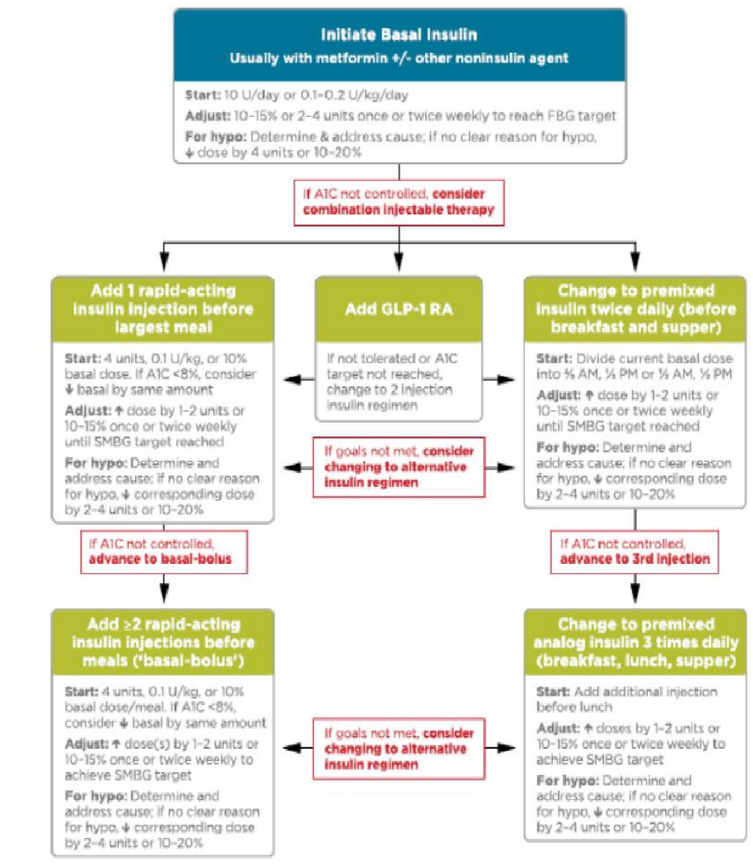
- Consider initiating insulin therapy (with or without additional agents) in patients with newly diagnosed type 2 diabetes who are symptomatic and/or have A1C ≥10% (86 mmol/mol) and/or blood glucose levels ≥300 mg/dL (16.7 mmol/L). **E**

Diabetes Care 35:1364–1379, 2012

- Iniciar insulina basal (0,2 UI/kg/d) con ajuste de dosis por el paciente.
- Pauta basal plus / bolo-basal.
- Dos dosis de insulina premezclada.
- Añadir análogo de GLP-1.

Summary of Revisions: *Standards of Medical Care in Diabetes—2018*

Diabetes Care 2018;41(Suppl. 1):S4–S6 | https://doi.org/10.2337/dc18-SREV01

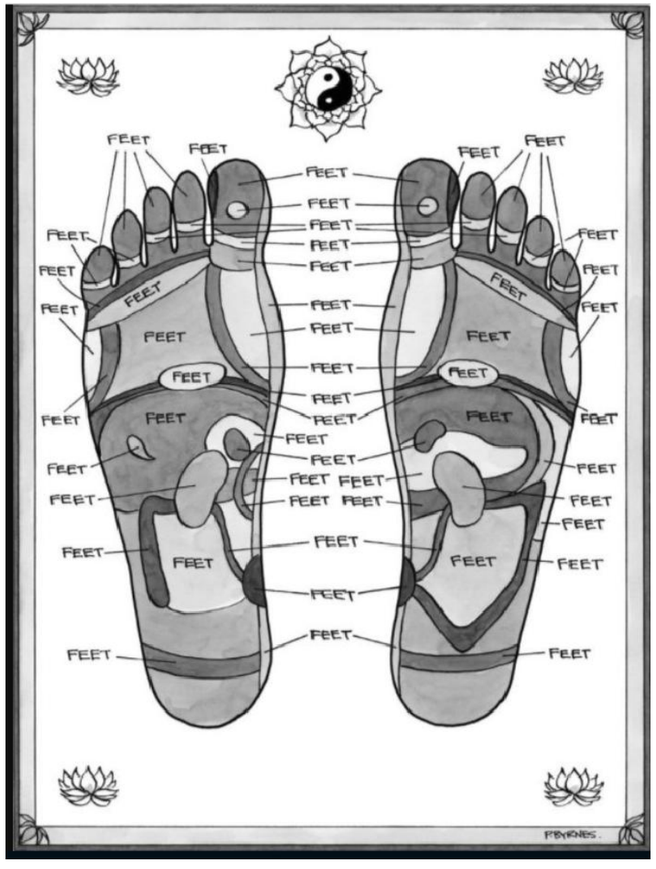


Conclusiones

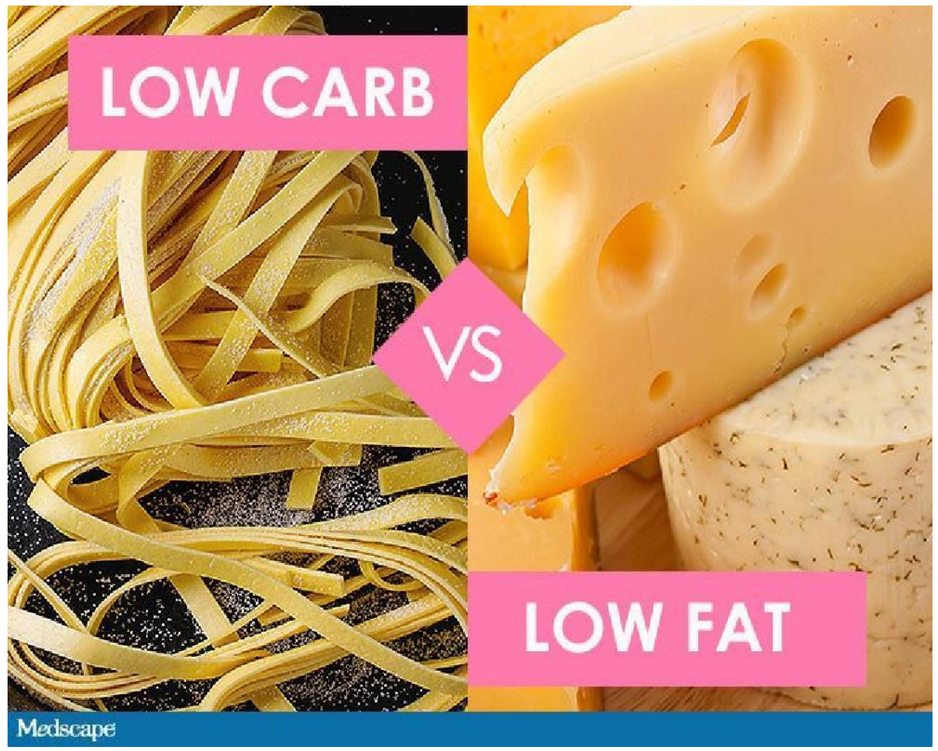
- Si existe sobrepeso u obesidad, la pérdida de peso debe considerarse un objetivo prioritario a lo largo del trascurso de la enfermedad.
- Los niveles de HbA1c como meta, deben individualizarse.
- El tratamiento debe ser personalizado, según las características del paciente, el coste y las preferencias personales.
- Minimizar el riesgo de hipoglucemias es siempre prioritario.
- Evitar el aumento de peso es otra prioridad.
- El tratamiento suele precisar de varios agentes, con mecanismos de acción complementarios.
- Hemos de reevaluar la efectividad de nuestra intervención, al principio cada 3 meses y, cuando el paciente está estable, con menos frecuencia.

Garber AJ et al. Endocr Pract 2017;23:207-238

Muchas gracias !




SUGAR
VS
ARTIFICIAL SWEETENERS
Medscape


LOW CARB
VS
LOW FAT
Medscape