DIABETES
NOVEDADES 2014/15

Ángel Sánchez Rodríguez

Medicina Interna

USAL.

Salamanca

VNiVERSiDAD D SALAMANCA

SECUENCIA

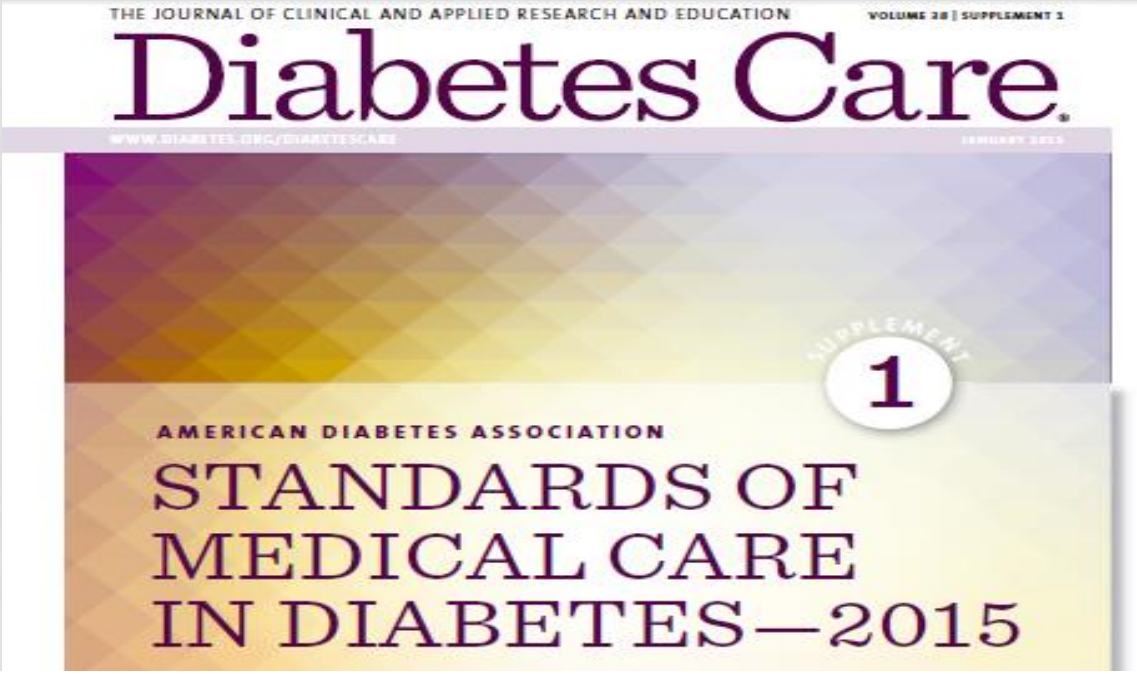
- Nuevas Guías/Consensos
- Novedades en opciones terapéuticas:
  - ✓Agonistas GLP1-1. (+Asociaciones)
  - ✓SGLT-2/SGLT-1
  - ✓IDPP-4
  - ✓Nuevas insulinas. – Nuevas coformulaciones
- Temas puntuales: Diabetes y FRCV.
- Nuevas hipótesis fisiopatológicas. Nuevas dianas

Management of Hyperglycemia in Type 2 Diabetes, 2015: A Patient-Centered Approach

Update to a Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes

Silvio E. Inzucchi,[1] Richard M. Bergenstal,[2] John B. Buse,[3] Michaela Diamant,[4] Ele Ferrannini,[5] Michael Nauck,[6] Anne L. Peters,[7] Apostolos Tsapas,[8] Richard Wender,[9,10] and David R. Matthews[11,12,13]

Diabetes Care 2015;38:140–149 | DOI: 10.2337/dc14-2441



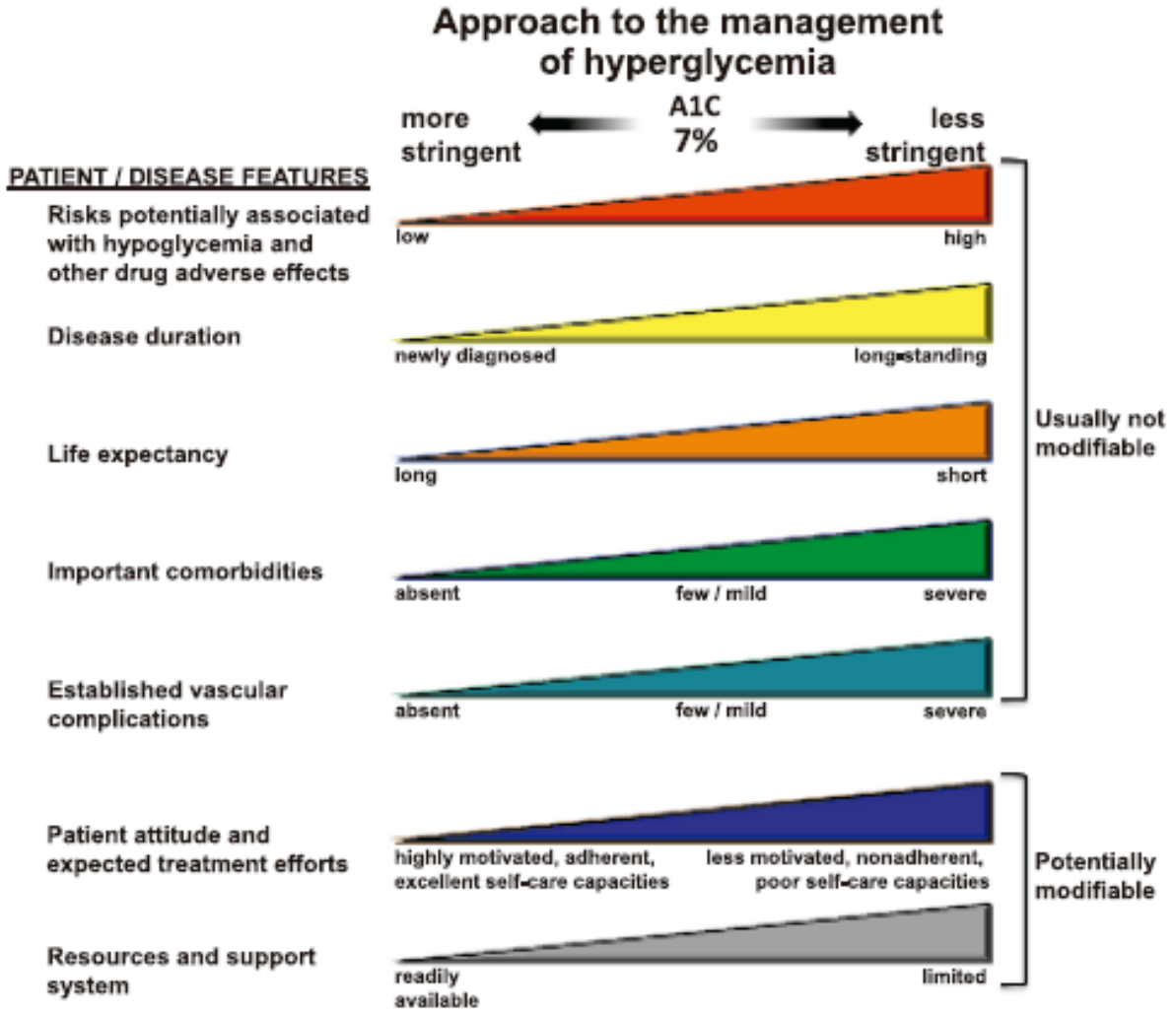
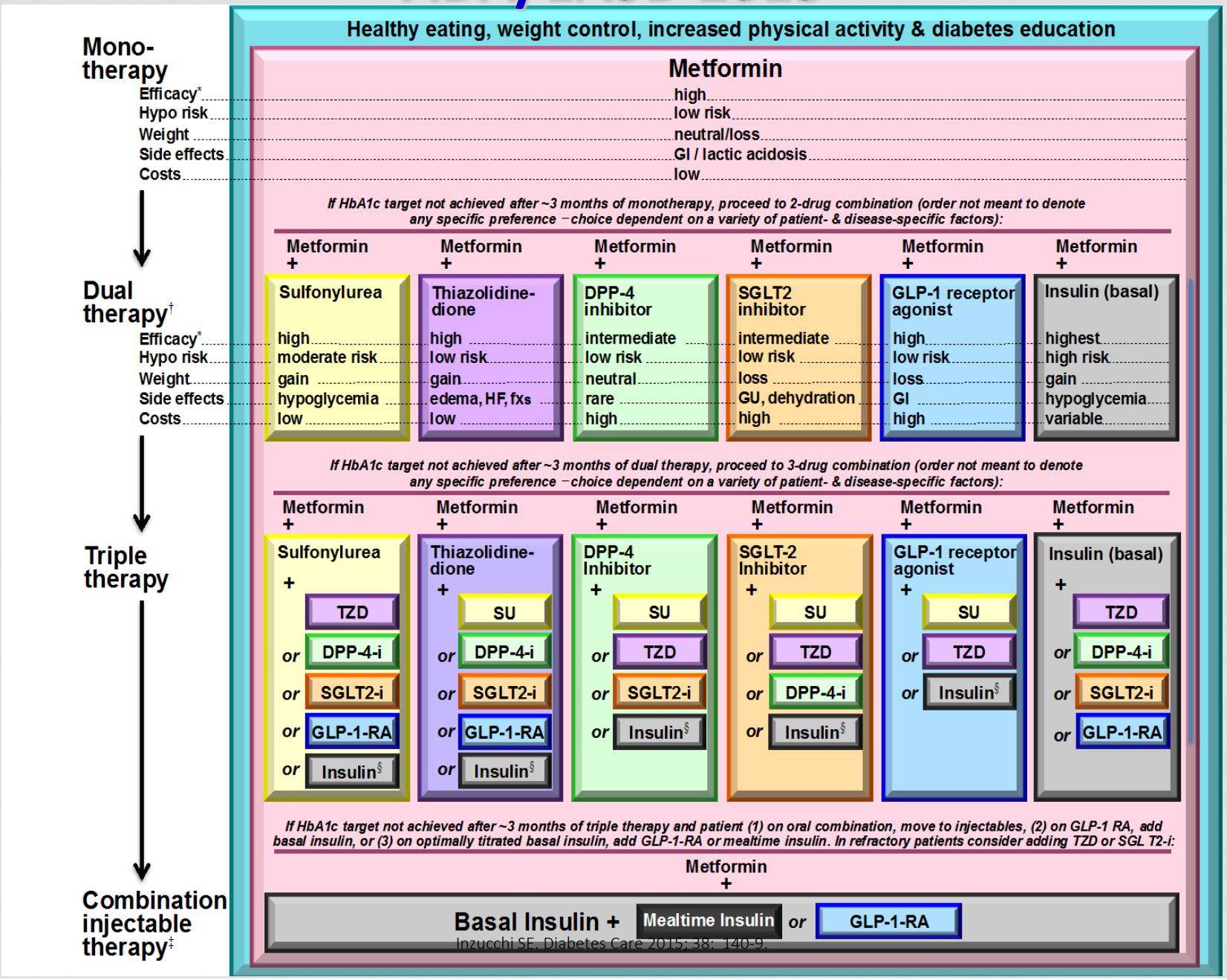


Figure 6.1—Depicted are patient and disease factors used to determine optimal A1C targets. Characteristics and predicaments toward the left justify more stringent efforts to lower A1C; those toward the right suggest less stringent efforts. Adapted with permission from Inzucchi et al. (45).

ADA/EASD 2015



Inzucchi SE. Diabetes Care 2015; 38: 140-9.

American Association of Clinical Endocrinologists and American College of Endocrinology Clinical Practice Guidelines for Developing a Diabetes Mellitus Comprehensive Care Plan

Writing Committee Cochairpersons

Yehuda Handelsman MD, FACP, FACE, FNLA

Zachary T. Bloomgarden, MD, MACE

George Grunberger, MD, FACP, FACE

Guillermo Umpierrez, MD, FACP, FACE

Robert S. Zimmerman, MD, FACE

ENDOCRINE PRACTICE Vol 21 No. 4 April 2015

GLYCEMIC CONTROL ALGORITHM

LIFESTYLE MODIFICATION
(Including Medically Assisted Weight Loss)

Entry A1c < 7.5%

MONOTHERAPY*

- ✓ Metformin
- ✓ GLP-1 RA
- ✓ SGLT-2i
- ✓ DPP-4i
- ✓ AGi
- ⚠ TZD
- ⚠ SU/GLN

If not at goal in 3 months proceed to Double Therapy

Entry A1c ≥ 7.5%

DUAL THERAPY*

MET or other 1st-line agent +

- ✓ GLP-1 RA
- ✓ SGLT-2i
- ✓ DPP-4i
- ⚠ TZD
- ⚠ Basal Insulin
- ✓ Colesevelam
- ✓ Bromocriptine QR
- ✓ AGi
- ⚠ SU/GLN

If not at goal in 3 months proceed to Triple Therapy

TRIPLE THERAPY*

MET or other 1st-line agent + 2nd-line agent +

- ✓ GLP-1 RA
- ✓ SGLT-2i
- ⚠ TZD
- ⚠ Basal insulin
- ✓ DPP-4i
- ✓ Colesevelam
- ✓ Bromocriptine QR
- ✓ AGi
- ⚠ SU/GLN

If not at goal in 3 months proceed to or intensify insulin therapy

Entry A1c > 9.0%

SYMPTOMS

NO	YES
DUAL Therapy OR TRIPLE Therapy	INSULIN ± Other Agents

ADD OR INTENSIFY INSULIN
Refer to Insulin Algorithm

LEGEND
- ✓ Few adverse events or possible benefits
- ⚠ Use with caution

* Order of medications listed represents a suggested hierarchy of usage

PROGRESSION OF DISEASE

Type 2 diabetes in adults: management of type 2 diabetes in adults

NICE guideline

Draft for consultation, January 2015

CONSENSOS

✓ Nuevas Guías Americanas ACE sobre diabetes y obesidad (Prof. Yohuda Handelsman)

✓Consenso Español de Diabetes y Obesidad (Dr. R. Gómez Huelgas y cols).

✓ Consenso sobre la detección y el manejo de la prediabetes. (SED) (Dr. Mata-Cases y cols).

✓Diabetes in older people: new insights and remaining challenges (Sinclair A. Lancet Diabetes Endocrinol. 2015: 3; 275-285)

ESTUDIO COMPARATIVO

- *Mejoría control glucémico prolongado*
- *GPP/GPA*
- *Fluctuaciones limitadas de glucemia*
- *Hipoglucemias*
- *Control de peso*
- *Control del riesgo cv*
- *Efectividad y tolerabilidad*
- *Seguimiento a largo plazo*

GLP-1R
SGLT-2
IDPP-4

- HbA1c
- Hipoglucemias
- Peso
- Lípidos
- PA
- Ef. beneficiosos RCV
- Tolerab. CV

New development in diabetes management.
Clin Ther 2014; 36: 477-84

Emerging New Therapies for the Treatment of Type 2 Diabetes Mellitus: Glucagon-like Peptide-1 Receptor Agonists

Christopher A. Lindamood; and James R. Taylor, PharmD, CDE

University of Florida, College of Pharmacy, Gainesville, Florida

Clin Ther 2015; 37: 483-93

REVIEWS

GLP-1 receptor agonists for individualized treatment of type 2 diabetes mellitus

Juris J. Meier

Nat Rev Endocrinol 2014; 8(12):728-42

Efficacy and tolerability of glucagon-like peptide-1 receptor agonists in patients with type 2 diabetes mellitus

Kira B. Harris and Delilah J. McCarty

Ther Adv Endocrinol Metab 2015; 6(1): 3-18

COMPARATIVOS DIRECTOS DE AGLP1. CAMBIOS EN HBA1C

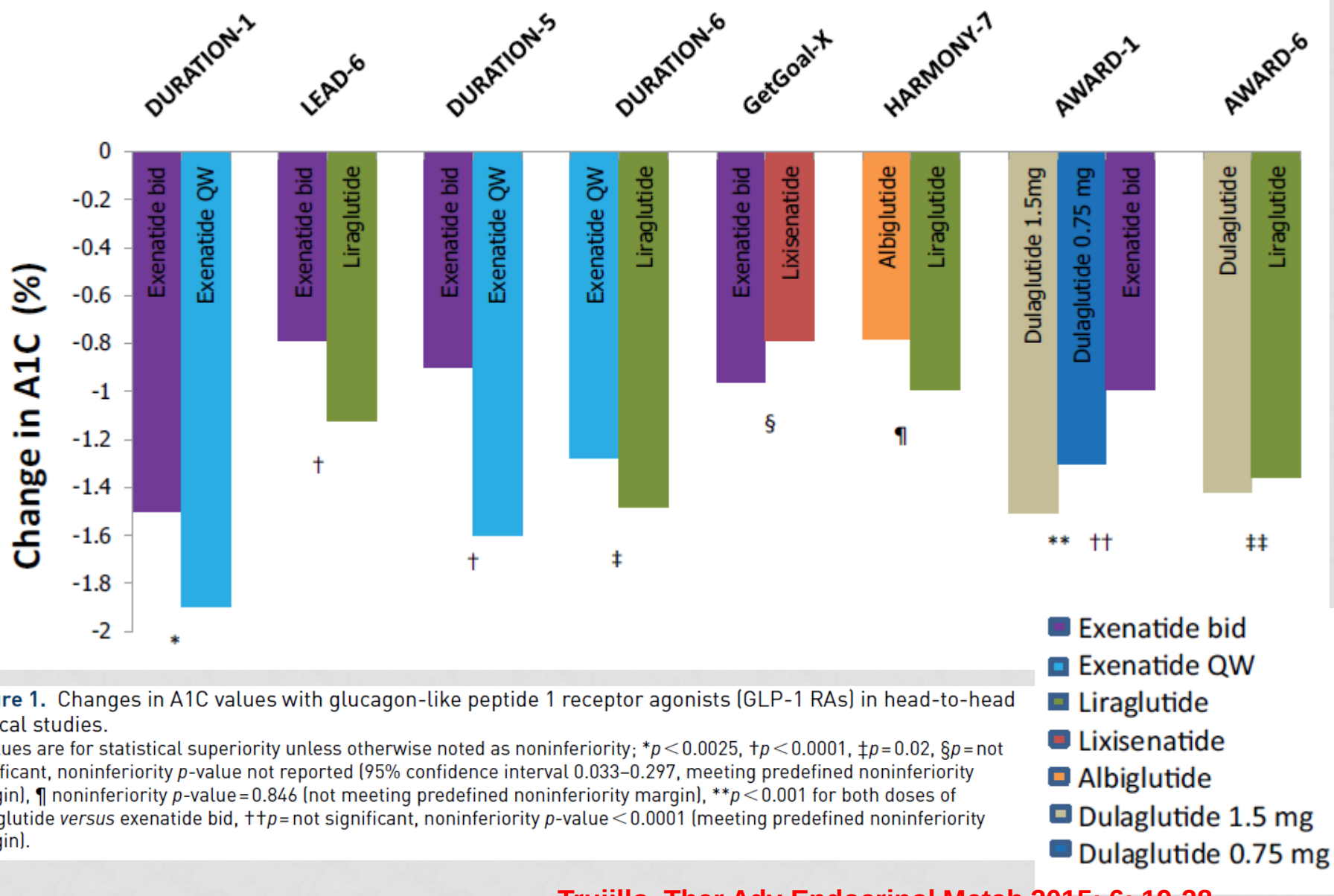


Figure 1. Changes in A1C values with glucagon-like peptide 1 receptor agonists (GLP-1 RAs) in head-to-head clinical studies.

p-values are for statistical superiority unless otherwise noted as noninferiority; *$p < 0.0025$, †$p < 0.0001$, ‡$p = 0.02$, §p = not significant, noninferiority p-value not reported (95% confidence interval 0.033–0.297, meeting predefined noninferiority margin), ¶ noninferiority p-value = 0.846 (not meeting predefined noninferiority margin), **$p < 0.001$ for both doses of dulaglutide *versus* exenatide bid, ††p = not significant, noninferiority p-value < 0.0001 (meeting predefined noninferiority margin).

Trujillo. Ther Adv Endocrinol Metab 2015; 6: 19-28.

COMPARATIVOS DIRECTOS DE AGLP1. CAMBIOS EN PESO.

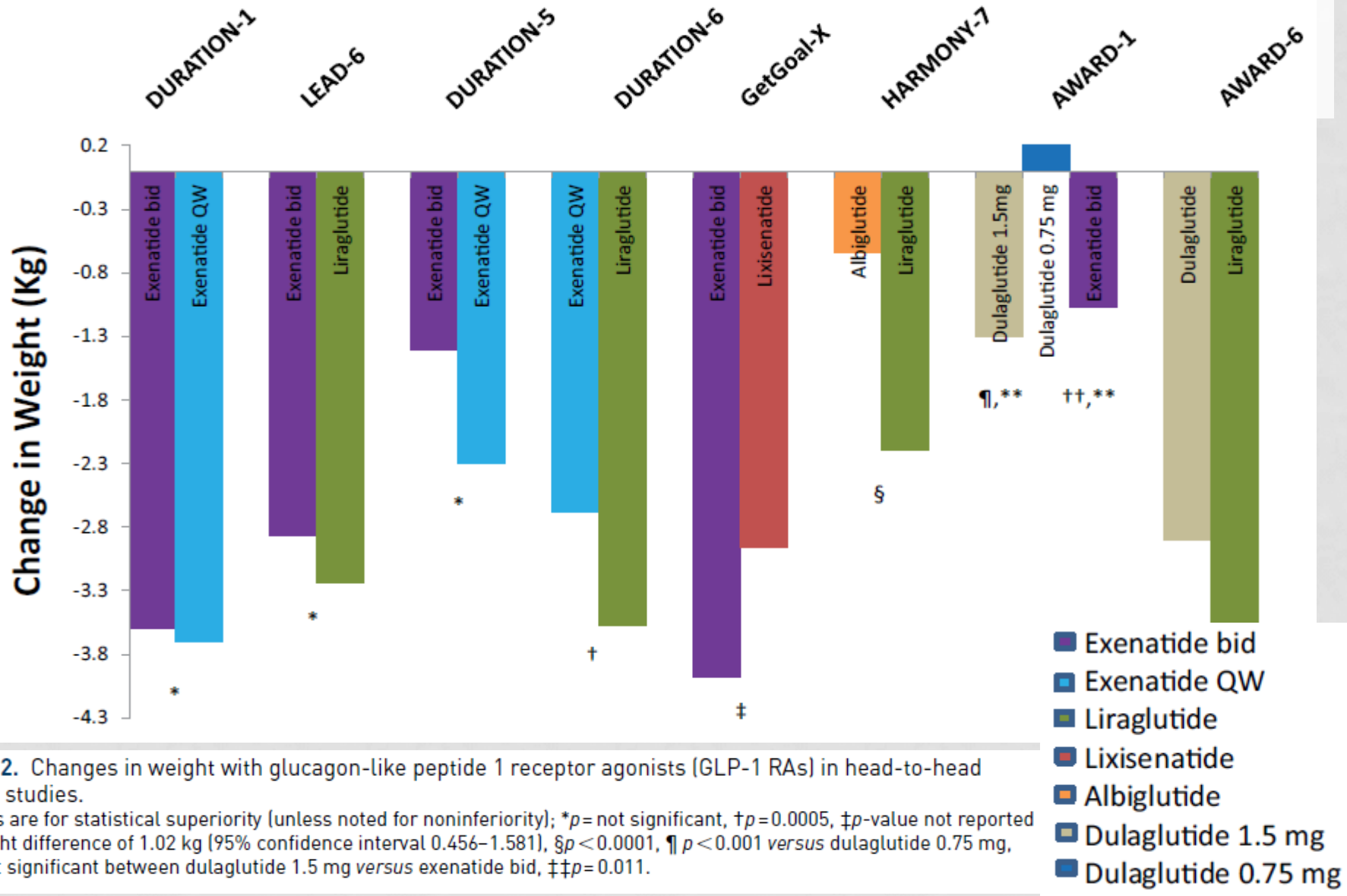


Figure 2. Changes in weight with glucagon-like peptide 1 receptor agonists (GLP-1 RAs) in head-to-head clinical studies.

p-values are for statistical superiority (unless noted for noninferiority); **p* = not significant, †*p* = 0.0005, ‡*p*-value not reported for weight difference of 1.02 kg (95% confidence interval 0.456–1.581), §$p < 0.0001$, ¶ $p < 0.001$ *versus* dulaglutide 0.75 mg, ***p* = not significant between dulaglutide 1.5 mg *versus* exenatide bid, ‡‡*p* = 0.011.

Trujillo. Ther Adv Endocrinol Metab 2015; 6: 19-28.

Circulation Research

JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association.

Cardiovascular Actions of Incretin-Based Therapies

John R. Ussher and Daniel J. Drucker

Circ Res. 2014;114:1788-1803
doi: 10.1161/CIRCRESAHA.114.301958
Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

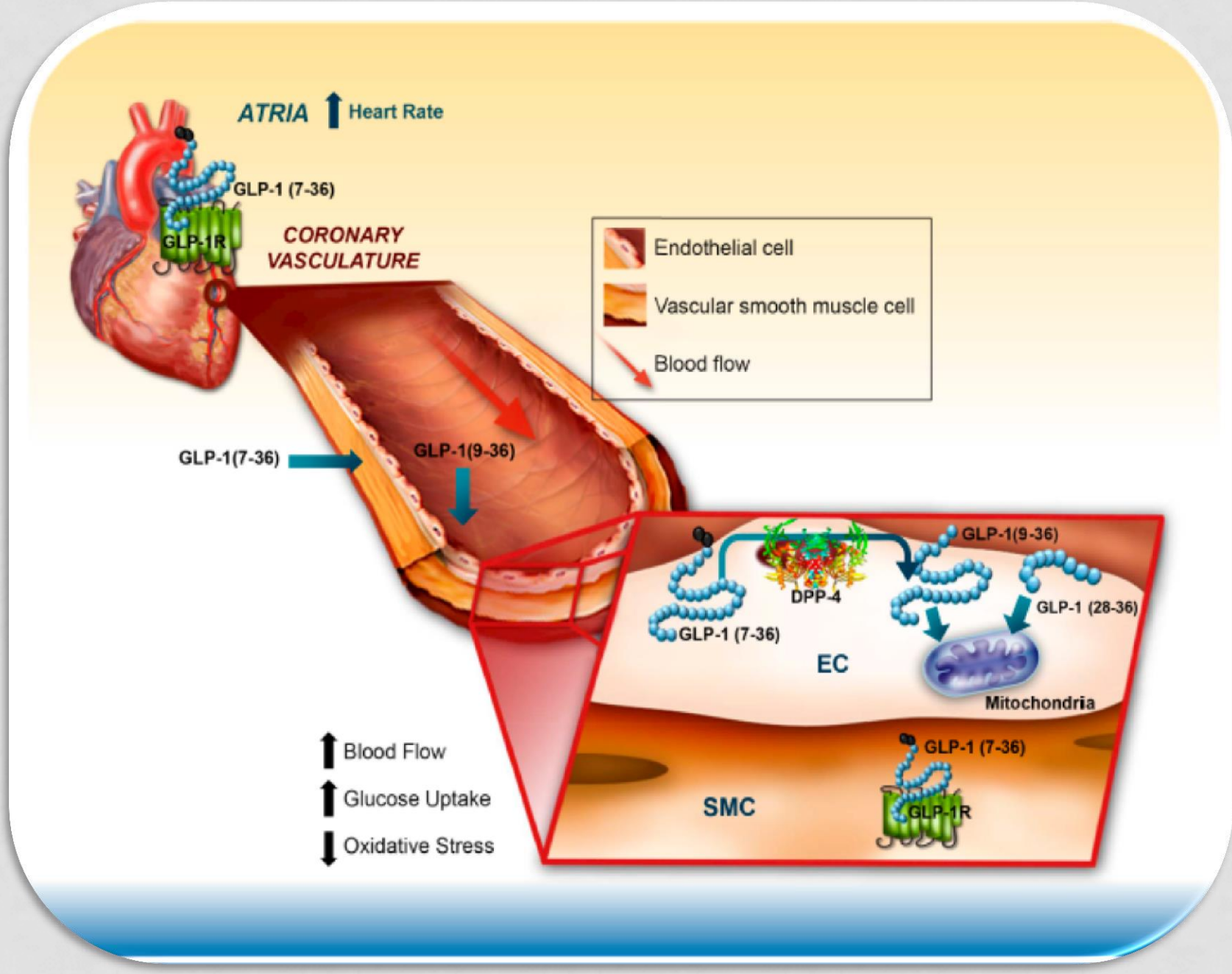
Print ISSN: 0009-7330. Online ISSN: 1524-4571

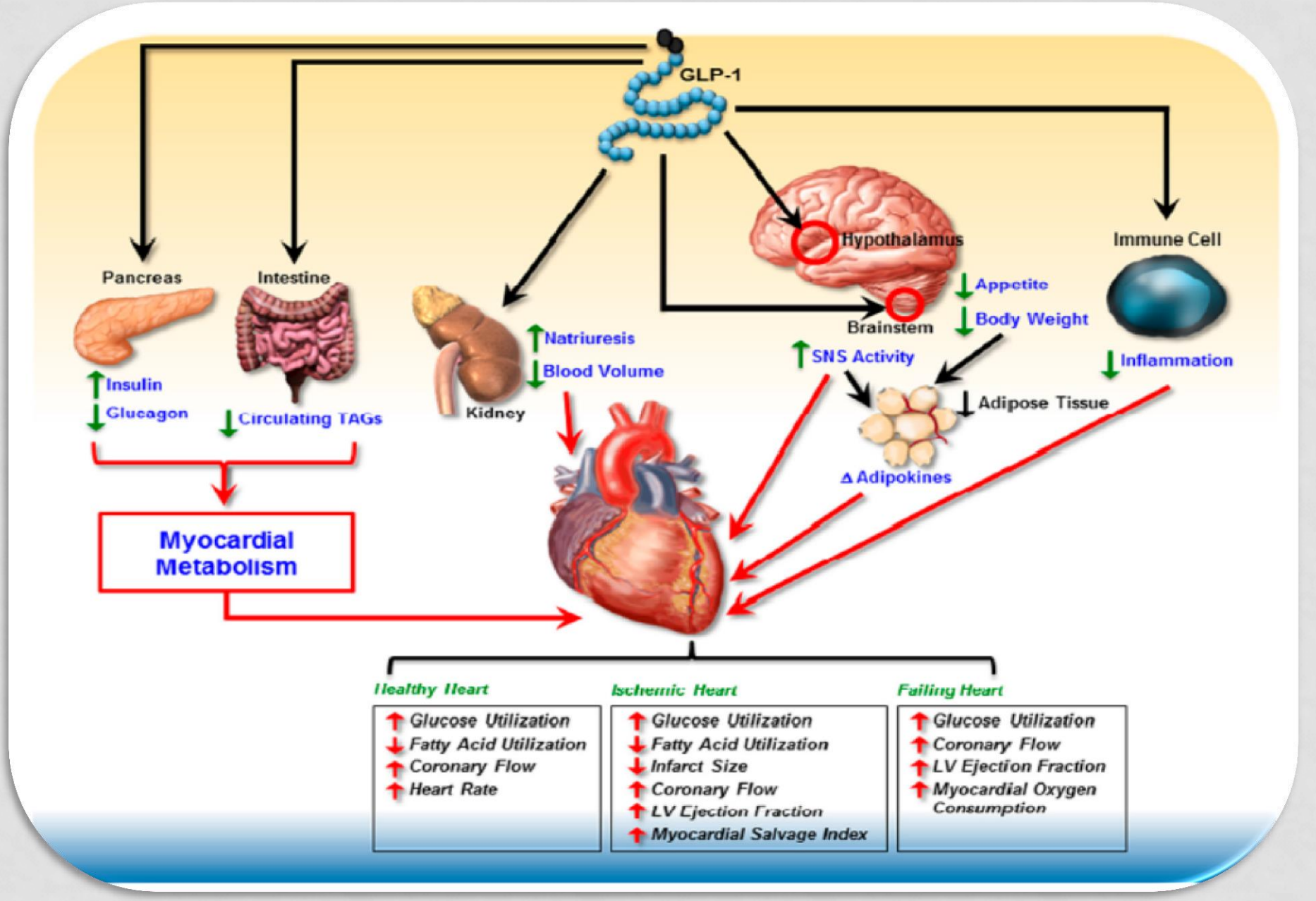
Clinical Therapeutics/Volume ▮, Number ▮, 2015

Cardiometabolic Effects of a New Class of Antidiabetic Agents

Cyrus V. Desouza, MBBS[1,2]; Namita Gupta, MBBS[2]; and Anery Patel, MBBS[2]

[1]Omaha Veterans Affairs Medical Center, Omaha, Nebraska; and [2]Department of Internal Medicine, Division of Diabetes, Endocrine, and Metabolism, University of Nebraska Medical Center, Omaha, Nebraska


ATRIA
Heart Rate
GLP-1 (7-36)
GLP-1R
CORONARY VASCULATURE
Endothelial cell
Vascular smooth muscle cell
Blood flow
GLP-1(7-36)
GLP-1(9-36)
GLP-1(9-36)
DPP-4
GLP-1 (28-36)
GLP-1 (7-36)
EC
Mitochondria
GLP-1 (7-36)
SMC
GLP-1R
Blood Flow
Glucose Uptake
Oxidative Stress


GLP-1
Pancreas
Intestine
Kidney
Hypothalamus
Brainstem
Immune Cell
Insulin
Glucagon
Circulating TAGs
Natriuresis
Blood Volume
Appetite
Body Weight
SNS Activity
Inflammation
Adipose Tissue
Δ Adipokines
Myocardial Metabolism
Healthy Heart
Glucose Utilization
Fatty Acid Utilization
Coronary Flow
Heart Rate
Ischemic Heart
Glucose Utilization
Fatty Acid Utilization
Infarct Size
Coronary Flow
LV Ejection Fraction
Myocardial Salvage Index
Failing Heart
Glucose Utilization
Coronary Flow
LV Ejection Fraction
Myocardial Oxygen Consumption

THE CARDIOVASCULAR SAFETY OF GLP-1 RECEPTOR AGONIST

RANDOMISED CLINICAL TRIALS INVESTIGATING LONG-TERM CARDIOVASCULAR OUTCOMES

Table 1 Randomised clinical trials investigating long-term cardiovascular outcomes with incretin-based therapies in people with T2D

Title	Trial acronym	Intervention	Enrolment	Study duration	Primary outcome measure	Date initiated (month/year)	Primary completion date (month/year)
GLP-1 receptor agonists							
A Randomized Double Blind, Placebo-controlled Clinical Trial to Assess the Effects of Taspoglutide (RO5073031) on Cardiovascular Outcomes in Subjects with Inadequately Controlled Type 2 Diabetes and Established Cardiovascular Disease/NCT01018173	T-EMERGE-8	Taspoglutide 20 mg once weekly	2118	Event-driven timeframe, ≤2 years anticipated	Time to a CV composite endpoint (CV death, acute MI, stroke or hospitalisation for unstable angina)	01/2010	Trial suspended 09/2010 due to high discontinuation rates (gastrointestinal intolerability and serious hypersensitivity reactions)
Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results - A Long Term Evaluation/NCT01179048	LEADER	Liraglutide 1.8 mg OD	9340	≤60 months	Time from randomisation to first occurrence of CV death, non-fatal MI or non-fatal stroke	08/2010	01/2016
Exenatide Study of Cardiovascular Event Lowering Trial: A Trial To Evaluate Cardiovascular Outcomes After Treatment With Exenatide Once Weekly In Patients With Type 2 Diabetes Mellitus/NCT01144338	EXSCEL	Exenatide 2 mg once weekly	9500	5.5 years	Time to first confirmed CV event in a composite CV endpoint	06/2010	03/2017
Evaluation of Cardiovascular Outcomes in Patients With Type 2 Diabetes After Acute Coronary Syndrome During Treatment With AVE0010 (Lixisenatide)/NCT01147250	ELIXA	Lixisenatide 20 µg OD	6000	203 weeks	Time to first confirmed CV event	06/2010	09/2014
Researching Cardiovascular Events With a Weekly Incretin in Diabetes/NCT01394952	REWIND	Dulaglutide 1.5 mg once weekly	9622	≤6.5 years	Time from randomisation to first occurrence of CV death, non-fatal MI or non-fatal stroke	07/2011	04/2019
Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects With Type 2 Diabetes/ NCT01720446	SUSTAIN 6	Semaglutide 0.5 mg or 1.0 mg once weekly	3260	≤148 weeks	Time from randomisation to first occurrence of CV death, non-fatal MI or non-fatal stroke	02/2013	01/2016

COMBINACIONES INSULINA/GLP-1

- **COMBINACIONES FIJAS**

✓Liraglutide+Degludec (IDEGLIRA)
✓Lixisenatide+ I. Glargina (LIXILAN)

1-year efficacy and safety of IdegLira in a 26-week extension study (Gough et al)

IdegLira *post hoc* analysis of DUAL I extension and DUAL II (King *et al.)*

1-YEAR EFFICACY AND SAFETY OF IDEGLIRA IN A 26-WEEK EXTENSION *STUDY (Gouth et al)*

Key results: IDegLira vs. IDeg or Lira alone.

	IDegLira vs. IDeg Estimate [95% CI]	*p*-value	IDegLira vs. Lira Estimate [95% CI]	*p*-value
HBA_{1c} change* (%-points)	–0.46 [–0.57; –0.34]	<0.0001	–0.65 [–0.76; –0.53]	<0.0001
FPG change* (mmol/L)	0.20 [–0.45; 0.05]	NS	–1.67 [–1.92; –1.42]	<0.0001
Weight change* (kg)	–2.80 [–3.34; –2.27]	<0.0001	2.66 [2.13; 3.20]	<0.0001
Hypoglycaemia†	0.63 [0.50; 0.79]	<0.0001	8.52 [6.09; 11.93]	<0.0001
Daily insulin dose‡ (units [U])	–23.4 [–26.4; –20.3]	<0.0001	NA	NA

The improved glycaemic control and more favourable safety profile seen for IdegLira in the extension trial supports the sustainability of IdegLira over at least 1 year of use.

DRUGS IN CONTEXT

FULL TEXT ARTICLE

ISSN 1740-4398

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REVIEW

Sodium-glucose co-transporter 2 (SGLT2) inhibitors: a growing class of antidiabetic agents

Eva M Vivian, PharmD, MS, BC-ADM, CDE

School of Pharmacy, University of Wisconsin, Madison, WI, USA

Drugs in Context 2014; 3: 212264.

SGLT-2 / SGLT-1 INHIBIDORES

COMPUESTO

- ✓ Dapaglifocina
- ✓ Canaglifocina
- ✓ Empaglifocina
- ✓ Topoglifocina
- ✓ Sotaglifocina (Inhibidor dual)

M. CELULARES

- ✓ Inhibidores SGLT-2 en tub. renal proximal

ACCIÓN FISIOL.

- Reab. glucosa
- -> Secrec. gLucosa
- glucosuria

VENTAJAS

- ✓ No hipogluc.
- ✓ Disminución peso
- ✓ Disminución PA
- ✓ Todos estados

INCONVENIENTES

- ✓ I. genitales/urinarias
- ✓ Poliuria
- ✓ Depleción de volumen
- ✓ Hipotensión
- ✓ Aumento LDL
- ✓ Aumento creatinina

Drugs in Context 2014; 3: 212264.

I-DPP-4

COMPUESTO	M. CELULARES	ACCIÓN FISIOL.	VENTAJAS	E. COLATER-
✓ Sitagliptina ✓ Vildagliptina ✓ Saxagliptina ✓ Linagliptina ✓ **Alogliptina**	✓ Inh. DPP-4 ✓ > Incretinas activas pp	> Secrec. Insulina (glucosa-depen) < Secrec. Glucosa (glucosa- depen)	✓ No hipogluc. ✓ Peso neutro ✓ Buena tolerancia	✓ P. Aguda ✓ Hospitalización IC ✓ Angio edema ✓ Urticaria ✓ Precio Alto

Nauck, NA. Efficacy and security of Alogliptine. Intern. J. Clin. Pract. 2014

✓ E. TECOS (Seguridad y RCV sitagliptina)
✓The Guard Study.Diabetes,Obesity Metabol,2015
✓Incretin-based drugs and the risk of HF.Diabetes Care 2015;38:277-84
✓Meta-análisis (Monami/Ling)

THE AMERICAN JOURNAL of MEDICINE®

New Developments in Insulin Therapy for Type 2 Diabetes

Christopher Sorli, MD, FACE

Department of Diabetes, Endocrinology and Metabolism, Billings Clinic, Billings, Mont.

Am J Med. 2014; 127(10): S39-48

DEGLUDEC

- Insulina basal
- Perfil acción estable y prolongada
- Reducción variabilidad farmacocinética

Estudio Comparativo con I. glargina

- HbA1c: similar
- GPA: > Degludec
- Dosis total insulina : < Degludec
- RR Hipoglucémias → Nocturna no severa
  RR Hipoglucémias → Diurna no severa
- Eventos severos no significativos

Insulina- Degludec versus insulina glargine in type 1 and type 2 diabetes mellitus: a meta-analysis of endpoint.
Diabetes Ther. 2014: 5 (2) 435-446

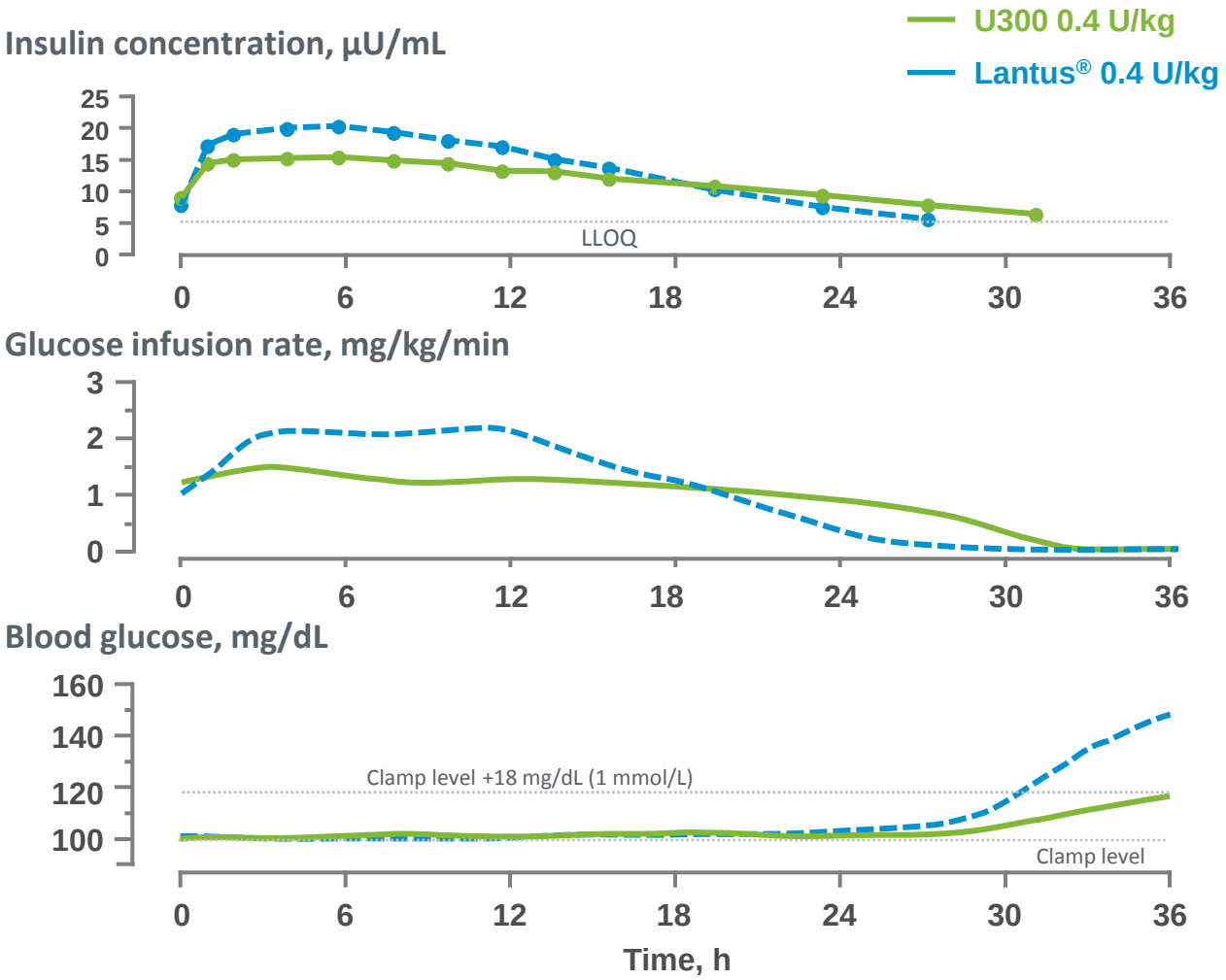
U300

Glargina 300 U/ml

Nuevo análogo de Insulina basal

U300 está en desarrollo clínico y aún no ha sido aprobada por ninguna agencia reguladora.
U300 se ha presentado a la EMA y la FDA para su revisión.

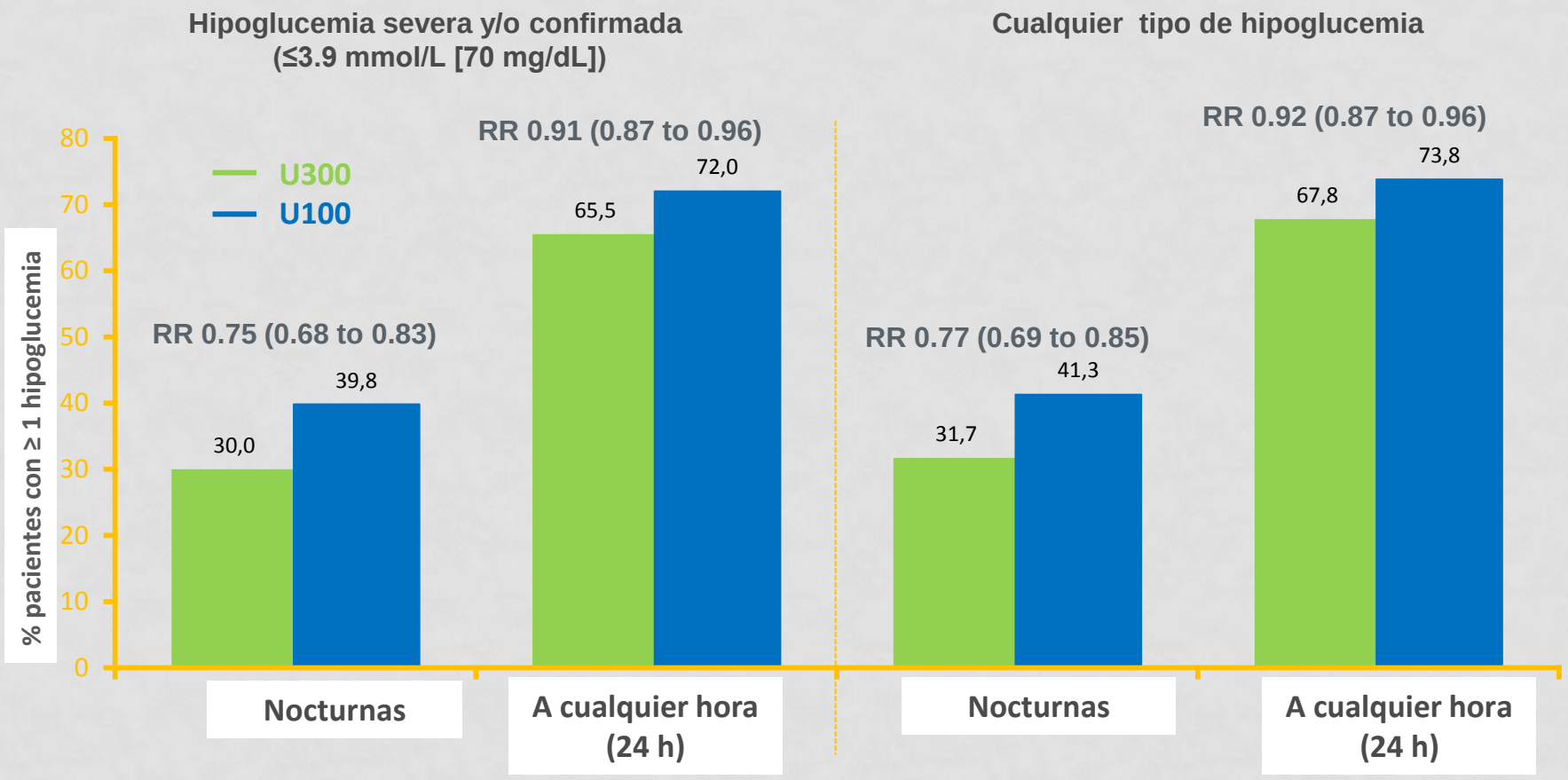
La liberación más controlada y gradual / perfil PK más constante y prolongado y un efecto reductor de la glucosa durante más de 24 horas



Euglycemic clamp study in T1DM in steady state (8 days' treatment)

Becker RHA et al. Diabetes Care. 2014 Aug 22. pii: DC_140006. [Epub ahead of print]

Reducción significativa de hipoglucemias severas y/o confirmadas o de cualquier tipo



Hipoglucemia confirmada <3.0 mmol/L (54 mg/dL), U300 redujo significativamente la proporción de pacientes con eventos confirmados/severos vs U100 a cualquier hora del día y de la noche

Ritzel R et al. New insulin glargine 300 U/mL: Glycemic control and hypoglycemia in a meta-analysis of Phase 3ª EDITION clinical trials in people with T2DM. Poster presentation on EASD 2014. Abstract 963 Available at http://www.easdvirtualmeeting.org/resources/18908 Accessed November 2014

Diferencia pequeña pero significativa en el aumento de peso con U300 vs Lantus

Diferencia media MC entre grupos (6º mes)
-0,28 (IC 95% -0,55 a -0,01) kg
P=0,039

W: semanas; M: meses

Ritzel R et al. New insulin glargine 300 U/mL: Glycemic control and hypoglycemia in a meta-analysis of Phase 3ª EDITION clinical trials in people with T2DM. Poster presentation on EASD 2014. Abstract 963 Available at http://www.easdvirtualmeeting.org/resources/18908 Accessed November 2014

Clinical Therapeutics/Volume 36, Number 8, 2014

Inhaled Insulin: A Breath of Fresh Air? A Review of Inhaled Insulin

Tricia Santos Cavaiola, MD; and Steven Edelman, MD

University of California, San Diego, San Diego, California

Insulina inhalada (acción rápida) (AFREZZA)

- Estudio comparativo

  3017 diab.

  Insulina basal +A
  Insulina basal + I. Aspart.

  ↓ HbA1c < Ins. Aspart
  ↓ Hipoglucemias

- Exigencias:
  - ✓ Ensayo clínico:
    - ✓ Potenciales tumores
    - ✓ Efecto sobre f. pulmonar
    - ✓ Riesgo cardiovascular
  - ✓ Efectos colaterales:
    - ✓ Broncoespasmo
    - ✓ Irritación faringe
    - ✓ Hipoglucemias

Inhaled insulin: a review of inhaled insulin
Clin Ther 2014; 36 (8) 1275-89

IDEGASP

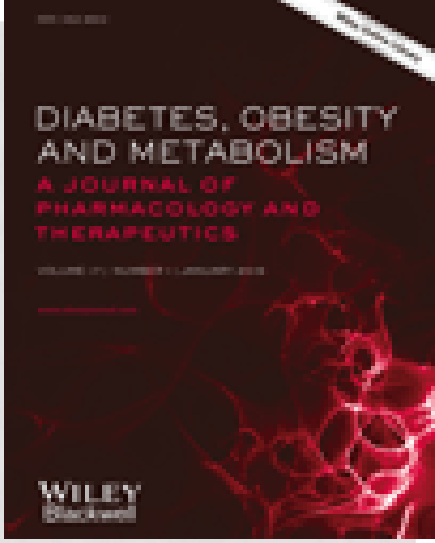
- Insulina Degludec/ Insulina Aspart (IDEGASP)
- Conformación soluble de análogos de insulina de acción larga y de acción corta.
- Objetivo; cobertura insulina basal y prandial.
  - Eficacia
  - Seguridad
  - Tolerabilidad
  - Potencia clínica

Insulin Degludec Aspart: The first Co-formulation of insulin analogues.

Diabetes Ther 2014: 5 ; 65-72

Ensayo clínico

DIABETES, OBESITY AND METABOLISM
A JOURNAL OF PHARMACOLOGY AND THERAPEUTICS



Contrasting weight changes with LY2605541, a novel long-acting insulin, and insulin glargine despite similar improved glycaemic control in T1DM and T2DM†

S. J. Jacober[1], J. Rosenstock[2], R. M. Bergenstal[3], M. J. Prince[1], Y. Qu[1] & J. M. Beals[1]

Diabetes, Obesity and Metabolism 16: 351–356, 2014.

ELSEVIER

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Atherosclerosis Supplements 15 (2014) 1–15

ATHEROSCLEROSIS
SUPPLEMENTS

www.elsevier.com/locate/atherosclerosis

The use of statins in people at risk of developing diabetes mellitus: Evidence and guidance for clinical practice

Naveed A. Sattar [a,*], Henry Ginsberg [b,1], Kausik Ray [c], M. John Chapman [d], Marcello Arca [e], Maurizio Averna [f], D. John Betteridge [g], Deepak Bhatnagar [h], Elena Bilianou [i],

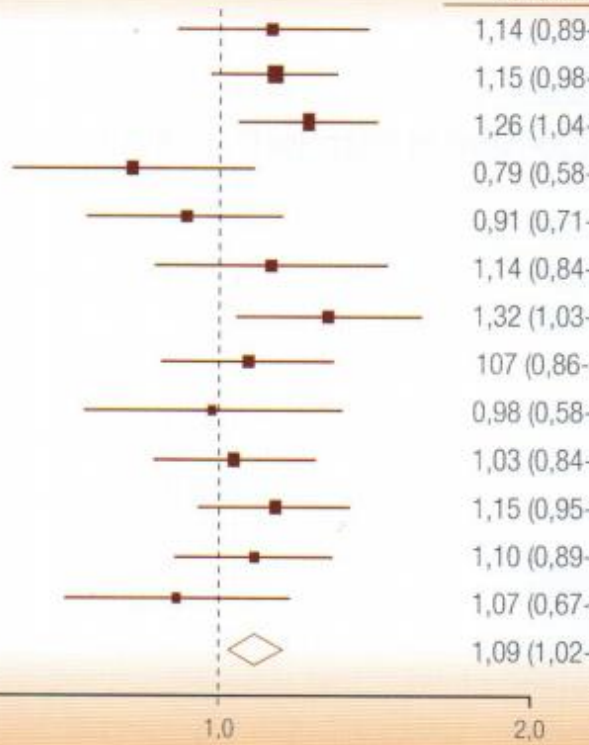
Statins and glycemic control in individuals with diabetes:
A systematic review and meta-analysis

Erqou, S et al.
Diabetologia 2014; 57:2444

Figura 2

El tratamiento con estatinas está asociado con un mayor riesgo de DM2 (metanálisis de Sattar)

	n	Estatina		Placebo o control		OR (95% CI)	Peso (%)
		Eventos	Tasa	Eventos	Tasa		
ASCOT-LLA	7773	154	11,9	134	10,5	1,14 (0,89-1,46)	7,07
HPS	14573	335	9,2	293	8,0	1,15 (0,98-1,35)	13,91
JUPITER	17802	270	16,0	216	12,8	1,26 (1,04-1,51)	11,32
WOSCOPS	5974	75	5,2	93	6,5	0,79 (0,58-1,10)	4,24
LIPID	6997	126	6,0	138	6,5	0,91 (0,71-1,71)	6,53
CORONA	3534	100	20,9	88	18,5	1,14 (0,84-1,55)	4,05
PROSPER	5023	165	20,5	127	15,8	1,32 (1,03-1,69)	6,94
MEGA	6086	172	10,8	164	10,1	107 (0,86-1,35)	8,03
AFCAPS/TEXCAPS	6211	72	4,5	74	4,6	0,98 (0,58-1,38)	3,76
4S	4242	198	17,3	193	16,8	1,03 (0,84-1,28)	8,88
ALL HAT	6087	238	16,4	212	14,4	1,15 (0,95-1,41)	10,23
GISSI HF	3378	225	34,8	215	32,1	1,10 (0,89-1,35)	9,50
GISSI PREV	3460	96	27,5	105	30,6	1,07 (0,67-1,20)	4,94
Global (I^2=11,2% [95% CI 0,0-50,2%])						1,09 (1,02-1,17)	100



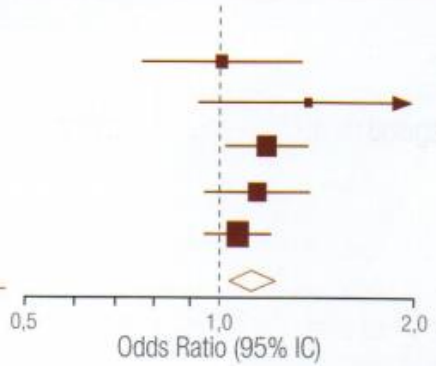
Adaptado de Sattar NA, et al. Atherosclerosis Supplements , 2014; 5 (2014): 1-15.

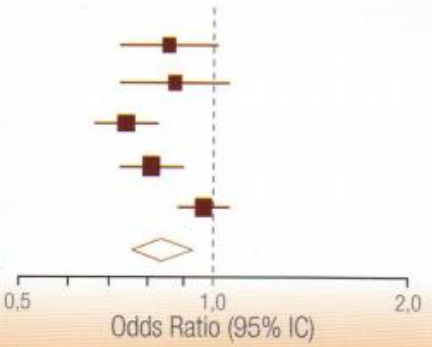
Sattar M. Atherosclerosis, 2014; 5: 1-15

Figura 3

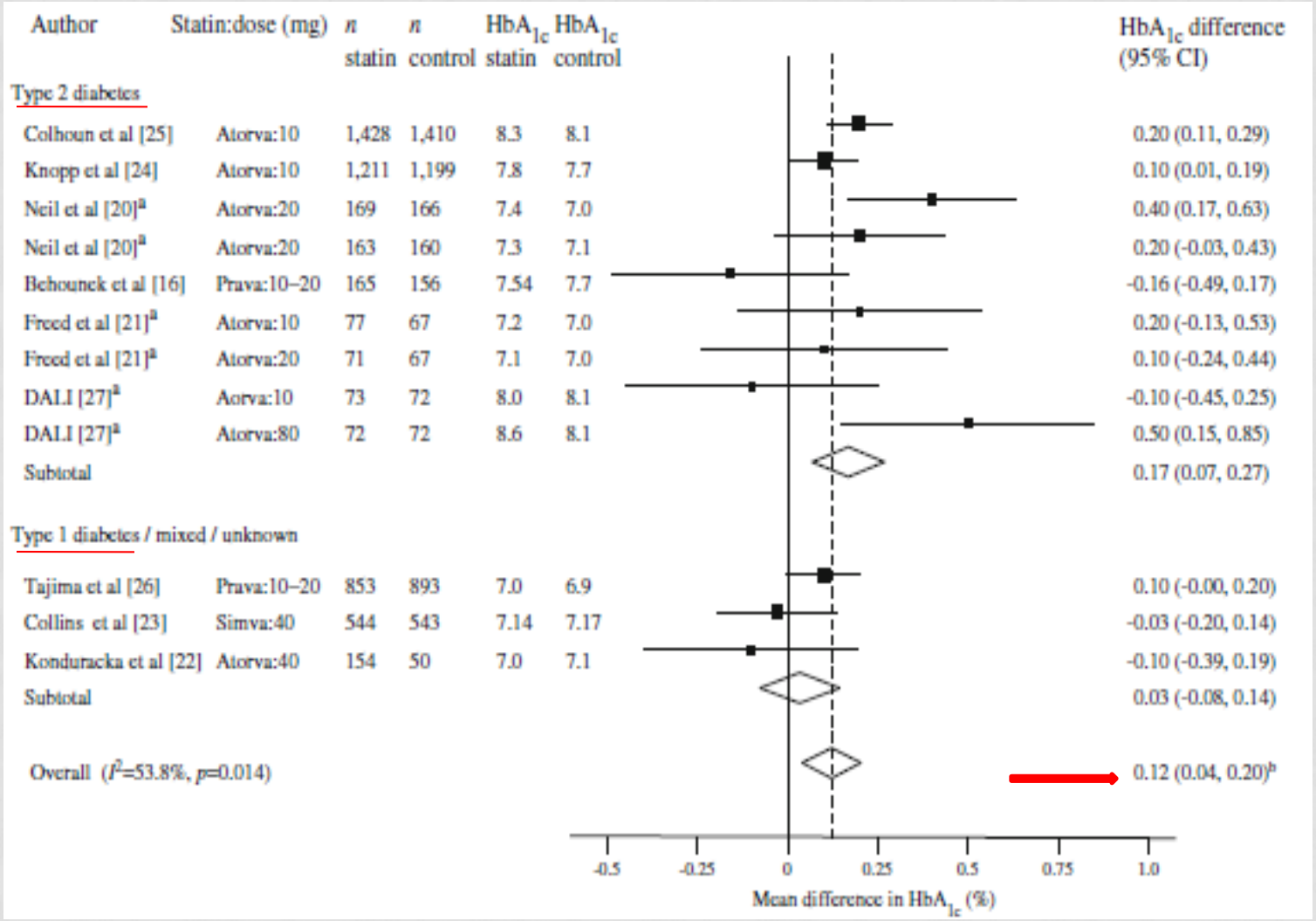
Los efectos diabetogénicos de las estatinas son dosis dependiente (metanálisis de Preiss)

	Casos/Total, Nº (%)		
	Dosis intensa	Dosis moderada	OR (95% IC)
Incidencia de diabetes			
PROVE IT_ TIM 22, 2004	101/1707 (5,9)	99/1688 (5,9)	1,0 1 (0,76-1,34)
A to Z , 2004	65/1768 (3,7)	47/ 1736 92,7)	1,37 (0,94-2,01)
TNT, 2005	418/3798 (3,7)	358/3797 (9,4)	1,19 (1,02-1,38)
IDEAL, 2005	240/3737 (6,4)	209/3724 (5,6)	1,15 (0,95-1,40)
SEARCH, 2010	625/5398 (11,6)	587/5399 (10,9)	1,07 (0,95-1,21)
Odds ratio de datos agrupados	1449/16408 (8,8)	1300/16344 (8,0)	1,12 (1,04-1,22)
Heterogeneidad; I^2 =0%; P=,60			
Incidencia de ECV			
PROVE IT_TIM 22, 2004	315/1707 (18,4)	355/1688 (21,0)	0,85 (0,72-1,01)
A to Z, 2004	212/1768 (12,0)	234/1736 (13,5)	0,87 (0,72-1,07)
TNT, 2005	647/3798 (17,0)	830/3797 (21,9)	0,73 (0,65-0,82)
IDEAL, 2005	776/3737 (20,8)	917/3724 (24,6)	0,80 (0,72-0,89)
SEARCH, 2010	1184/5398 (21,9)	1214/5399 (22,5)	0,97 (0,88-1,06)
Odds ratio de datos agrupados	3134/16408 (19,1)	1214/5399 (22,5)	0,84 (0,75-0,94)
Heterogeneidad; I^2= 74%; P=0,004			

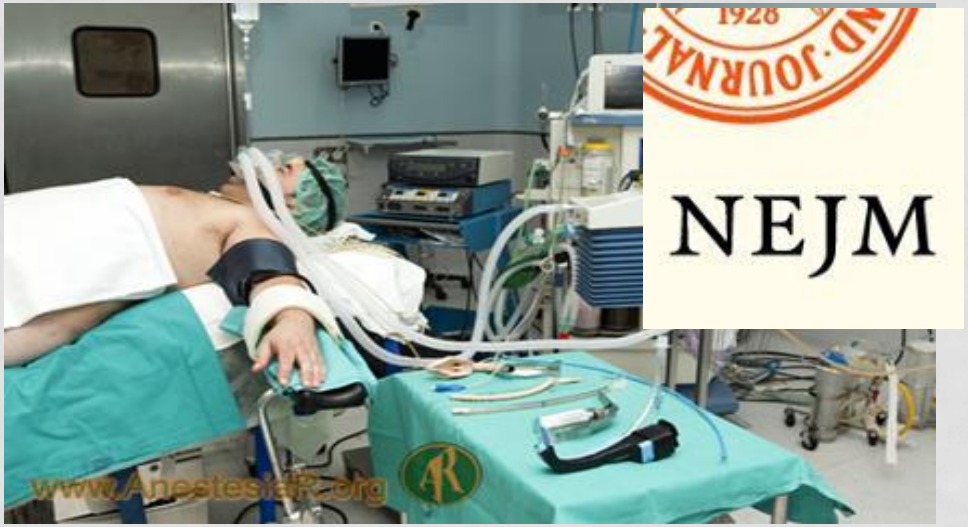




Adaptado de Preiss D, J Am Med Assoc 2011;305:2556-64.



Diferencia media en la HbA1c en los 9 ensayos de diabetes con estatinas.



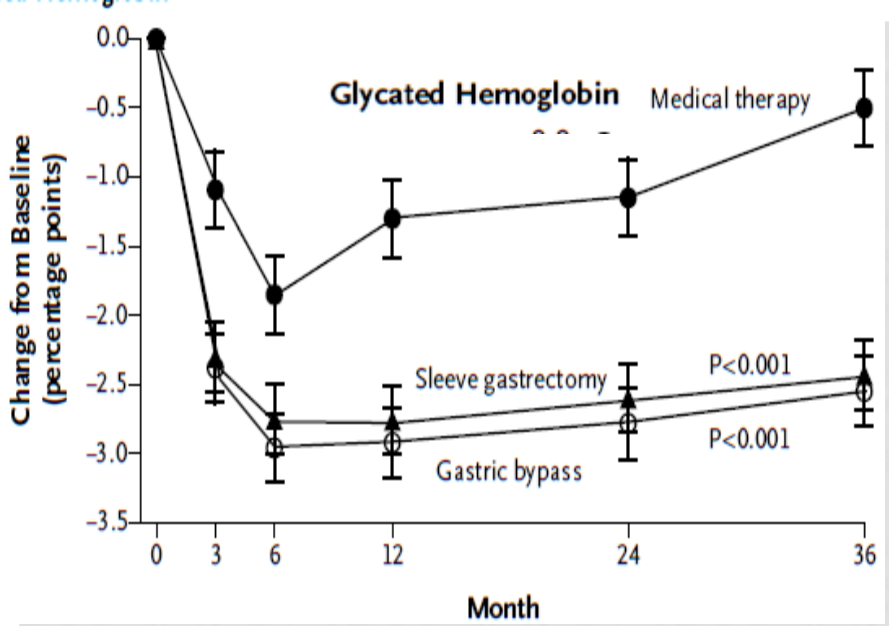
Bariatric Surgery versus Intensive Medical Therapy for Diabetes -3 Year Outcomes

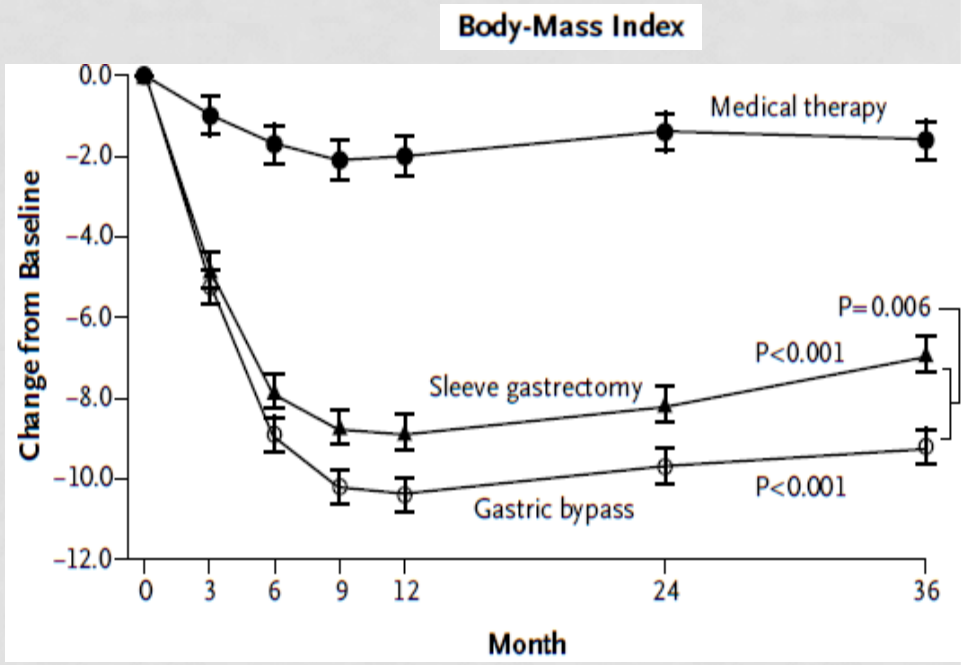
Schauer PR, Bhatt DL, Kirwan JP, Wolski K, Brethauer SA, Navaneethan SD, Aminian A, Pothier CE,Kim ÉSH, Nissen SE, Kashyyap SR For the STAMPEDE Investigators.

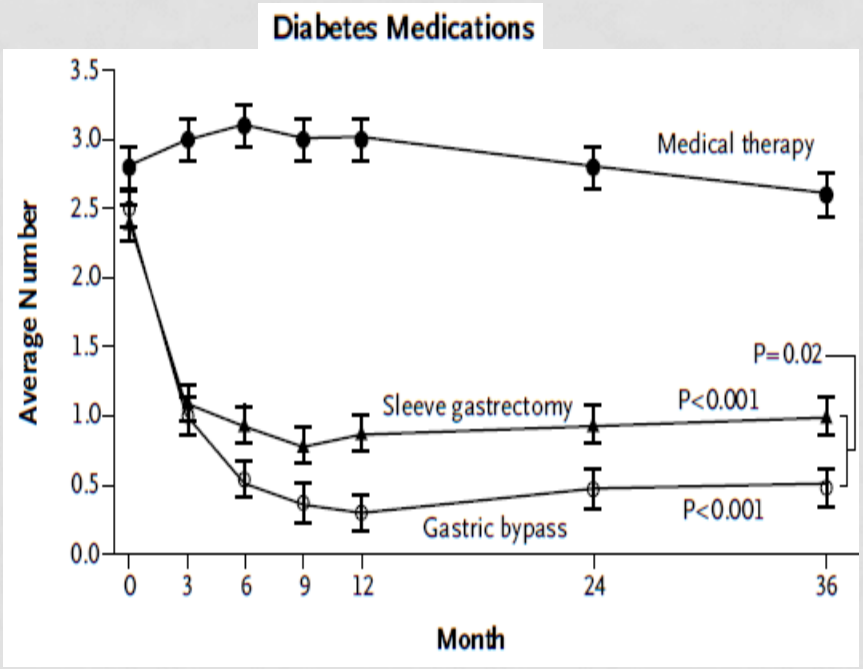
N Engl J Med 2014;370: 2002-13

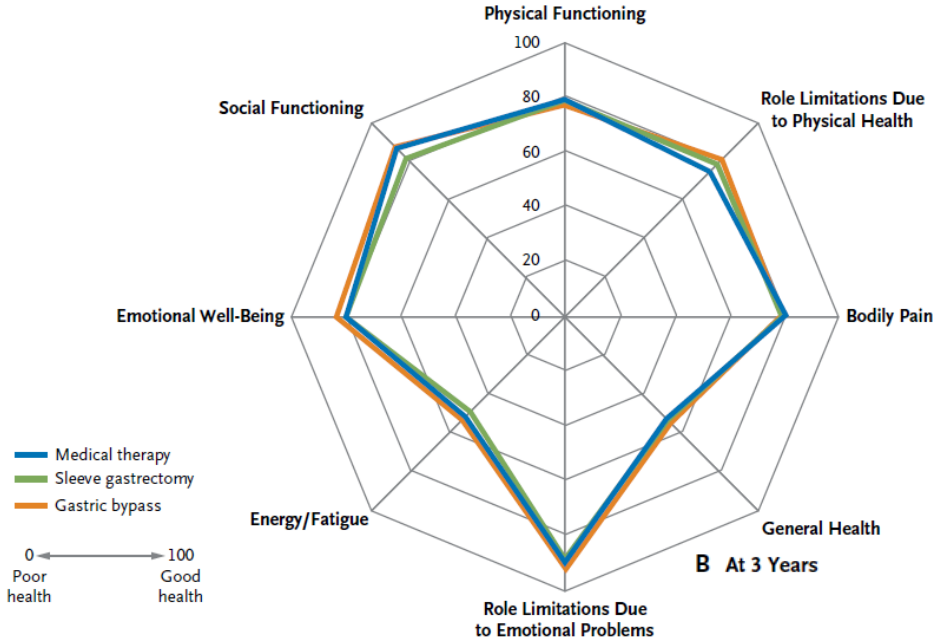
Comparación datos basales y a los 3 años

Objetivo	Tratamiento medico a	Bypass Gástrico b	Gastrectomía sleeve c	Valor p
HbA1c % Basal 3 años	 9.0±1.4 8.4±2.2	 9.2±1.4 6.7±1.3	 9.5±1.7 7.0±1.3	 <0.001 a/b a/c b/c
Peso cambio 3 años kg % cambio de basal	 -4.3±8.3 -4.2±8.3	 -26-2±10.6 -24.5±9.1	 -21.3±9.7 -21.1±8.9	 <0.001 a/b a/c b/c
% cambio de **LDL** **HDL** **TG**	 2.5±29.9 4.6±20.7 -21.5	 16.9±54.5 34.7±27.3 -45.5	 14.5±52.5 35.9±31.0 -31.5	 <0.001 a/b a/c 0.01 a/b a/c


Glycated Hemoglobin
Change from Baseline (percentage points)
0.0
−0.5
−1.0
−1.5
−2.0
−2.5
−3.0
−3.5
Medical therapy
Sleeve gastrectomy
Gastric bypass
P<0.001
P<0.001
0
3
6
12
24
36
Month


Body-Mass Index
Change from Baseline
0.0
−2.0
−4.0
−6.0
−8.0
−10.0
−12.0
Medical therapy
Sleeve gastrectomy
Gastric bypass
P=0.006
P<0.001
P<0.001
0
3
6
9
12
24
36
Month

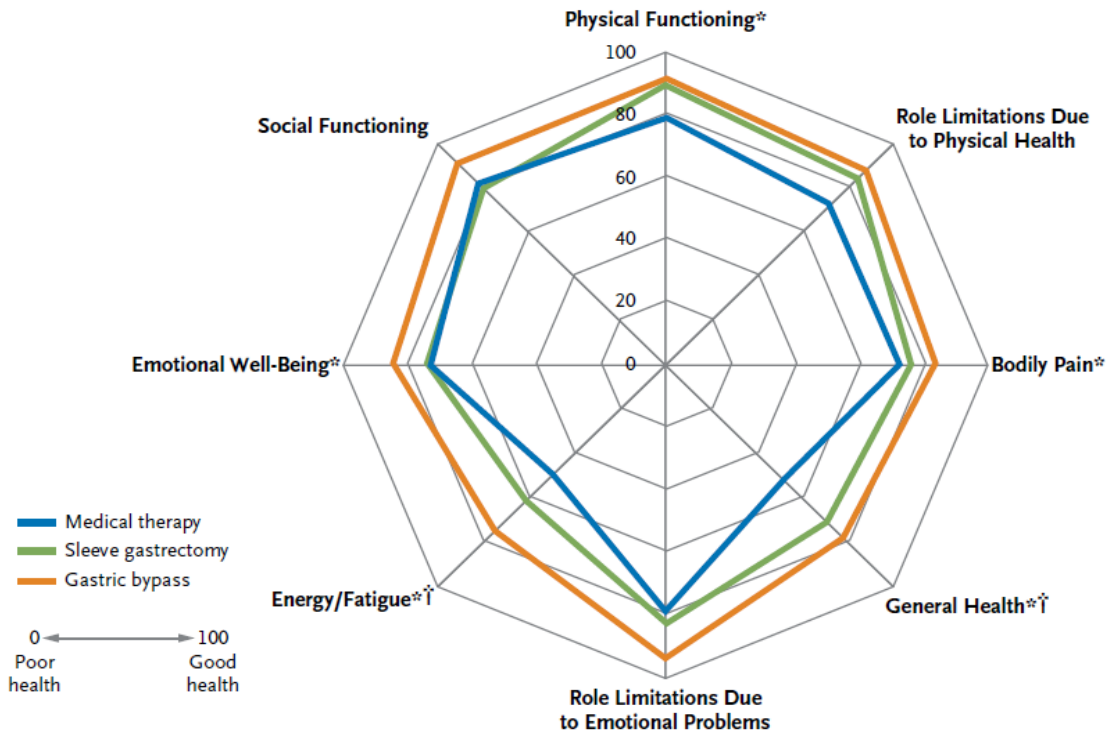

Diabetes Medications
Average Number
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
Medical therapy
Sleeve gastrectomy
Gastric bypass
P=0.02
P<0.001
P<0.001
0
3
6
9
12
24
36
Month



Scores de calidad de vida basal

- Terapia médica
- Gastrectomia sleeve
- Bypass gástrico

Scores de calidad de vida
a los 3 años postrandomización



NEJM

Follow-up of Blood-Pressure Lowering and Glucose Control in Type 2 Diabetes

Zoungas S, Chalmer J, Neal B, Billot L, Li Q, Hirakawwa Y, Arima H, Monaghan H, Joshi R, Colagiuri S, Cooper ME, Glasziou P, Grobbee D,Harnet P, Harrap S, Heller S, Lisheng L, Mancia G, Marre M, Matthews DR, Mogensen CE, Perkovic V, Poulter N, Rodger A, Williams B, MacMahon S, Patel A, and Woodward M for the ADVANCE-ON Collaborative Group

N Engl J MED 2014; 371: 1392-406

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 4, 2013 VOL. 368 NO. 14

Primary Prevention of Cardiovascular Disease with a Mediterranean Diet

Ramón Estruch, M.D., Ph.D., Emilio Ros, M.D., Ph.D., Jordi Salas-Salvadó, M.D., Ph.D., Maria-Isabel Covas, D.Pharm., Ph.D., Dolores Corella, D.Pharm., Ph.D., Fernando Arós, M.D., Ph.D., Enrique Gómez-Gracia, M.D., Ph.D., Valentina Ruiz-Gutiérrez, Ph.D., Miquel Fiol, M.D., Ph.D., José Lapetra, M.D., Ph.D., Rosa Maria Lamuela-Raventos, D.Pharm., Ph.D., Lluís Serra-Majem, M.D., Ph.D., Xavier Pintó, M.D., Ph.D., Josep Basora, M.D., Ph.D., Miguel Angel Muñoz, M.D., Ph.D., José V. Sorlí, M.D., Ph.D., José Alfredo Martínez, D.Pharm, M.D., Ph.D., and Miguel Angel Martínez-González, M.D., Ph.D., for the PREDIMED Study Investigators*

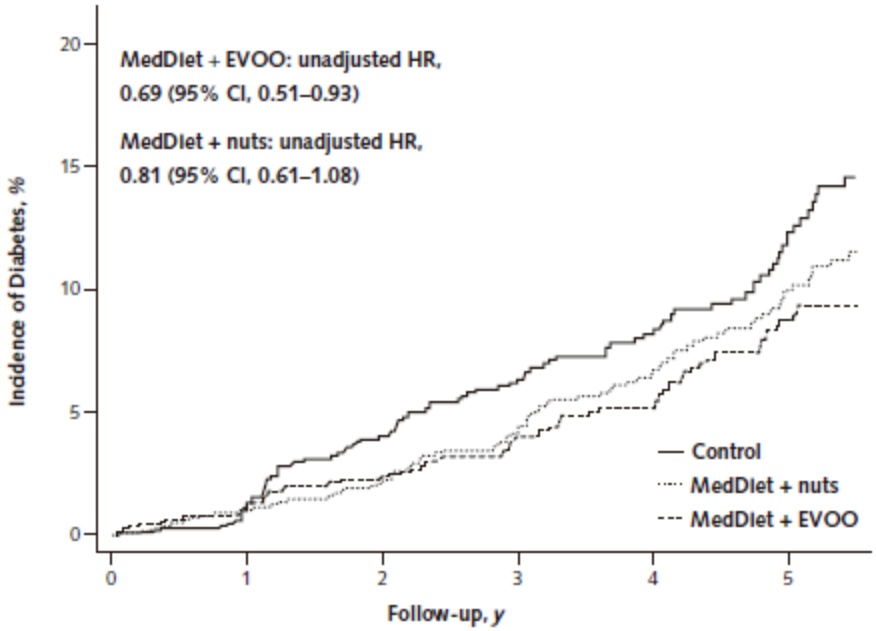
Annals of Internal Medicine | ORIGINAL RESEARCH

Prevention of Diabetes With Mediterranean Diets

A Subgroup Analysis of a Randomized Trial

Jordi Salas-Salvadó, MD, PhD*; Mònica Bulló, PhD; Ramón Estruch, MD, PhD; Emilio Ros, MD, PhD; Maria-Isabel Covas, DPharm; Núria Ibarrola-Jurado, RD, PhD; Dolores Corella, DPharm, PhD; Fernando Arós, MD, PhD; Enrique Gómez-Gracia, MD, PhD; Valentina Ruiz-Gutiérrez, PhD; Dora Romaguera, MD, PhD; José Lapetra, MD, PhD; Rosa Maria Lamuela-Raventós, DPharm, PhD; Lluis Serra-Majem, MD, PhD; Xavier Pintó, MD, PhD; Josep Basora, MD, PhD; Miguel Angel Muñoz, MD, PhD; José V. Sorlí, MD, PhD; and Miguel A. Martínez-González, MD, PhD*

Figure 2. **Cumulative incidence of diabetes (or either diabetes or death).**



Participants at risk, *n*						
MedDiet + EVOO	1154	1110	998	832	681	489
MedDiet + nuts	1240	1173	1000	775	629	427
Control	1147	1053	900	679	521	366

NUEVAS DIANAS

- **Factor de transcripción FOX 01**
- **GPR-119**

Wang, Z. Cell Metabolism 2014; 19: 872-882

Reiter, R. Arch Pharm Res 2014; 37: 671-678

Investigación básica

CellPress

Cell Metabolism
Article

Pancreatic β Cell Dedifferentiation in Diabetes and Redifferentiation following Insulin Therapy

Zhiyu Wang,[1,3] Nathaniel W. York,[3] Colin G. Nichols,[2,3] and Maria S. Remedi[2,3,*]
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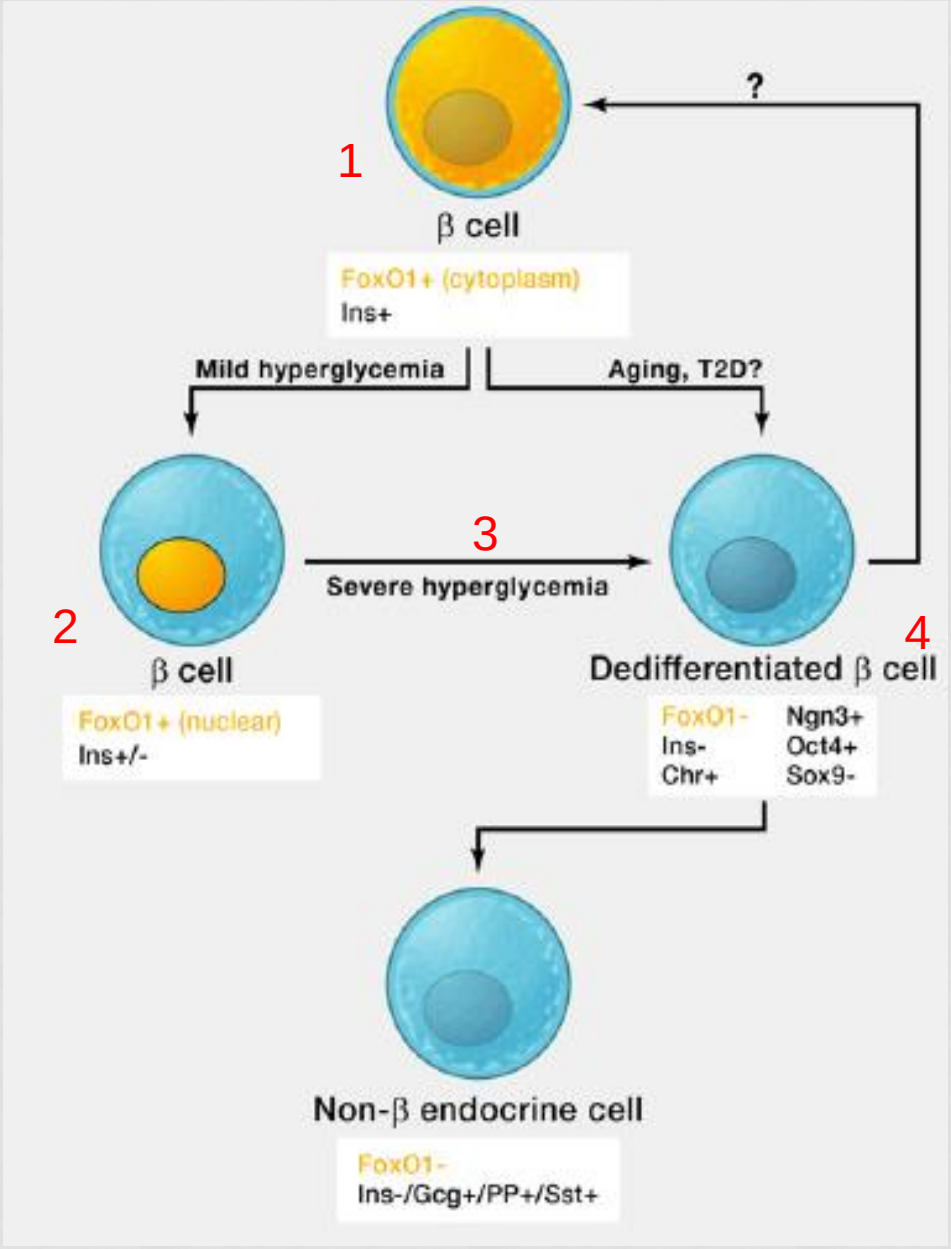
http://dx.doi.org/10.1016/j.cmet.2014.03.010

Cell Metabolism 2014; 19:872-882



1Normoglucemia: FOXO1 se localiza en el citoplasma de las células maduras productoras de insulina+

2 Hiperglucemia ligera: FOXO1 se localiza también en el núcleo

3 Hiperglucemia severa: FOXO1 disminuye significativamente en las células β con disminución prod. Insulina.

4 La edad y la DM2 favorecerían pérdida de FOXO1 y por tanto DEDIFERENCIACION de las Células B (Insulina- y Cromogranina+ llegando a expresar neurogenina 3 (marcador de células progenitoras)

Una reversión de las células desdiferenciadas a células funcionales seria de valor terapéutico.

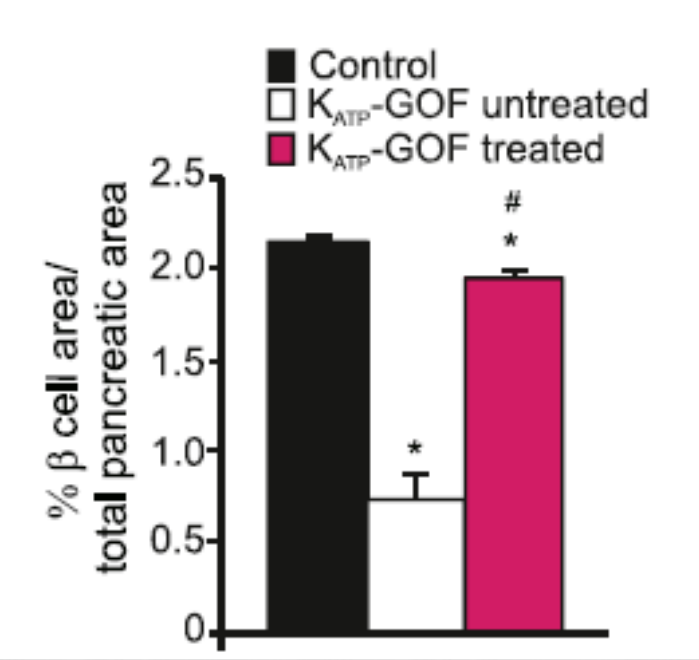
Talchai C et al, Cell 2012

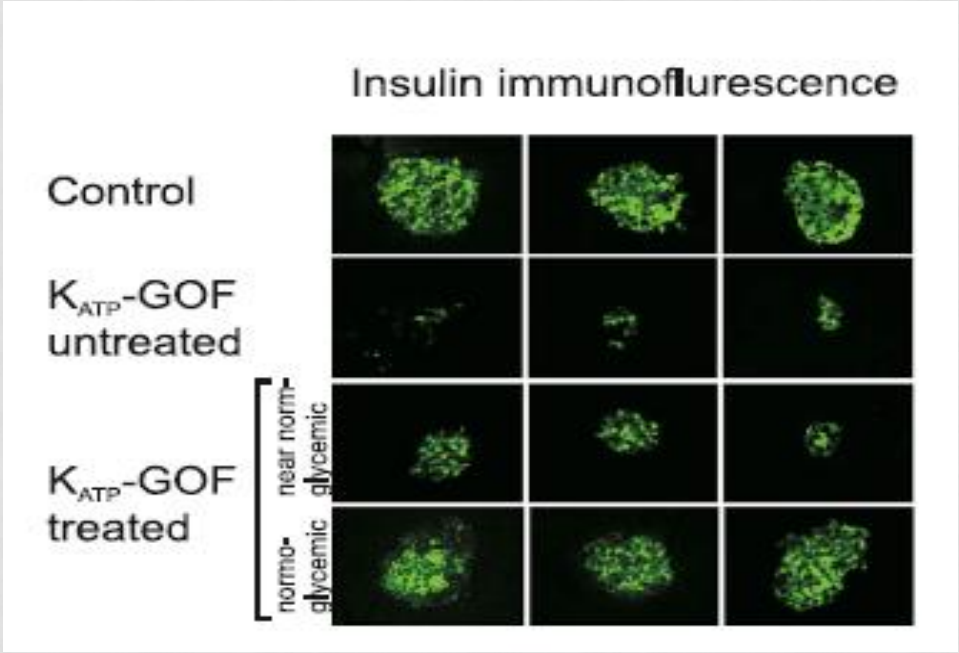
Para evaluar si la pérdida de insulina, por parte de la célula beta, era un proceso reversible si los niveles de glucosa se normalizan, los ratones diabéticos se dividieron en dos grupos:

- No tratados
- Tratados crónicamente con insulina (implantación de pellets de lenta liberación)

D

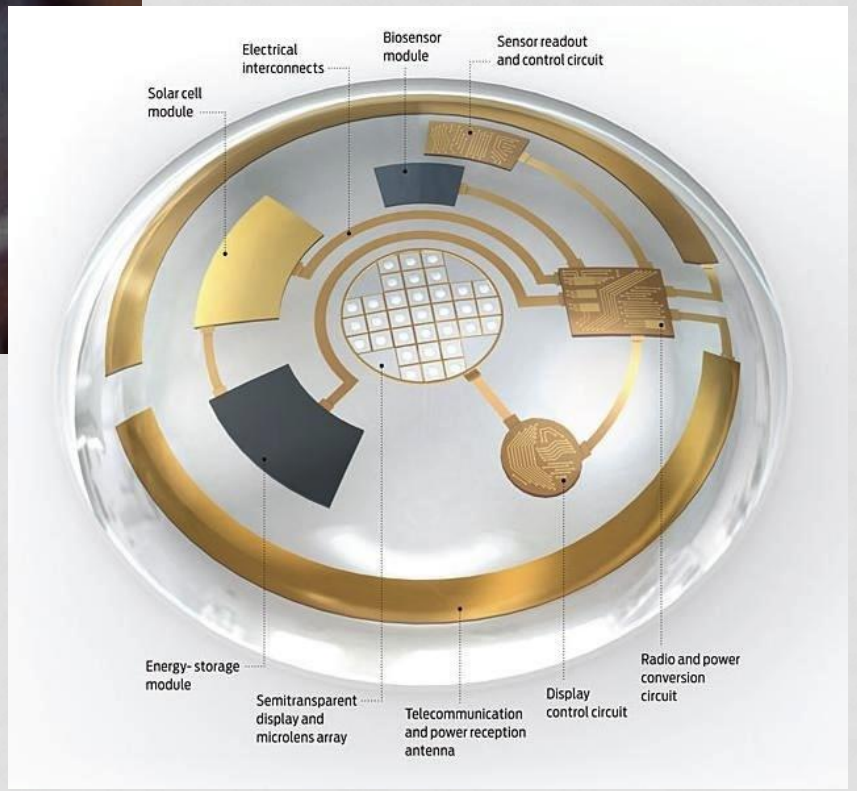
Nº de células beta + y el contenido de insulina de éstas se recuperó





Wang et al. Cell Metabolism 19, 872–882, 2014

NUEVO SISTEMA DE CONTROL



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