Diabetes Tipo 2

10ª JORNADA DE ACTUALIZACIÓN TERAPÉUTICA DE LA redGDPS

CASOS CLÍNICOS E INVESTIGACIÓN

redGDPS

Zaragoza, 20 y 21 de octubre de 2017

Algoritmo de insulinización redGDPS 2017

Situaciones generales

Manel Mata Cases

EAP La Mina. Sant Adrià de Besòs ICS SAP Litoral (Barcelona)

Institut Català de la Salut

IDIAP Jordi Gol

USR Barcelona

DAP_Cat

Grup de Recerca Epidemiològica en Diabetis des de l´Atenció Primària

ciberdem

Centro de Investigación Biomédica en Red de Diabetes y Enfermedades Metabólicas Asociadas

Fundación redGDPS

Red de Grupos de Estudio de la Diabetes EN ATENCIÓN PRIMARIA DE LA SALUD

Diabetes Tipo 2

10ª JORNADA DE ACTUALIZACIÓN TERAPÉUTICA DE LA redGDPS

CASOS CLÍNICOS E INVESTIGACIÓN

redGDPS

Zaragoza, 20 y 21 de octubre de 2017

Conflictos de interés:

Honorarios de ASTRA-ZENECA, BAYER, BOEHRINGER, FERRER, GSK, LILLY, MENARINI, MERCK, MSD, NOVARTIS, NOVONORDISK, SANOFI y SERVIER por la participación en Advisory Boards, cursos y ponencias sobre la DM2

Manel Mata Cases

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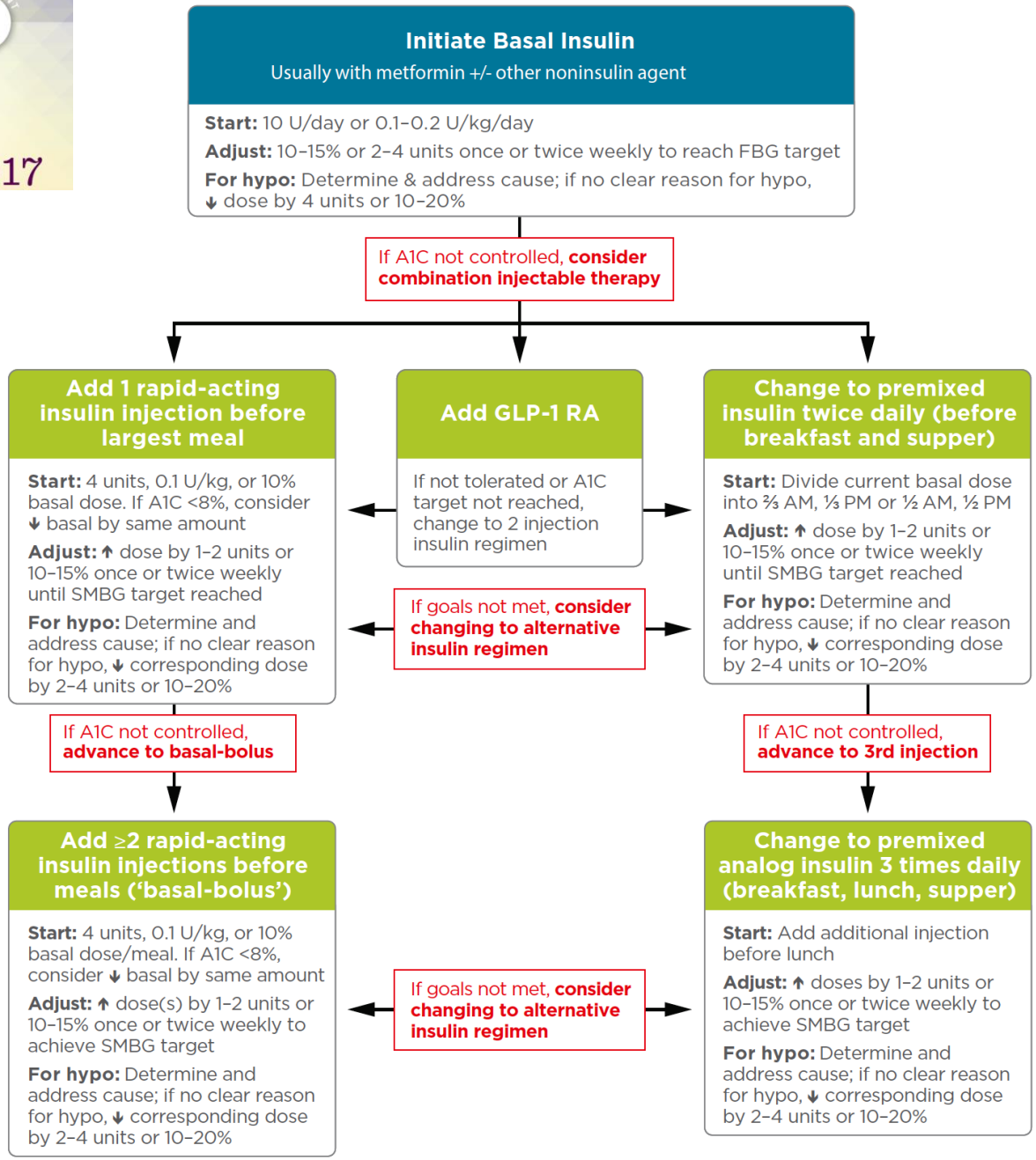
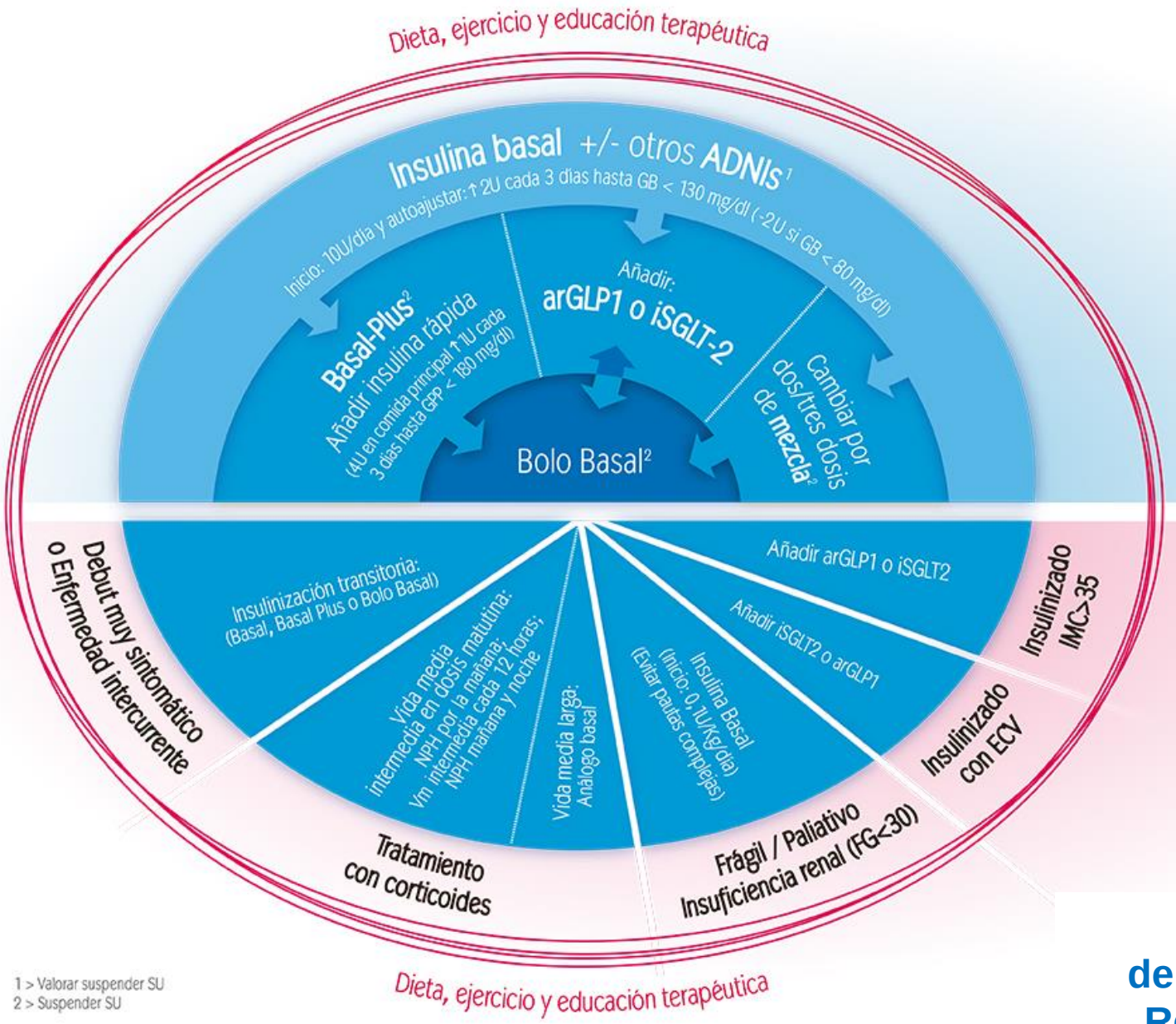
Red de Grupos de Estudio de la Diabetes EN ATENCIÓN PRIMARIA DE LA SALUD



ADA 2017. Combination injectable therapy for Type 2 diabetes

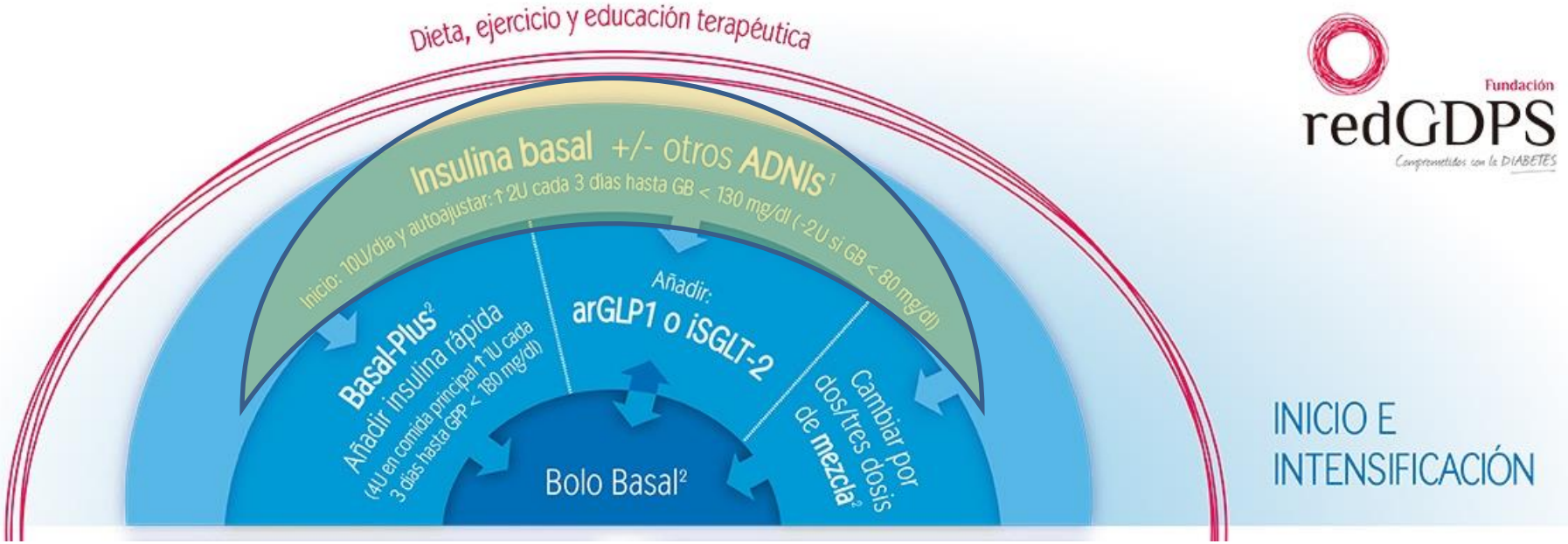


1 > Valorar suspender SU
2 > Suspender SU

Fundación redGDPS
Comprometidos con la DIABETES

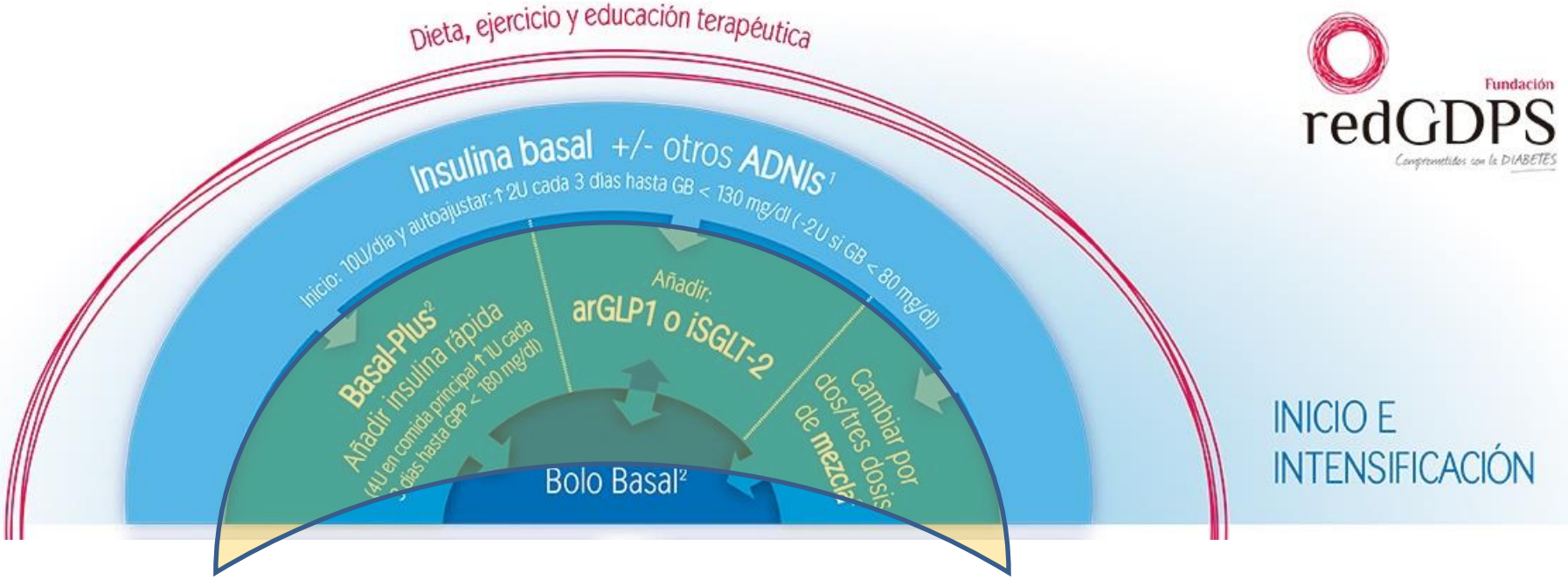
Algoritmo de insulinización RedGDPS 2017

Inicio con insulina basal



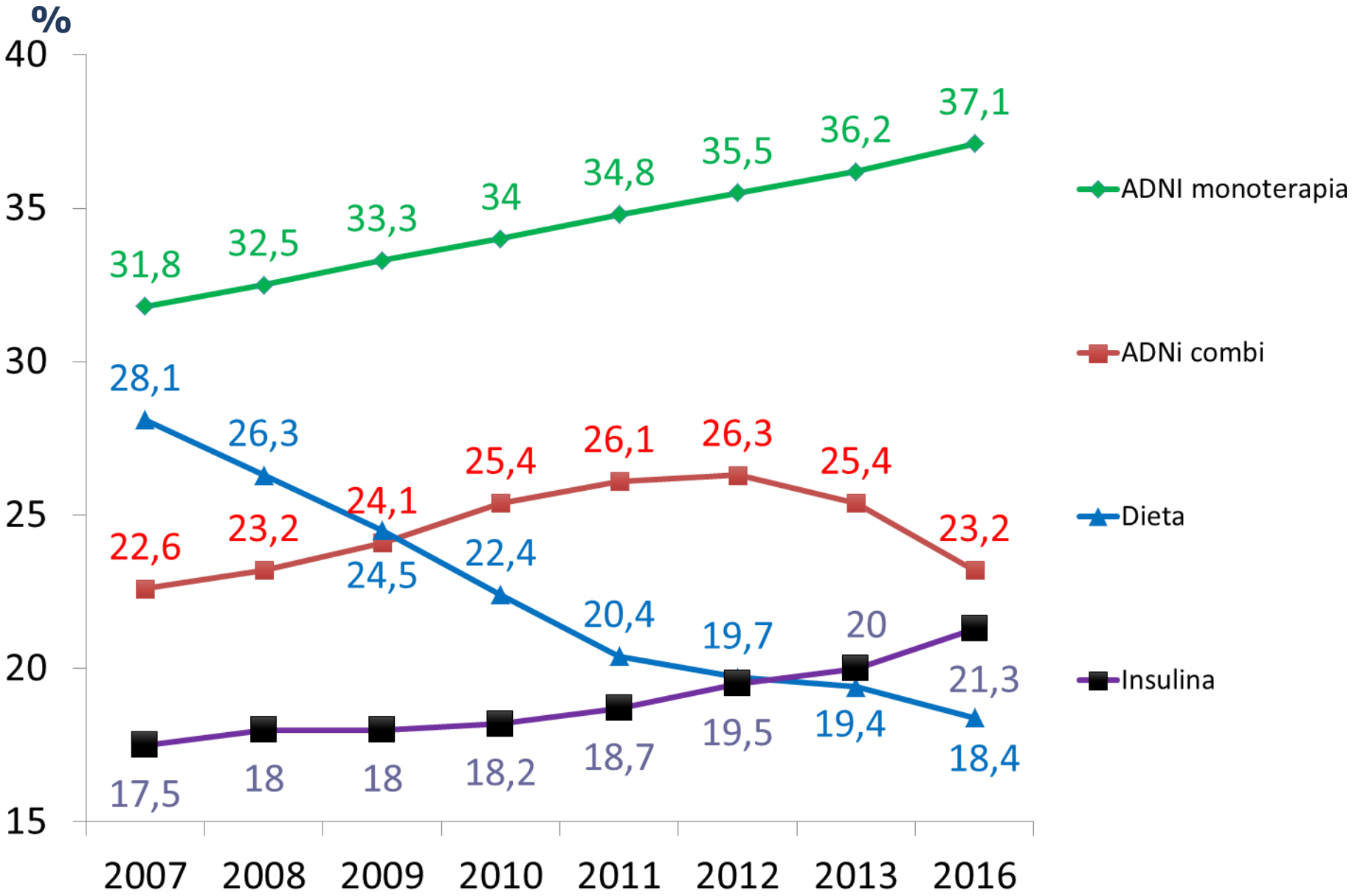
Algoritmo de insulinización RedGDPS 2017

Y si el control no es suficiente con insulina basal, que añadimos?



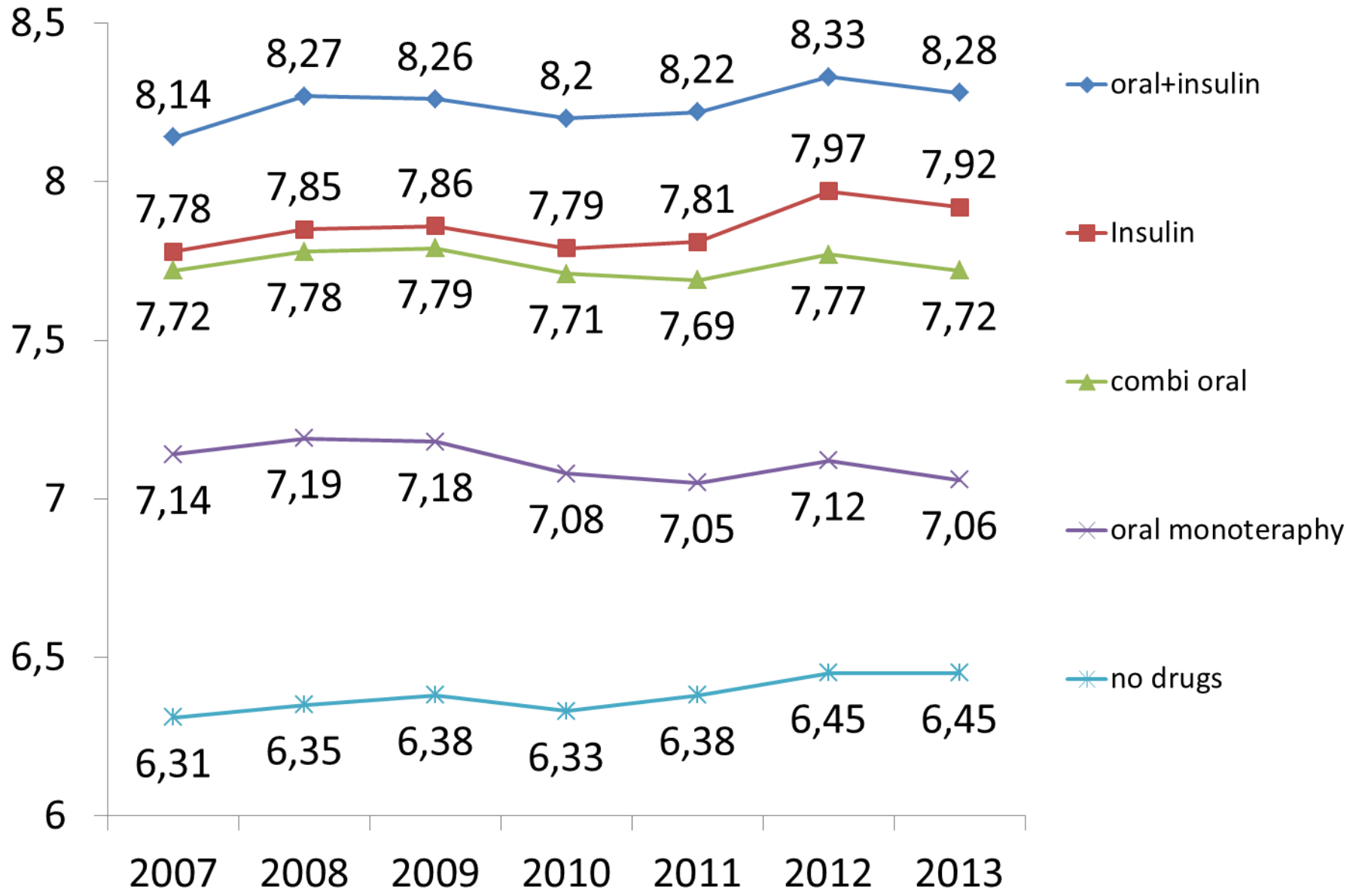
Algoritmo de insulinización RedGDPS 2017

SIDIAP Catalunya: Pacientes en cada escalón terapeútico . 2007-2016



Mata-Cases M et al. BMJ Open 2016 doi:10.1136/bmjopen-2016-012463
Datos 2016 no publicados

Catalunya: HbA1c media en cada escalón terapeútico



Mata-Cases M et al. BMJ Open 2016 doi:10.1136/bmjopen-2016-012463

Cuantos pacientes se controlan adecuadamente con una inyección de insulina basal?

Porcentaje de pacientes que consiguen el objetivo de HbA1c<7% en ensayos clínicos comparativos:

1 NPH vs 1 Glargina [1]	58%	vs	58%
1 NPH vs 1 Glargina [2]	58%	vs	58%
1 Glargina vs 1-2 Detemir [3]	52%	vs	52%
1 Glargina vs 1 Degludec [4]	54%	vs	52%

1. *Riddle M et al. Diabetes Care 2003; 26:3080−6*
2. *Yki-Jarvinen H et al . Diabetologia 2006;49:442-51.*
3. *Rosenstock J et al. Diabetologia. 2008;51(3):408-16.*
4. *Zinman et al. Diabetes Care 2012;35:2464–71*

Diabetes & Metabolism

Mata-Cases et al., J Diabetes Metab 2014, 5:2
http://dx.doi.org/10.4172/2155-6156.1000338

Research Article Open Access

Treatment of Hyperglycaemia in Type 2 Diabetic Patients in a Primary Care Population Database in a Mediterranean Area (Catalonia, Spain)

Manel Mata-Cases[1,2*], Dídac Mauricio[2,3], Irene Vinagre[4], Rosa Morros[2,5], Eduard Hermosilla[2], Francesc Fina[2,6], Magdalena Rosell-Murphy[2], Conxa Castell[7], Josep Franch-Nadal[2,8], Bonaventura Bolíbar[2,5]

Econtrol 2009: Control glucémico de los pacientes tratados con insulina

Insulina + ADOs N=29.095 (10.1%)	
HbA1c, media %	8.1 ± 1.6
HbA1c≤ 7% (%)	24.3
IMC, Kg/m^2 ± DE	30.6 ±5.3
Insulina monoterapia N=21.710 (7.6%)	
HbA1c, media %	7.9 ±1.7
HbA1c≤ 7% (%)	32.9
IMC, Kg/m^2 ± DE	28.6 ±5.1

Mata-Cases M et al. J Diabetes Metab. 2014 5:2. doi: 10.4172/2155-6156.1000338

Journal of Diabetes •• (2016) •–••

ORIGINAL ARTICLE

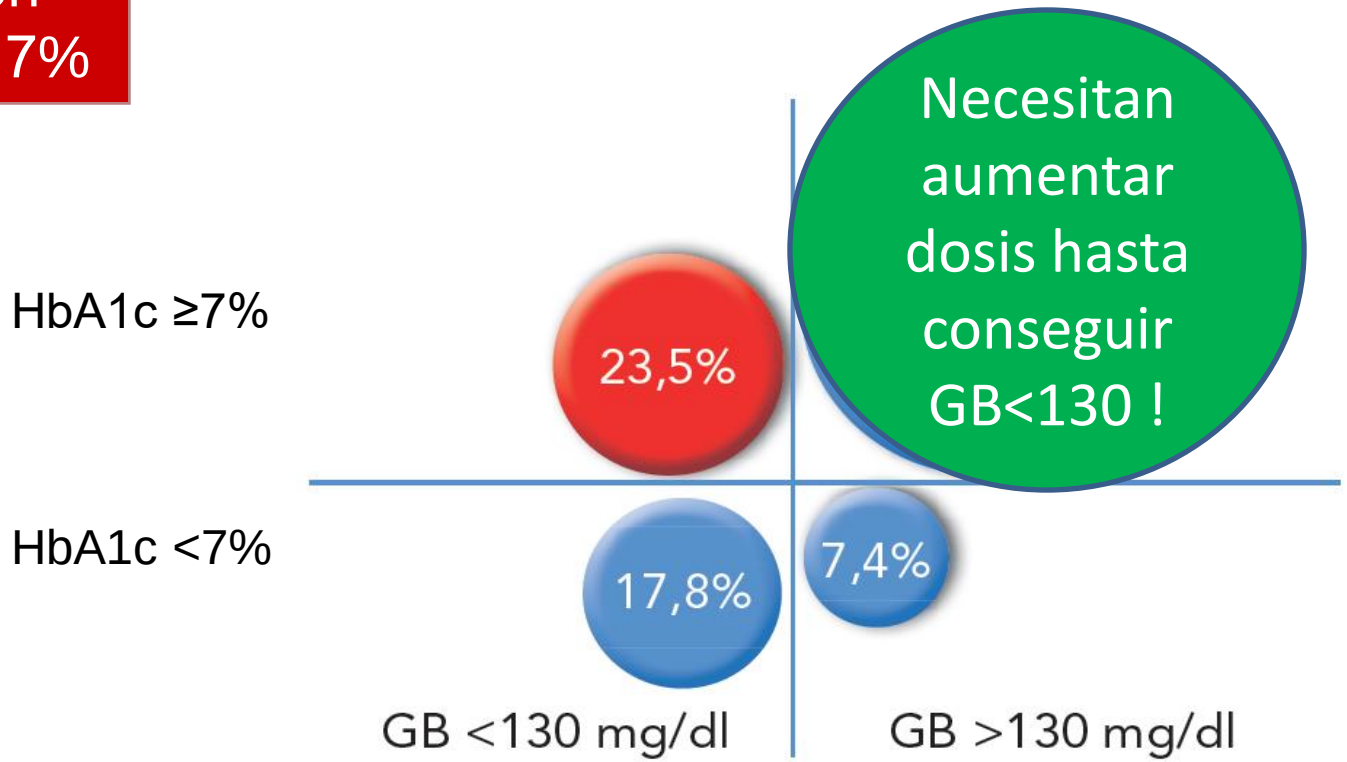
Clinical characteristics of type 2 diabetic patients on basal insulin therapy with adequate fasting glucose control who do not achieve HbA1c targets

Manel Mata-Cases,[1,2,5] Dídac Mauricio[1,4,5] and Josep Franch-Nadal[1,3,5]

Estudio eControl en Catalunya, 2010

9.899 Pacientes con DM2 tratados con insulina basal.

¾ tienen HbA1c ≥ 7%



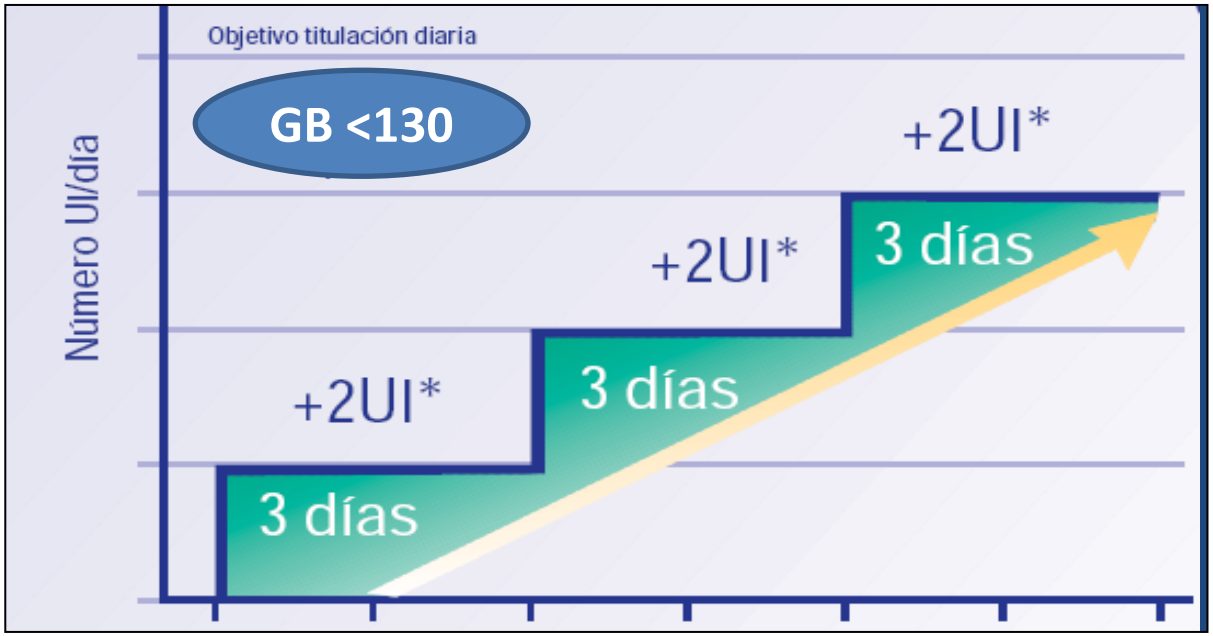
Mata-Cases M et al. J Diabetes. 2016 Jan 8. doi: 10.1111/1753-0407.12373

AMERICAN DIABETES ASSOCIATION
STANDARDS OF MEDICAL CARE IN DIABETES—2017

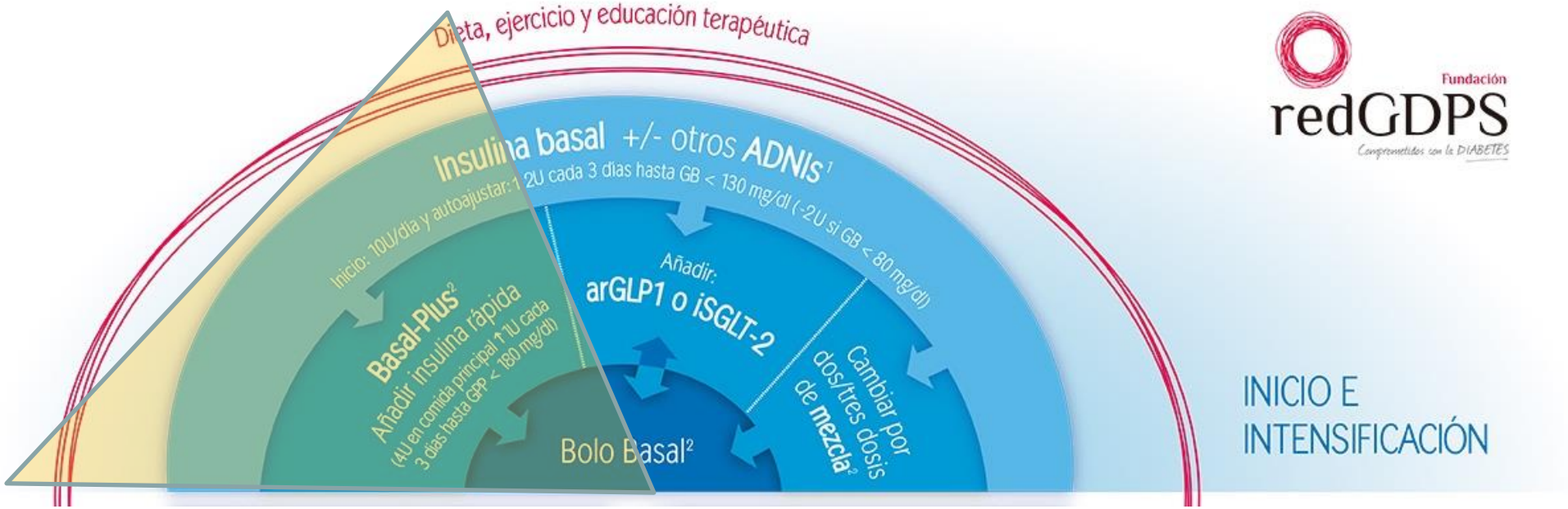
Initiate Basal Insulin

Usually with metformin +/- other noninsulin agent

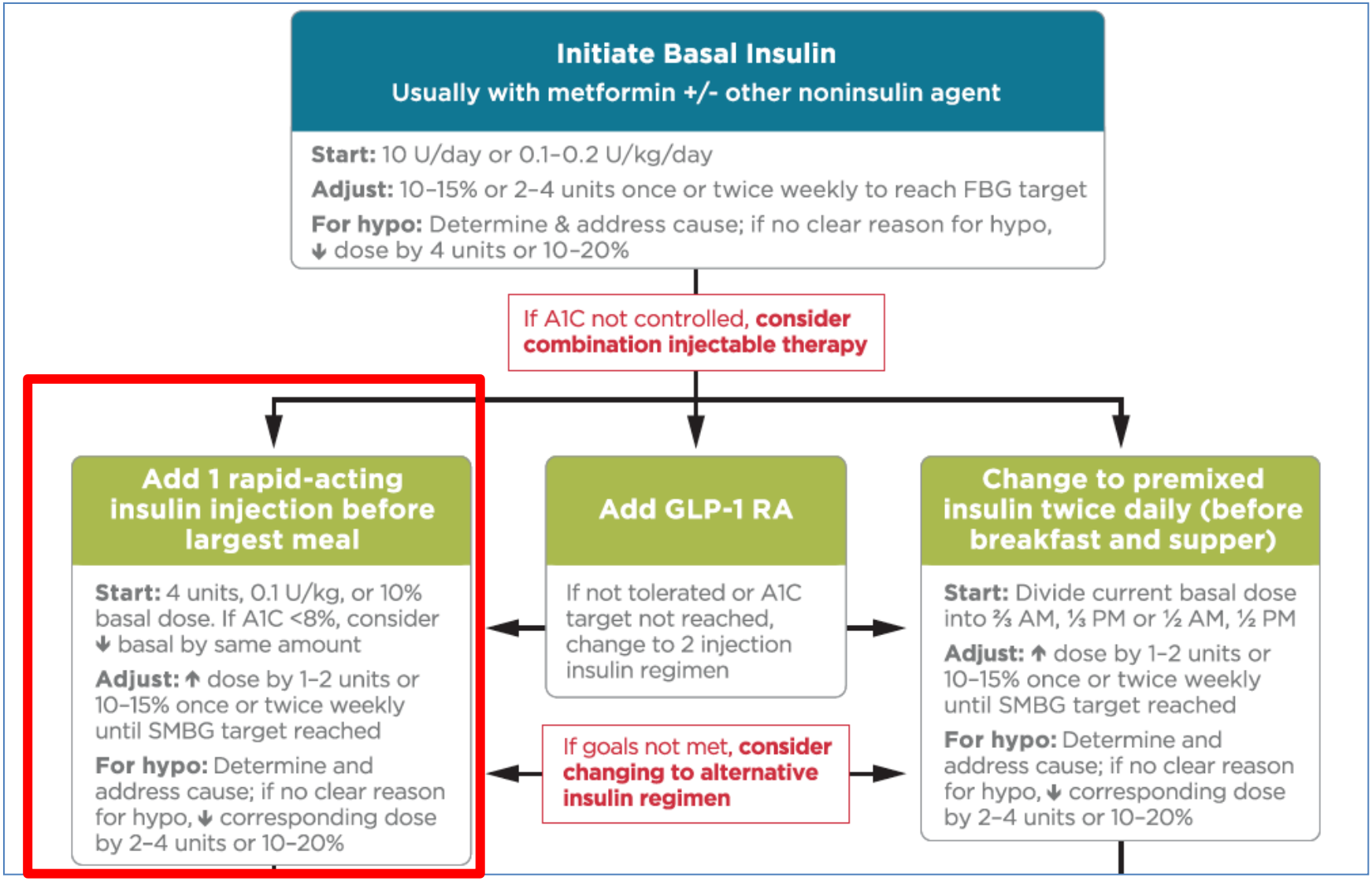
Iniciar con 10 U y aumentar 2U cada 3 días
↓ 2U si glucemia<80 mg/dl



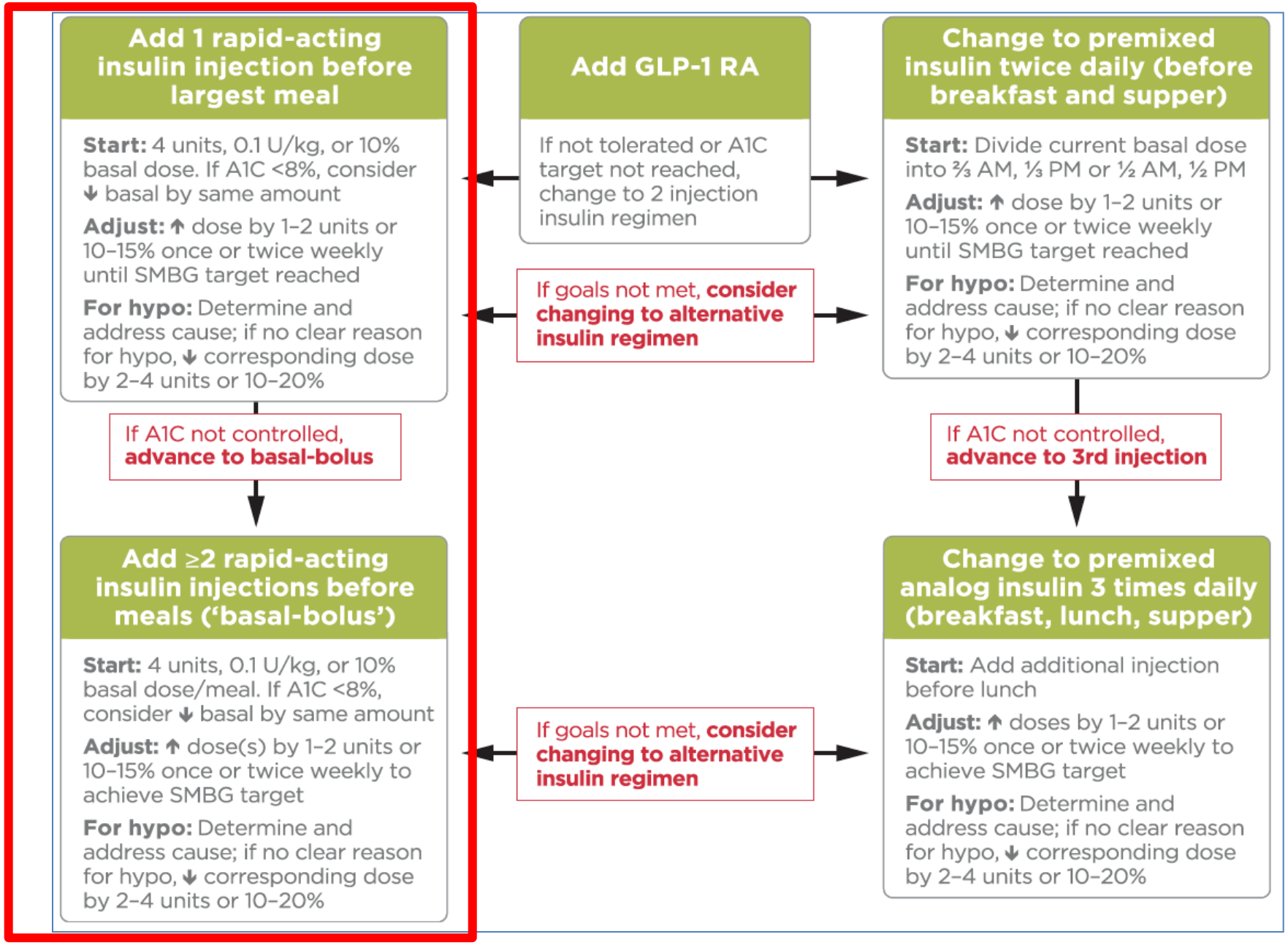
Paciente tratado con insulina basal y mal control:
1. Añadir insulina prandial



Algoritmo de insulinización RedGDPS 2017



ADA 2017. Combination injectable therapy for T2DM



ADA 2017. Combination injectable therapy for T2DM

1-2-3 Study

1, 2 ó 3 dosis de insulina prandial (glulisina) añadidas a insulina basal (glargina)

N= 100
N= 101
N= 102

	HbA1c	Hipos graves	Peso
1.	-2,75%	7%	+ 3,8
2.	-2,79%	8%	+ 4,1
3.	-2,87%	16%	+ 3,9

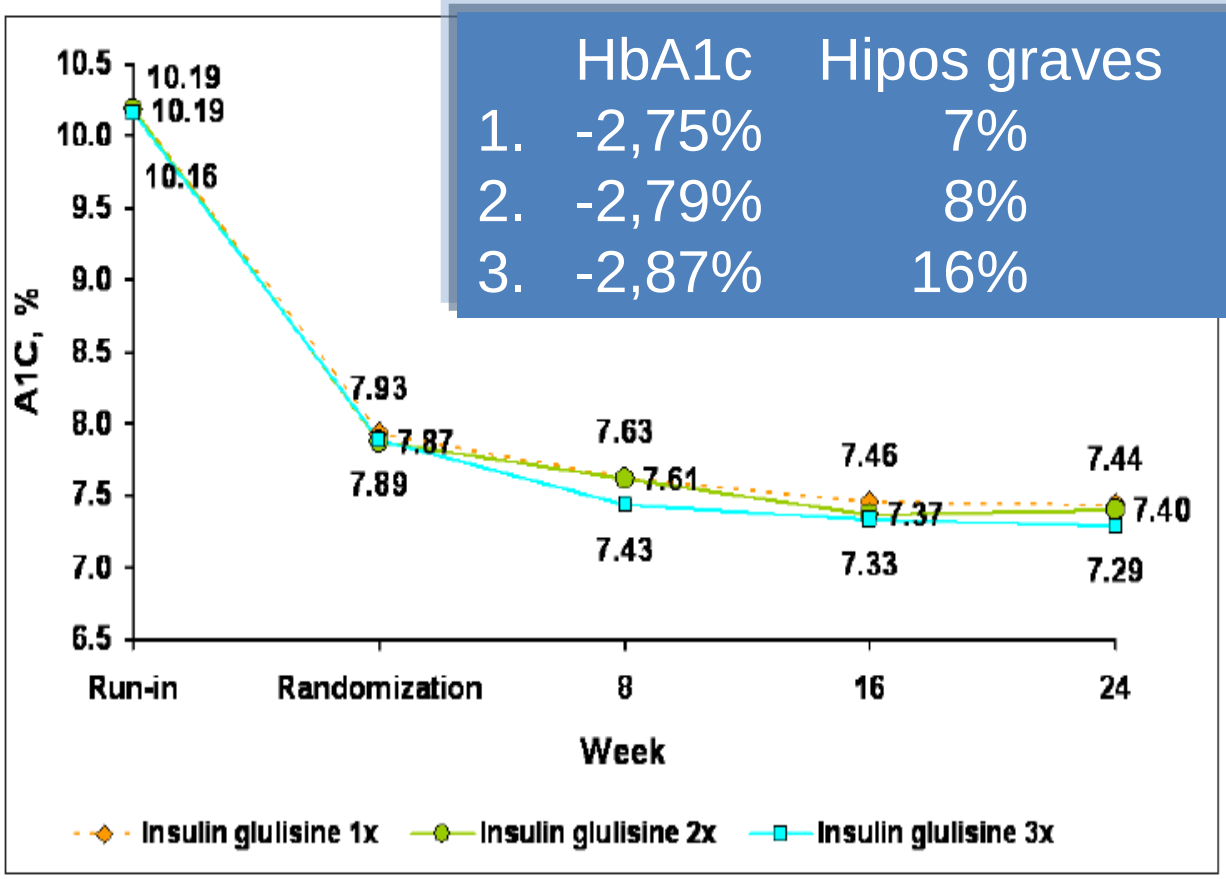
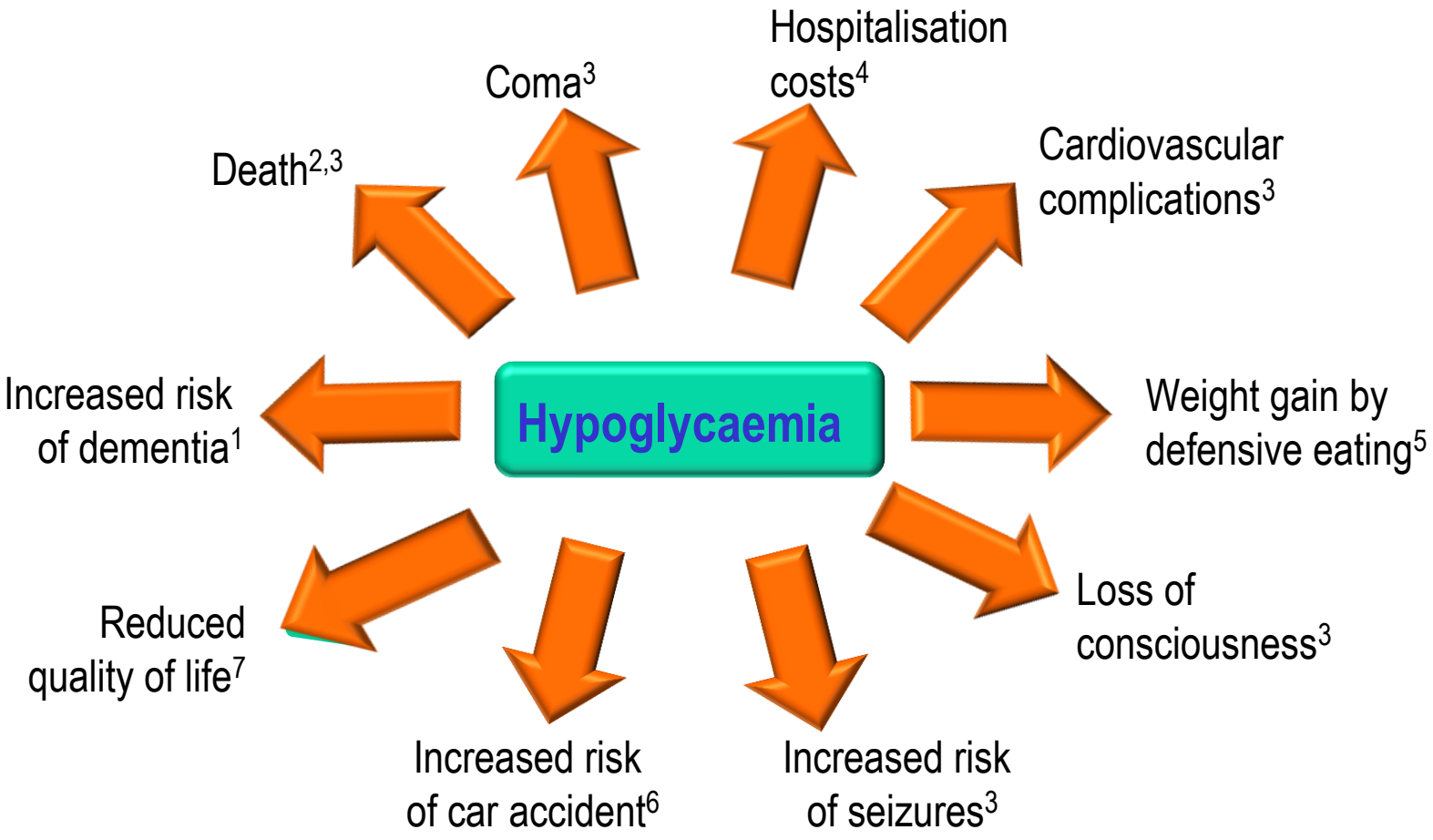


Fig. 3. Glycated hemoglobin A_{1c} (A1C) levels. Insulin glulisine 1× = insulin glulisine administered before the meal of greatest glycemic impact; insulin glulisine 2× = insulin glulisine administered before the 2 meals of greater glycemic impact; insulin glulisine 3× = insulin glulisine administered before all 3 meals.

Davidson MB, et al. Endocr Pract. 2011;17(3):395-403

The consequences of hypoglycaemia



[1]Whitmer RA, et al. *JAMA.* 2009; 301: 1565– 72; [2]Bonds DE, et al. *BMJ.* 2010; 340: b4909; [3]Barnett AH. *Curr Med Res Opin.* 2010; 26: 1333–1342; [4]Jönsson L, et al. *Value Health.* 2006; 9: 193–198; [5]Foley JE, Jordan J. *Vasc Health Risk Manag.* 2010; 6: 541–548; [6]Begg IS, et al. Can J Diabetes. 2003; 27: 128–140; [7]McEwan P, et al. *Diabetes Obes Metab.* 2010; 12: 431–436.

Acta Diabetol (2016) 53:377–392
DOI 10.1007/s00592-015-0803-3

ORIGINAL ARTICLE

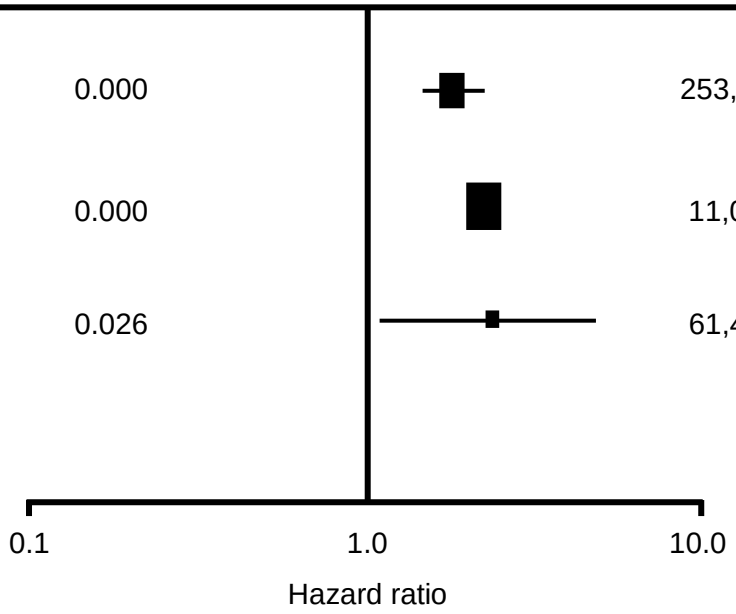
Hypoglycemia and risk of vascular events and mortality: a systematic review and meta-analysis

Jong Shiuan Yeh[1] · Shih-Hsien Sung[2,6,7] · Hui-Mei Huang[5] · Huei-Ling Yang[5] · Li-Kai You[3] · Shao-Yuan Chuang[8] · Po-Chieh Huang[3] · Pai-Feng Hsu[4,6,7] · Hao-Min Cheng[3,6,7] · Chen-Huan Chen[3,6,7]

The findings of this systematic review support the speculation that hypoglycemia is a risk factor for adverse vascular events and mortality.

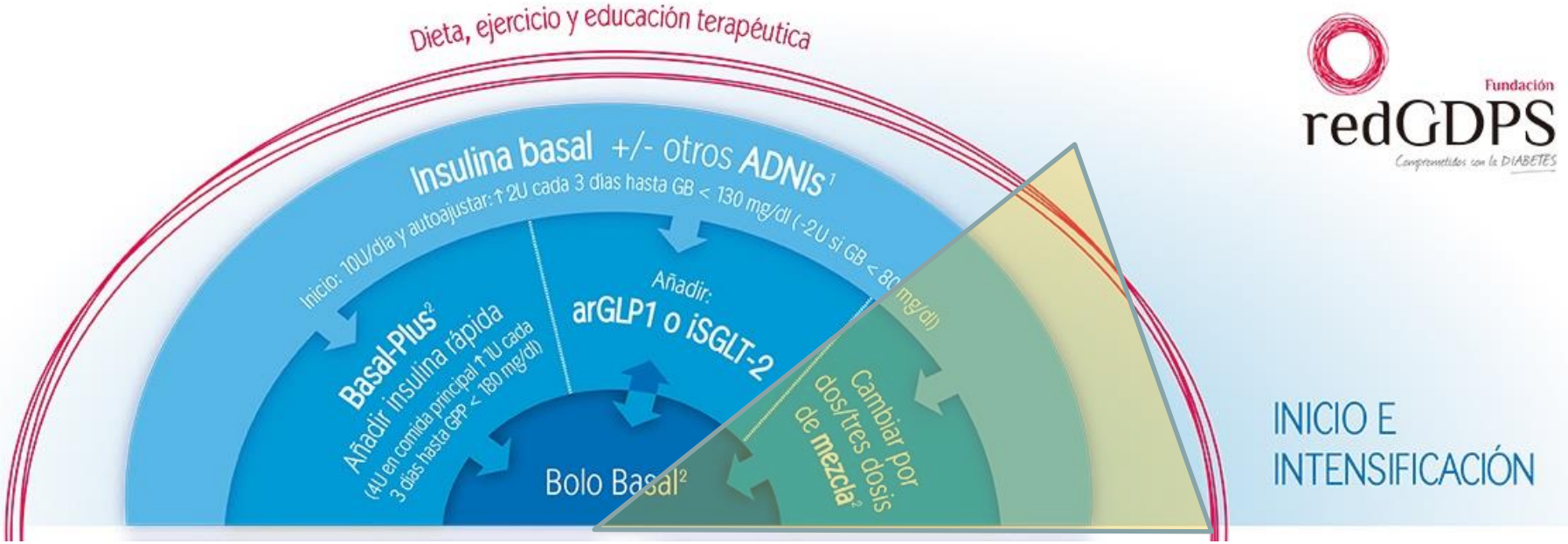
325,835 subjects (19 RCT)

	Hazard ratio [95% CI]	*p*-value	Number of patients
Total mortality	1.8 [1.5; 2.2]	0.000	253,390
Cardiovascular mortality	2.2 [2.0; 2.4]	0.000	11,011
Major cardiovascular event	2.3 [1.1; 5.0]	0.026	61,434

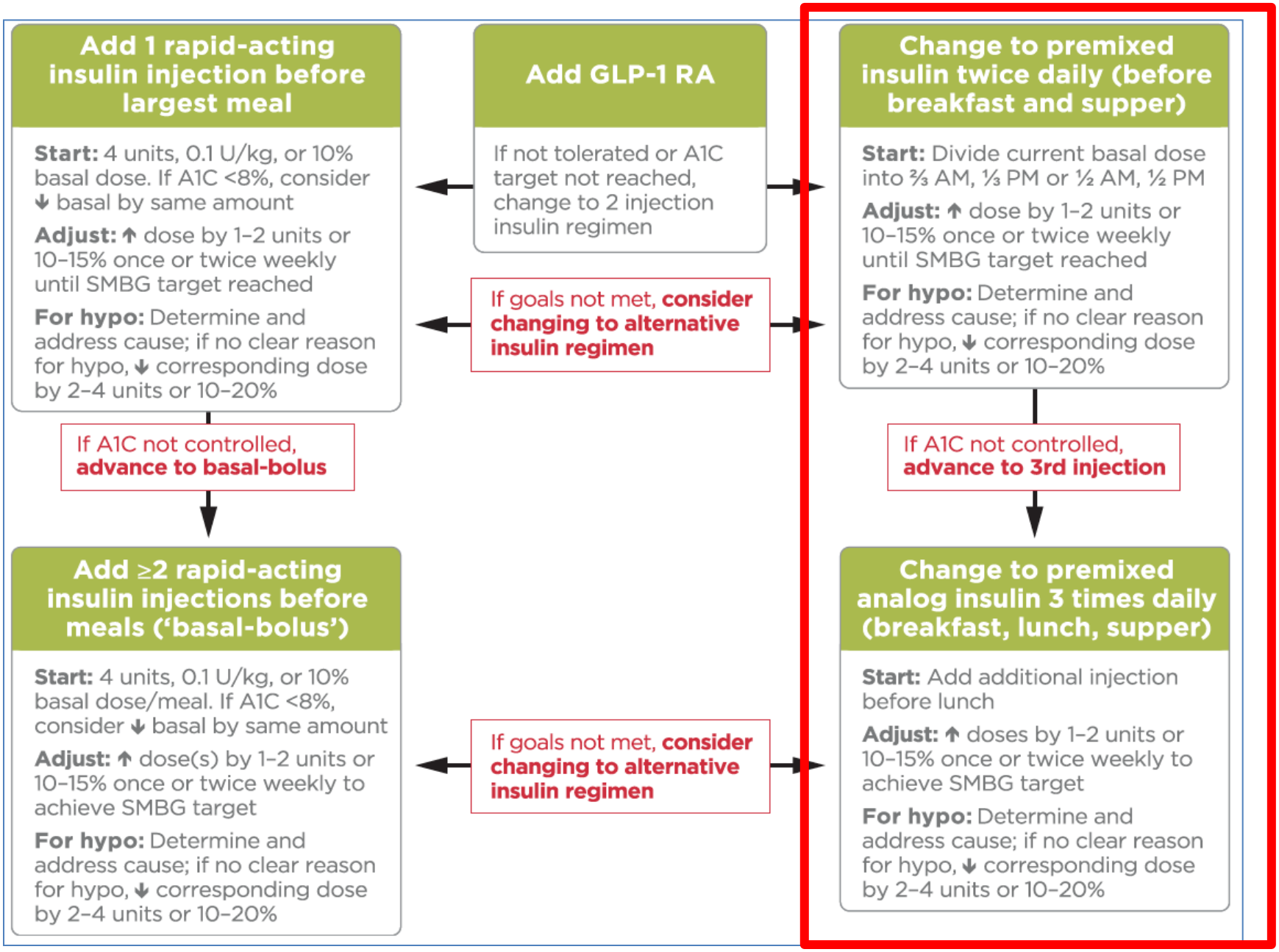


Yeh JS et al. Acta Diabetol 2016; 53:377–92

Pacientes tratado con insulina basal y mal control:
2. Pasar a dos dosis de insulina premezclada



Algoritmo de insulinización RedGDPS 2017



ADA 2017. Combination injectable therapy for T2DM

DIABETICMedicine
DOI: 10.1111/dme.12694

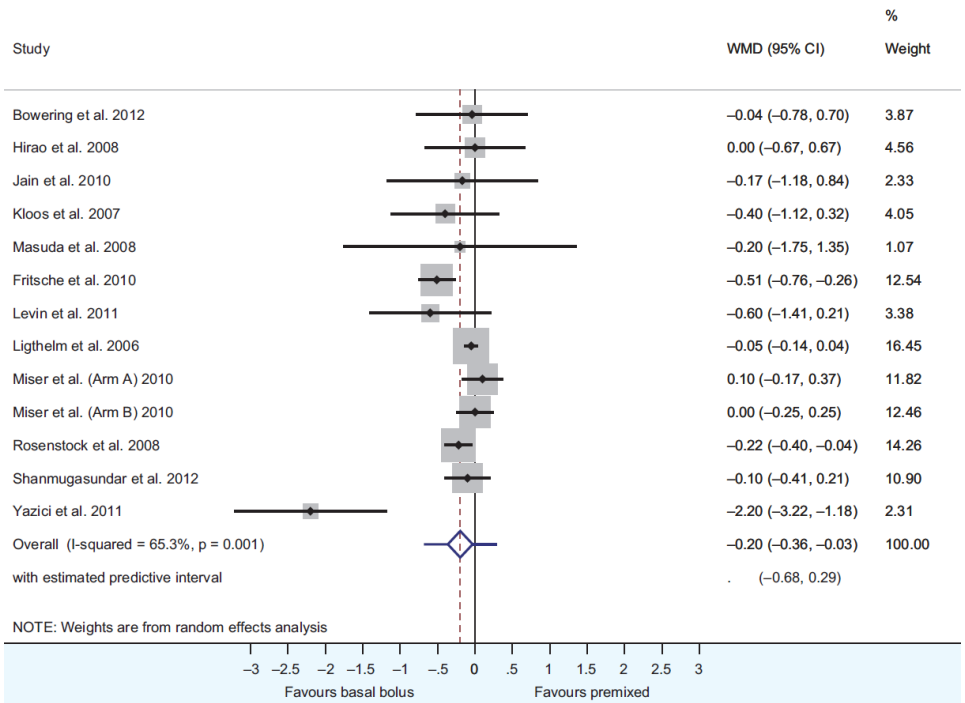
Systematic Review or Meta-analysis

Biphasic vs basal bolus insulin regimen in Type 2 diabetes: a systematic review and meta-analysis of randomized controlled trials

C. Wang, J. Mamza and I. Idris

15 ensayos clínicos aleatorizados, 4.384 pacientes

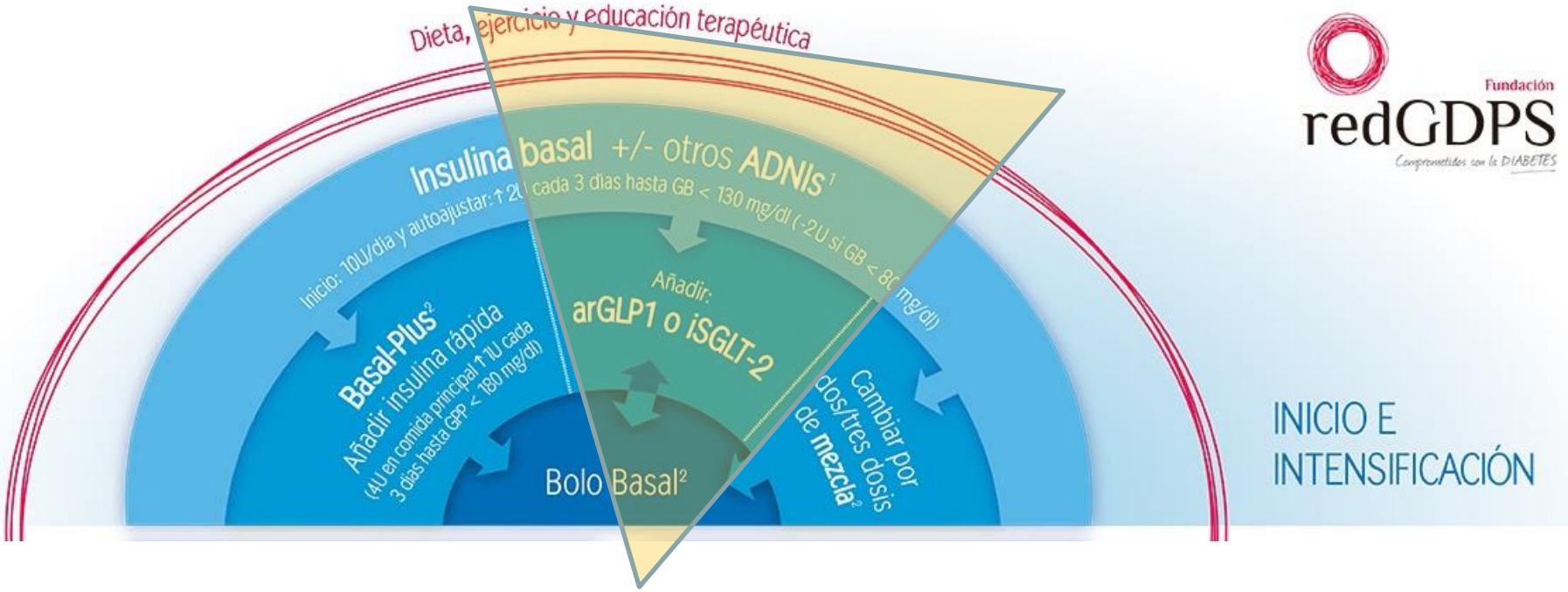
Basal-bolo vs Bifásica: Reducción HbA1c



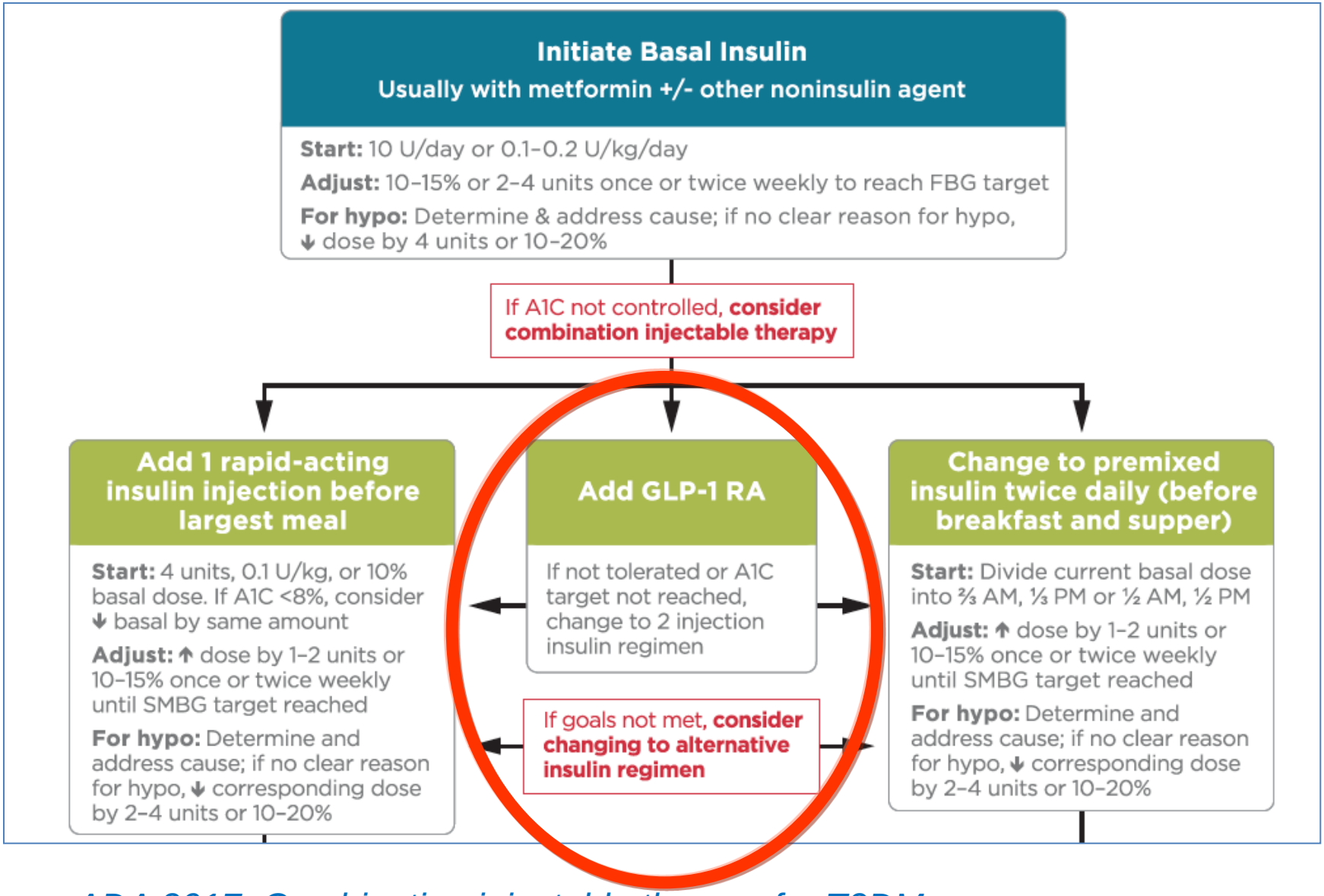
Las reducciones de HbA1c con la pauta basal-bolo fueron algo mayores (-0,20), pero no significativas, a expensas de mayores dosis diarias e incremento de peso (+0,9kg), pero sin un mayor riesgo de hipoglucemia

Wang C et al. Diabet Med. 2015; 32: 585–94

Paciente tratado con insulina basal y mal control:
3. Añadir insulina arGLP1 o iSGLT-2



Algoritmo de insulinización RedGDPS 2017



ADA 2017. Combination injectable therapy for T2DM

AMERICAN DIABETES ASSOCIATION
1
STANDARDS OF MEDICAL CARE IN DIABETES—2017

Summary of Revisions

Diabetes Care 2017;40(Suppl. 1):S4–S5 | DOI: 10.2337/dc17-S003

To reflect new evidence showing an association between B12 deficiency and long-term metformin use, a recommendation was added to consider periodic measurement of B12 levels and supplementation as needed.

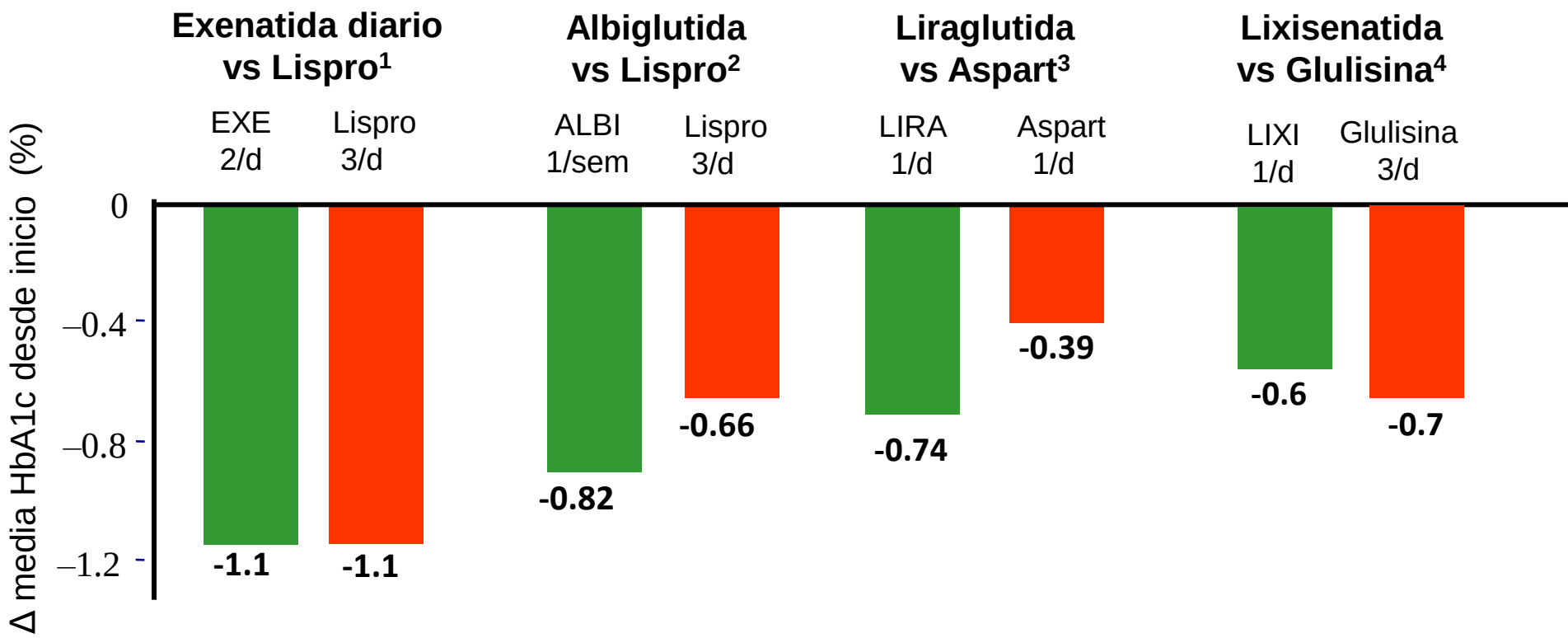
Based on the results of two large clinical trials, a recommendation was added to consider empagliflozin or liraglutide in patients with established cardiovascular disease to reduce the risk of mortality.

The algorithm for the use of combination injectable therapy in patients with type 2 diabetes (**Fig. 8.2**) has been changed to reflect studies demonstrating the noninferiority of basal insulin plus glucagon-like peptide 1 receptor agonist versus basal insulin plus rapid-acting insulin versus two daily injections of premixed insulin, as well as studies demonstrating the noninferiority of multiple dose premixed insulin regimens versus basal-bolus therapy.

Due to concerns about the affordability of antihyperglycemic agents, new tables were added showing the median costs of noninsulin agents (**Table 8.2**) and insulins (**Table 8.3**).

Figure 8.1, antihyperglycemic therapy in type 2 diabetes, was updated to acknowledge the high cost of insulin.

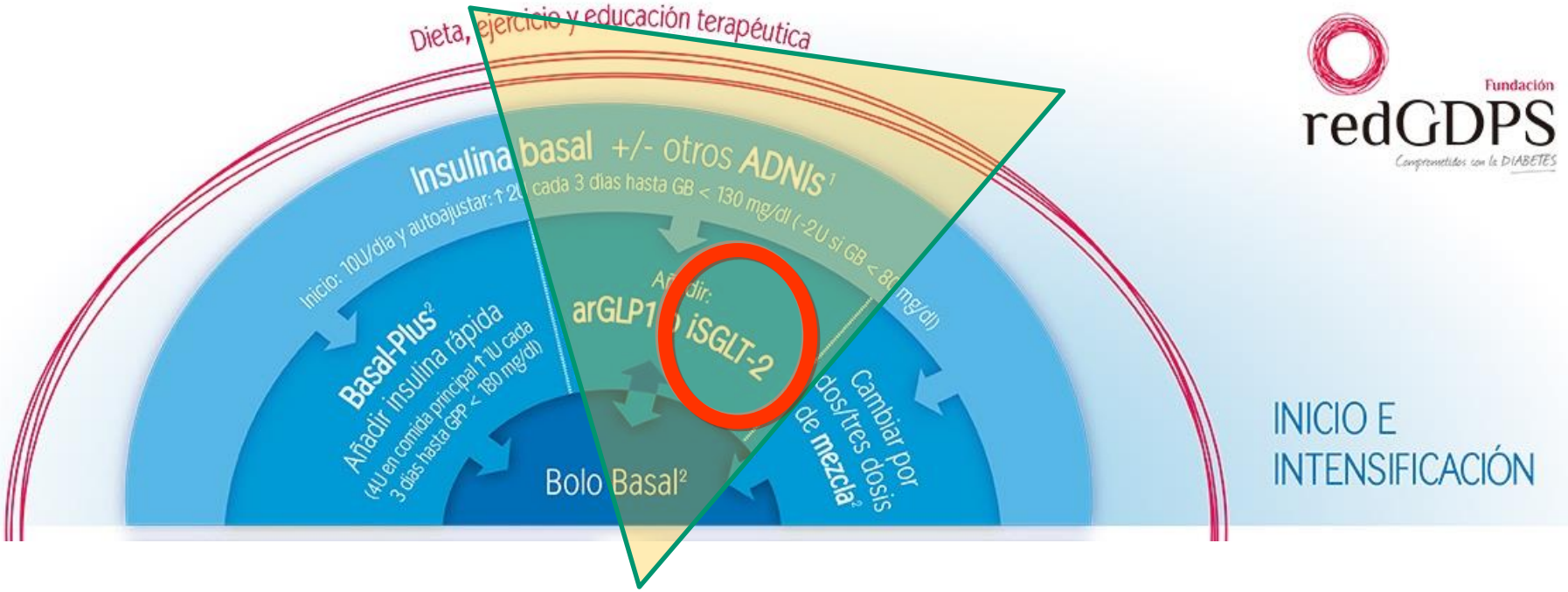
Agonistas del receptor del GLP-1 vs insulina rápida en pacientes tratados con insulina basal



	EXE 2/d	Lispro 3/d	ALBI 1/sem	Lispro 3/d	LIRA 1/d	Aspart 1/d	LIXI 1/d	Glulisina 3/d
ΔPeso (kg):	-2.5	+2.1	-0.7	+0.8	-2.8	+0.9	-0.6	+1.4
Hipos graves:	2.1	5.2	1.0	2.1	1.0	8.2	0	0

1. Diamant M, et al, . Diabetes Care. 2014;37(10):2763-73
2. Rosenstock J et al. Diabetes Care 2014; 37(8):2317-25
3. Mathieu C et al. Diabetes Obes Metab. 2014;16(7):636-44
4. Rosenstock J et al. Poster ADA 2015; Boston, USA

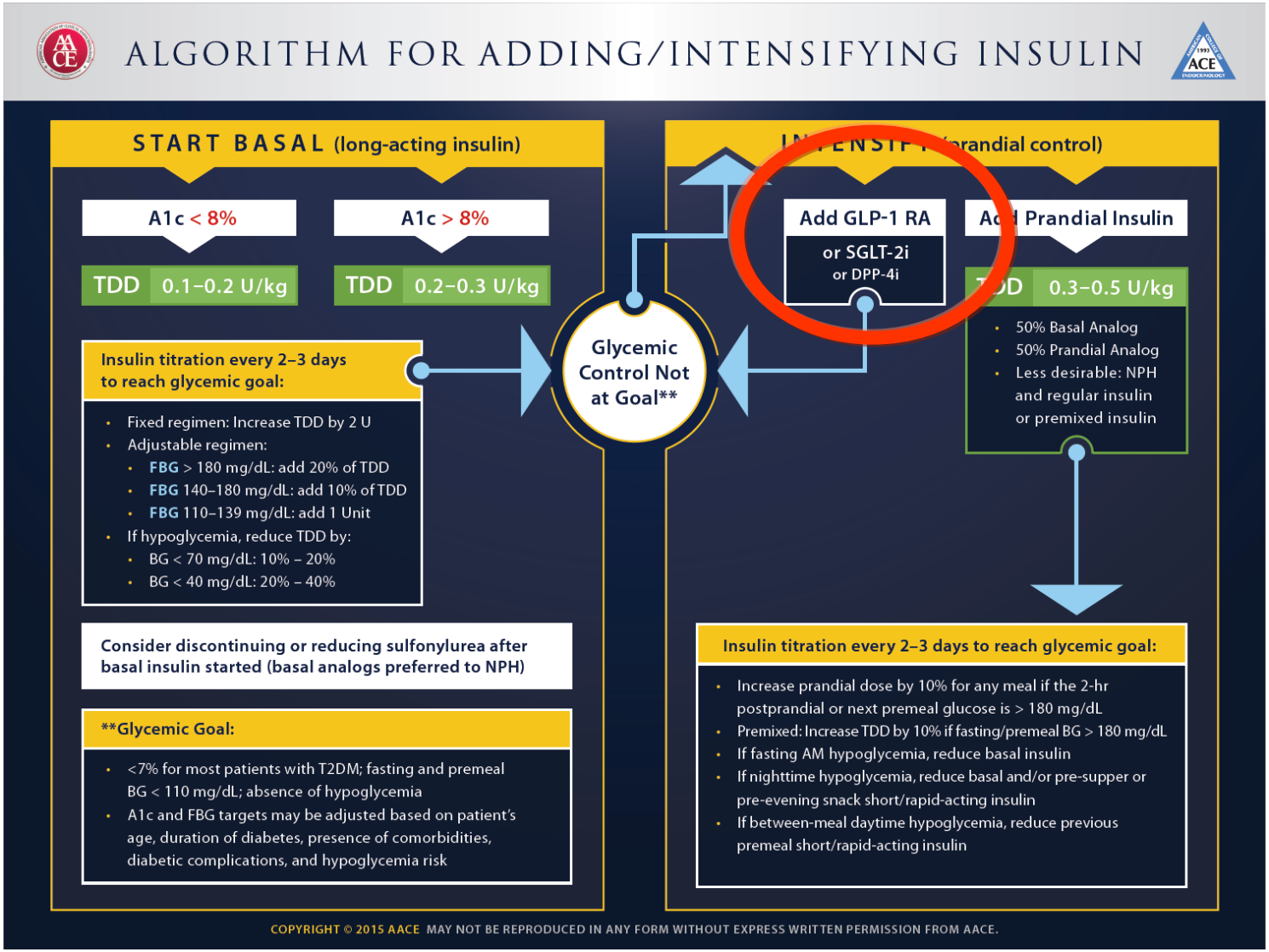
Paciente tratado con insulina basal y mal control:
3. Añadir insulina arGLP1 o iSGLT-2



Algoritmo de insulinización RedGDPS 2017

Algoritmo para añadir o intensificar insulina

Asociación Americana de Endocrinólogos Clínicos (AACE) 2015



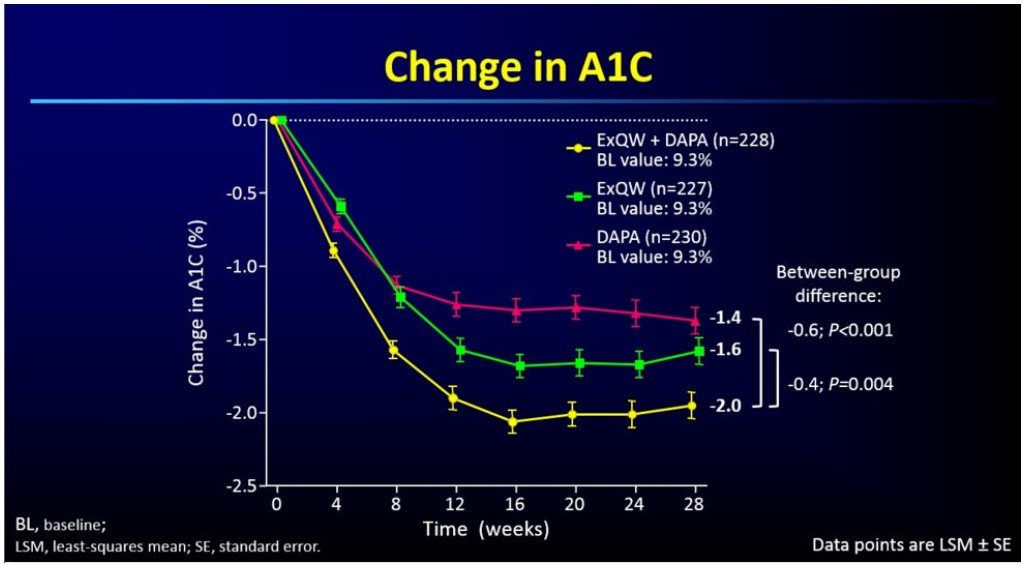
Garber AJ et al. Endocr Pract. 2015;21(4):438-47

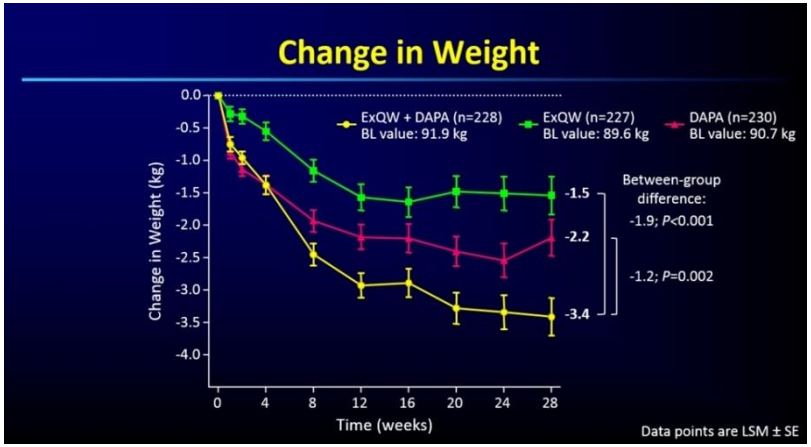
Exenatide once weekly plus dapagliflozin once daily versus exenatide or dapagliflozin alone in patients with type 2 diabetes inadequately controlled with metformin monotherapy (DURATION-8): a 28 week, multicentre, double-blind, phase 3, randomised controlled trial

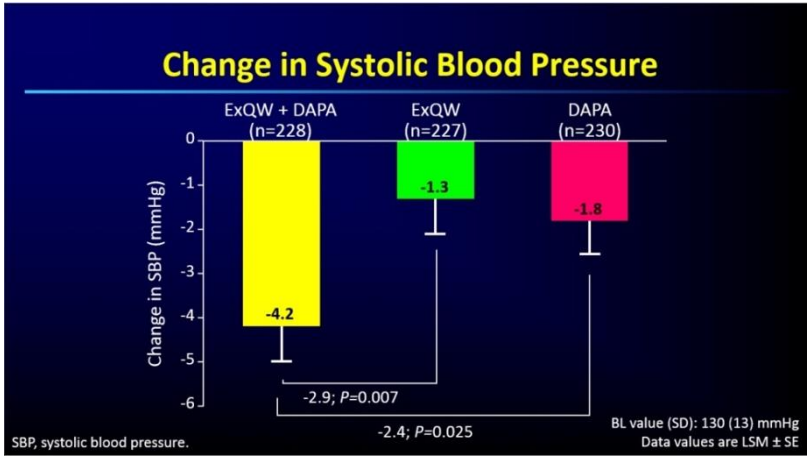
Juan P Frías, Cristian Guja, Elise Hardy, Azizuddin Ahmed, Fang Dong, Peter Öhman, Serge A Jabbour*

arGLP-1 vs iSGLT-2
Estudio DURATION 8

Dapagliflozina vs Exenatida semanal vs la combinación de ambos
N= 695 DM2 tratados con metformina, duración 24 semanas







	Exe	Dapa	Exe+Dapa
↓ HbA1c	1,6	1,4	2,0
↓ Peso	1,5	2,2	3,4
↓ PAS	1,3	1,8	4,2

Frías JP et al. Lancet Diabetes & Endocrinol. 2016; 4(12): 1004 - 1016

CONCLUSIONES

1. La pauta de insulina basal consigue un buen control en poco más de la mitad de los casos. Si no se consigue, se recomienda añadir insulina prandial (pautas basal-plus y basal-bolo), pasar a 2 dosis de insulinas premezcladas o añadir un arGLP-1 o un iSGLT2.

2. Las pautas mixtas son igual de eficaces que las pautas basal plus o basal-bolo y, aunque son más difíciles de ajustar, son útiles en pacientes estables en los que no se pretende un control muy estricto.

CONCLUSIONES

3. En pacientes obesos tratados con insulina basal y control deficiente la adición de un arGLP1 es tan eficaz como la insulina prandial, con menos pinchazos, menor incremento de peso e hipoglucemias.

4. Por razones de coste/efectividad los arGLP1 se deberían priorizar en pacientes con IMC>35 y suspenderlos si a los 6 meses no se reduce la HbA1c ≥1% y el peso ≥3% (NICE).

5. Aunque no hay estudios comparativos entre iSGLT2 e insulina prandial, son una buena opción en pacientes obesos, con ECV y como alternativa cuando no se consiguen los objetivos con un arGLP1.


Diabetes Tipo 2
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CASOS CLÍNICOS E INVESTIGACIÓN
redGDPS
Zaragoza, 20 y 21 de octubre de 2017
Gracias

Efectos cardiovasculares de los antidiabéticos. Resumen de los principales ensayos clínicos

Estudio	Año	Fármaco	MACE	IC
UKPDS34	1998	Metformina	↓ 39%	Neutro
PROactive	2005	Pioglitazona	↓ 16%	↑ 41%
ADVANCE	2008	Gliclacida	Neutro	Neutro
HOME	2009	Metformina	↓ 39%	Neutro
RECORD	2012	Rosiglitazona	Neutro	↑ 110%
ORIGIN	2012	Glargina	Neutro	Neutro
SAVOR	2013	Saxagliptina	Neutro	↑ 26%
EXAMINE	2013	Alogliptina	Neutro	↑ 19% (ns)
TECOS	2015	Sitagliptina	Neutro	Neutro
ELIXA	2015	Lixisenatida	Neutro	Neutro
EMPA-REG	2015	Empagliflozina	↓ 14%	↓ 35%
IRIS	2016	Pioglitazona	↓ 24%	↑ 15%
LEADER	2016	Liraglutida	↓ 24%	Neutro
CANVAS	2017	Canagliflozina	↓ 14%	↓ 33%
EXSCEL	2017	Exenatide sem	Neutro	Neutro

perspective

Diabetes, Obesity and Metabolism 18: 454–462, 2016.

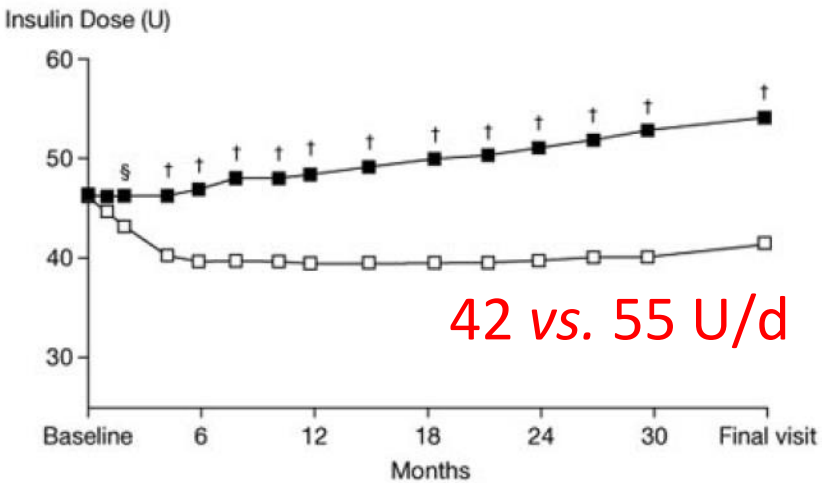
Revitalization of pioglitazone: the optimum agent to be combined with a sodium-glucose co-transporter-2 inhibitor

R. A. DeFronzo[1], R. Chilton[2], L. Norton[1], G. Clarke[3], R. E. J. Ryder[4] & M. Abdul-Ghani[1]

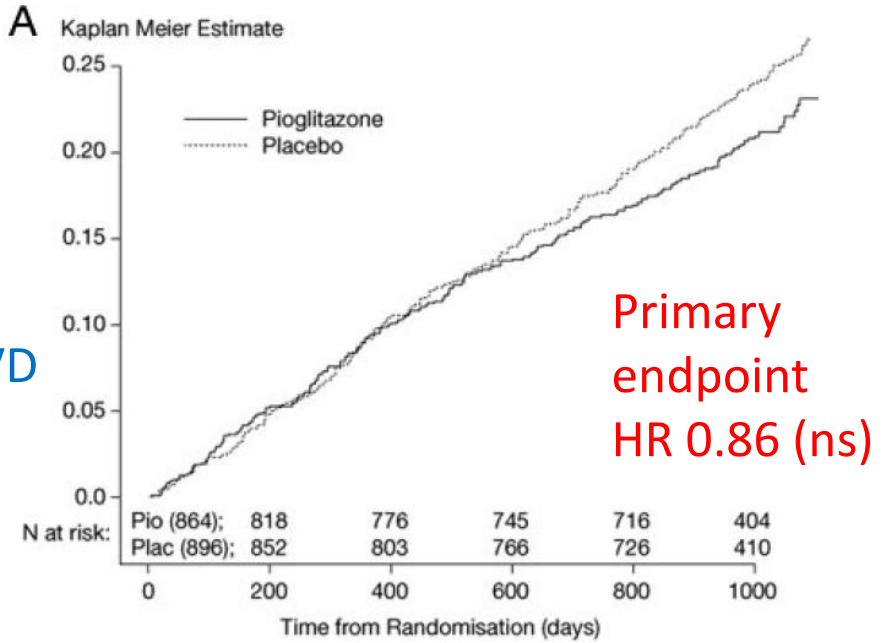
Pioglitazone Use in Combination with Insulin in the Prospective Pioglitazone Clinical Trial in Macrovascular Events Study (PROactive19)

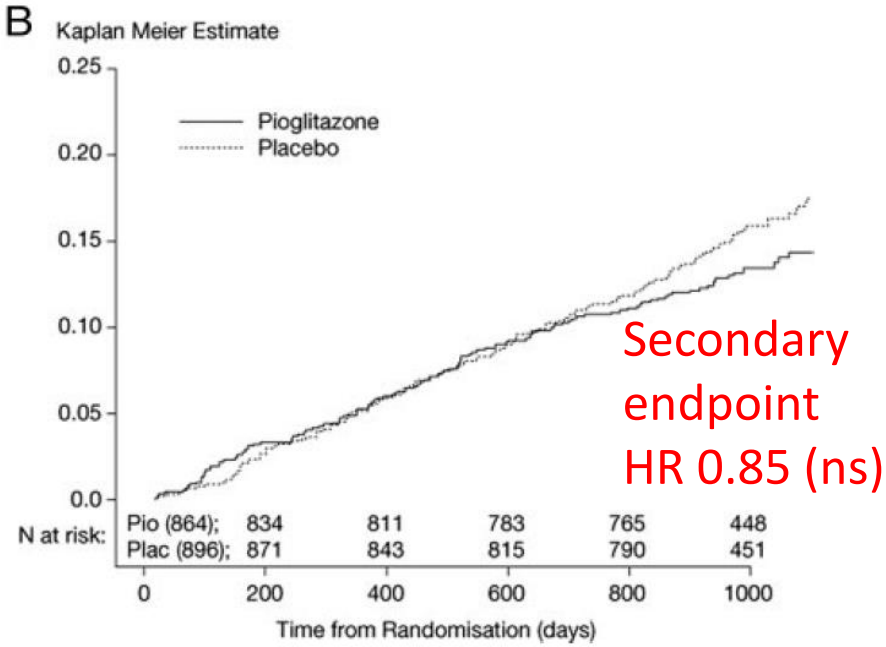
Bernard Charbonnel, Ralph DeFronzo, Jaime Davidson, Ole Schmitz, Kare Birkeland, Valdis Pirags, and André Scheen, on behalf of the PROactive investigators

N= 864 (Pio) vs 896 (pbo) insulin treated + CVD



Heart Failure:	13.5 *vs* 10.5%
Edema:	30.8 *vs* 18.2%
Weight:	+4.2 *vs* +0.1 kg
Fractures:	5.1 vs 2.5%





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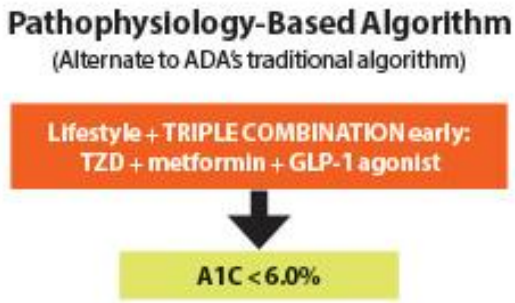
perspective

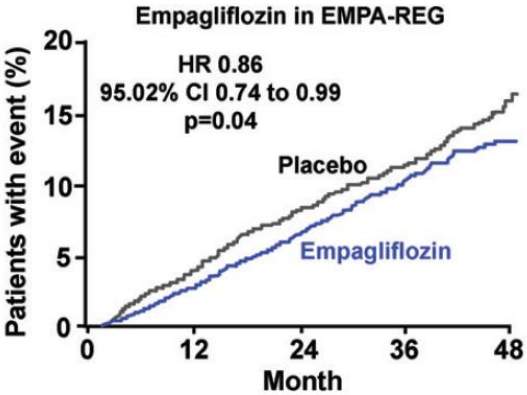
Diabetes, Obesity and Metabolism 18: 454–462, 2016.

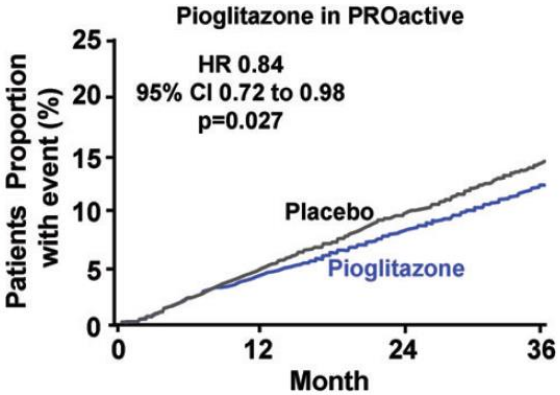
Revitalization of pioglitazone: the optimum agent to be combined with a sodium-glucose co-transporter-2 inhibitor

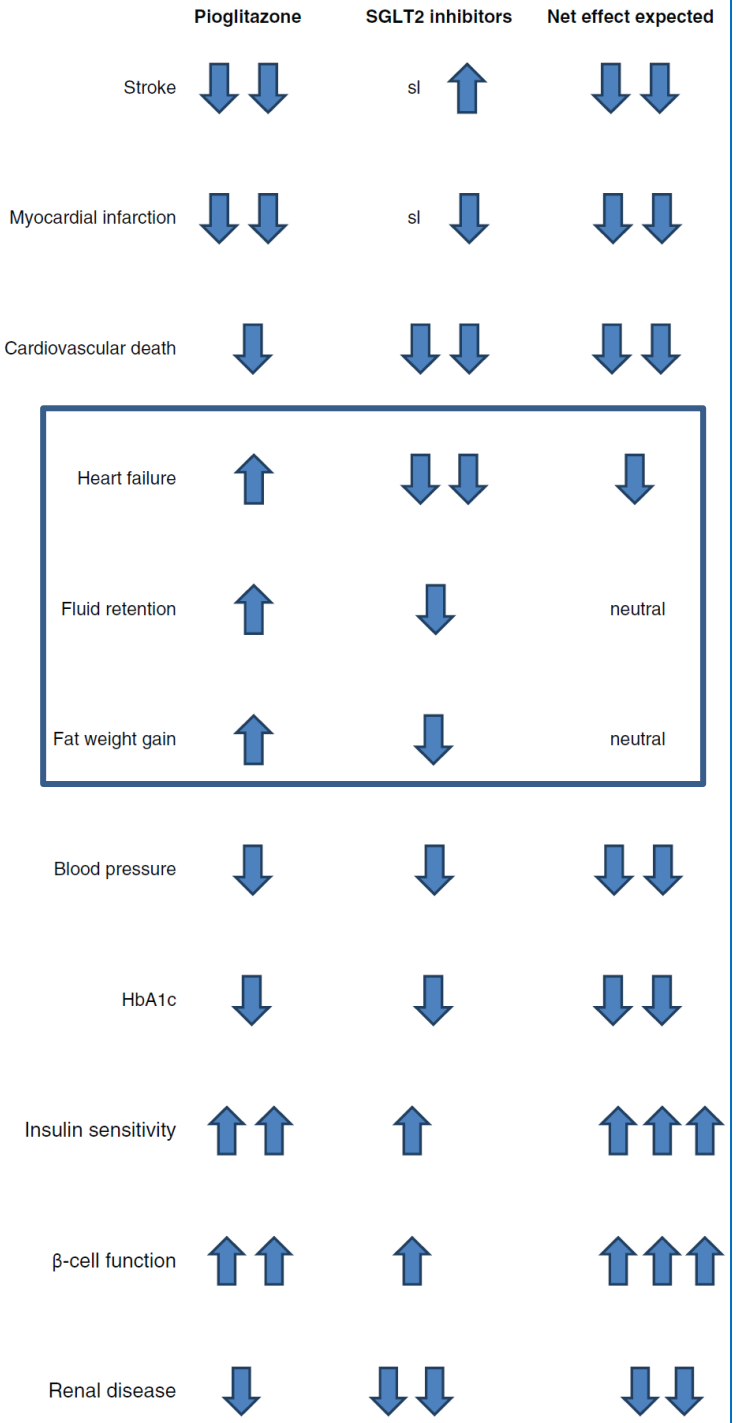
R. A. DeFronzo[1], R. Chilton[2], L. Norton[1], G. Clarke[3], R. E. J. Ryder[4] & M. Abdul-Ghani[1]



TZD, thiazolidinediones GLP-1 agonist, glucagon-like peptide 1 agonist







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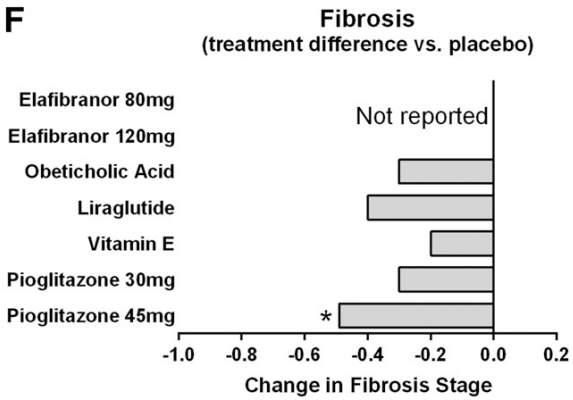
Management of Nonalcoholic Fatty Liver Disease in Patients With Type 2 Diabetes: A Call to Action

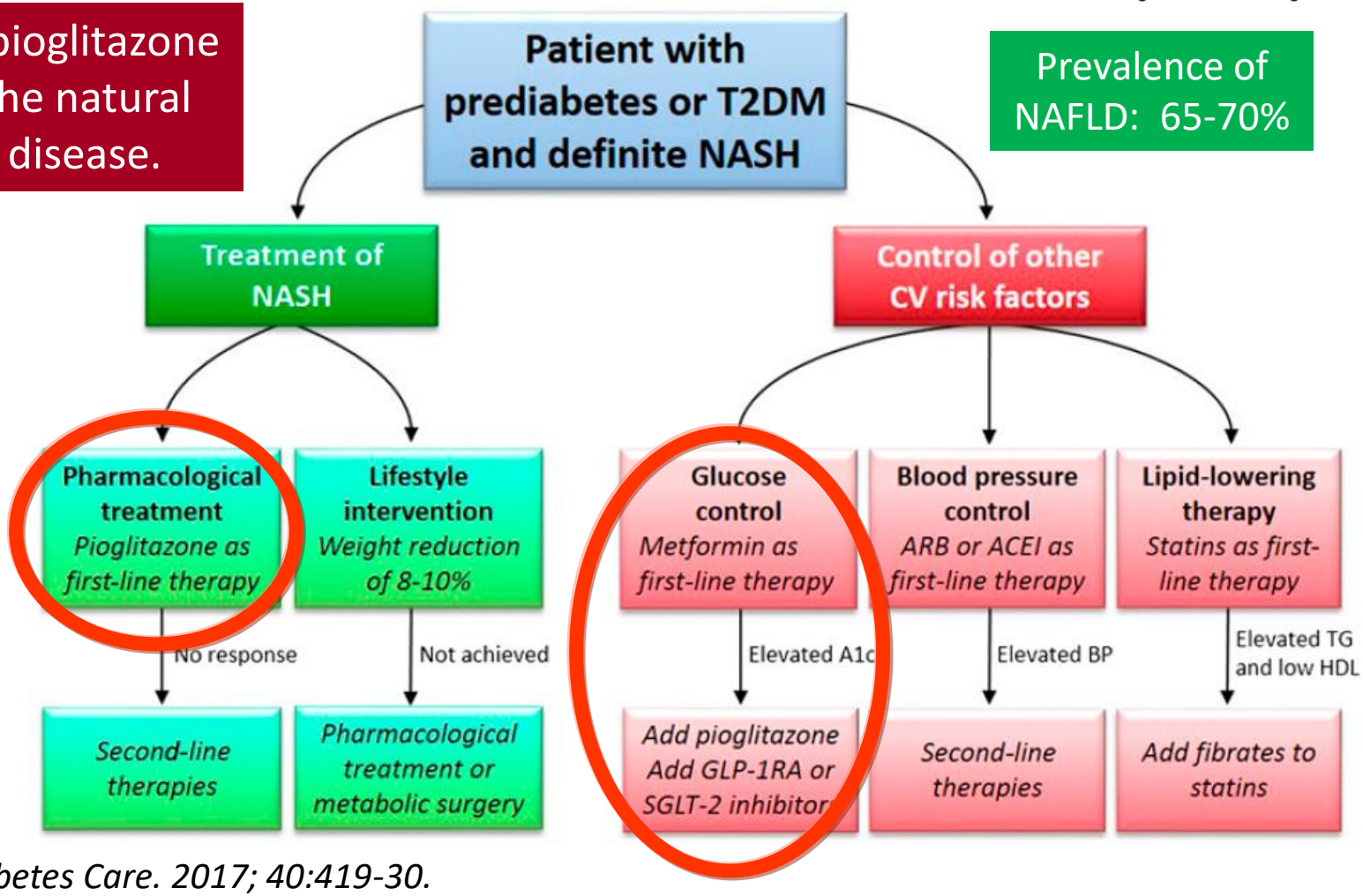
Fernando Bril[1] and Kenneth Cusi[1,2]

Diabetes Care 2017;40:419–430 | DOI: 10.2337/dc16-1787



In summary, pioglitazone may change the natural history of the disease.

Prevalence of NAFLD: 65-70%



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