Farmacogenètica al servei del tractament personalitzat de la diabetis tipus 2

José Carlos Flórez, MD, PhD

17.3.17

MGH 1811

BROAD INSTITUTE


adidas
SIEMENS


Olé
COMPARTIMOS LA PASIÓN
El Cielón aplastado


L'ÉQUIPE
INQUALIFIABLE
FC Barcelone 6-1 Paris SG


BARCELONA - PSG
6:1
PIERWSZY MECZ 8:4
I STAŁ SIĘ CUD!!!


888 sport.it
STADIO
Corriere dello Sport
La Juve ha deciso: obiettivo De Sciglio
CHAMPIONS: BARÇA PAZZESCO, RIMONTA STORICA (6-1)
DA LEGGENDA!


6 1
Suárez le ganó el duelo a Cavani en un histórico partido en el Camp Nou
BARCA ÉPICO


SPORT
SOIS LEYENDA
6 1

Farmacogenética

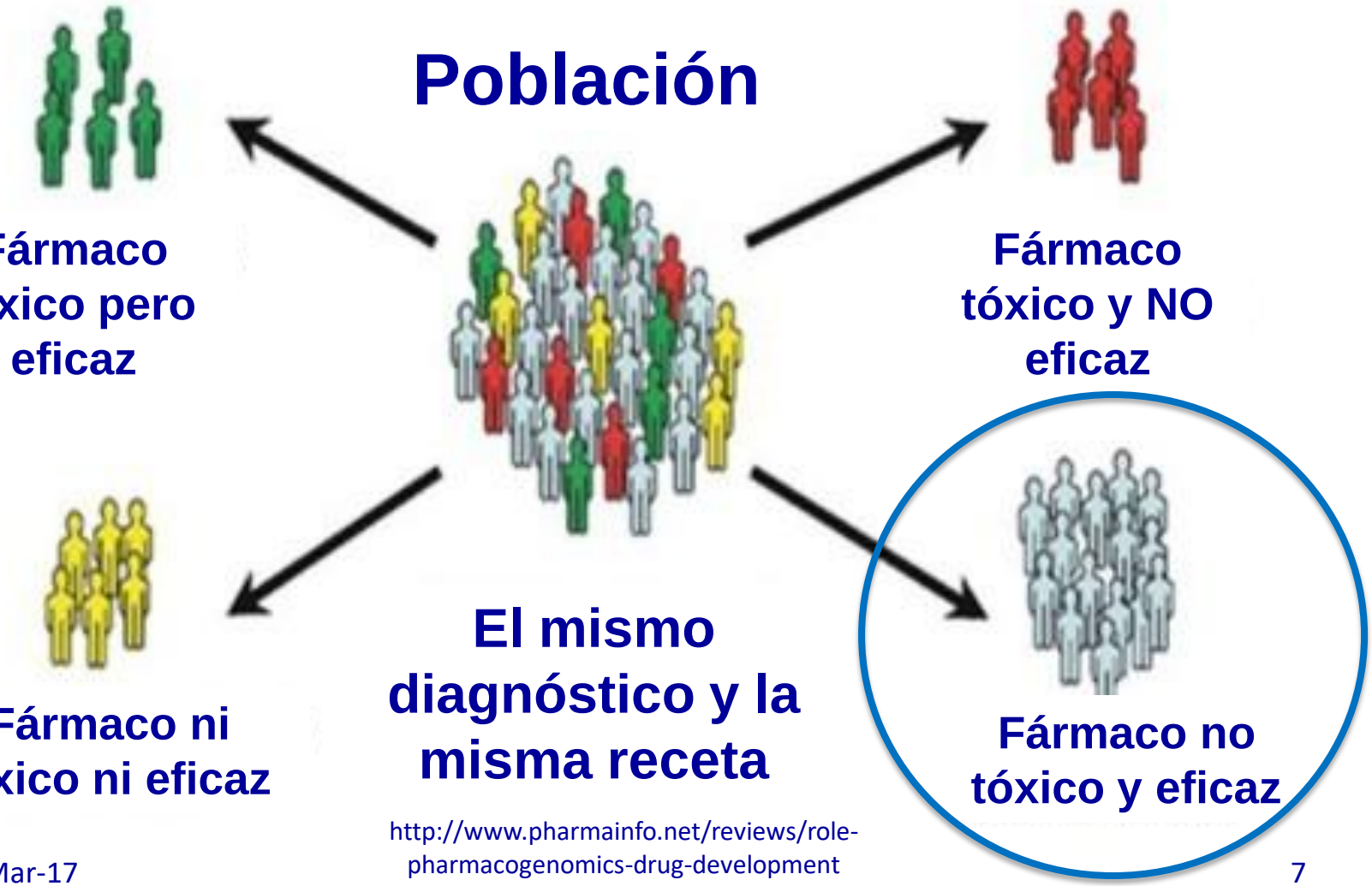
Farmacogenética: definición

- El estudio de las diferencias genéticas en las vías metabólicas que inciden en la respuesta terapéutica del individuo y la intolerancia al fármaco
- El fármaco funciona mejor o peor dependiendo del contexto genético
- Trascender el paradigma del “paciente medio”, superar el enfoque de un tratamiento único para todos

Los pacientes responden de forma diferente al mismo fármaco

Metabolismo rápido **Metabolismo normal** **Metabolismo lento**

El mismo fármaco puede ser tóxico o eficaz en personas distintas



http://www.pharmainfo.net/reviews/role-pharmacogenomics-drug-development

Las diferencias genéticas pueden ayudar a distinguir quienes van a responder de quienes no van a responder

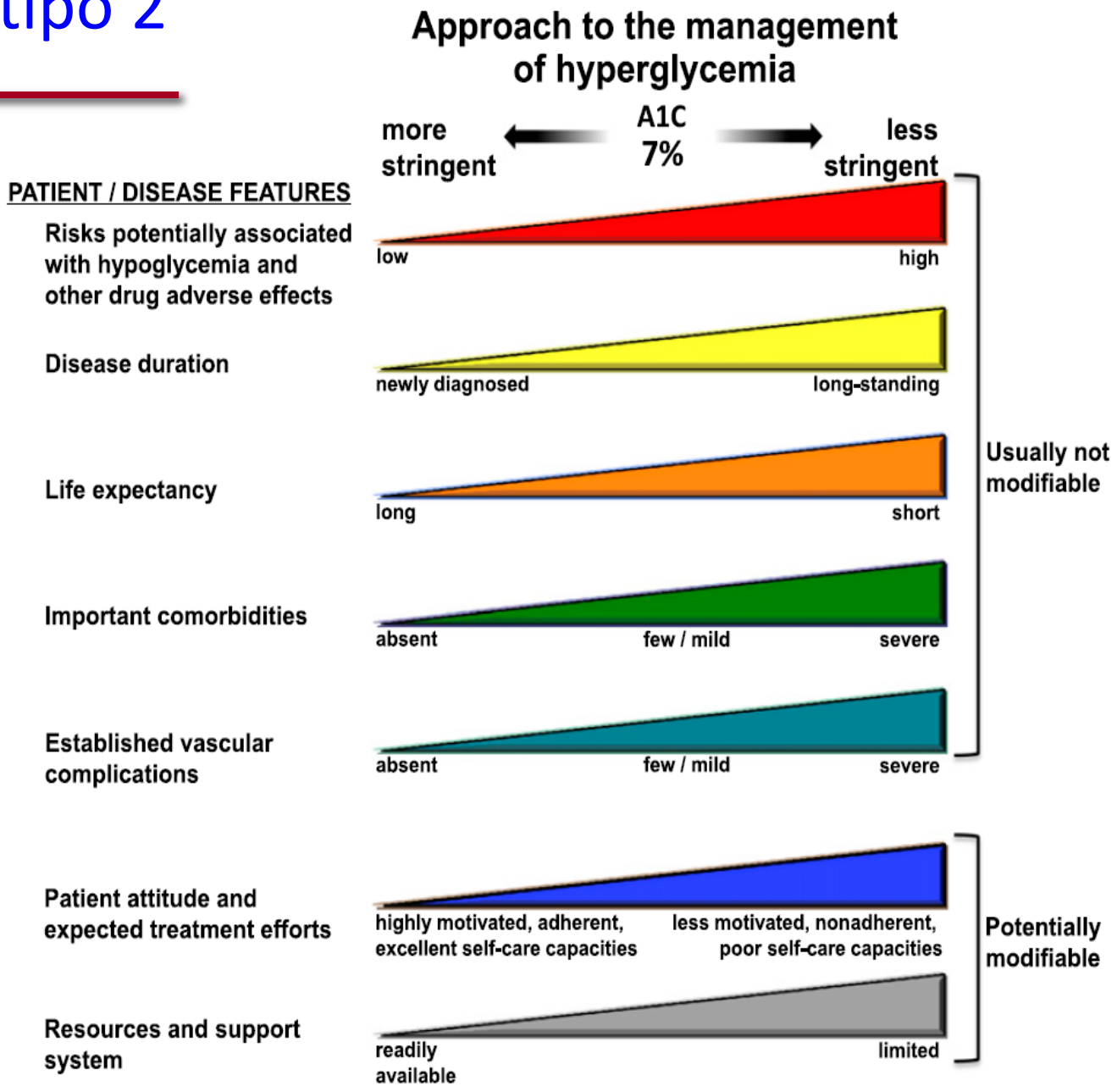
http://www.actionbioscience.org/biotechnology/ethical_issues_in_pharmacogenetics.html

Medicina de precisión (o personalizada)

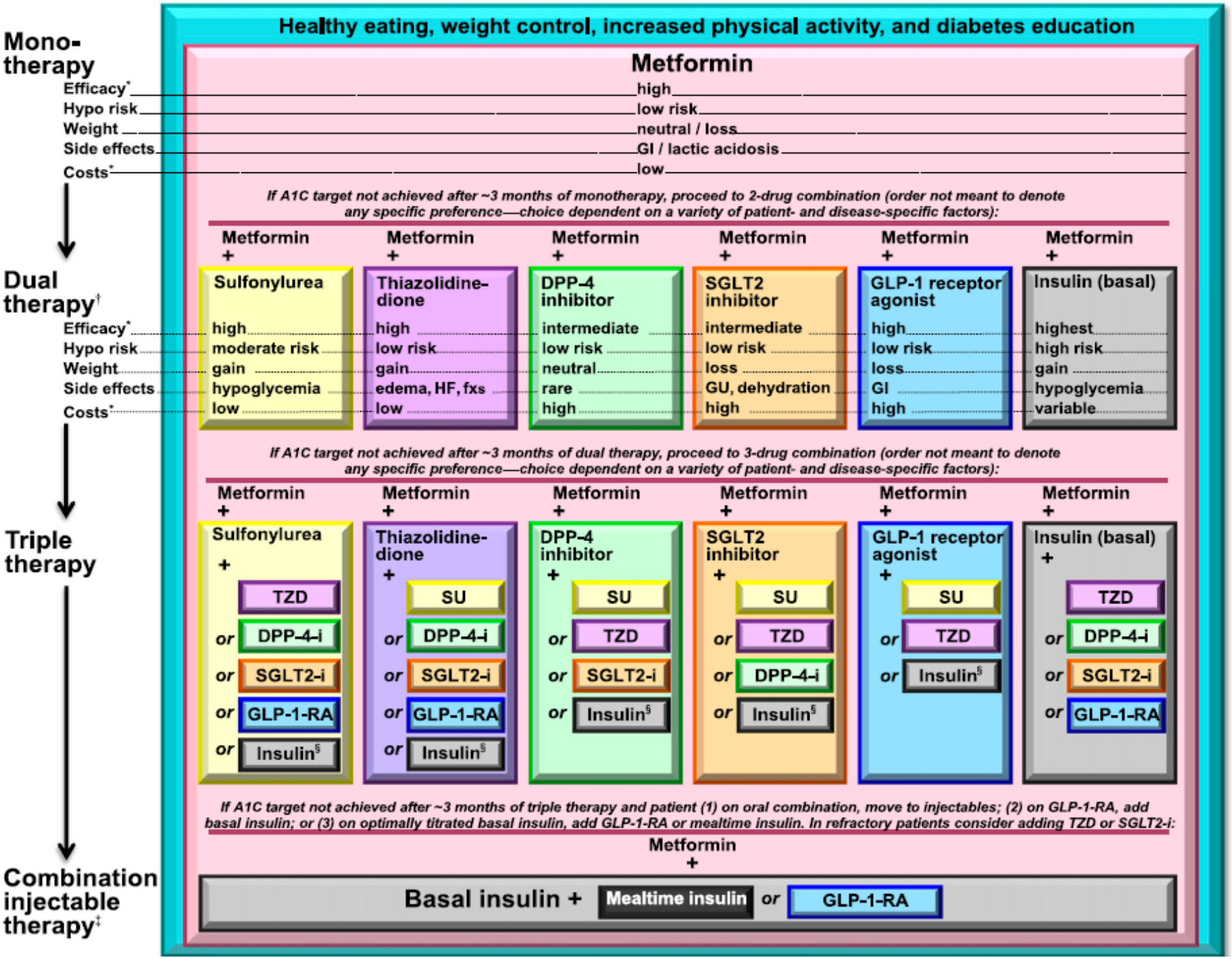
U.S. Precision Medicine Initiative

En la diabetes tipo 2

Un paso adelante…
Pero insuficiente



Suggested citation: American Diabetes Association. Glycemic targets. Sec. 6. In Standards of Medical Care in Diabetes—2015. *Diabetes Care 2015;38(Suppl. 1):S33–S40*


Healthy eating, weight control, increased physical activity, and diabetes education
Mono-therapy
Metformin
Efficacy* high
Hypo risk low risk
Weight neutral / loss
Side effects GI / lactic acidosis
Costs* low
If A1C target not achieved after ~3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference—choice dependent on a variety of patient- and disease-specific factors):
Dual therapy†
Efficacy* Hypo risk Weight Side effects Costs*
Metformin + Sulfonylurea: high / moderate risk / gain / hypoglycemia / low
Metformin + Thiazolidine-dione: high / low risk / gain / edema, HF, fxs / low
Metformin + DPP-4 inhibitor: intermediate / low risk / neutral / rare / high
Metformin + SGLT2 inhibitor: intermediate / low risk / loss / GU, dehydration / high
Metformin + GLP-1 receptor agonist: high / low risk / loss / GI / high
Metformin + Insulin (basal): highest / high risk / gain / hypoglycemia / variable
If A1C target not achieved after ~3 months of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference—choice dependent on a variety of patient- and disease-specific factors):
Triple therapy
Metformin + Sulfonylurea + TZD or DPP-4-i or SGLT2-i or GLP-1-RA or Insulin§
Metformin + Thiazolidine-dione + SU or DPP-4-i or SGLT2-i or GLP-1-RA or Insulin§
Metformin + DPP-4 inhibitor + SU or TZD or SGLT2-i or Insulin§
Metformin + SGLT2 inhibitor + SU or TZD or DPP-4-i or Insulin§
Metformin + GLP-1 receptor agonist + SU or TZD or Insulin§
Metformin + Insulin (basal) + TZD or DPP-4-i or SGLT2-i or GLP-1-RA
If A1C target not achieved after ~3 months of triple therapy and patient (1) on oral combination, move to injectables; (2) on GLP-1-RA, add basal insulin; or (3) on optimally titrated basal insulin, add GLP-1-RA or mealtime insulin. In refractory patients consider adding TZD or SGLT2-i:
Combination injectable therapy‡
Metformin +
Basal insulin + Mealtime insulin or GLP-1-RA

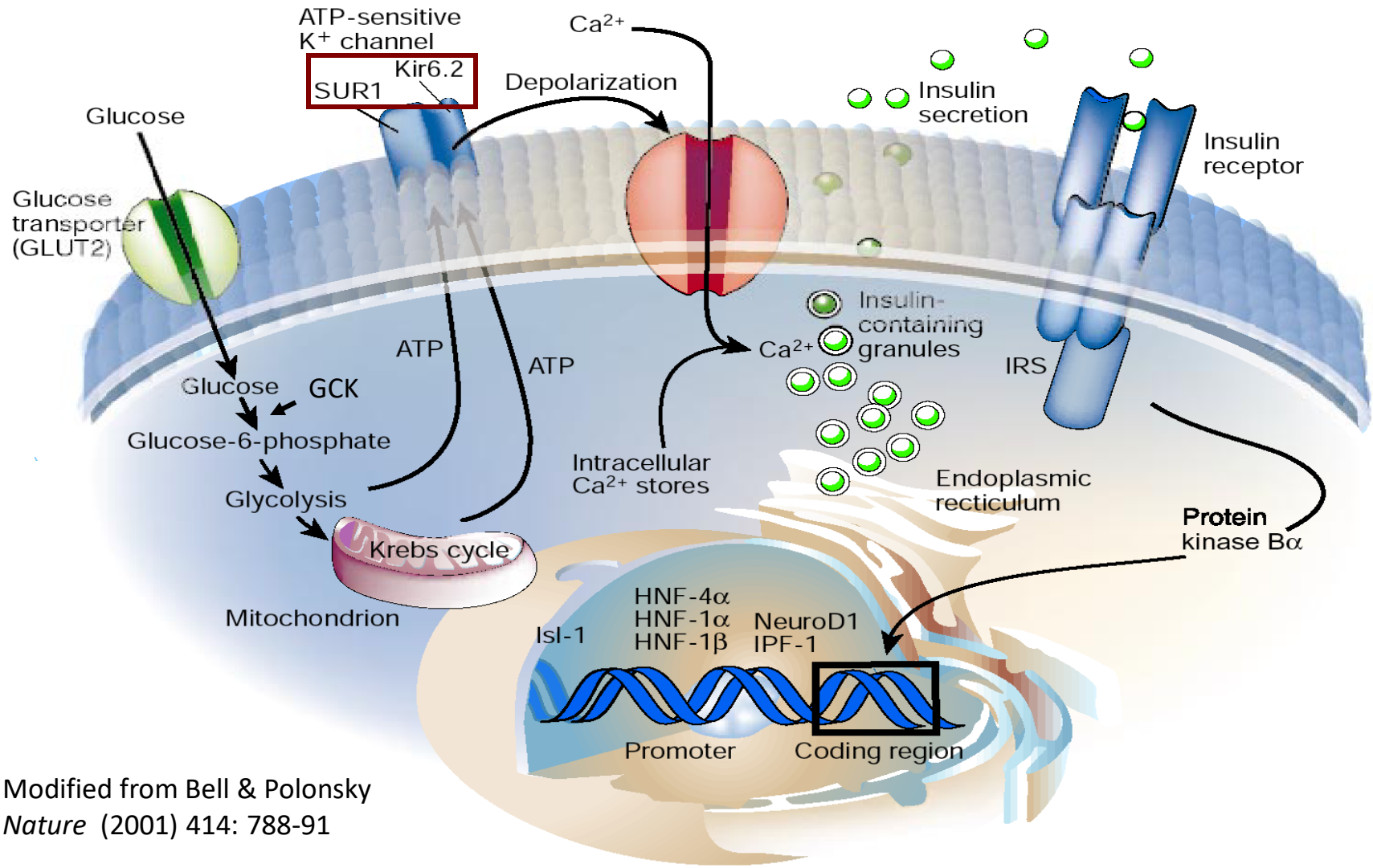
La promesa de la farmacogenética

1. Utilidad clínica: estratificación
   - Predicción
   - Pronóstico
   - Respuesta
   - Tolerabilidad
2. Identificación de dianas: terapéutica
   - Heterogeneidad clínica
   - Clases de fármacos diversas
   - Mecanismos nuevos
3. Prueba de concepto: descubrimiento
   - Perturbación farmacológica revela la fisiología del gen diana

Precedente:

La diabetes monogénica

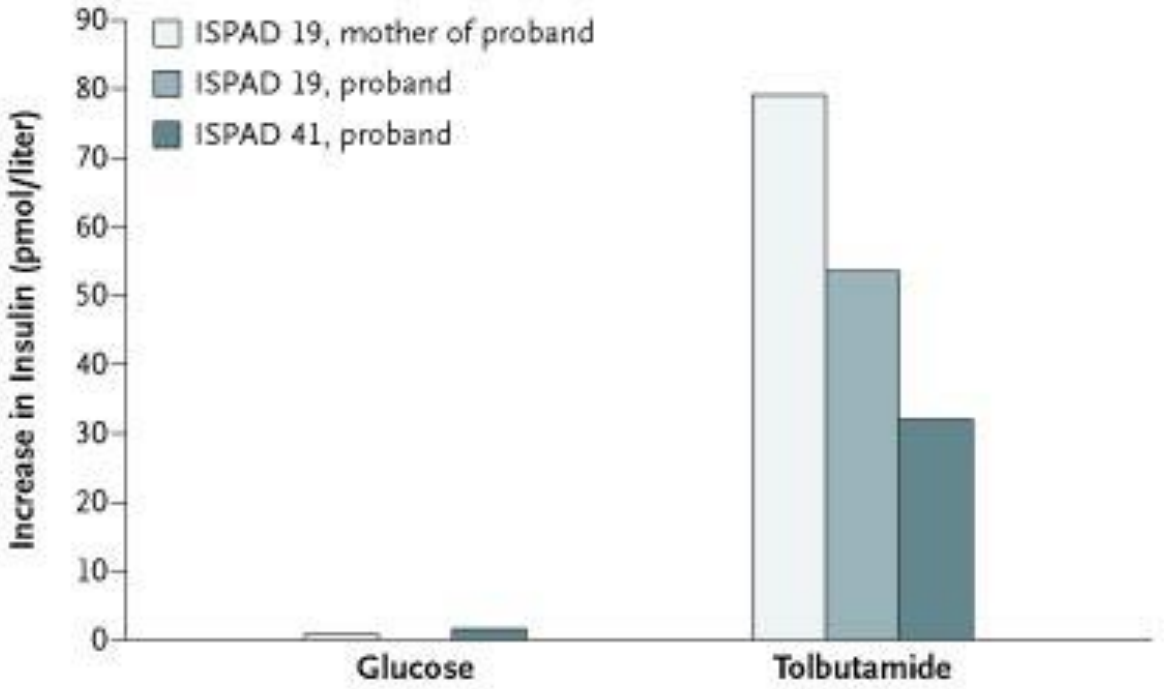
Diabetes neonatal



Modified from Bell & Polonsky
Nature (2001) 414: 788-91

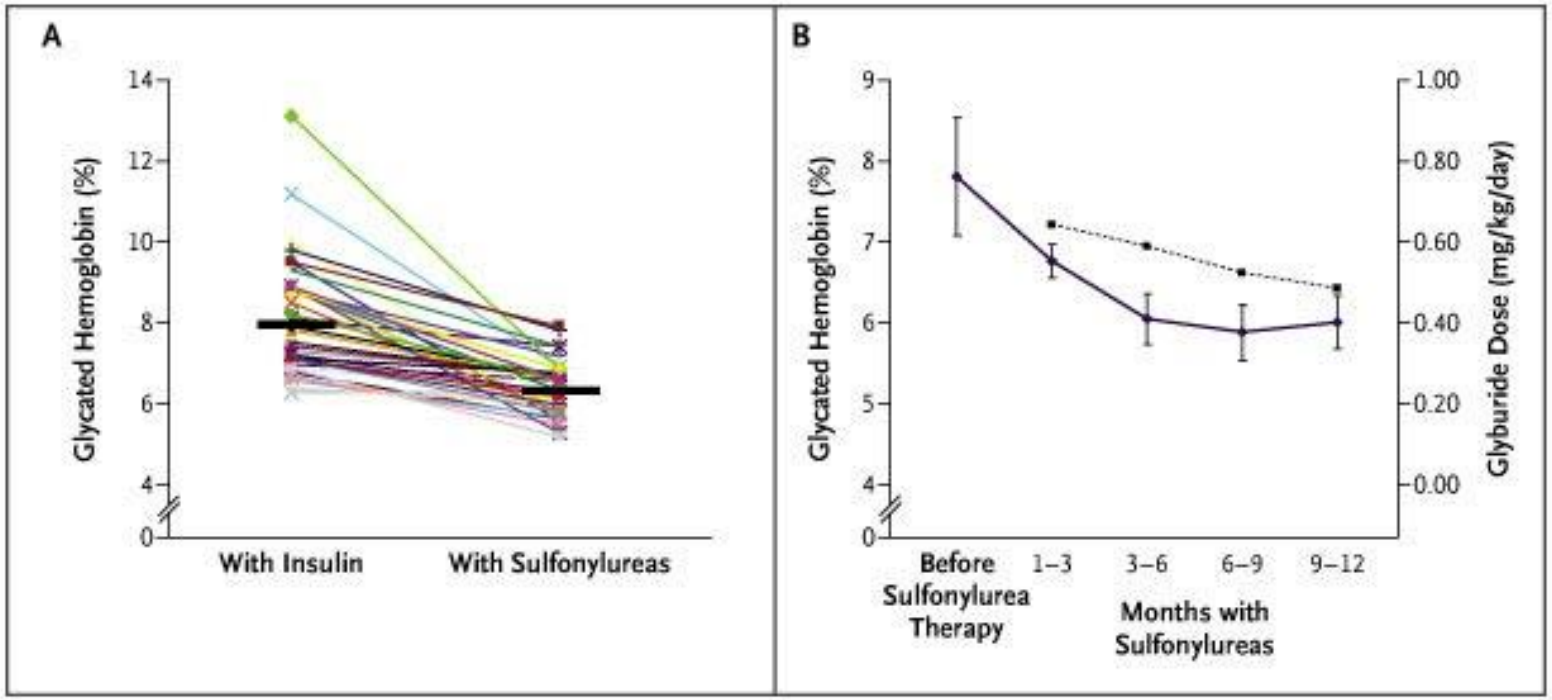
La farmacogenética en la diabetes monogénica

Mutaciones en *KCNJ11*



Gloyn A *et al.* N Engl J Med 2004;350:1838-1849

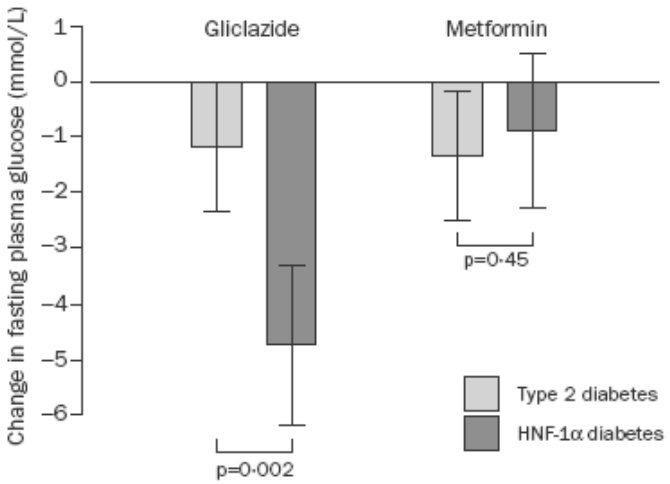
Cambio en HbA1c con sulfonilureas



Pearson E *et al.,* N Engl J Med 2006;355:467-477

Otro ejemplo: MODY 3

- Tipo más frecuente
- Mutaciones en HNF1α (*HNF1A*)
- Ensayo clínico randomizado con cruce de brazos en 36 adultos
- La respuesta a sulfonilureas y metformina comparada entre portadores de mutaciones en *HNF1A* y sujetos con diabetes tipo 2
- El grupo de *HNF1A* demuestra una respuesta 5 veces superior a la sulfonilurea que a la metformina
- La respuesta del grupo *HNF1A* a la sulfonilurea fue 4 veces superior que la del grupo diabetes tipo 2



Pearson *et al., Lancet* 2003;362:1275-1281

Sulfonilureas

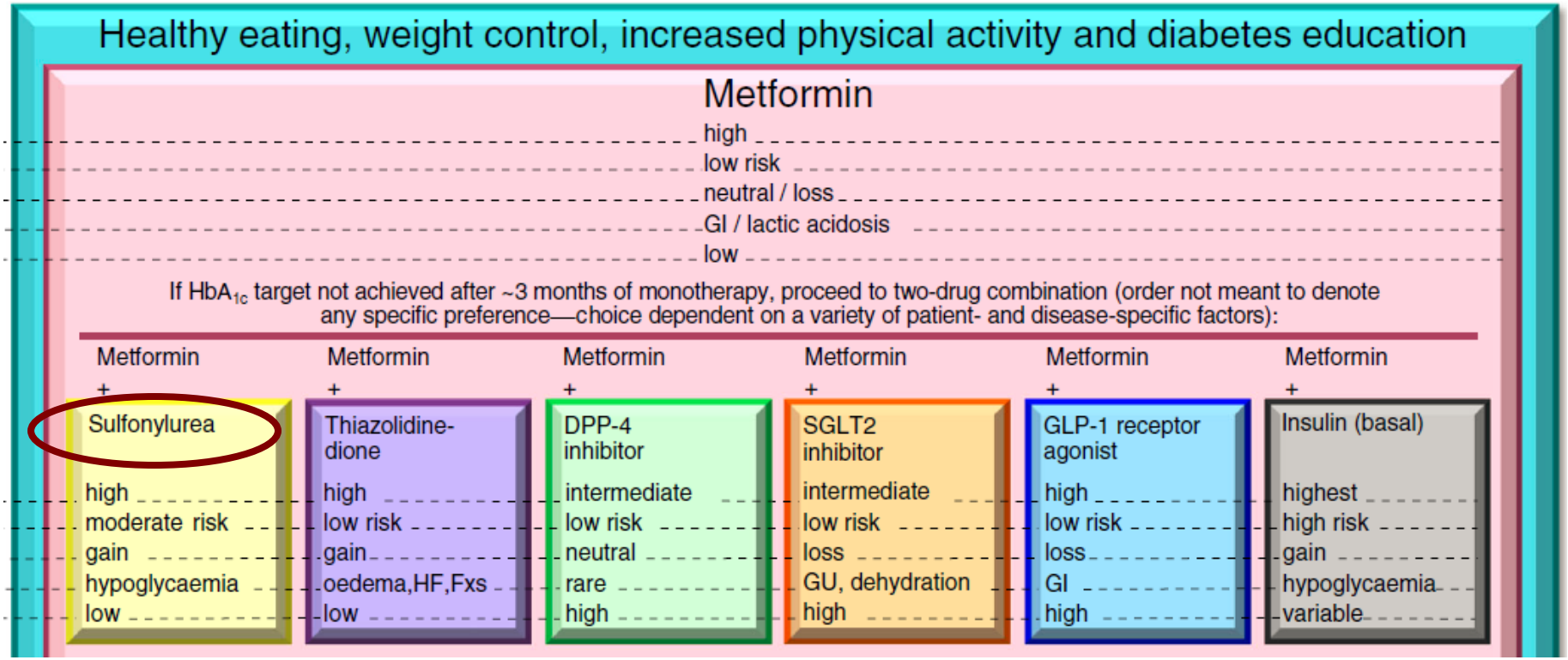
Diabetes tipo 2

POSITION STATEMENT

Management of hyperglycaemia in type 2 diabetes, 2015: a patient-centred approach. Update to a Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes

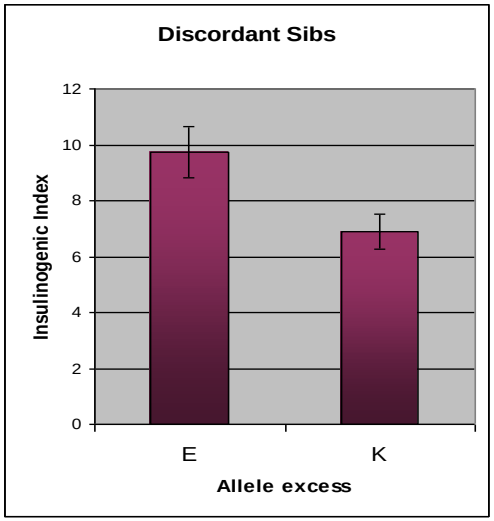
Silvio E. Inzucchi · Richard M. Bergenstal · John B. Buse · Michaela Diamant · Ele Ferrannini · Michael Nauck · Anne L. Peters · Apostolos Tsapas · Richard Wender · David R. Matthews

Diabetologia 2015
Diabetes Care 2015

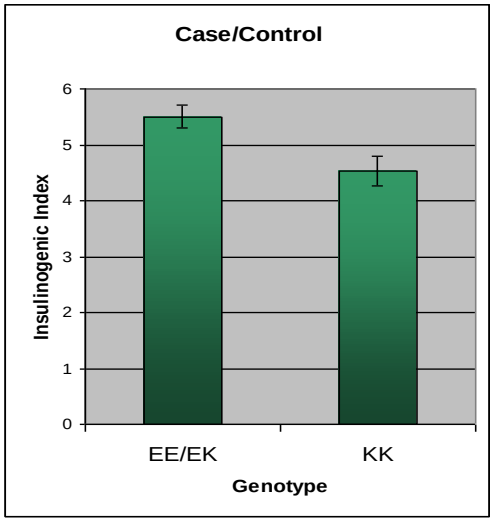


Kir6.2 E23K y riesgo de la diabetes tipo 2

K vs E	OR	*P*	95% CI	N
Meta-analysis, previous data *	1.14	0.0002	1.06 – 1.22	6417
Scand/Canada samples	1.17	0.003	1.05 – 1.32	3413
USA/Poland samples	1.15	0.001	1.05 – 1.26	4470
Meta-analysis, all data	1.15	$< 10^{-7}$	1.09 – 1.21	14300



P <0.01



P <0.02

* Gloyn *et al.*, *Diabetes* 2003

Florez *et al.*, *Diabetes* 2004

Correlación quasi-perfecta entre *ABCC8* A1369S y *KCNJ11* E23K

61	62	63		65		67			70			73		75
G	A	T	A	C	A	C	A	T	C	C	T	C	T	G
G	G	T	A	C	G	C	A	G	G	C	T	C	T	G
G	G	T	A	C	G	C	A	G	C	C	T	T	T	G
G	G	T	A	C	G	C	A	G	G	T	T	T	T	G
G	A	T	A	C	A	C	G	G	G	T	C	T	C	A
G	A	T	A	C	A	C	G	T	C	C	T	C	T	G
G	G	T	A	C	G	C	A	G	C	C	T	C	T	G
G	G	T	A	C	G	C	A	G	C	C	T	T	C	A

A	G	G	G	T	G	C	G	G	G	T	C	T	T	G
A	G	G	G	T	G	G	G	G	G	T	C	T	T	G
A	G	G	G	T	G	C	G	G	G	T	C	T	C	A
G	G	G	G	T	G	C	G	G	G	T	C	T	T	G
G	G	G	G	T	G	C	G	G	G	T	C	T	C	A

E23K

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61	62	63		65		67			70			73		75
G	A	T	A	C	A	C	A	T	C	C	T	C	T	G
G	G	T	A	C	G	C	A	G	G	C	T	C	T	G
G	G	T	A	C	G	C	A	G	C	C	T	T	T	G
G	G	T	A	C	G	C	A	G	G	T	T	T	T	G
G	A	T	A	C	A	C	G	G	G	T	C	T	C	A
G	A	T	A	C	A	C	G	T	C	C	T	C	T	G
G	G	T	A	C	G	C	A	G	C	C	T	C	T	G
G	G	T	A	C	G	C	A	G	C	C	T	T	C	A

A	G	G	G	T	G	C	G	G	G	T	C	T	T	G
A	G	G	G	T	G	G	G	G	G	T	C	T	T	G
A	G	G	G	T	G	C	G	G	G	T	C	T	C	A
G	G	G	G	T	G	C	G	G	G	T	C	T	T	G
G	G	G	G	T	G	C	G	G	G	T	C	T	C	A

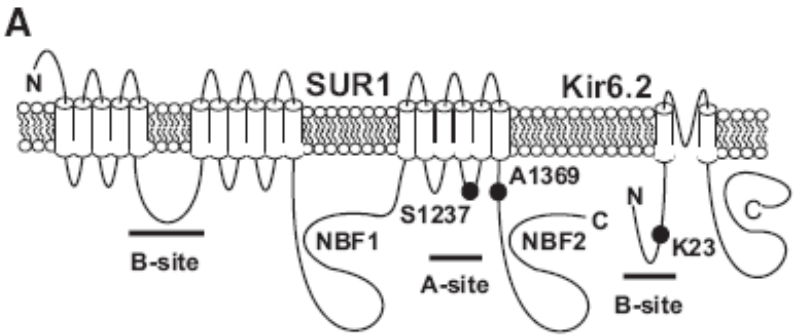
<1%

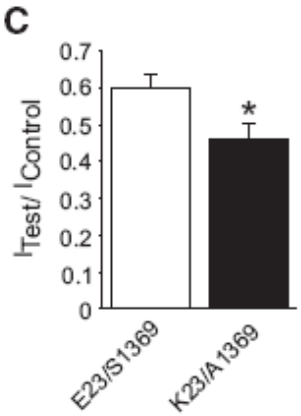
A	G	G	G	C	A	C	A	T	C	C	T	C	T	G

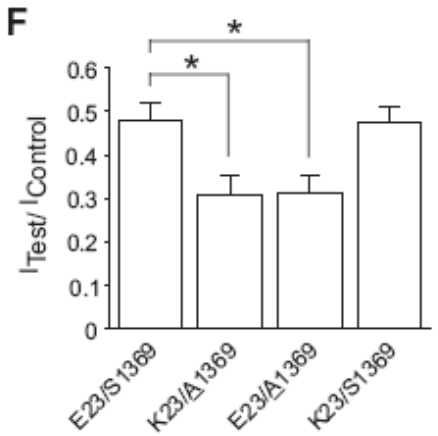
A1369S E23K

Florez *et al., Diabetes* 53:1360–1368, 2004

Caracterización funcional





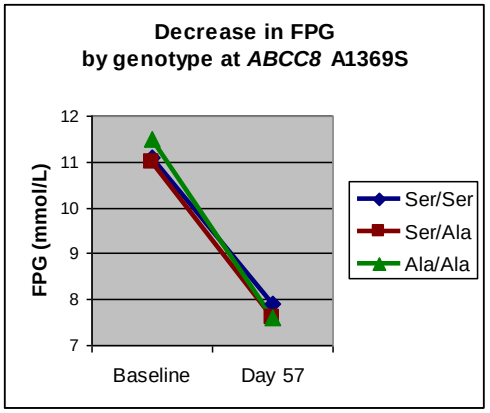


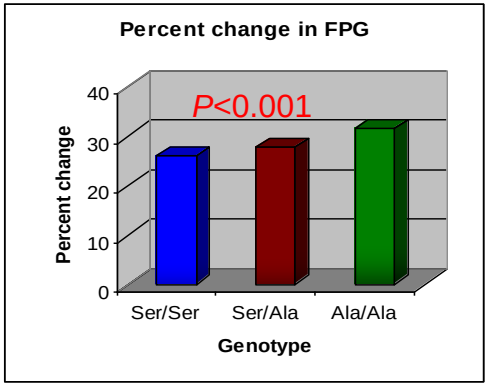
Hamming *et al.*
Diabetes 2009;58:2419-2424

Ser1369Ala Variant in Sulfonylurea Receptor Gene *ABCC8* Is Associated With Antidiabetic Efficacy of Gliclazide in Chinese Type 2 Diabetic Patients

- 23 hospitales en China
- Dos cohortes independientes (n=661 and n=607)
- Debut de la DM en los últimos 5 años, sin tratamiento por 2 meses
- Gliclazida 40 mg dos veces al día por 2 meses
- 25 SNPs en 11 genes
- Porcentaje del cambio en glucosa

Feng *et al. Diabetes Care* 31:1939–1944, 2008





Metformina

Genes candidato

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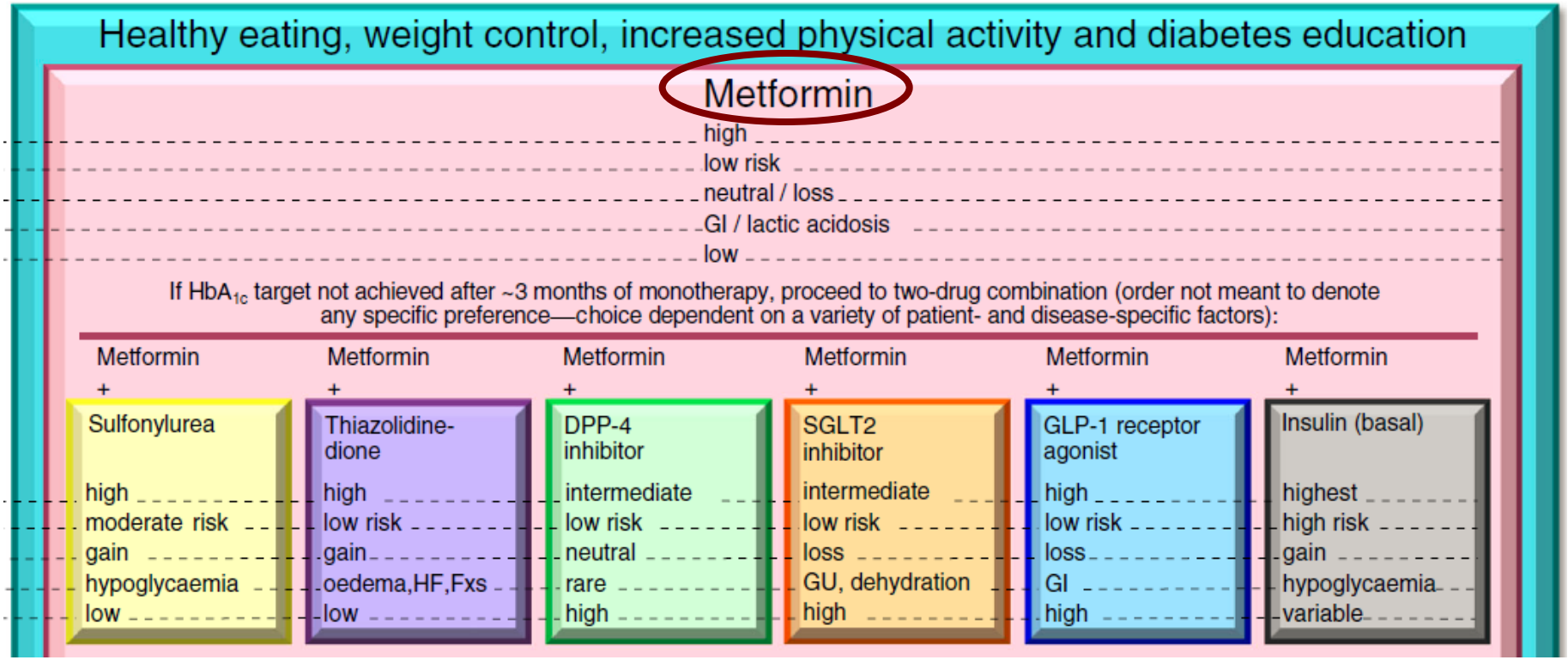
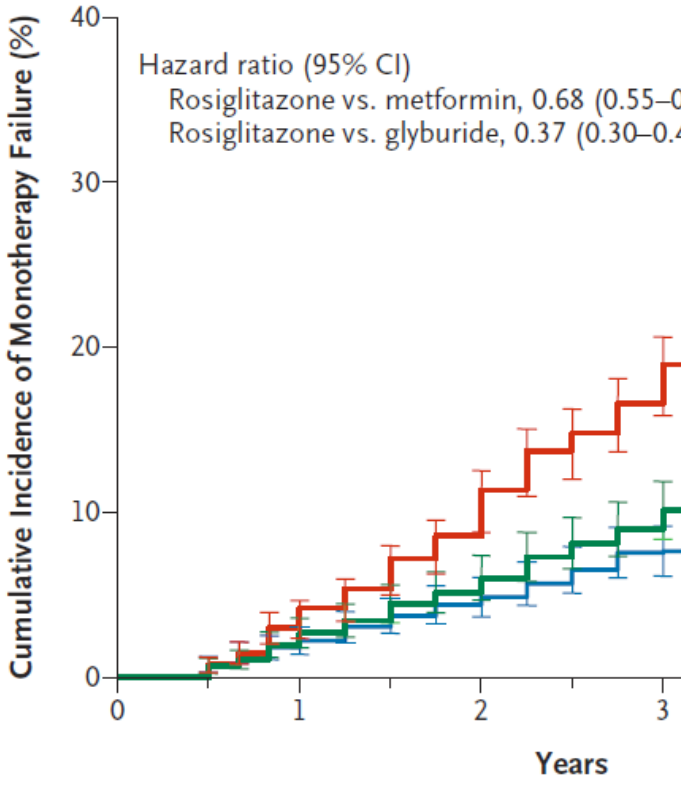
Diabetologia 2015
Diabetes Care 2015

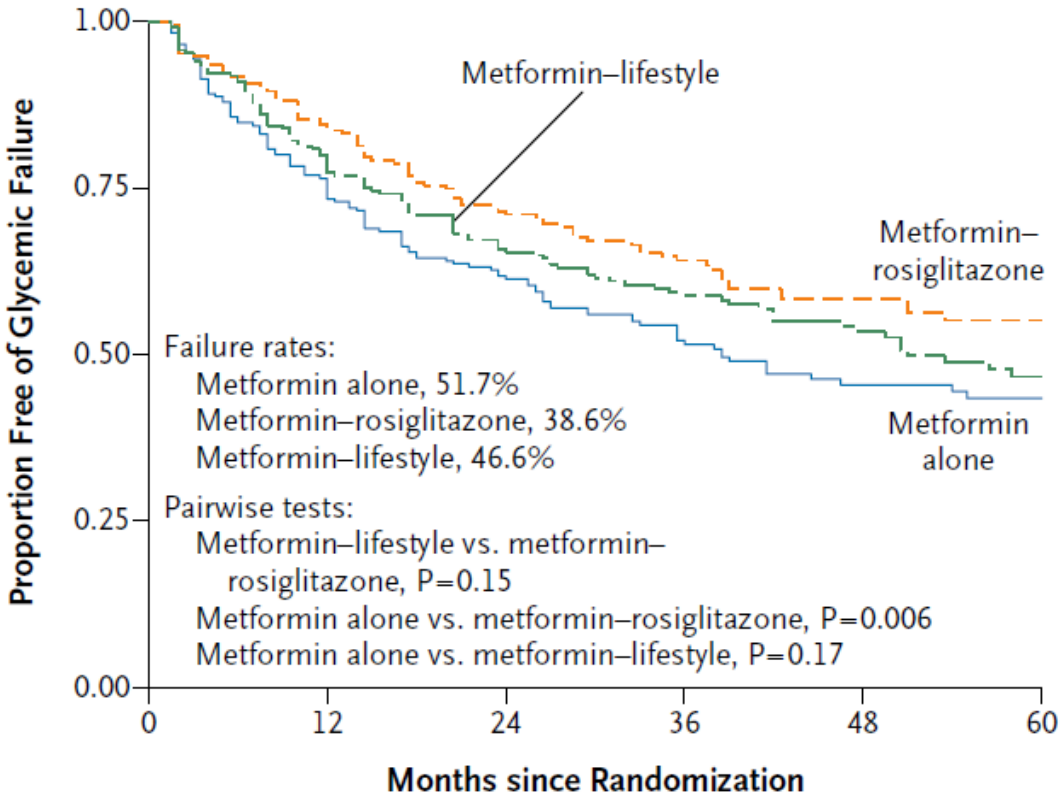


La metformina no siempre es eficaz

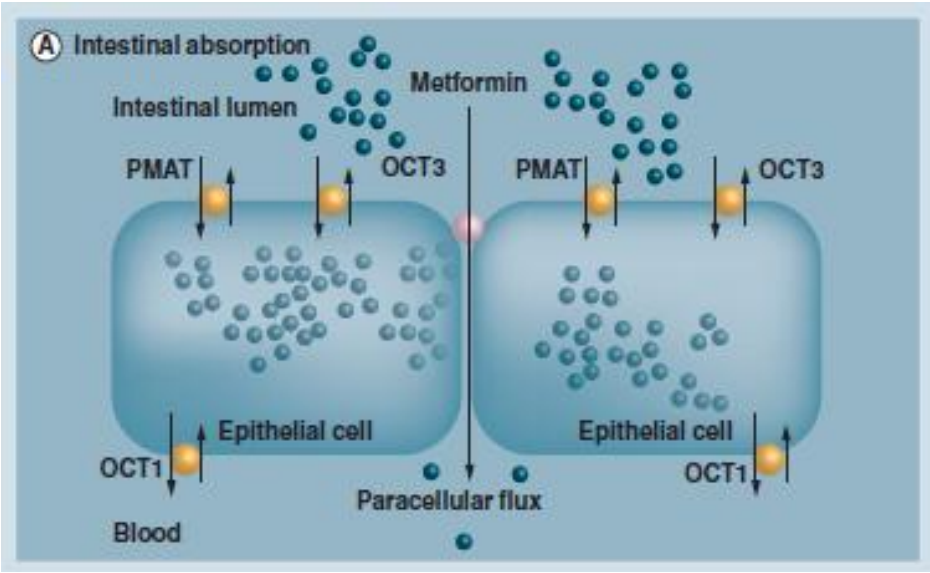
ADOPT (*NEJM* 2006)

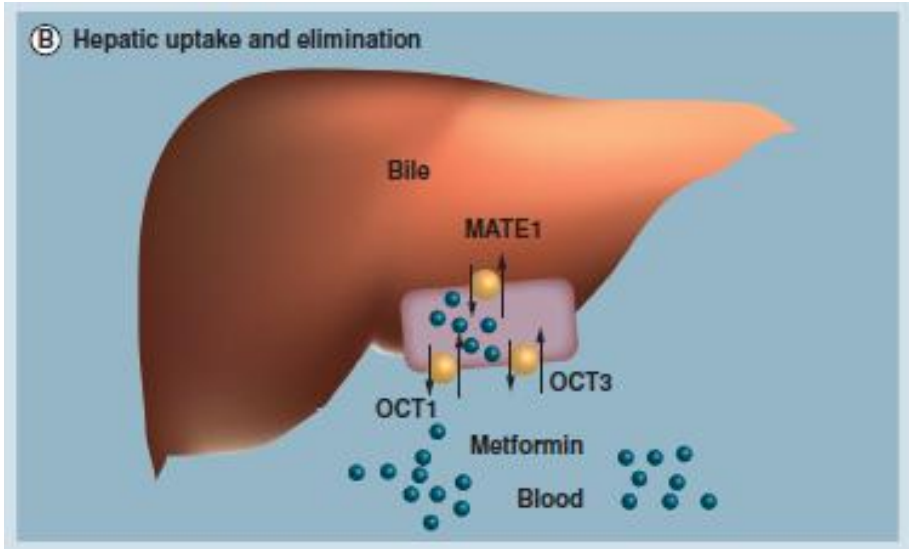


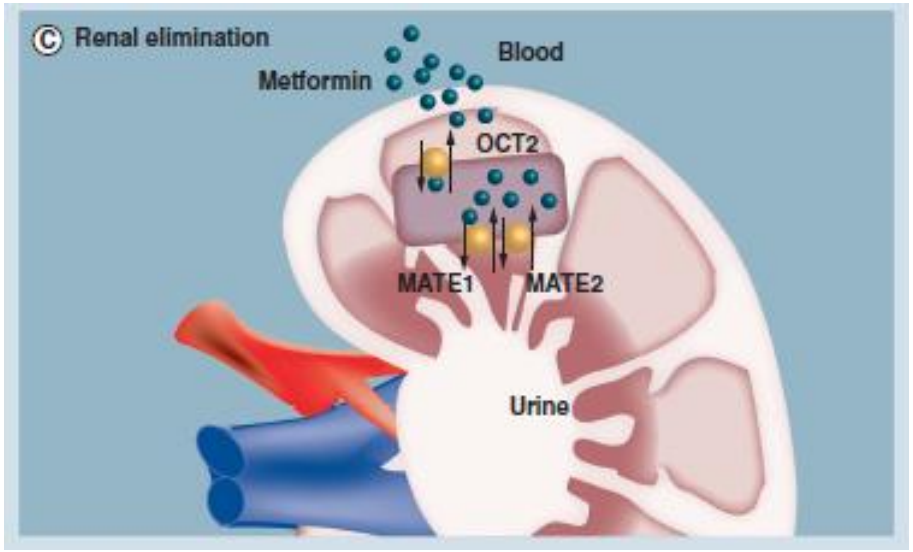
TODAY (*NEJM* 2012)



Metabolismo de la metformina

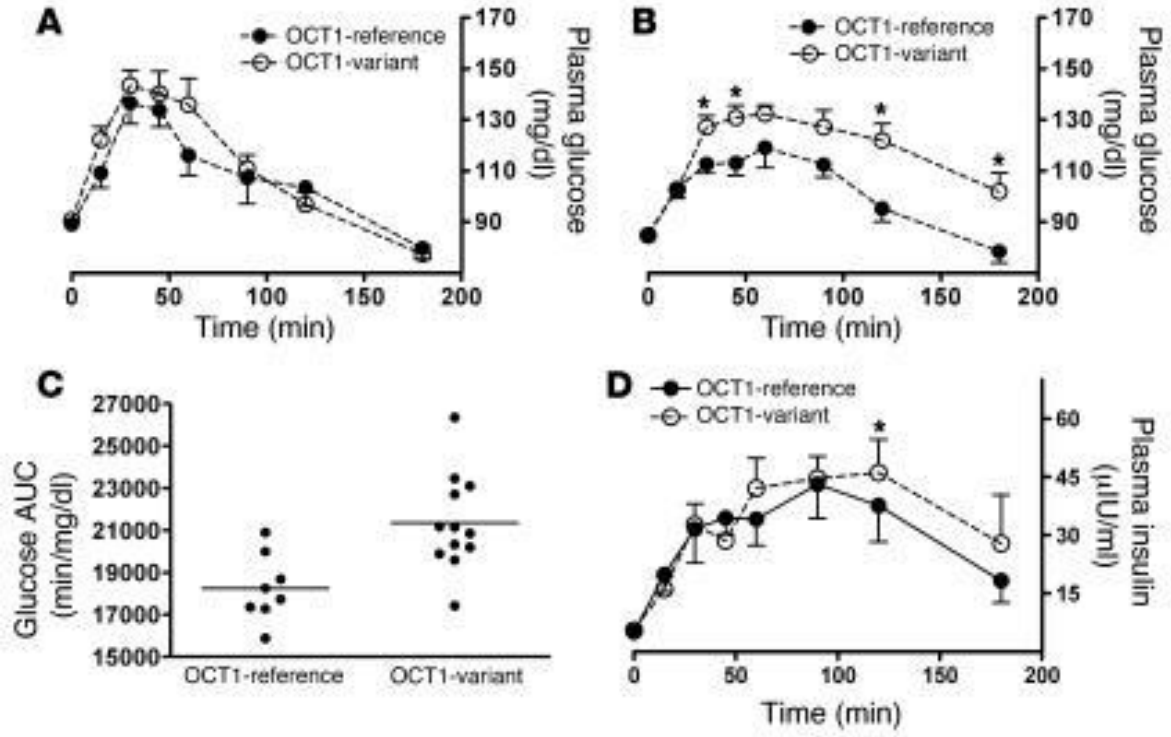






Rena, Pearson, Sakamoto
Diabetes Management
2012;2:439–452

OCT1 y el transporte de metformina

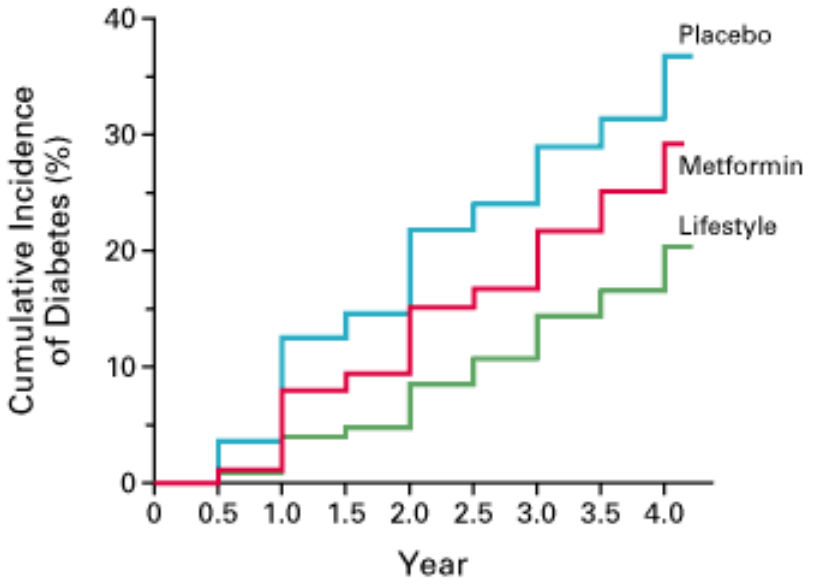


8 sujetos sanos portadores de alelos referencia comparados a 12 sujetos sanos portadores de al menos un alelo de función reducida

Shu *et al., JCI* 2007 117:1422-1431

Farmacogenética de la diabetes: El Diabetes Prevention Program

- 3234 personas con intolerancia a la glucosa
- Randomizadas a placebo, estilo de vida o metformina
- 585 pacientes adicionales inicialmente randomizados a troglitazona
- Seguidos durante 4 años
- DNA extraído

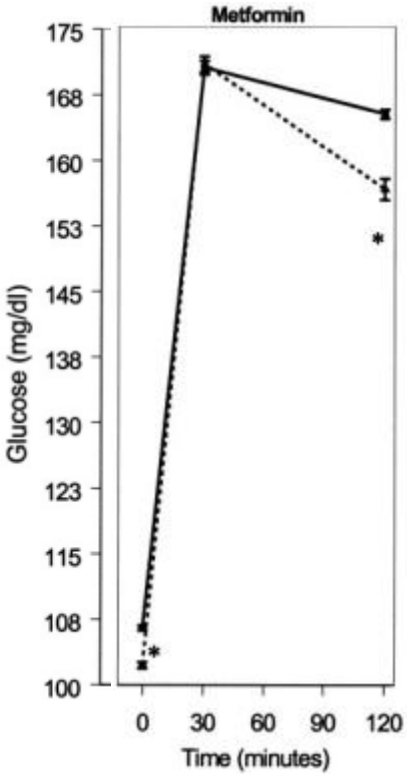


DPP Research Group
NEJM 346:393-403, 2002

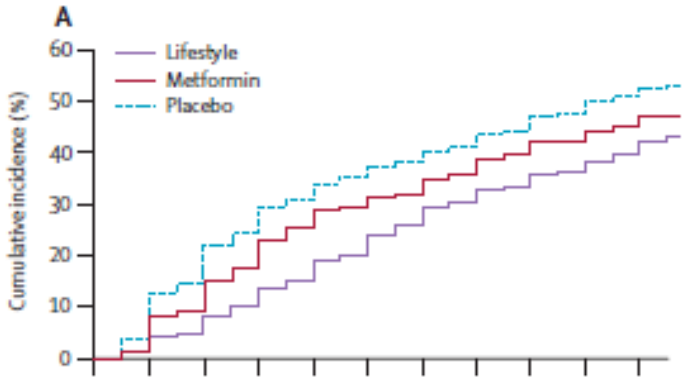
Reducción de riesgo: 31% metformina
58% estilo de vida

Efectos sostenidos en glucosa y peso

Glucosa en ayunas
y 2h después de 1 año

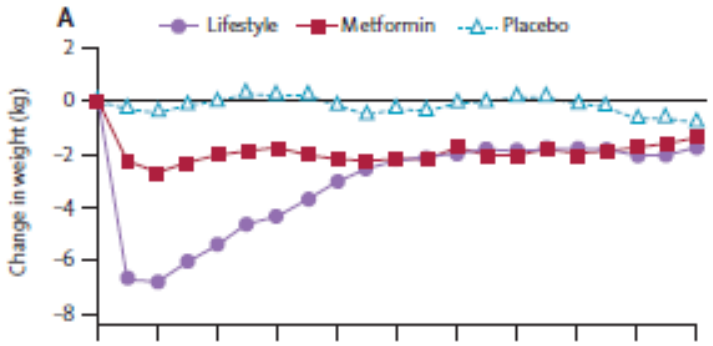


DPP Research Group
Diabetes 2005



Incidencia de diabetes

Peso



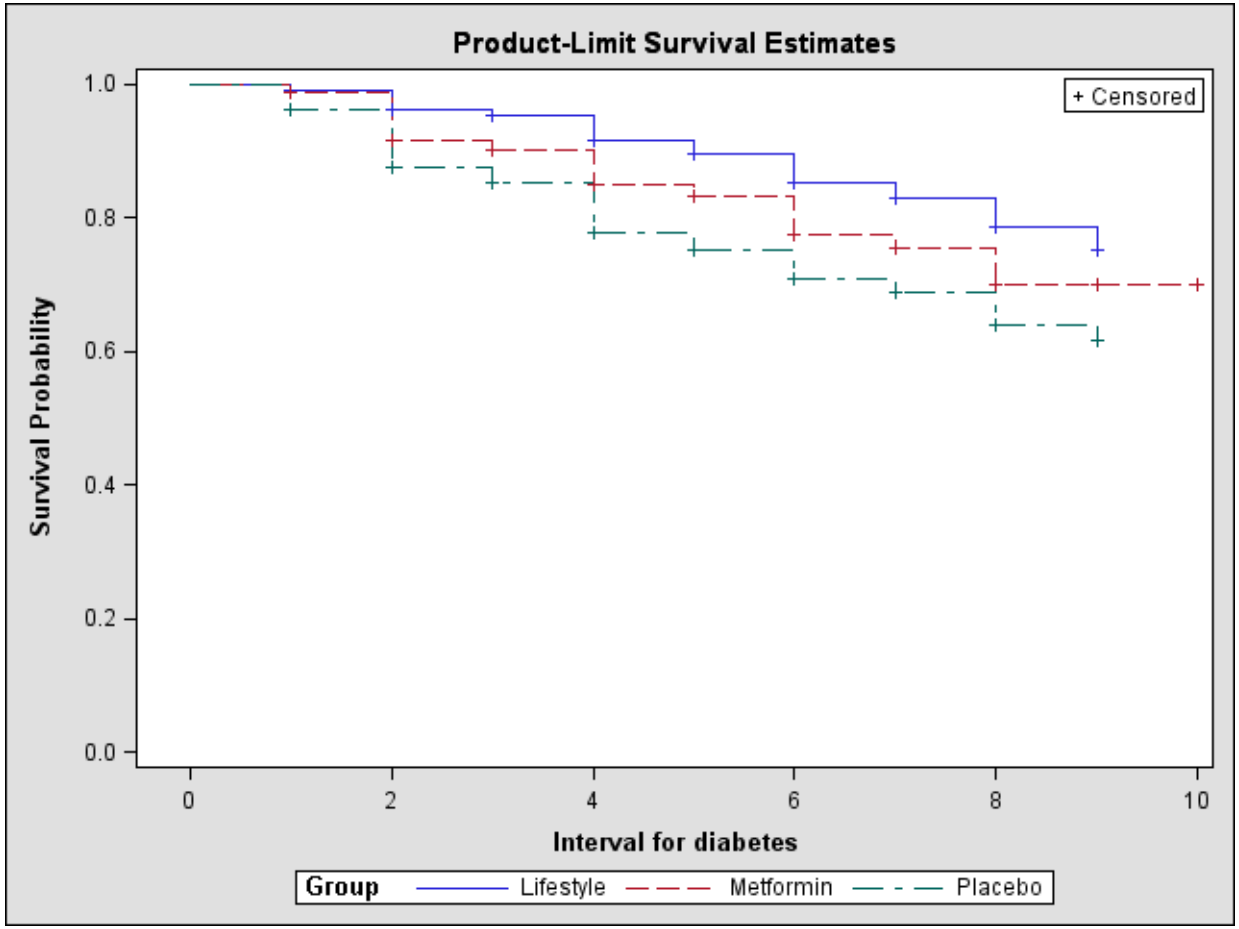
DPP Research Group, *The Lancet* 2009

Análisis de haplotipos en OCT1

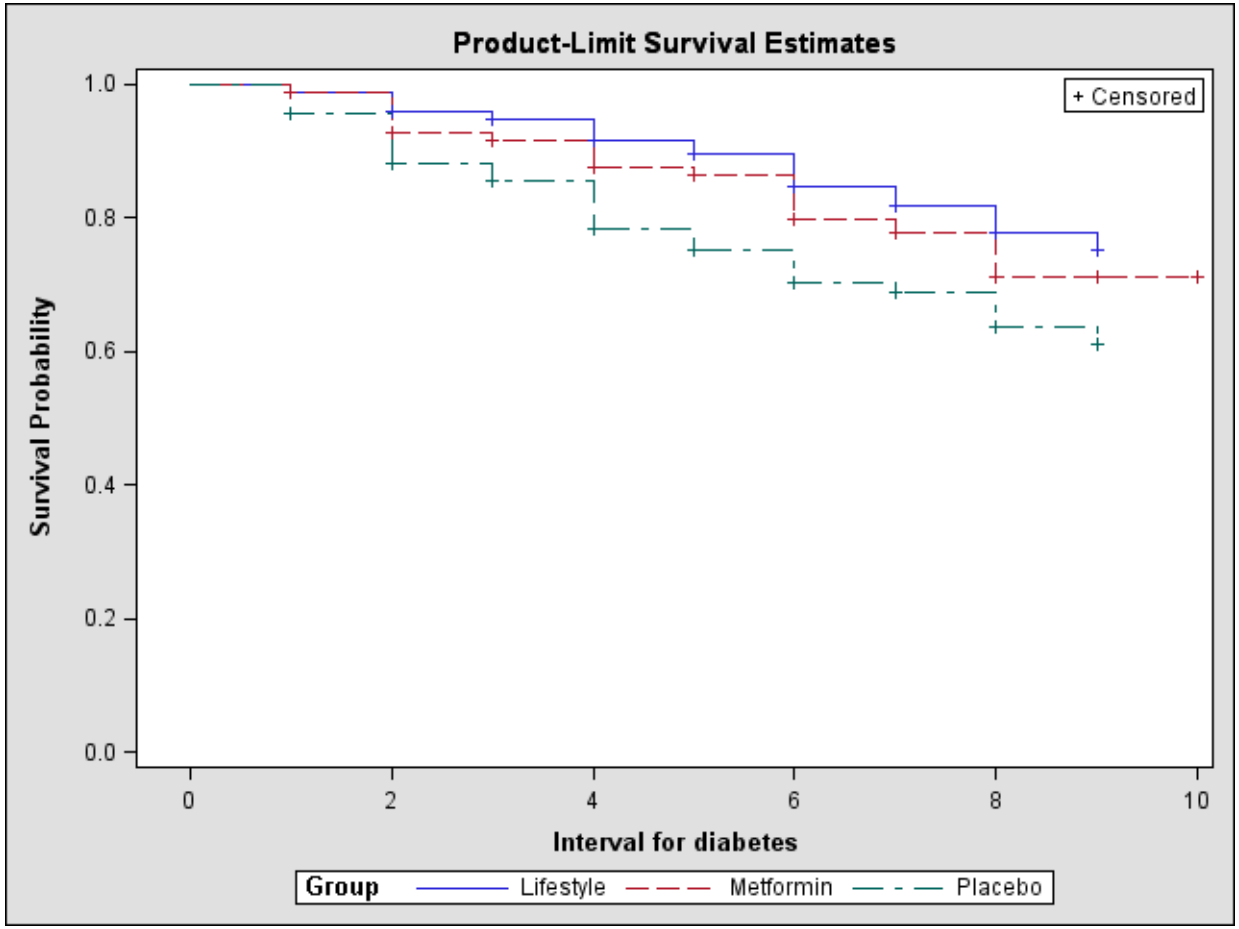
Haplotype	61	160	341	401	408	420	465	Frequency	Hap x Met p-value	Placebo HR (95% CI)	Met HR (95% CI)
CCCGGIG	R	F	P	G	V	M	G	0.42 – 0.59	ref	ref	ref
CCCGAIG	R	F	P	G	M	M	G	0.03 – 0.24	0.41	1.01(0.78 – 1.30)	1.18 (0.88 – 1.56)
CCCGGDG	R	F	P	G	V	del	G	0.06 – 0.29	0.74	1.19 (0.91 – 1.55)	1.25 (0.92 – 1.71)
CGCGAIG	R	L	P	G	M	M	G	0.03 – 0.11	**0.01**	1.01(0.72 – 1.41)	**1.84* (1.31 – 2.61)**
TGCGAIG	C	L	P	G	M	M	G	0.004 – 0.08	0.80	1.05 (0.69 – 1.60)	1.09 (0.68 – 1.77)
CCTGGIG	R	F	L	G	V	M	G	0.01 – 0.08	0.83	1.34 (0.83 – 2.17)	1.54 (0.88 – 2.72)
CCCGGDA	R	F	P	G	V	del	R	0.00 – 0.02	0.99	1.04(0.54 – 2.00)	1.08 (0.50 – 2.34)
CGCAAIG	R	L	P	S	M	M	G	0.00 – 0.02	0.14	1.07(0.50 – 2.30)	**2.39** (1.06 – 5.38)**

Toni Pollin, Jose Florez, Sook Wah Yee, Kathleen Jablonski, Jarred McAteer, Andy Taylor, Bill Knowler, Kathy Giacomini, Alan Shuldiner

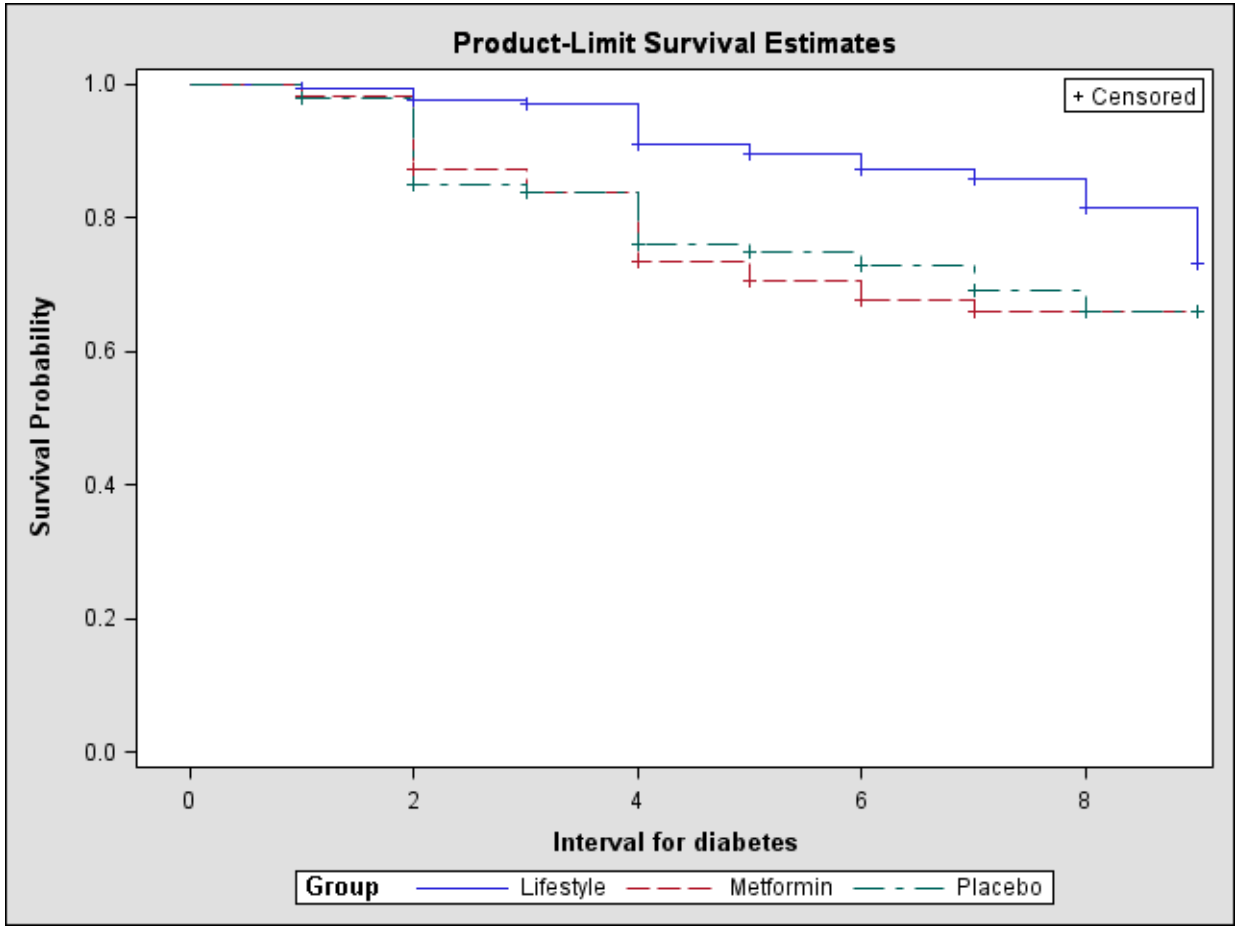
Supervivencia sin diabetes: todos (n=2,945)



Ausencia de Arg61-Leu160 (n=2,362)

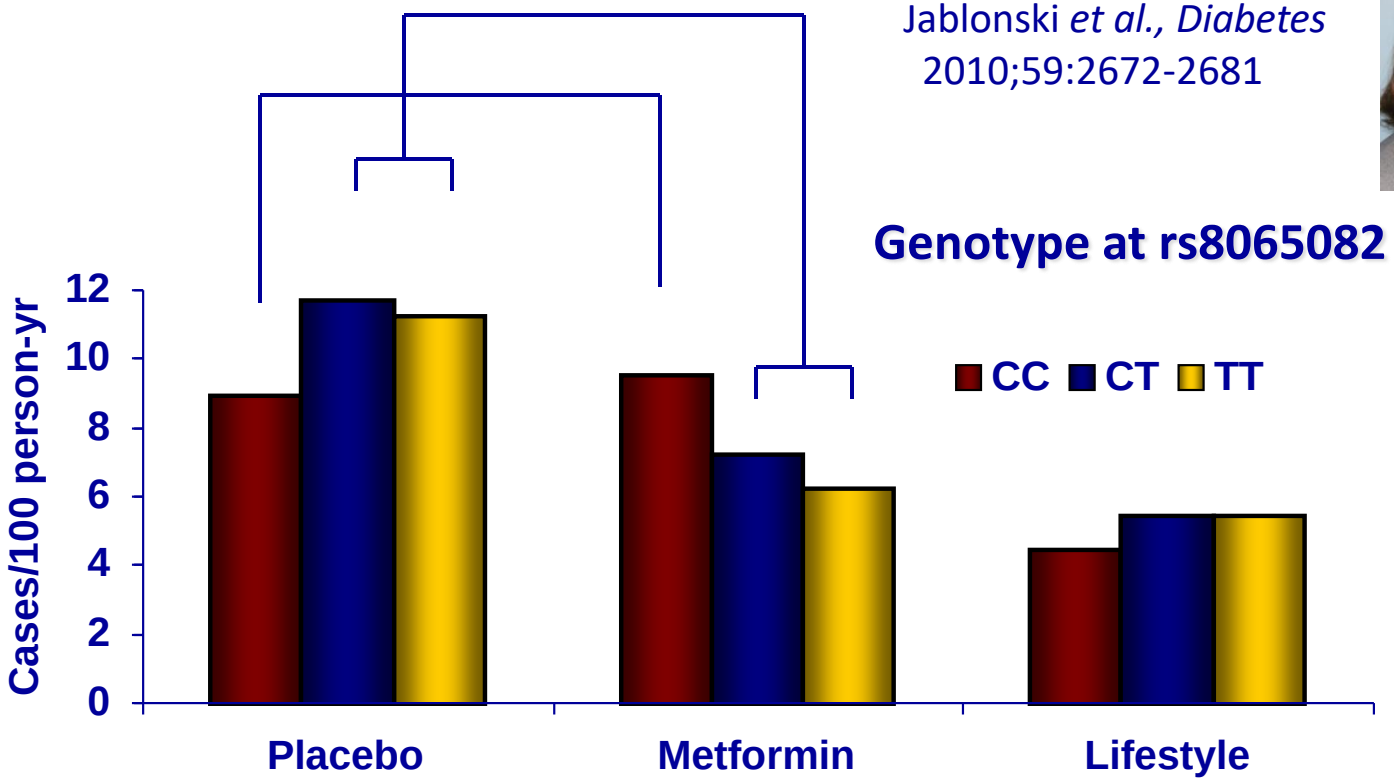


Portadores de Arg61-Leu160 (n=583)



SLC47A1: incidencia de diabetes en el DPP

Jablonski *et al., Diabetes* 2010;59:2672-2681



Efectos adversos

Tanja Dujic,[1] Kaixin Zhou,[2] Louise A. Donnelly,[2] Roger Tavendale,[2] Colin N.A. Palmer,[2] and Ewan R. Pearson[2]

Association of Organic Cation Transporter 1 With Intolerance to Metformin in Type 2 Diabetes: A GoDARTS Study

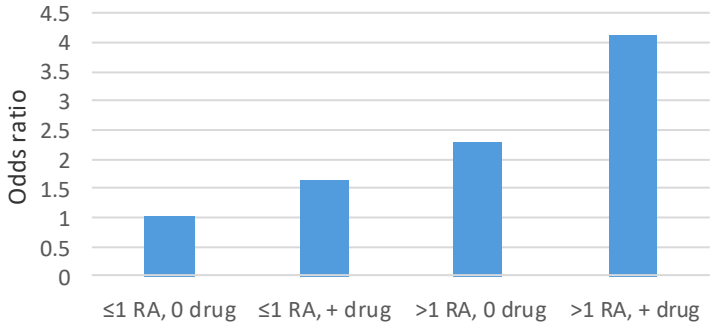
Diabetes 2015;64:1786–1793 | DOI: 10.2337/db14-1388

Table 2—Logistic regression model of metformin intolerance

	OR (95% CI)	*P*
Age	1.10 (1.08–1.12)	<0.001
Sex (females vs. males)	1.85 (1.33–2.57)	<0.001
Weight	0.99 (0.98–1.00)	0.064
Use of OCT1-inhibiting drugs	1.64 (1.20–2.25)	0.002
Two reduced-function OCT1 alleles	2.41 (1.48–3.93)	<0.001

Logistic regression analysis included 205 intolerant and 1,650 tolerant patients.

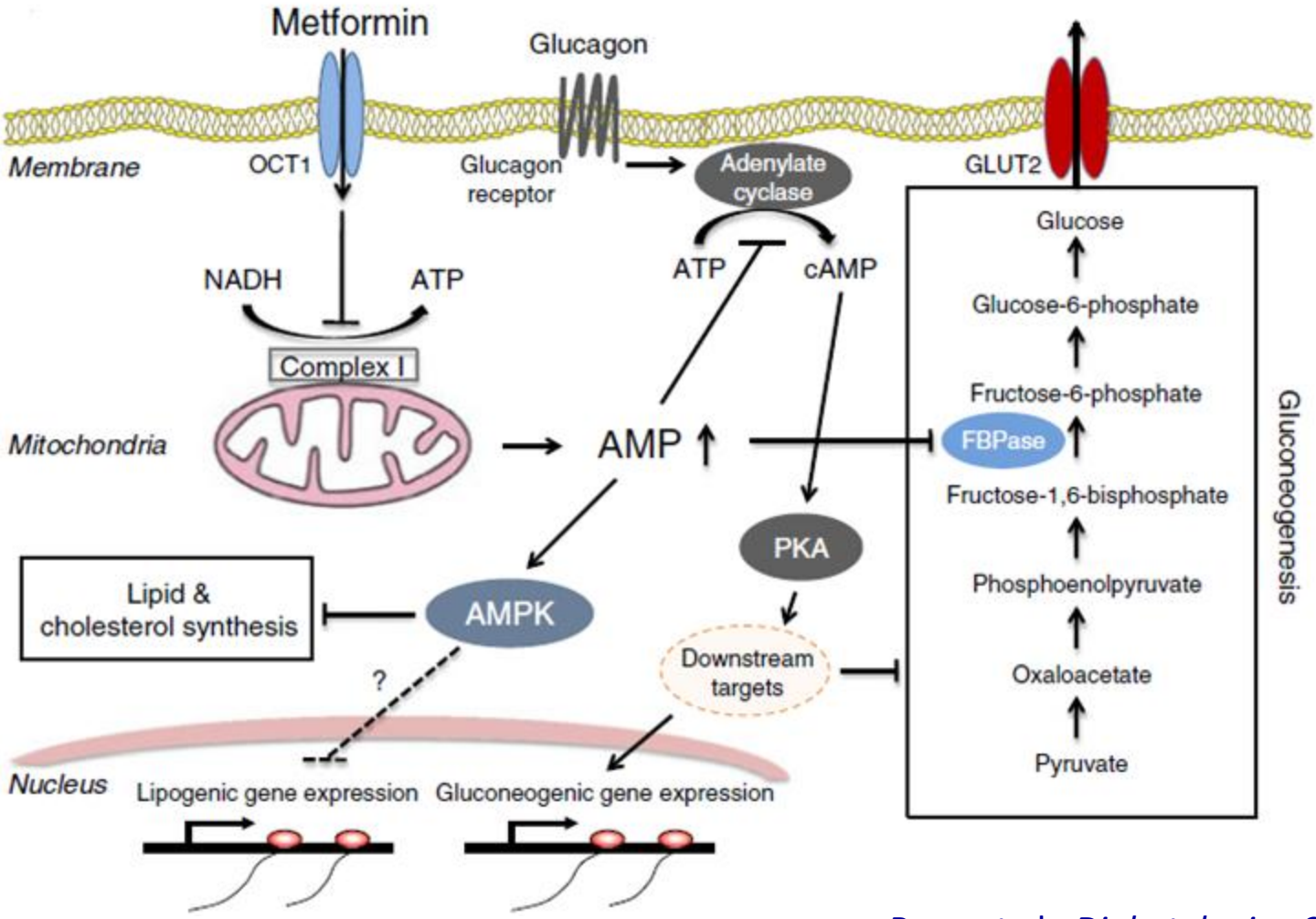
Combined effect of OCT1 genotype and drug on metformin intolerance



Metformina: estudios genómicos

1. Diana molecular
2. Mecanismos
3. Estratificación

Metformina: Mecanismo de acción



Rena et al., *Diabetologia*., 2013

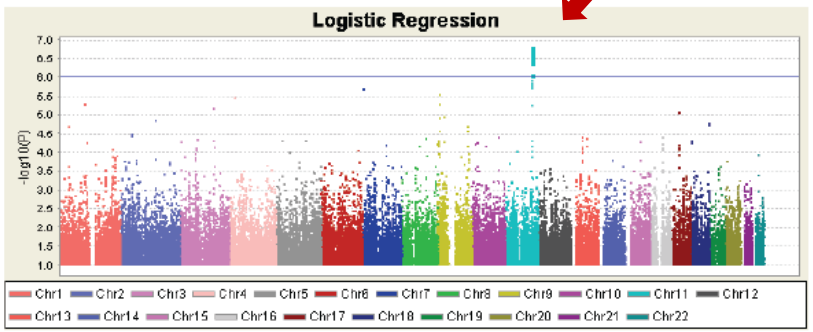
nature genetics

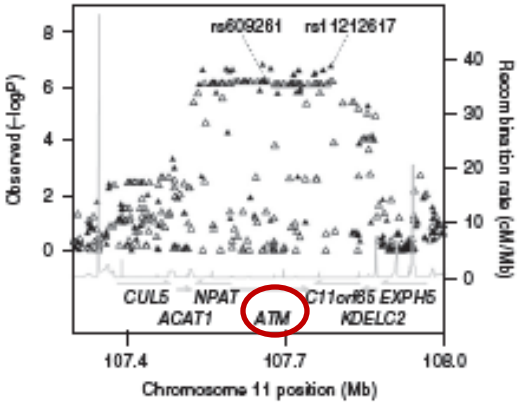
LETTERS

Un GWAS de respuesta la metformina

Common variants near *ATM* are associated with glycemic response to metformin in type 2 diabetes

The GoDARTS and UKPDS Diabetes Pharmacogenetics Study Group[1,2] & The Wellcome Trust Case Control Consortium 2[2]





The C Allele of *ATM* rs11212617 Does Not Associate With Metformin Response in the Diabetes Prevention Program

Jose C. Florez, md, phd[1,2,3]
Kathleen A. Jablonski, phd[4]
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Edward Horton, md[3,6]
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nature genetics

Consorcio MetGen

Variation in the glucose transporter ; associated with glycemic response to

Kaixin Zhou[1,46], Sook Wah Yee[2,46], Eric L Seiser[3], Nienke van Leeuwen[
Christopher J Groves[5], Ruth L Coleman[6], Amber A van der Heijden[7], Jol
Linda Zaharenko[11,12], Daniel M Rotroff[13,14], Mattijs Out[15,16], Kathleen A
Jozef Židzik[19], Albert M Levin[20], L Keoki Williams[21,22], Tanja Dujic[1,23]
Huan-Chieh Chien[2], Shiro Maeda[26,27], John S Witte[28–31], Longyang Wu
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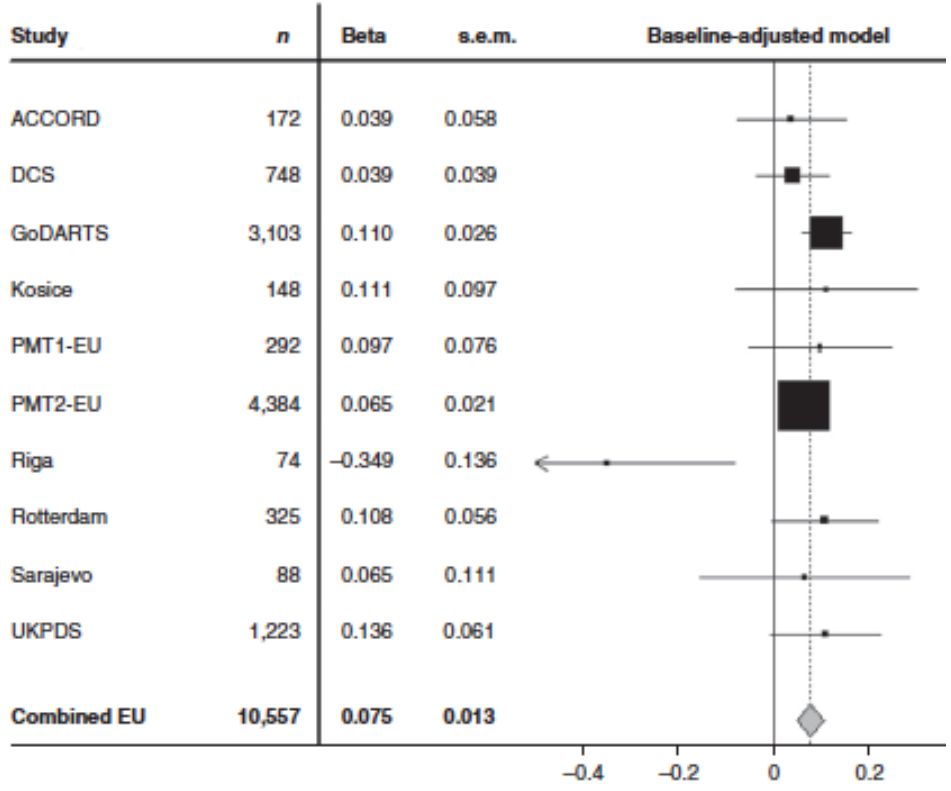
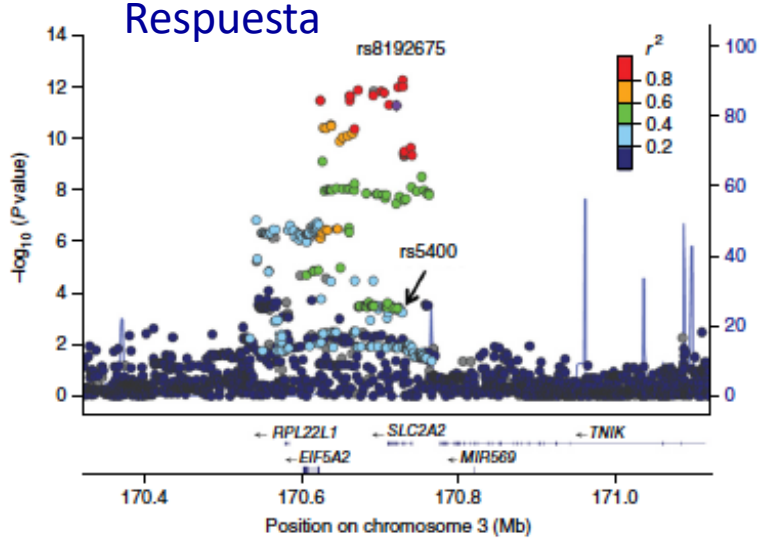
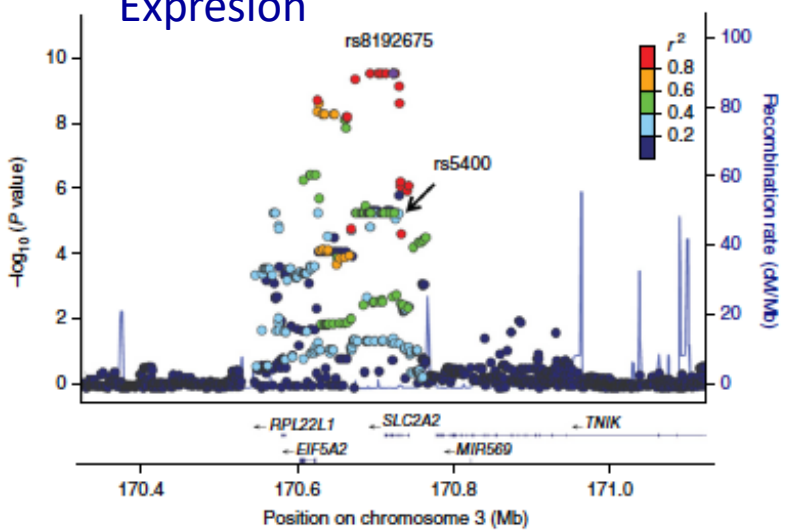
ACCORD Investigators[34], Calum Sutherland[1], Janis Klovins[11,12], Valdi
Bruno H Stricker[10,37], Alison A Motsinger-Reif[13], Michael J Wagner[38],
Rury R Holman[6], Mark I McCarthy[5,40,41], Monique M Hedderson[42], Co
Kathleen M Giacomini[2,29,47] & Ewan R Pearson[1,47]



Respuesta



Expresión



El futuro

PARTNERS HEALTHCARE

Mensajes clave

1. La diabetes monogénica (neonatal y MODY) demuestra que la información genética puede guiar a la terapéutica
2. Los efectos en la diabetes tipo 2 son mucho más modestos, pero podrían llegar a la relevancia clínica (~10 mg/dl)
3. Esta información podría alterar las dosis utilizadas, o conllevar la elección de otra clase de fármacos
4. Son necesarios los estudios de replicación, desenlaces clínicos y coste
5. La estrategia sólo será viable si el genotipado de todas las variantes con repercusión clínica se realiza una sola vez

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Graciès