Optimización del tratamiento antidiabético: ¿Cómo cambia mi práctica clínica como especialista y como médico de atención primaria?

Dr. Sergio Cinza Sanjurjo

@SergioCinza

scinzas@semergen.es

Médico de Familia

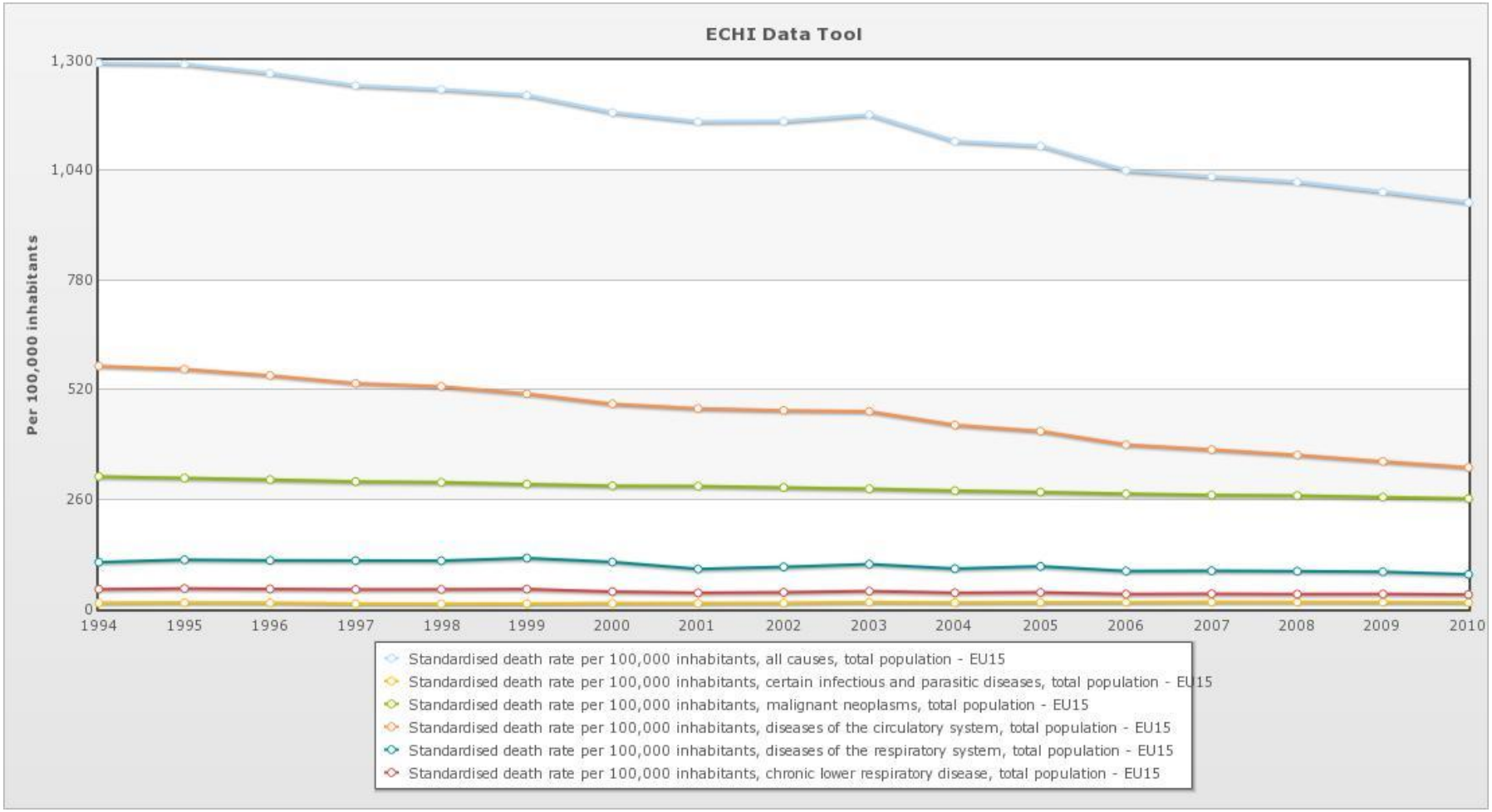
C.S. Porto do Son

Conflicto de intereses

- Almirall
- Astra Zeneca
- Boehringer-Ingelheim
- Esteve
- Lilly
- MSD
- Mundipharma
- Novartis
- Novo-Nordisk
- Sanofi-Aventis

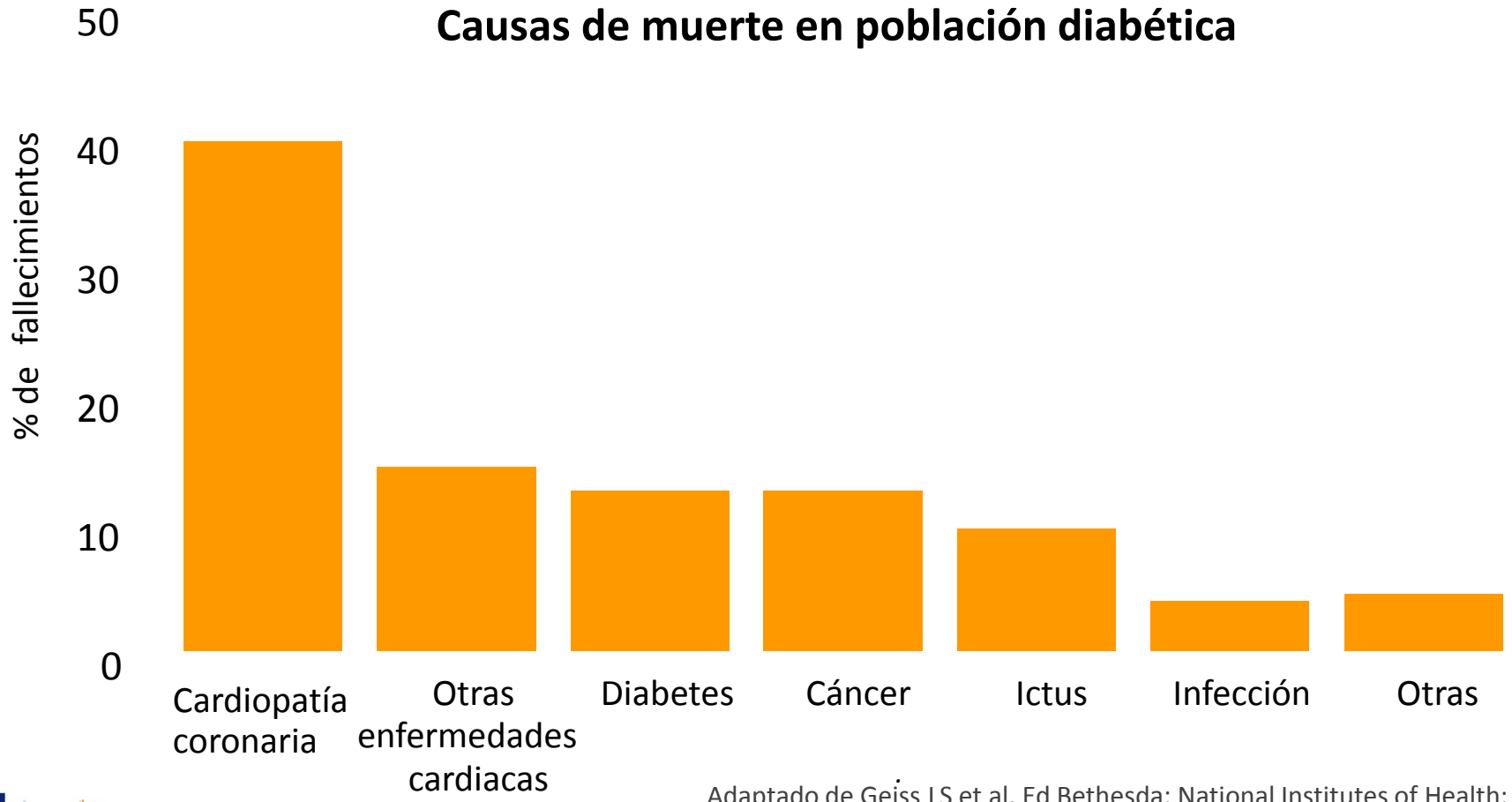
Aspectos importantes de la ECV y la DM en la población

ECV primera causa de mortalidad en UE



http://ec.europa.eu/health/dyna/echi/datatool/index.cfm?indlist=13

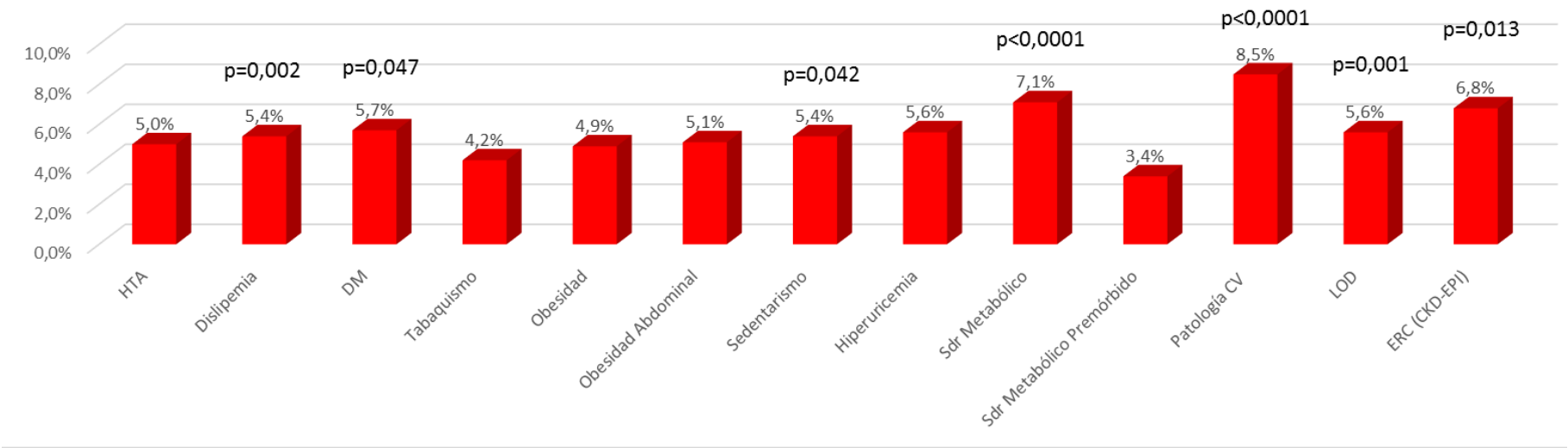
Las enfermedades cardiovasculares son responsables del 70% de las muertes en pacientes con diabetes

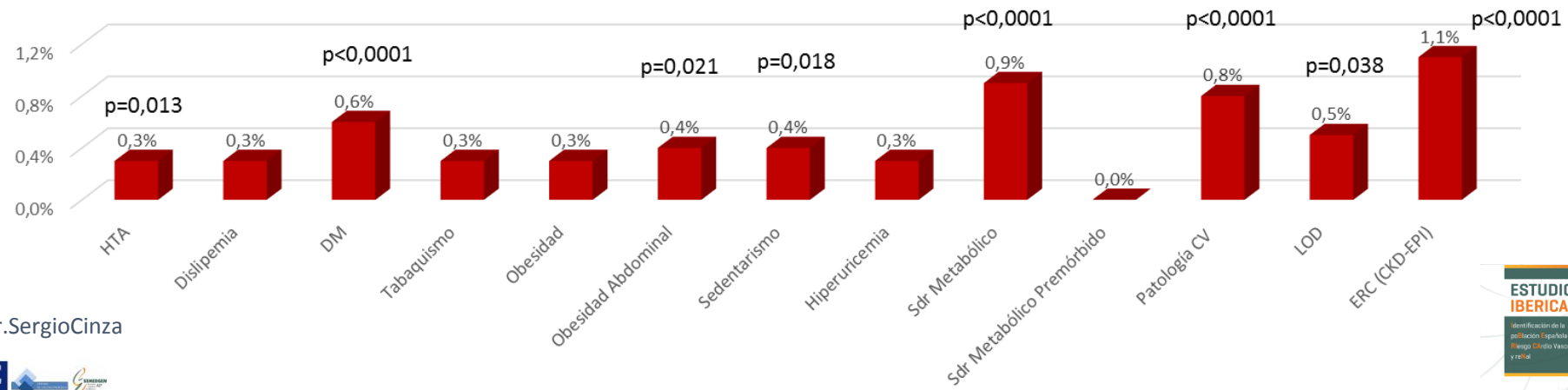


Adaptado de Geiss LS et al. Ed Bethesda: National Institutes of Health; 1995

Pronóstico CV: eventos CV

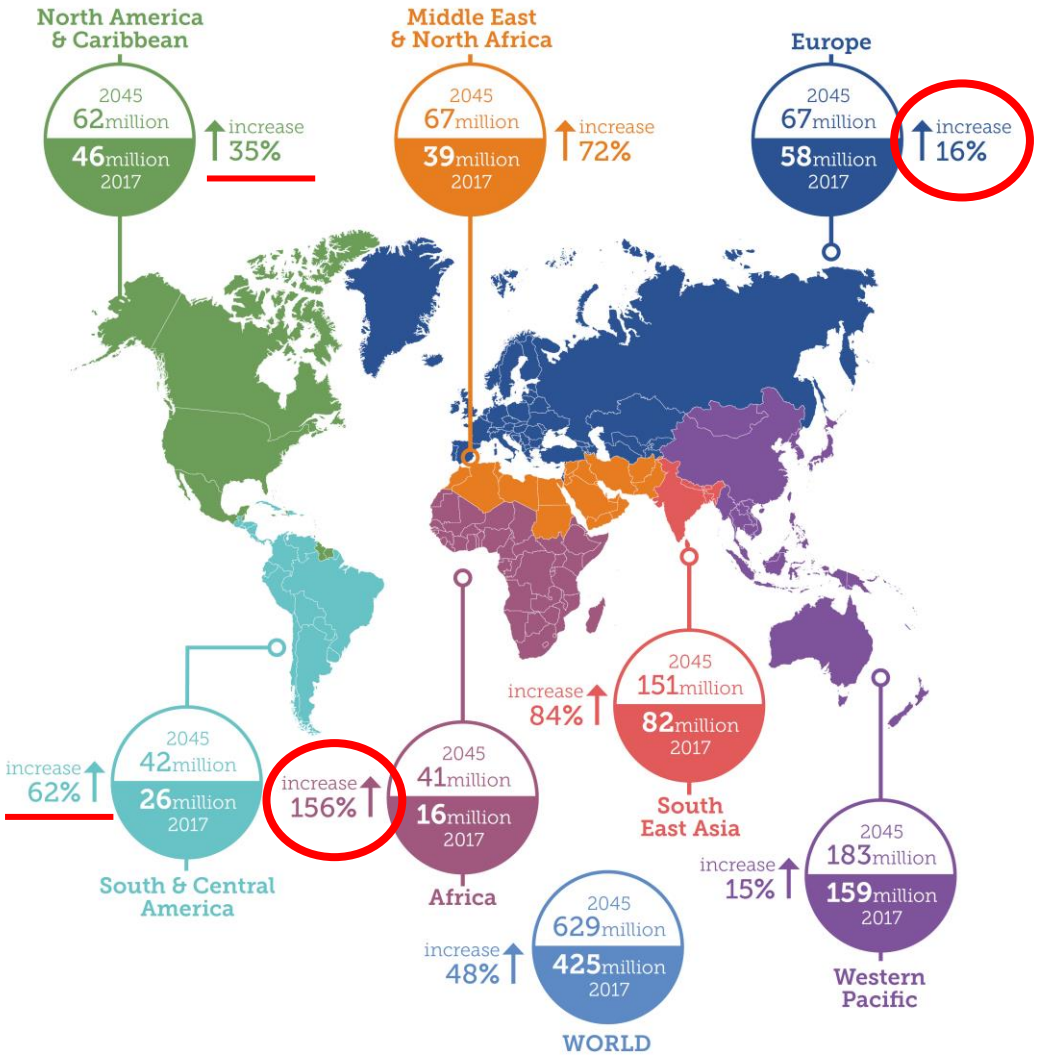
N=6.007





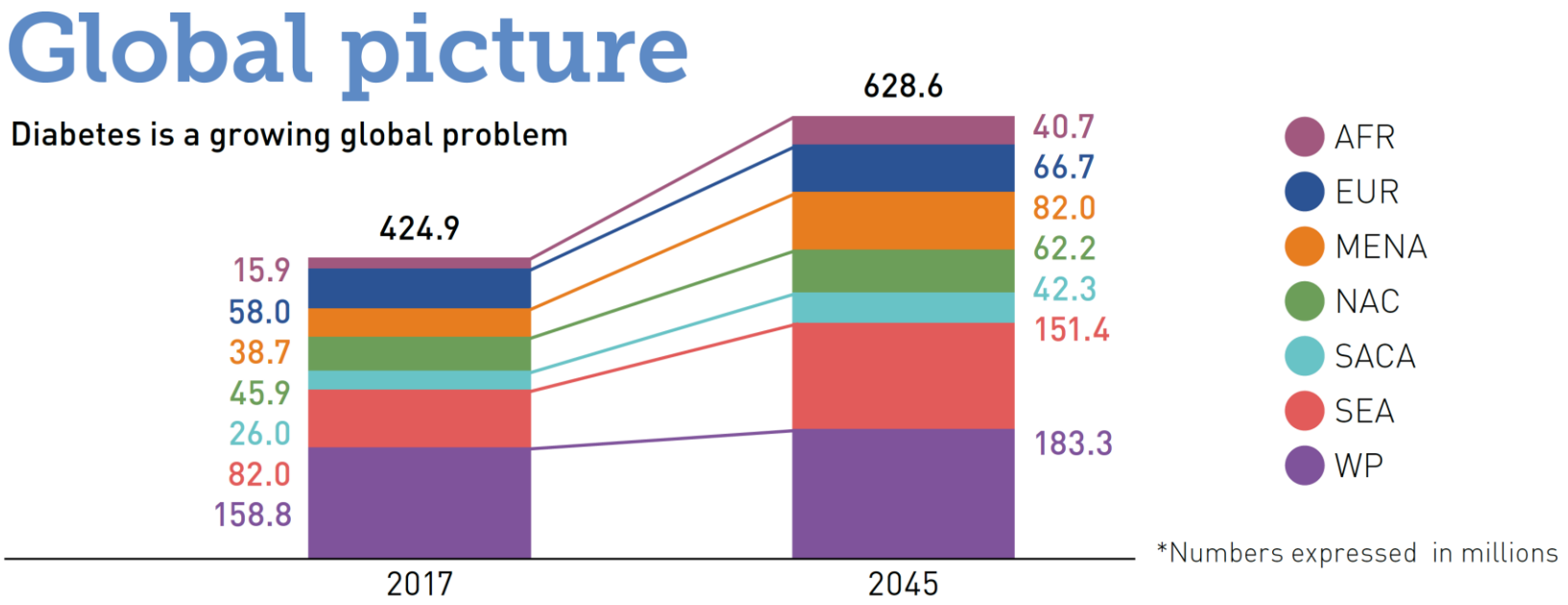
ESTUDIO IBERICAN

Atlas de diabetes 2017-2045



Atlas de diabetes de la IDF, 8ª edición 2017

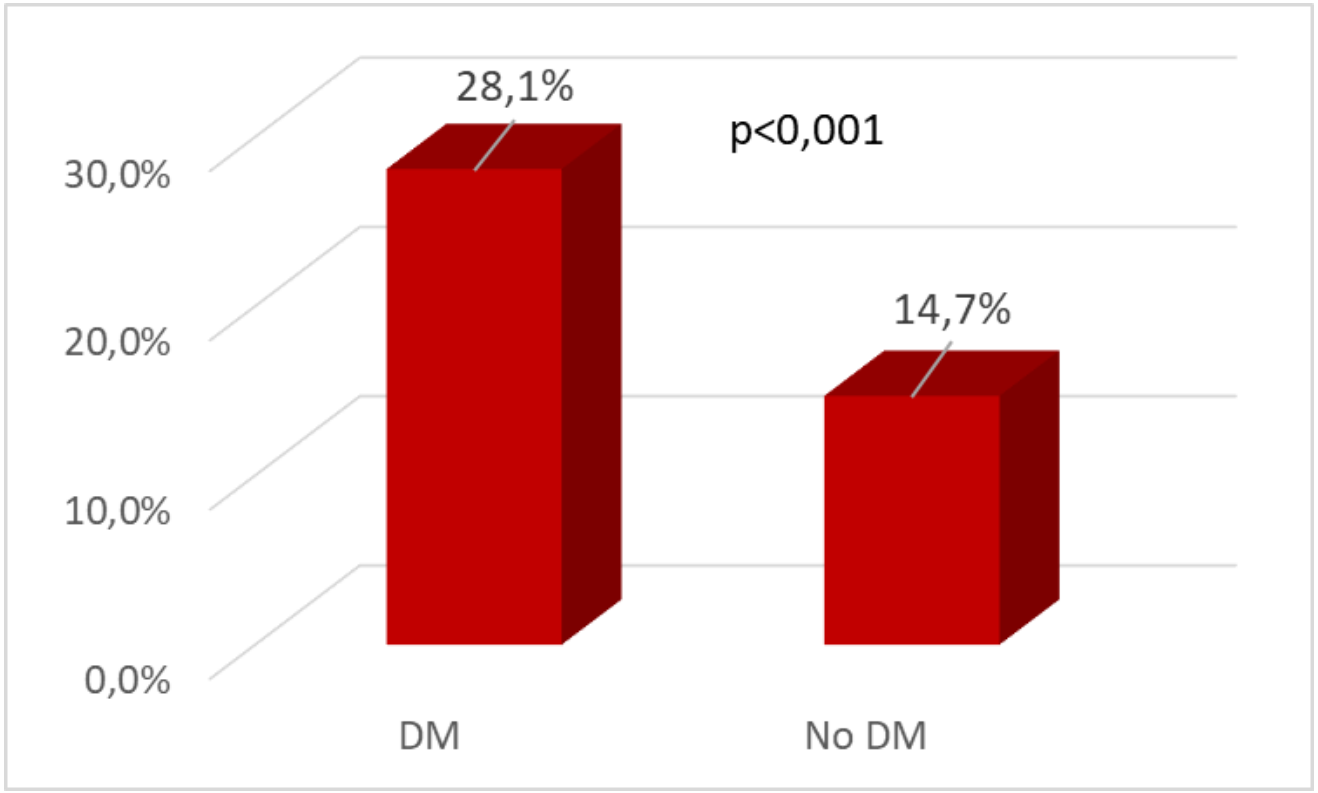
Atlas de diabetes 2017-2045



Atlas de diabetes de la IDF, 8ª edición 2017

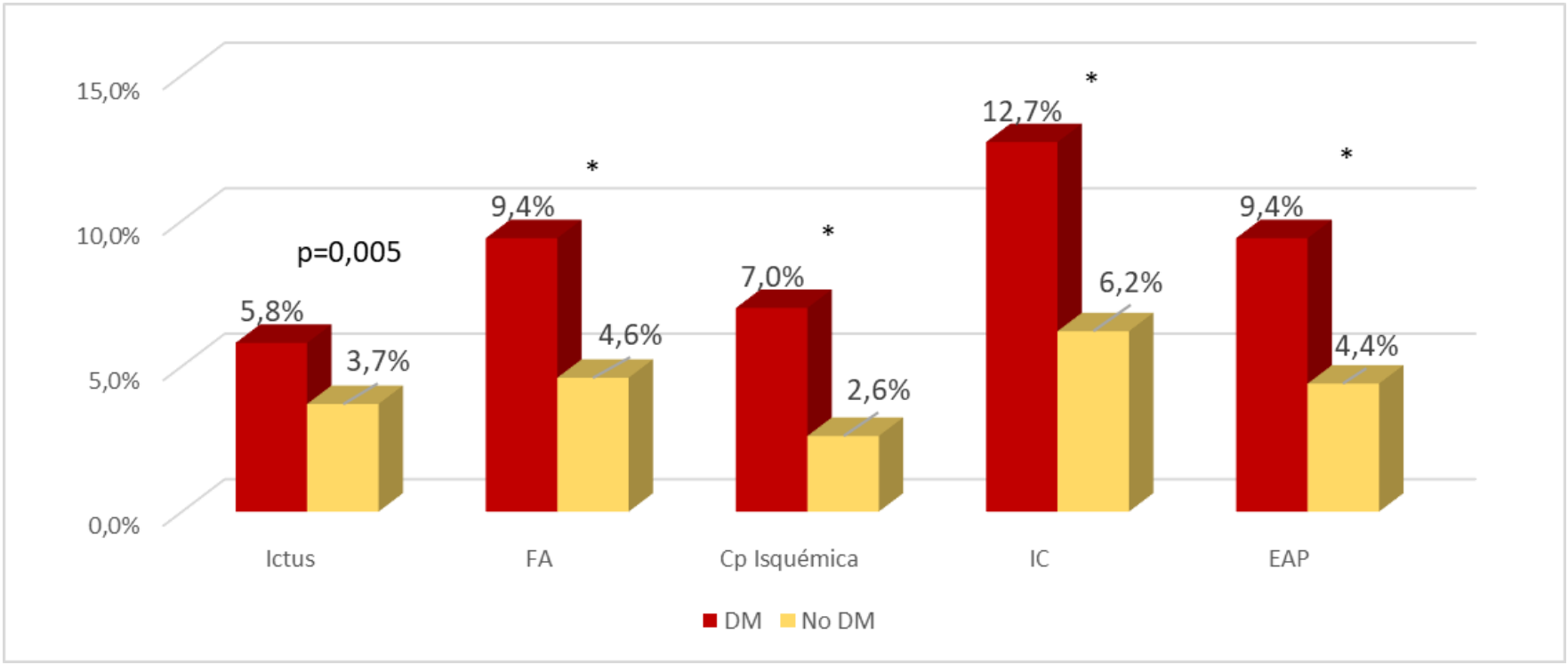
Enfermedad CV en DMt2

N=6.007



Enfermedad CV en DMt2

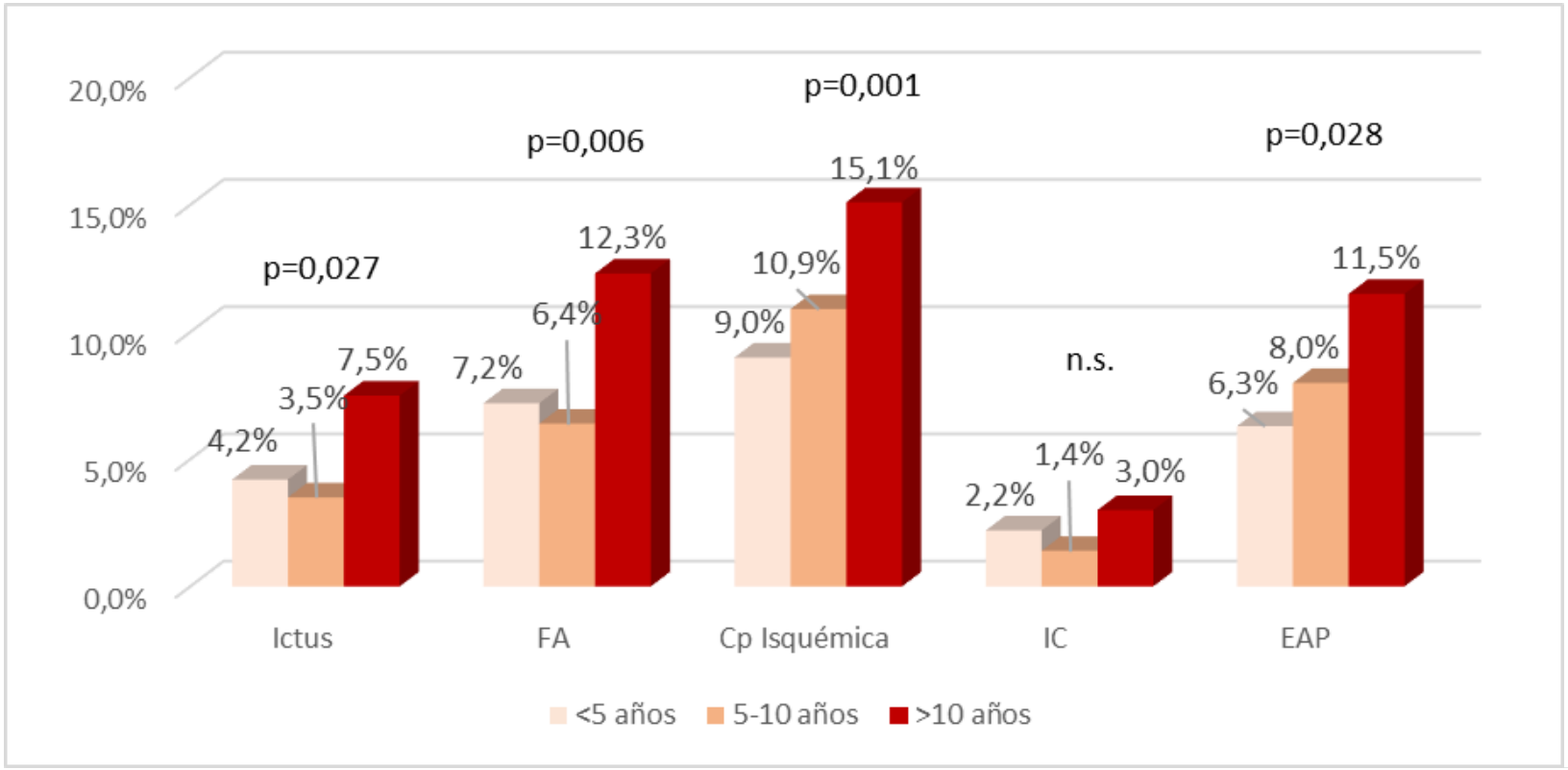
N=6.007



*: p<0,001

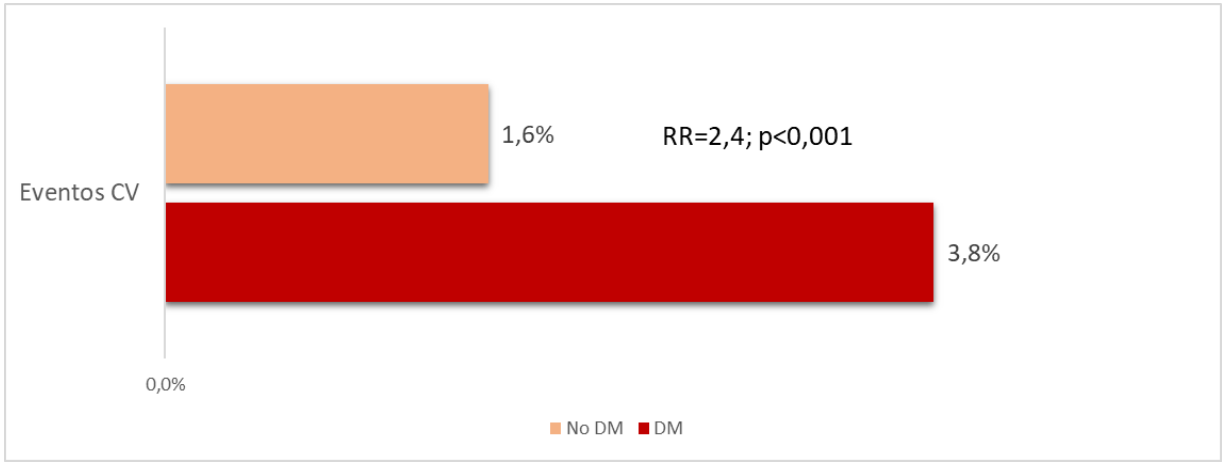
ECV en función de antigüedad DM

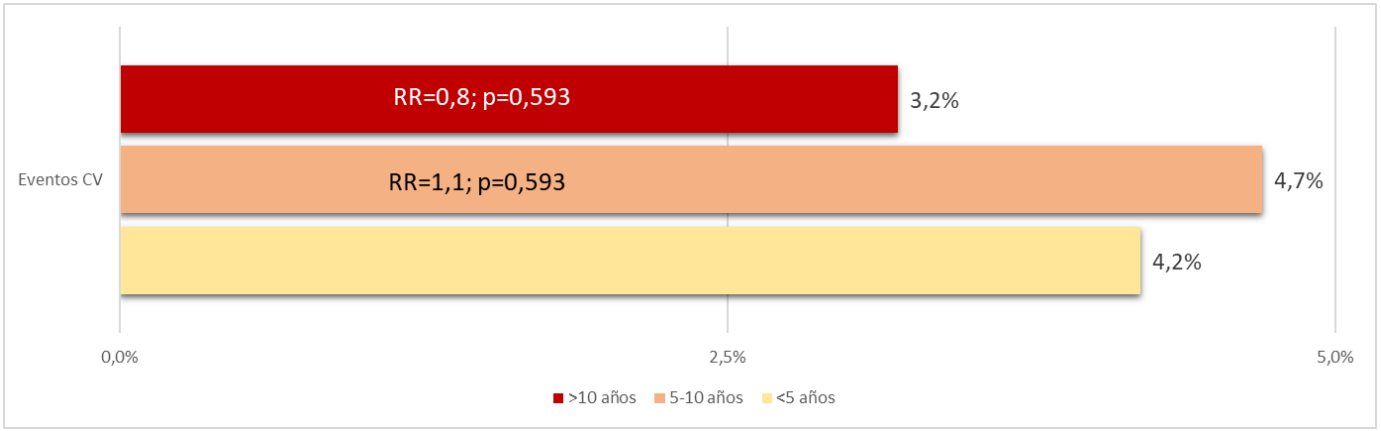
N=6.007



Eventos CV asociados a DM

N=6.007



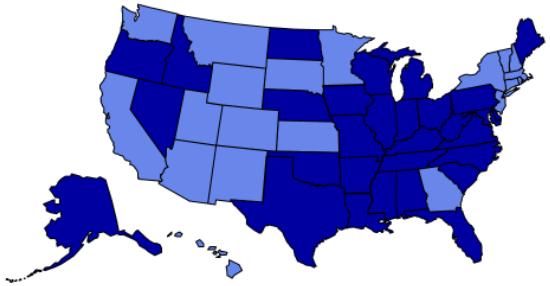


¿Factores asociados en el paciente diabético?

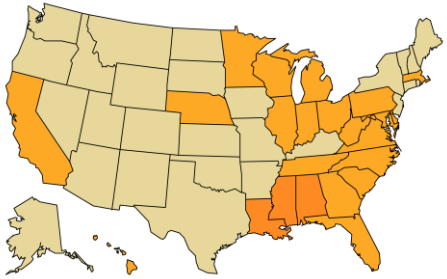
Prevalencia de DM ligada a los hábitos de vida

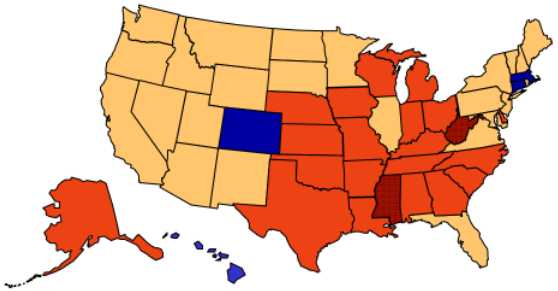
Obesidad

DM

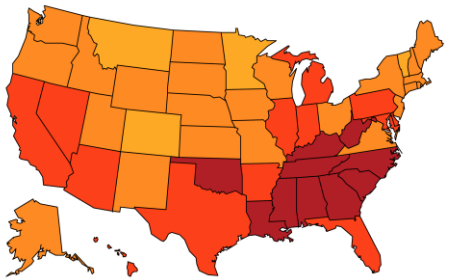


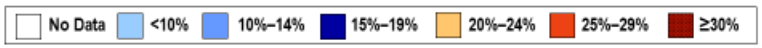
1996





2006





Asociación entre obesidad y DM

	Prevalence of type 2 diabetes and abdominal obesity						
	1999/2000	2001/2002	2	2009/2010	2011/2012	2013/2014	
Type 2 diabetes	3959	4492	4	5684	4966	5328	Mean change per year
20–44 years	2.3(1.4;3.1)n = 1614	3.4(2.0;4.8)n = 1892	2	2.5(1.7;3.3)n = 2381	3.5(2.5;4.5)n = 2141	3.3(2.6;4.0)n = 2265	0.04(−0.03;0.10)
45–64 years	11.8(9.5;14.2)1224	11.8(9.0;14.7)n = 1417	1	13.3(11.4;15.2)n = 1925	14.3(11.8;16.8)n = 1733	15.5(13.1;17.8)n = 1846	0.24(0.06;0.41)
≥65 years	18.4(14.2;22.6)n = 1121	18.5(15.9;21.1)n = 1183	2	25.7(22.6;28.7)n = 1378	22.4(19.5;25.3)n = 1092	24.6(22.2;27.0)n = 1217	0.46(0.23;0.69)
Total population	8.8(7.2–10.4)	9.3(7.8–10.8)	1	10.8(9.8–11.8)	11.0(9.5–12.5)	11.7(10.9–12.6)	0.19(0.09–0.28)
Abdominal obesity	3847	4296	4	5421	4709	5059	Mean change per year
20–44 years	36.5(32.0;41.1)n = 1582	36.6(34.5;38.7)n = 1835	4	42.3(38.4;46.3)n = 2298	43.8(39.1;48.5)n = 2064	48.1(45.8;50.4)n = 2193	0.71(0.45;0.97)
45–64 years	54.5(48.3;60.7)n = 1200	56.6(53.1;60.1)n = 1378	6	61.5(57.7;65.2)n = 1856	63.4(58.8;68.0)n = 1661	62.3(59.7;64.9)n = 1768	0.55(0.23;0.86)
≥65 years	60.0(55.1;64.8)n = 1065	62.5(59.3;65.7)n = 1083	6	68.0(65.2;70.9)n = 1267	68.3(63.0;73.6)n = 984	69.9(64.7;75.1)n = 1098	0.61(0.28;0.94)
Total population	47.4(42.6;52.2)	48.6(46.3;50.9)	5	54.0(51.0;57.0)	55.3(51.3;59.4)	57.2(55.9;58.5)	0.62(0.38;0.86)
Missing waist circumference	112	196	2	263	257	269	

Type 2 diabetes	Mean change per year
20–44 years	0.04(−0.03;0.10)
45–64 years	0.24(0.06;0.41)
≥65 years	0.46(0.23;0.69)
Total population	0.19(0.09–0.28)
Abdominal obesity	Mean change per year
20–44 years	0.71(0.45;0.97)
45–64 years	0.55(0.23;0.86)
≥65 years	0.61(0.28;0.94)
Total population	0.62(0.38;0.86)
Missing waist circumference	

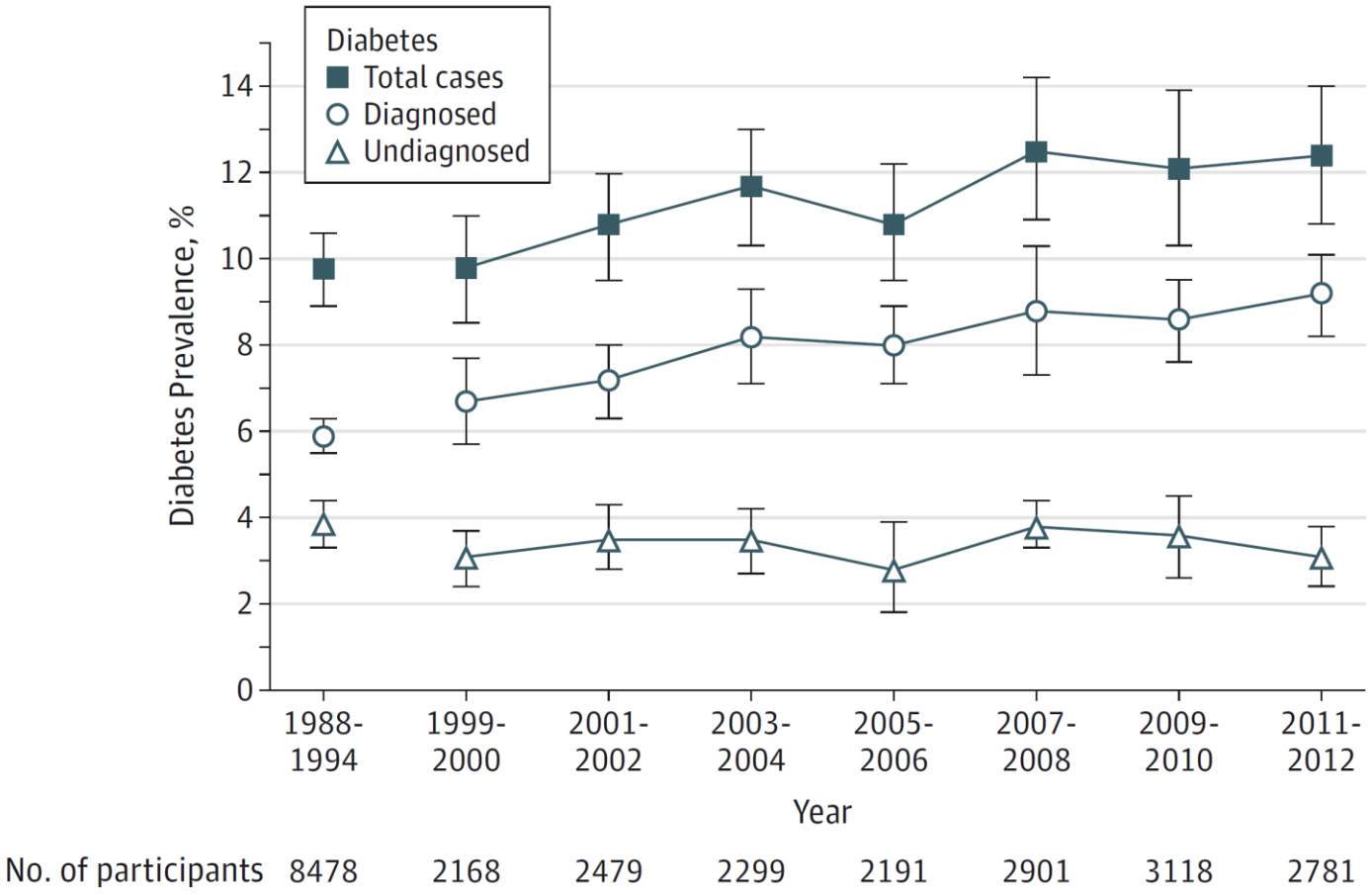
Caspard, et al. Recent trends in the prevalence of type 2 diabetes and the association with abdominal obesity lead to growing health disparities in the USA: An analysis of the NHANES surveys from 1999 to 2014. Diabetes Obes Metab 2018

Asociación entre obesidad y DM

No. of participants								
Obese	2324	727	732	815	820	1137	1302	1075
Overweight	2942	724	878	784	694	949	1009	852
Normal weight	3025	645	699	624	604	726	762	785

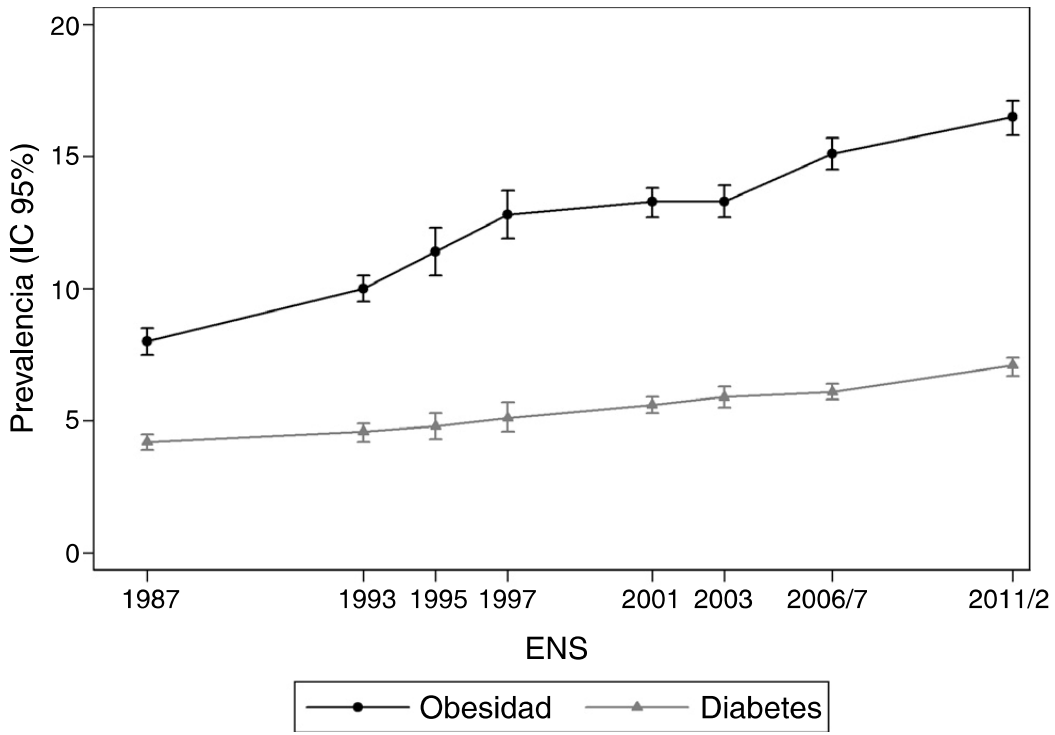
Menke, et al. Prevalence of and Trends in Diabetes Among Adults in the United States, 1988-2012. JAMA 2015

Asociación entre obesidad y DM



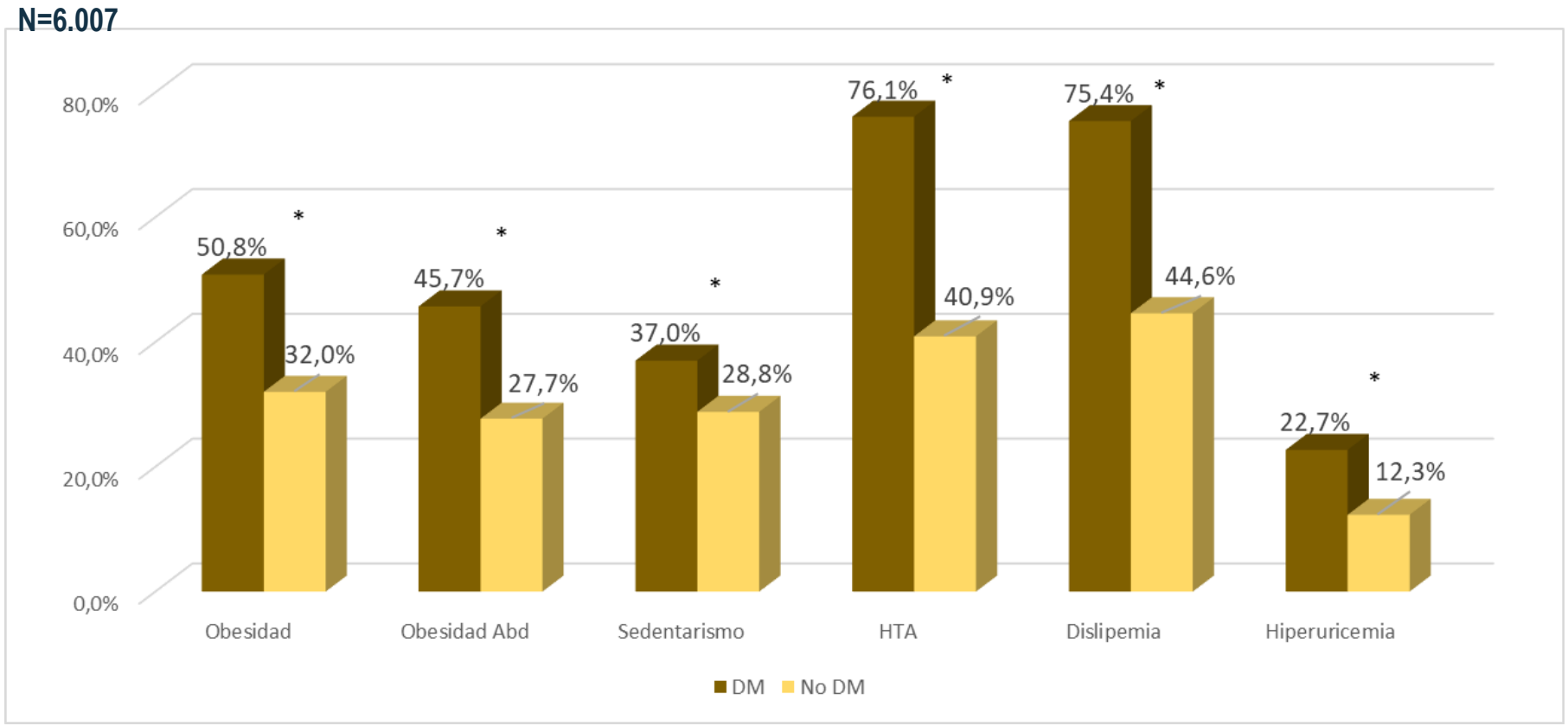
Menke, et al. Prevalence of and Trends in Diabetes Among Adults in the United States, 1988-2012. JAMA 2015

Relación entre obesidad y DM en España



Med Clin (Barc). 2017;**148(6)**:250–256

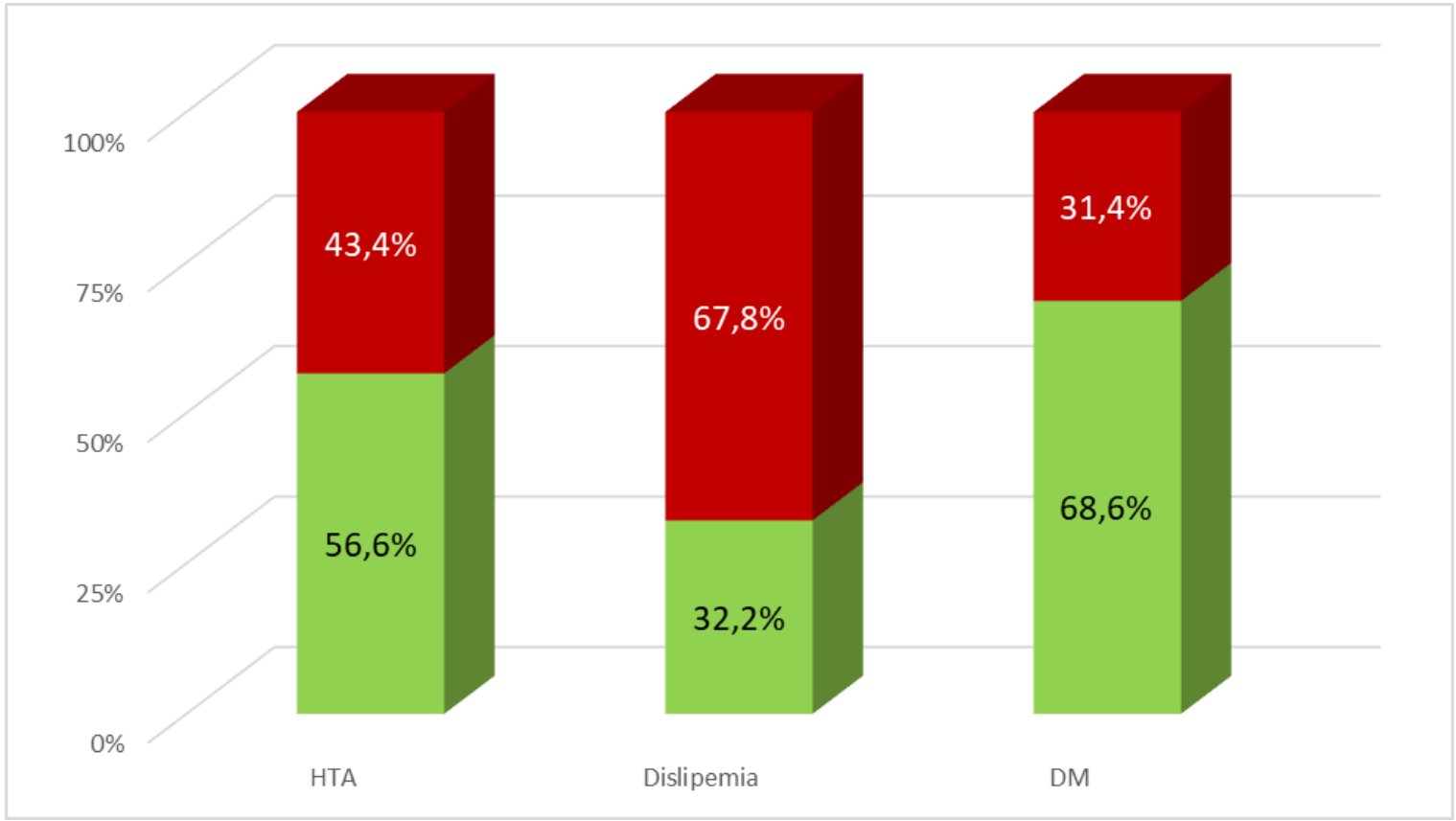
FRCV en pacientes con DM



*: p<0,001

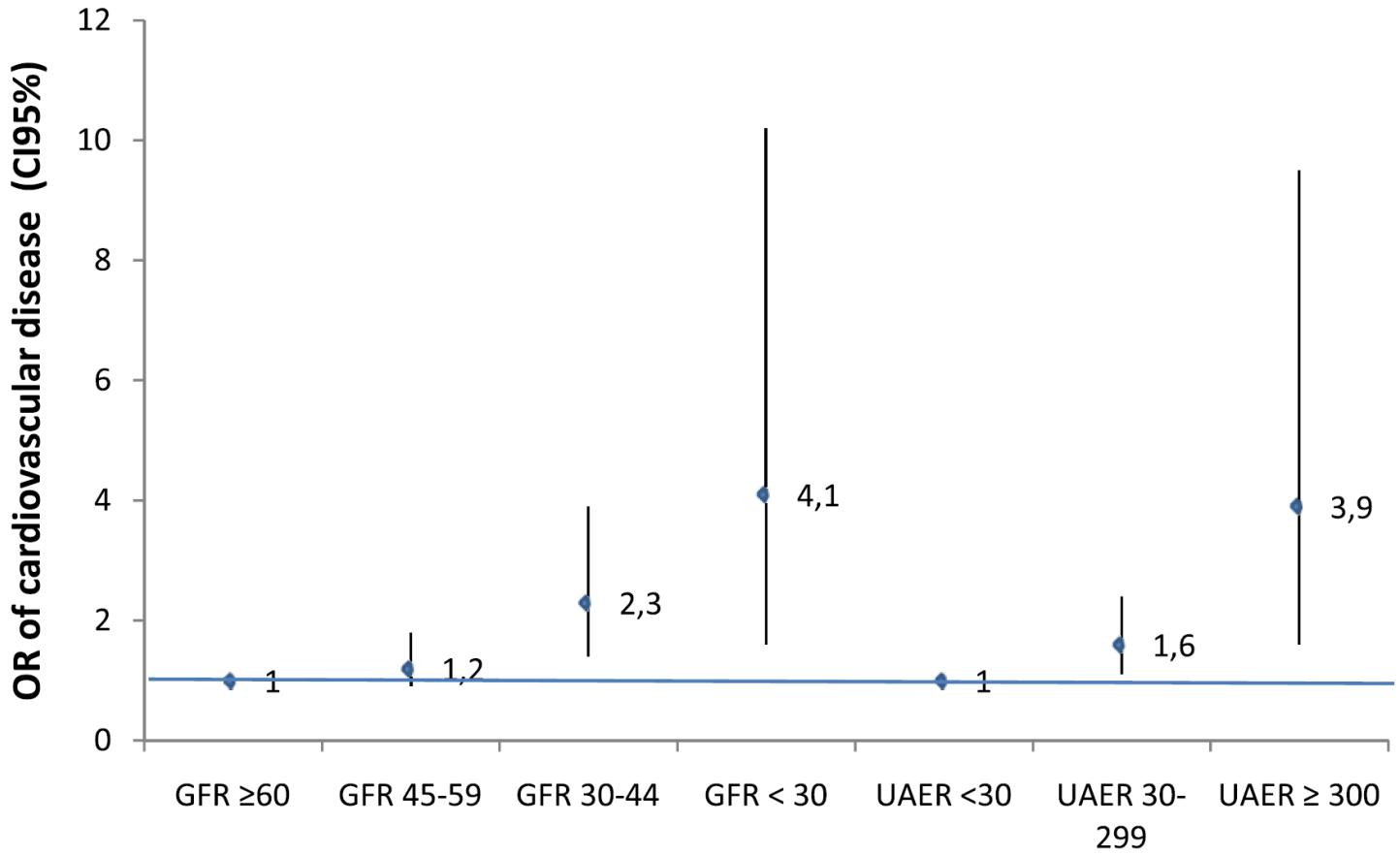
Grado de control de los FRCV

N=6.007



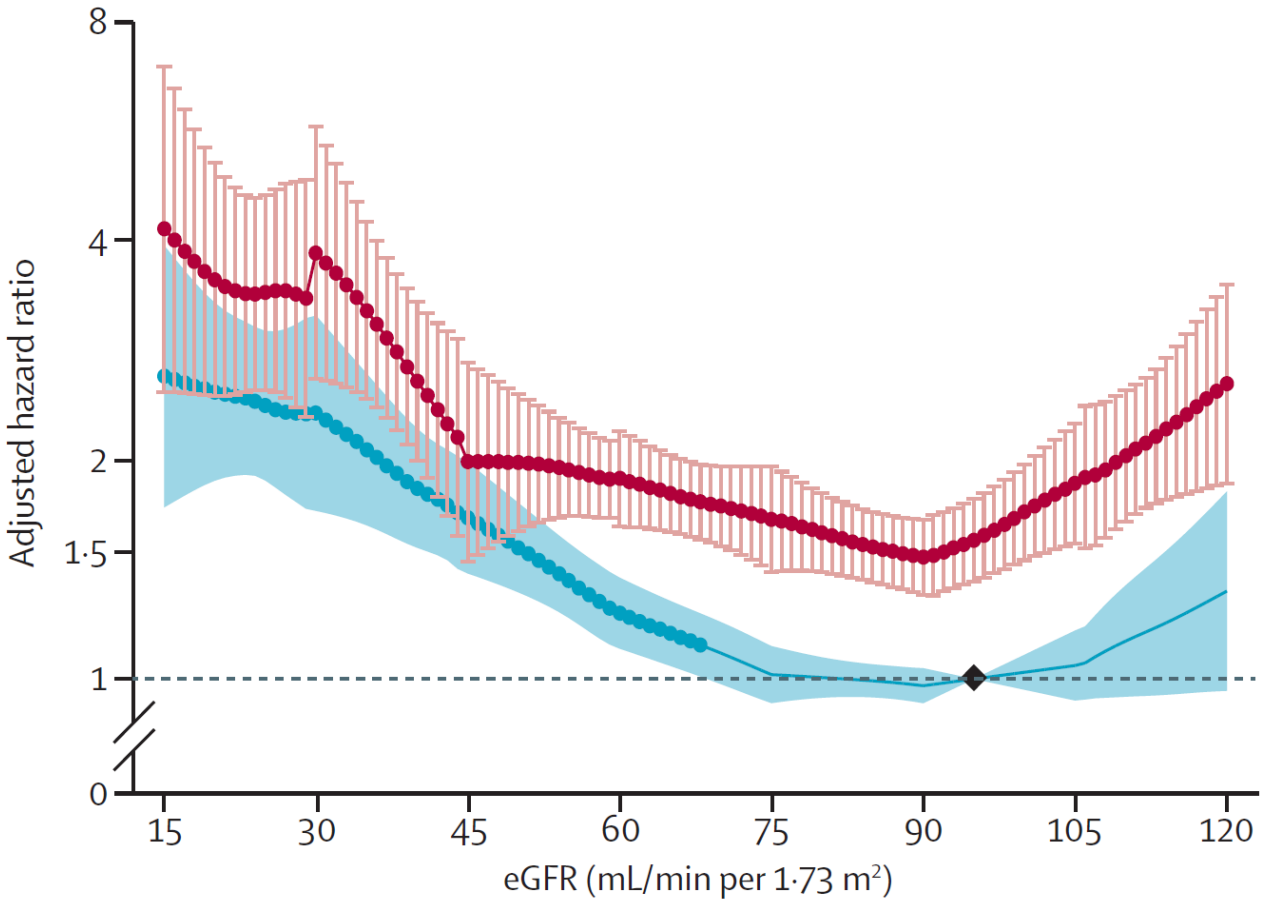
ESTUDIO IBERICAN

Relación entre la ERC y ECV en España



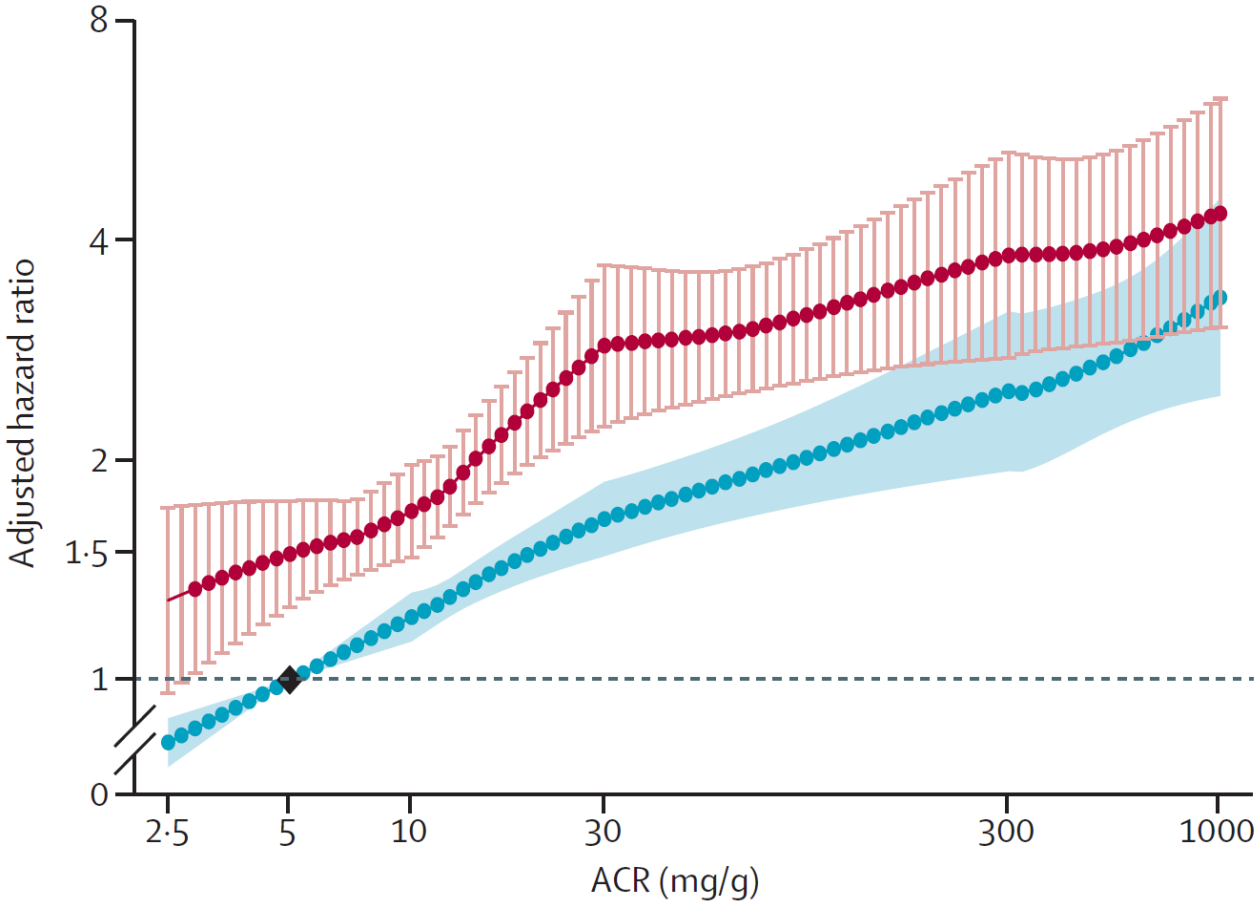
Rodríguez-Poncelas, et al. PERCEDIME2 study. BMC Nephrology 2014

Mortalidad cardiovascular por FGe



Fox, et al. Associations of kidney disease measures with mortality and end-stage renal disease in individuals with and without diabetes: a meta-analysis. Lancet 2012

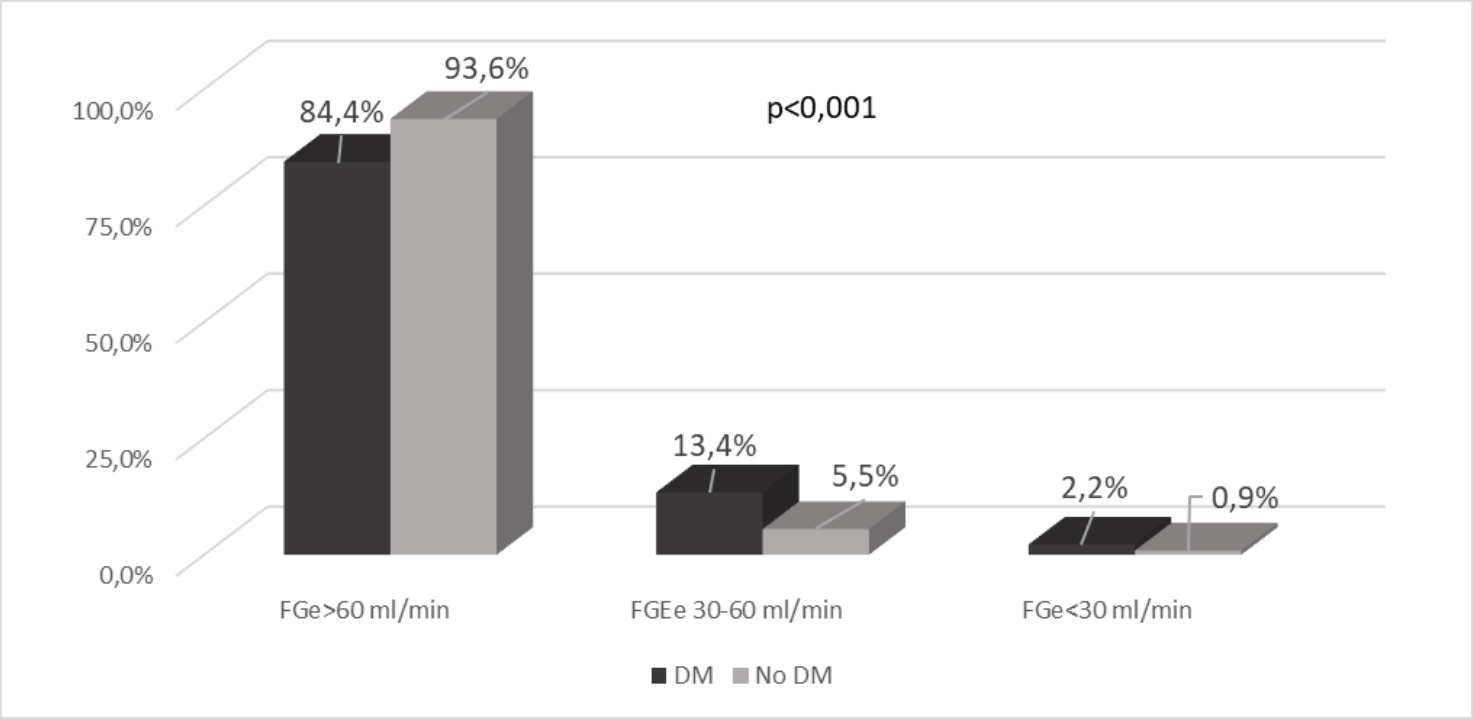
Mortalidad cardiovascular por Alb



Fox, et al. Associations of kidney disease measures with mortality and end-stage renal disease in individuals with and without diabetes: a meta-analysis. Lancet 2012

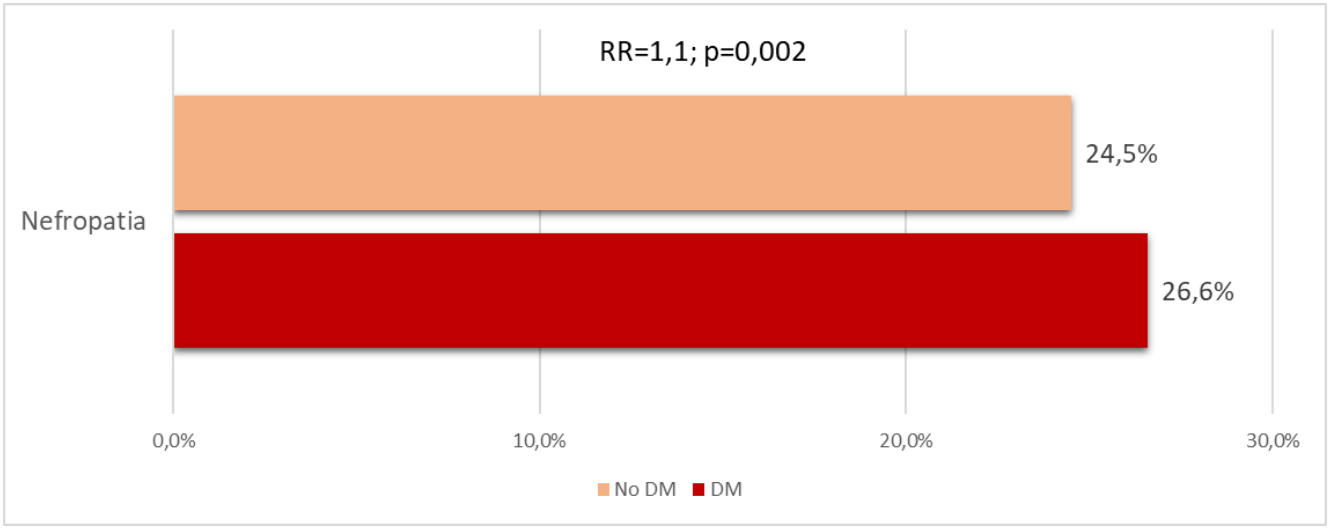
Enfermedad renal en DMt2

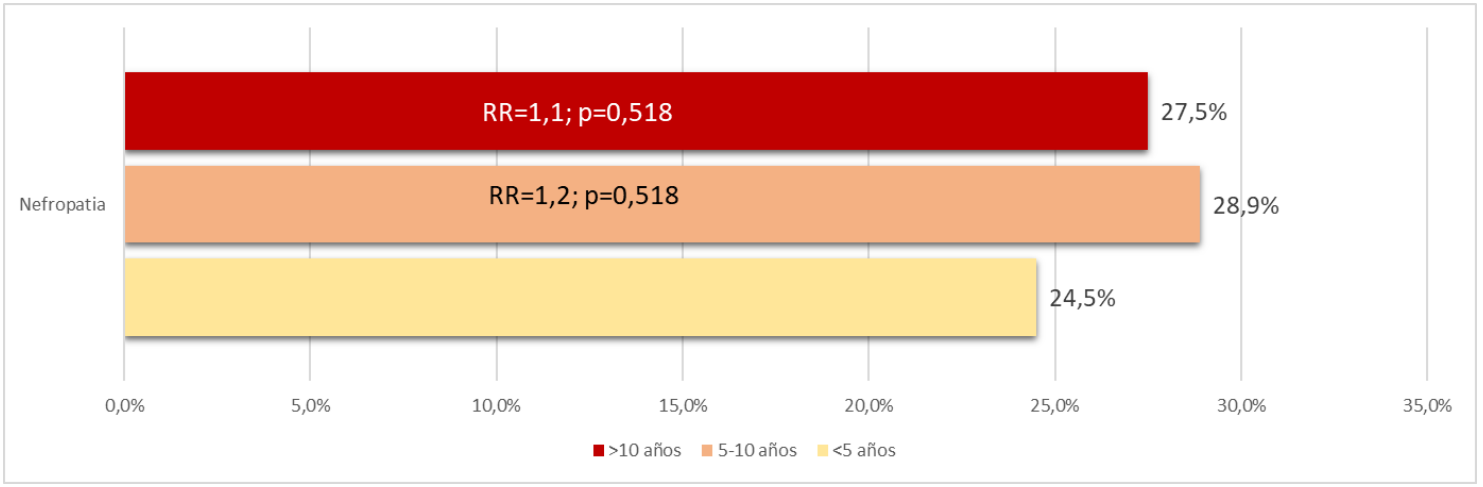
N=6.007



Eventos CV asociados a DM

N=6.007



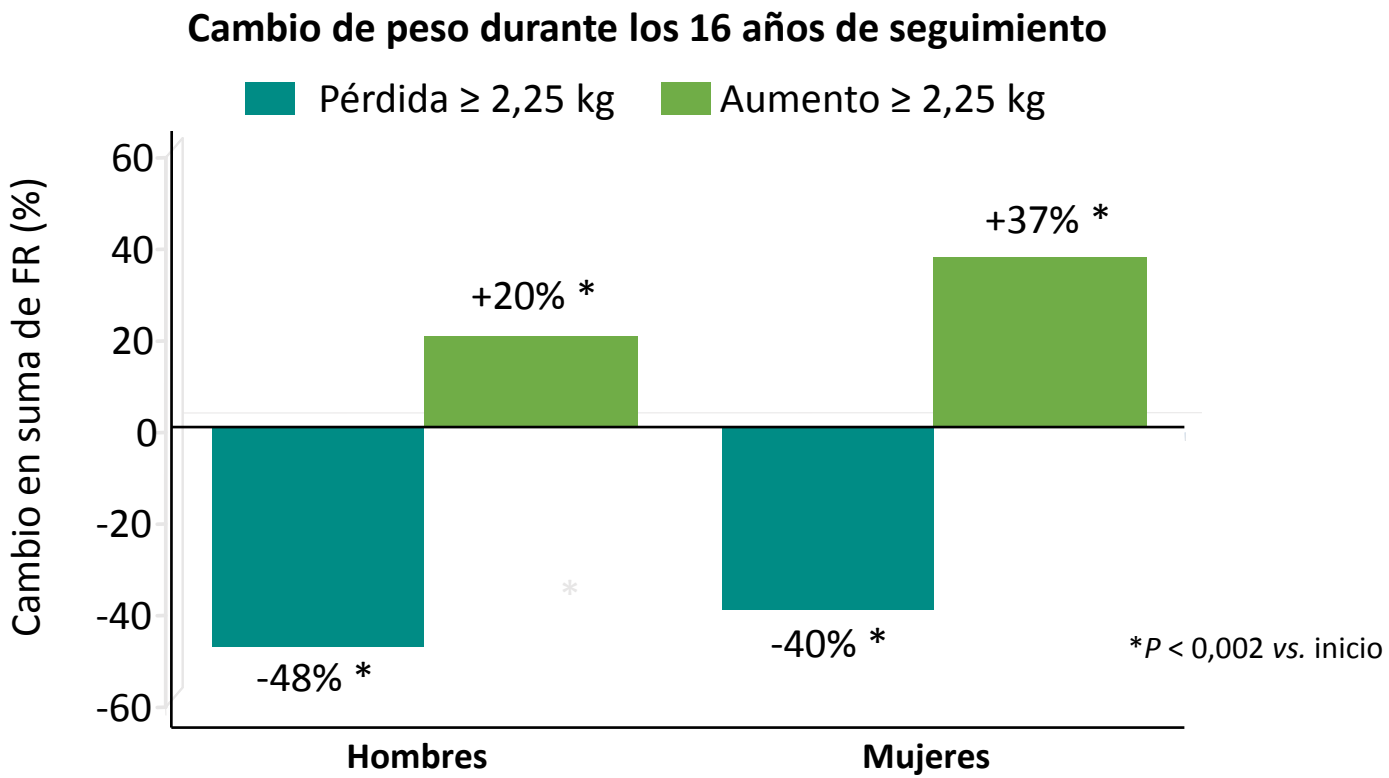


¿Cómo modificar el RCV del paciente diabético?

Modificaciones del peso

Repercusiones en el riesgo CV

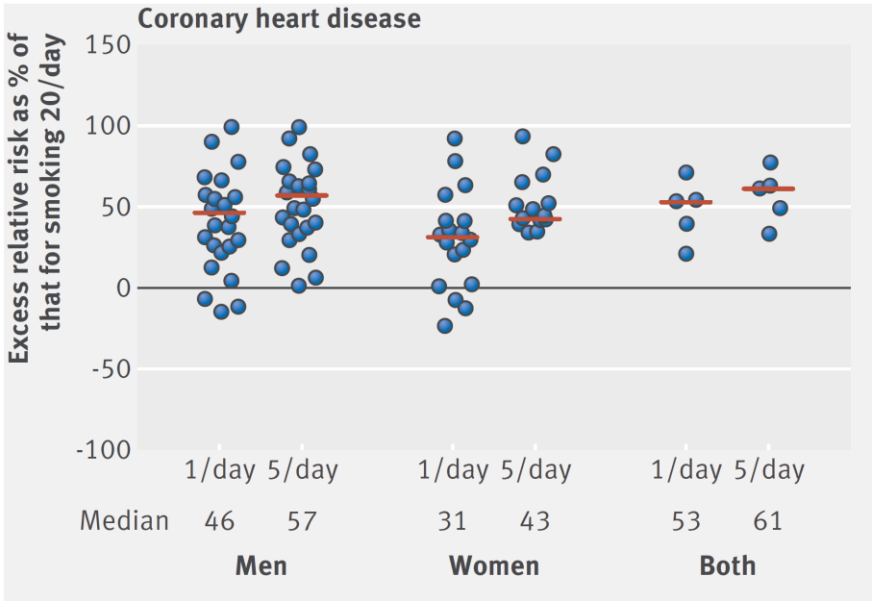
Relación entre el cambio de peso y la suma de factores de riesgo (FR) de la cardiopatía coronaria (CC): estudio Framingham Offspring

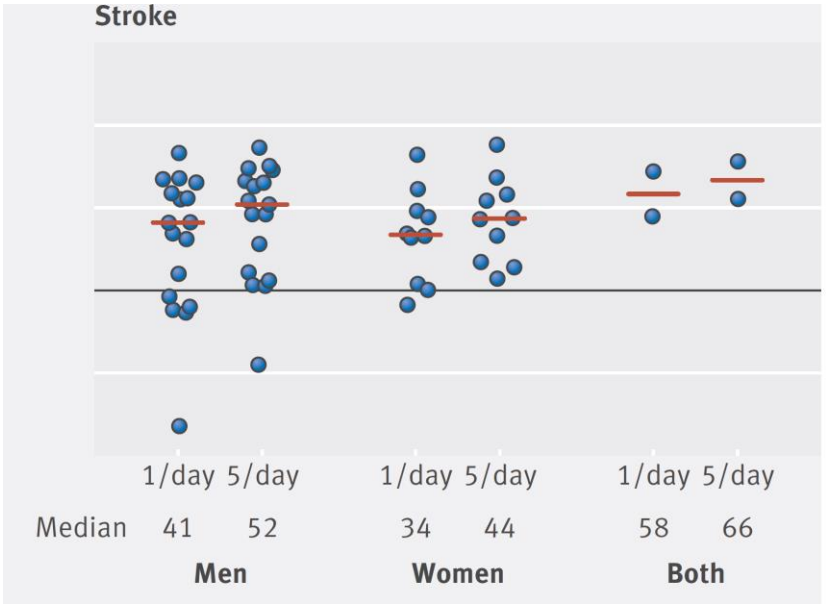


Wilson PWF et al. Arch Intern Med. 1999;159:1104-9.

Prevalencia de DM ligada a los hábitos de vida

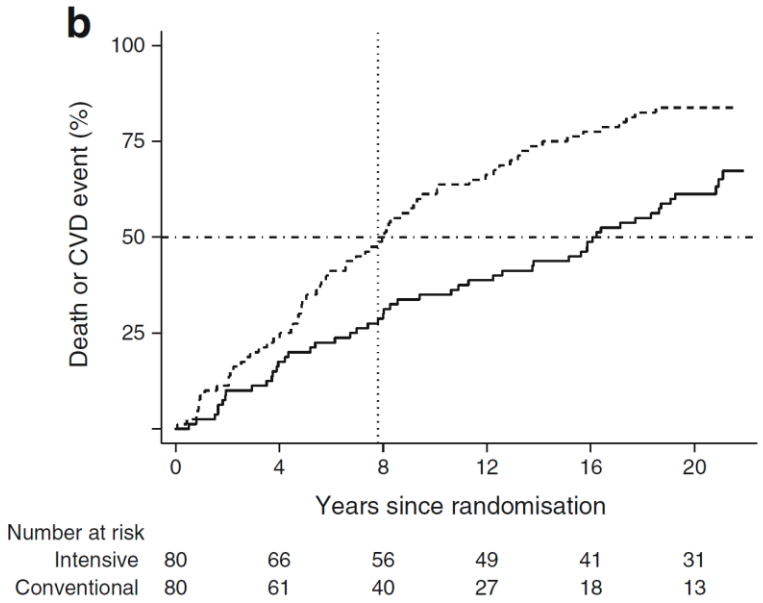
Abandono del tabaquismo: Objetivo=0 cig/día

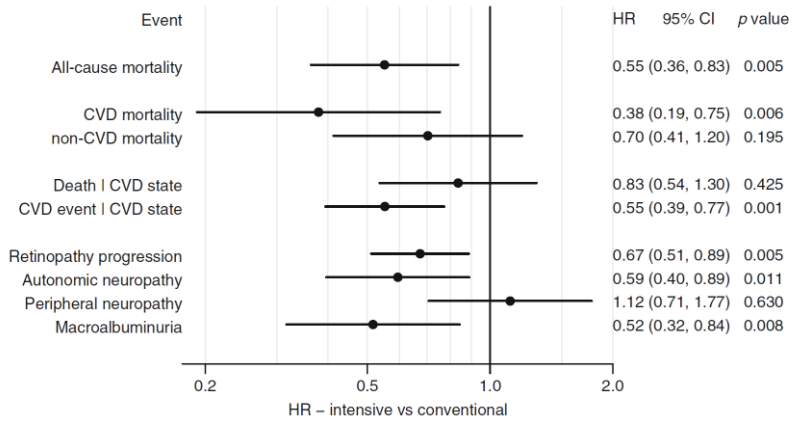




Hackshaw et al. Low cigarette consumption and risk of coronary heart disease and stroke: meta-analysis of 141 cohort studies in 55 study reports. BMJ 2018

El control intensivo de FRCV en diabéticos se asoció a menor tasa de ECV (Estudio STENO-2)

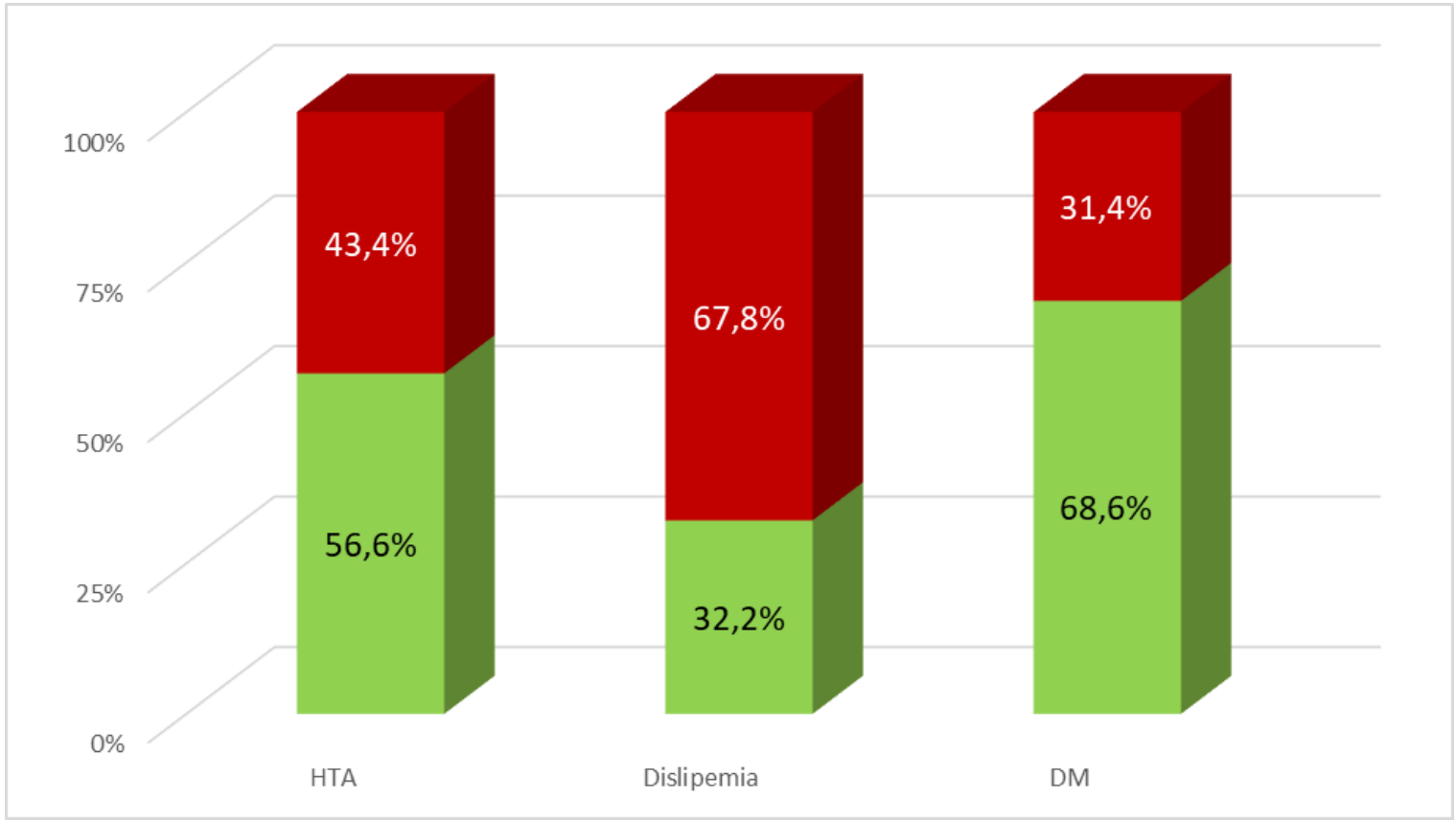




Gaede, P. Years of life gained by multifactorial intervention in patients with type 2 diabetes mellitus and microalbuminuria: 21 years follow-up on the Steno-2 randomised trial. Diabetologia 2016

Grado de control de los FRCV

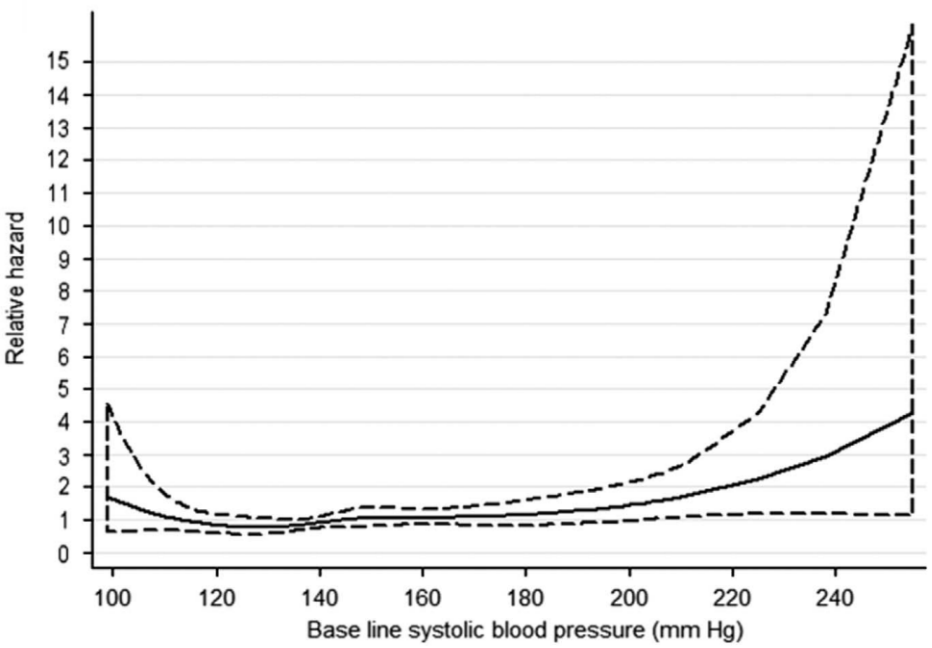
N=6.007



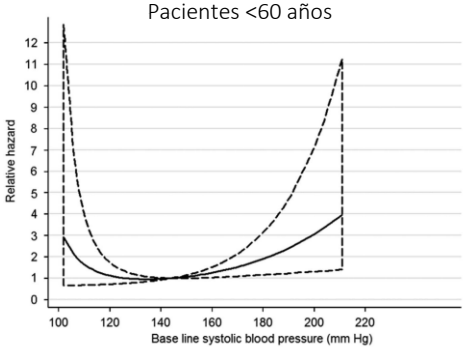
ESTUDIO IBERICAN

Reducir las cifras de PA excesivamente en pacientes diabéticos no aporta beneficio

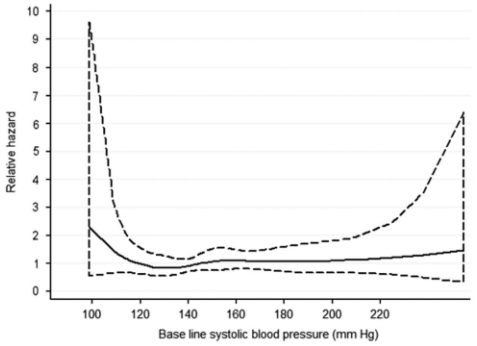
Pacientes que reciben tratamiento



Pacientes <60 años



Pacientes ≥60 años

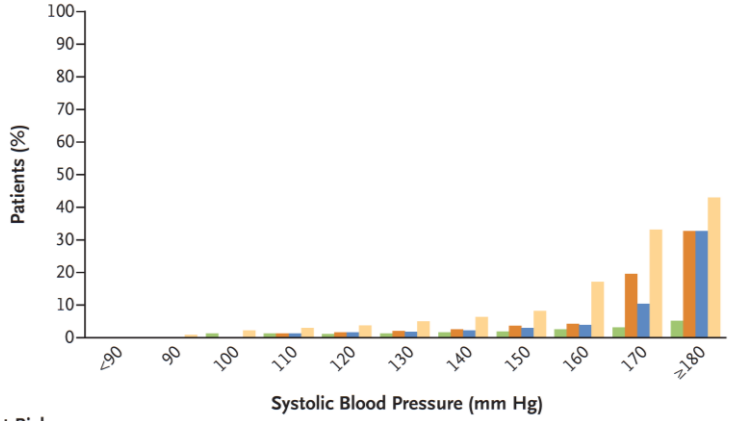


S Riyahi-Alam et al. Blood pressure and CVD in type 2 diabetes with hypertension. Journal of Human Hypertension. 2017

Relación entre PA ambulatoria y muerte cardiovascular

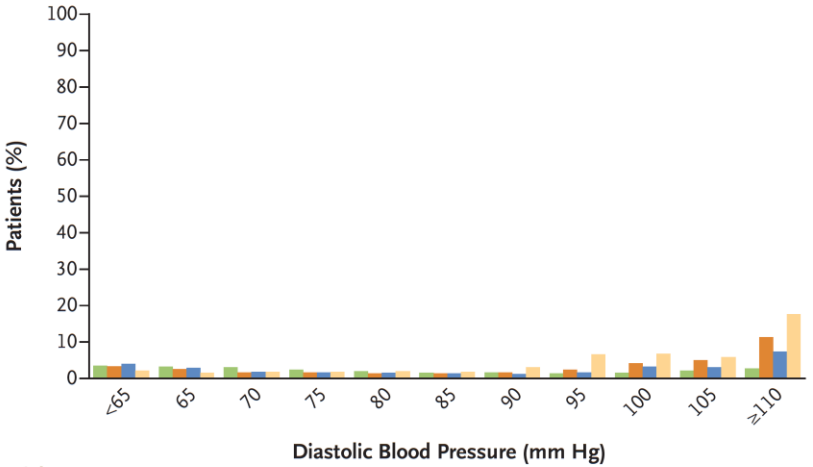
Clinic blood pressure | 24-Hr blood pressure | Daytime blood pressure | Nighttime blood pressure

C Risk of Death from Cardiac Causes across Systolic Blood-Pressure Values



No. at Risk											
Clinic	42	165	721	2,181	6,006	11,029	15,707	12,682	7,646	4,049	3,682
24-Hr	46	444	3,498	12,087	19,443	16,040	7,780	3,046	1,024	337	165
Daytime	35	301	2,349	8,912	17,332	18,075	10,437	4,233	1,510	500	226
Nighttime	648	3,983	12,419	17,691	14,205	8,149	3,927	1,747	690	268	183

D Risk of Death from Cardiac Causes across Diastolic Blood-Pressure Values

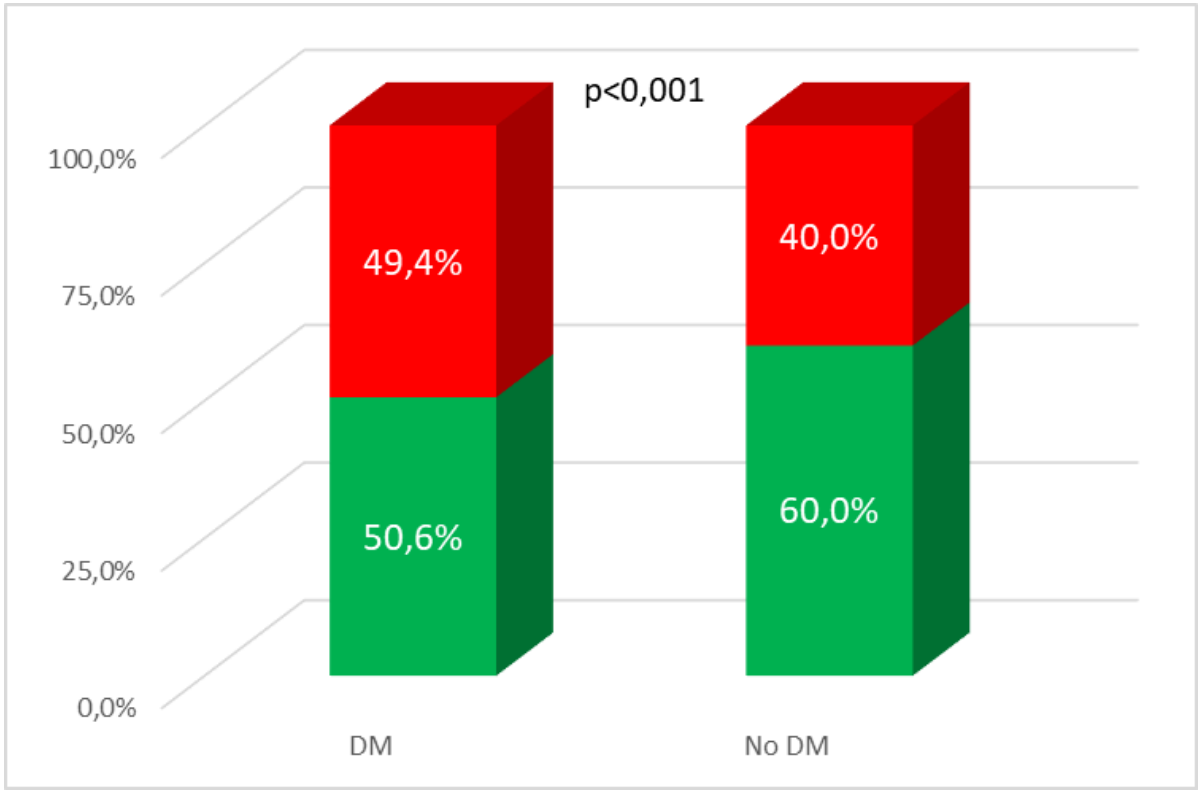


No. at Risk											
Clinic	2,064	2,273	4,822	6,454	10,124	11,043	11,826	7,314	4,604	1,797	1,589
24-Hr	8,026	8,523	11,844	12,668	10,316	6,765	3,403	1,422	616	222	105
Daytime	5,632	6,613	9,569	11,799	11,358	8,888	5,439	2,756	1,127	484	245
Nighttime	24,403	12,905	10,921	7,686	4,212	2,162	983	391	162	51	34

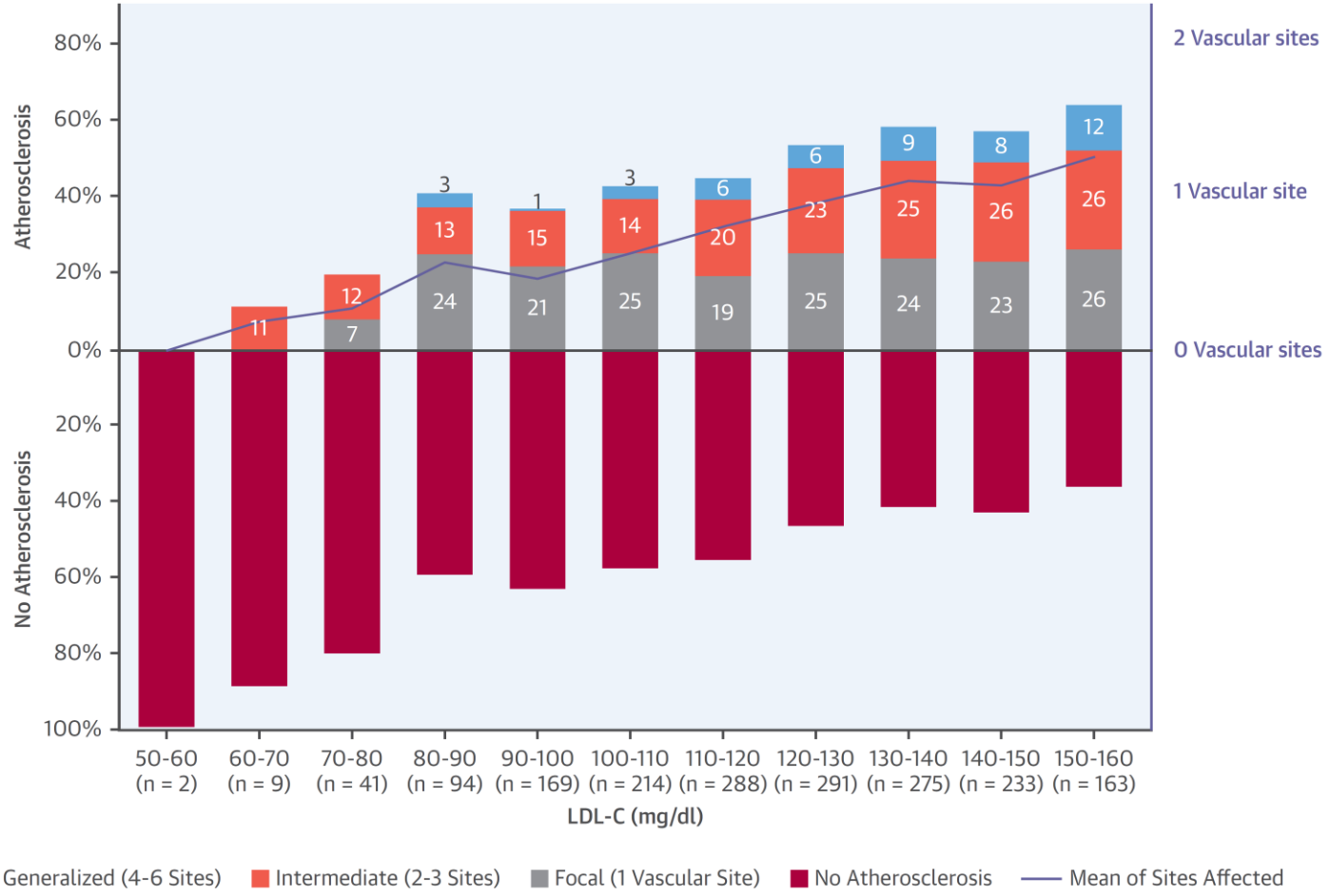
Banegas, et al. Relationship between Clinic and Ambulatory Blood-Pressure Measurements and Mortality. NEJM 2018

Control HTA en DMt2

N=6.007

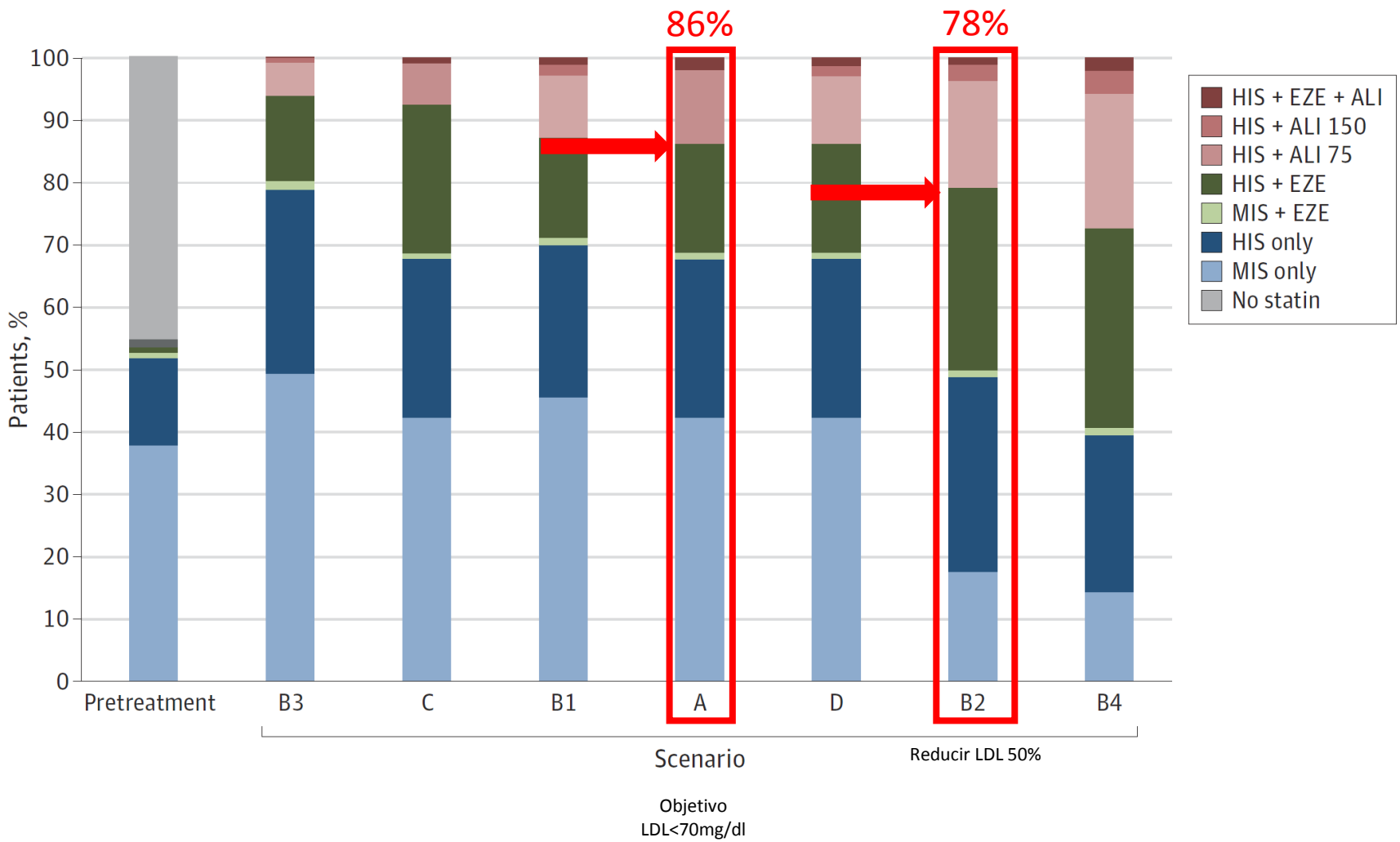


El desarrollo de aterosclerosis y territorios afectados tiene relación directa con el LDL



Fernández-Friera, L. et al. PESA (Progression of Early Subclinical Atherosclerosis) study population. J Am Coll Cardiol. 2017

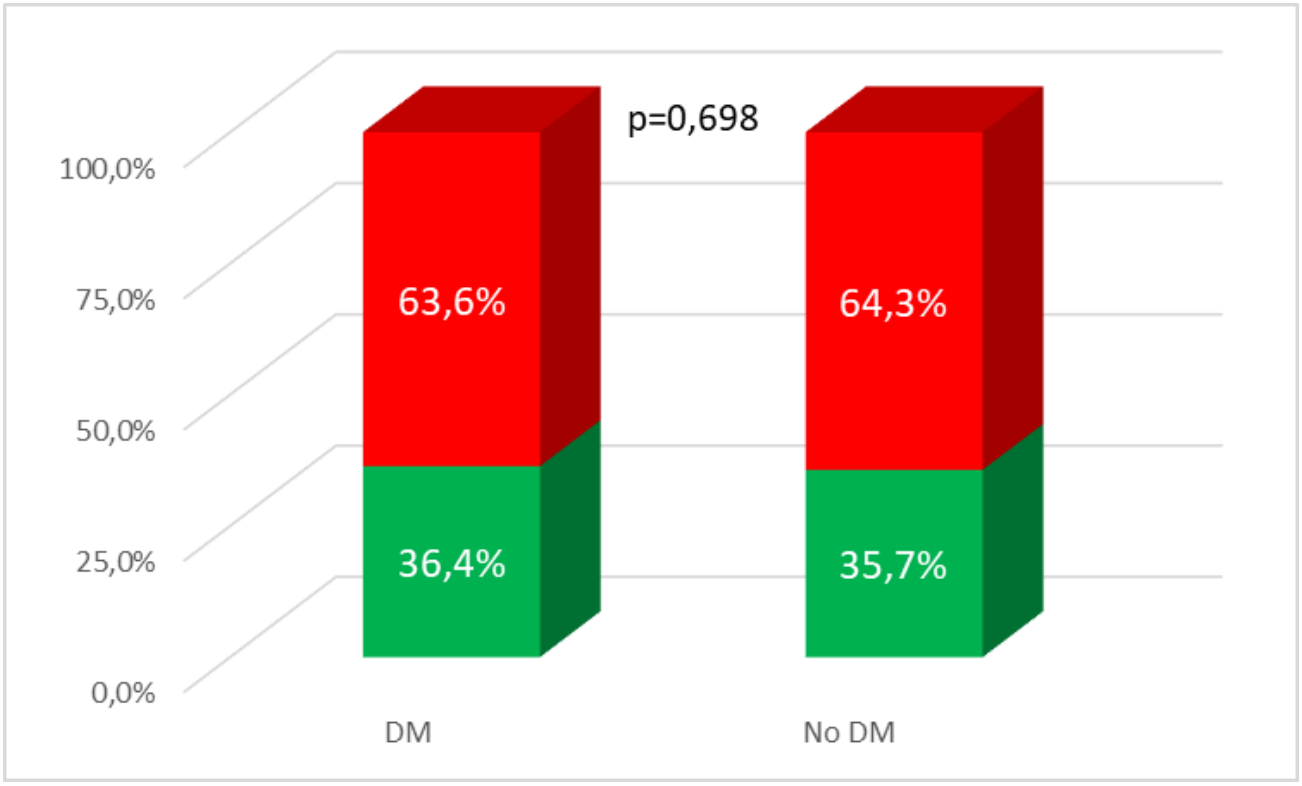
Objetivos terapéuticos con estatina+Eze



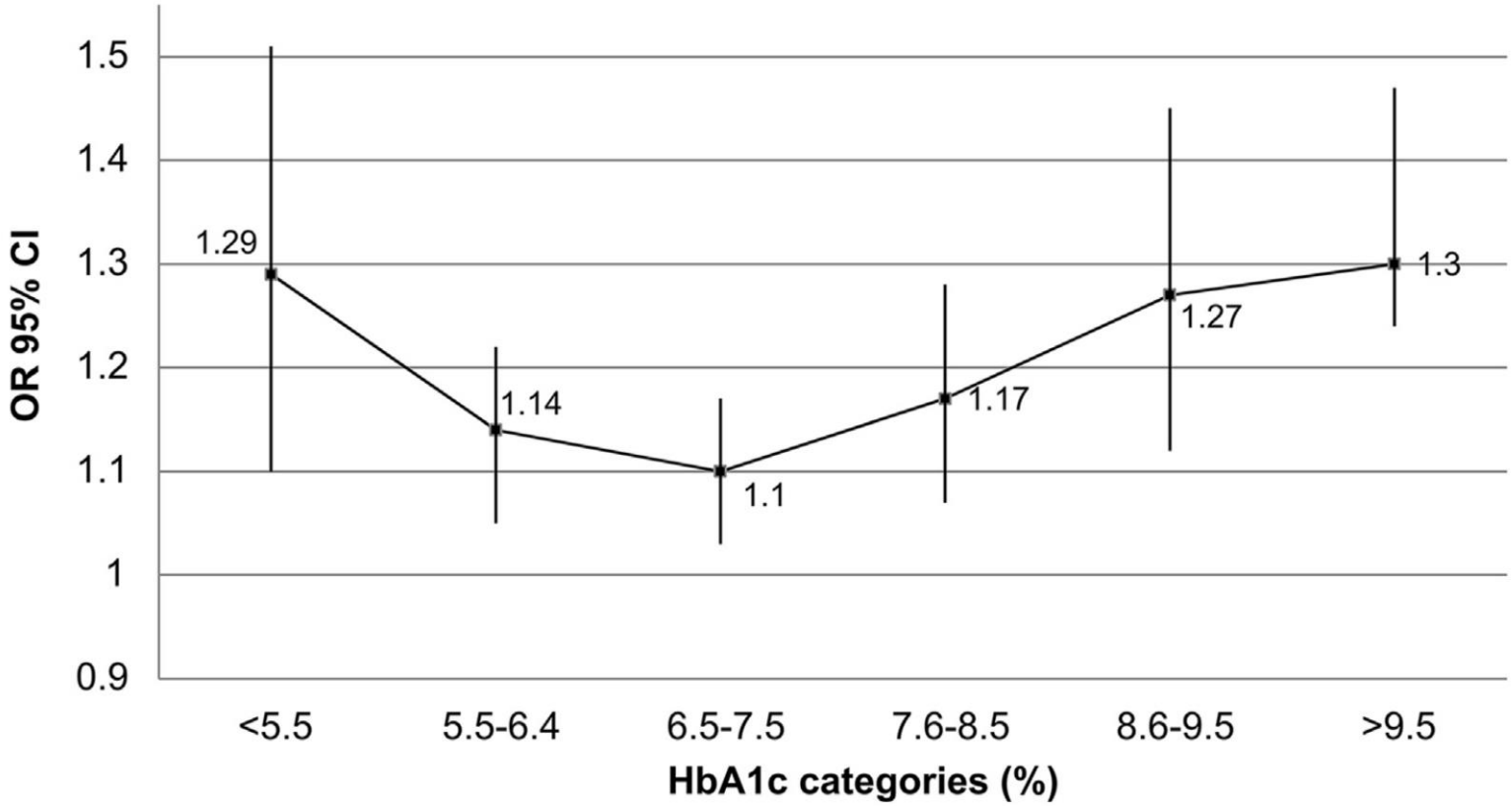
Cannon et al. Simulation of Lipid-Lowering Therapy Intensification for ASCVD. JAMA Cardiol 2017

Control dislipemia en DMt2

N=6.007



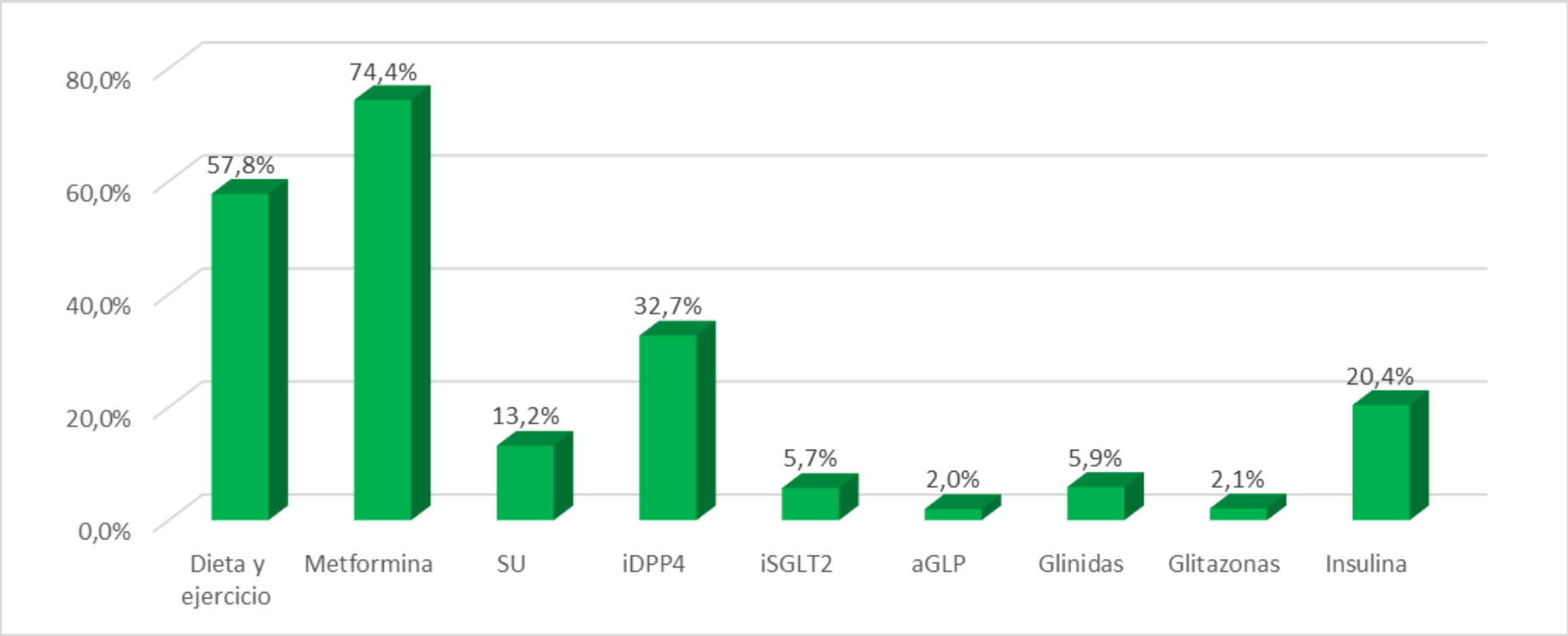
El descenso intensivo de la HbA1c no beneficia a la mortalidad por cualquier causa



Lawson, et al. Type 2 Diabetes Intensity and Outcomes in Heart Failure. JACC HF 2017

Terapias en DMt2

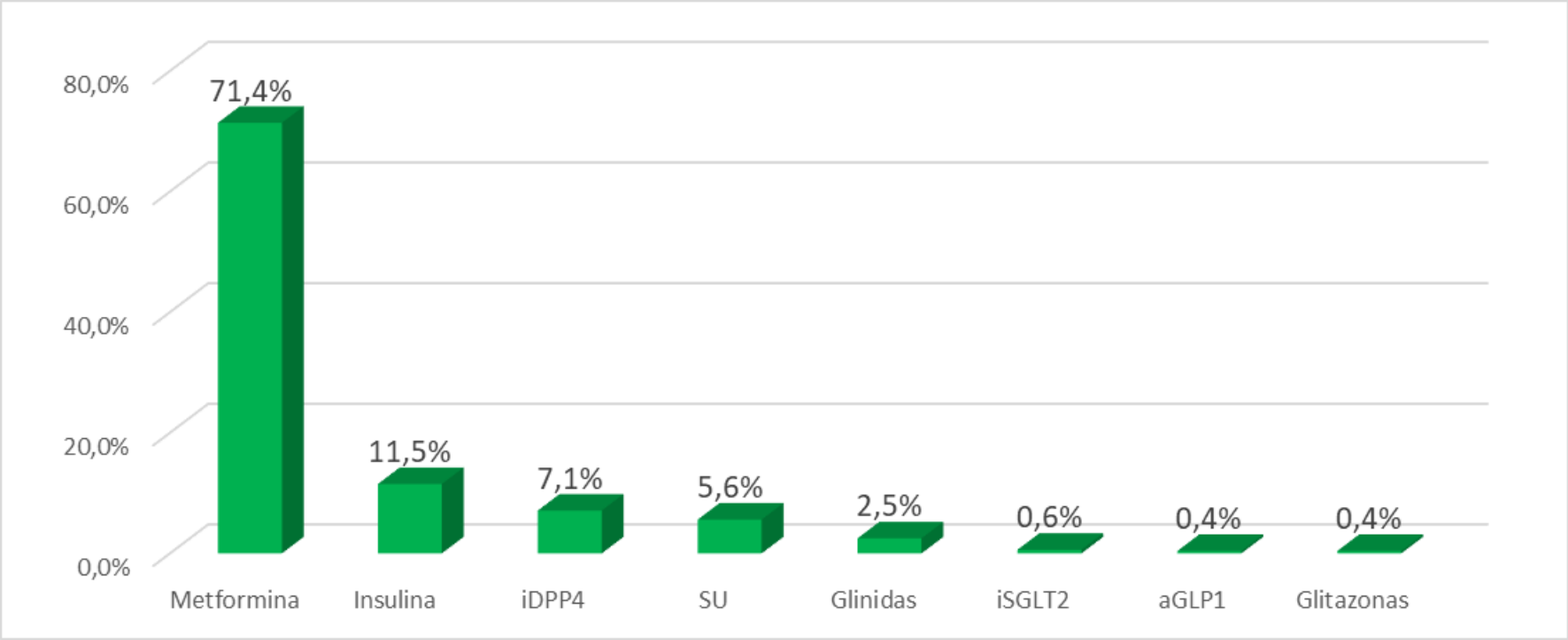
N=6.007



ESTUDIO IBERICAN
Identificación de la población Española de Riesgo Cardio Vascular y renal

Monoterapia en DMt2

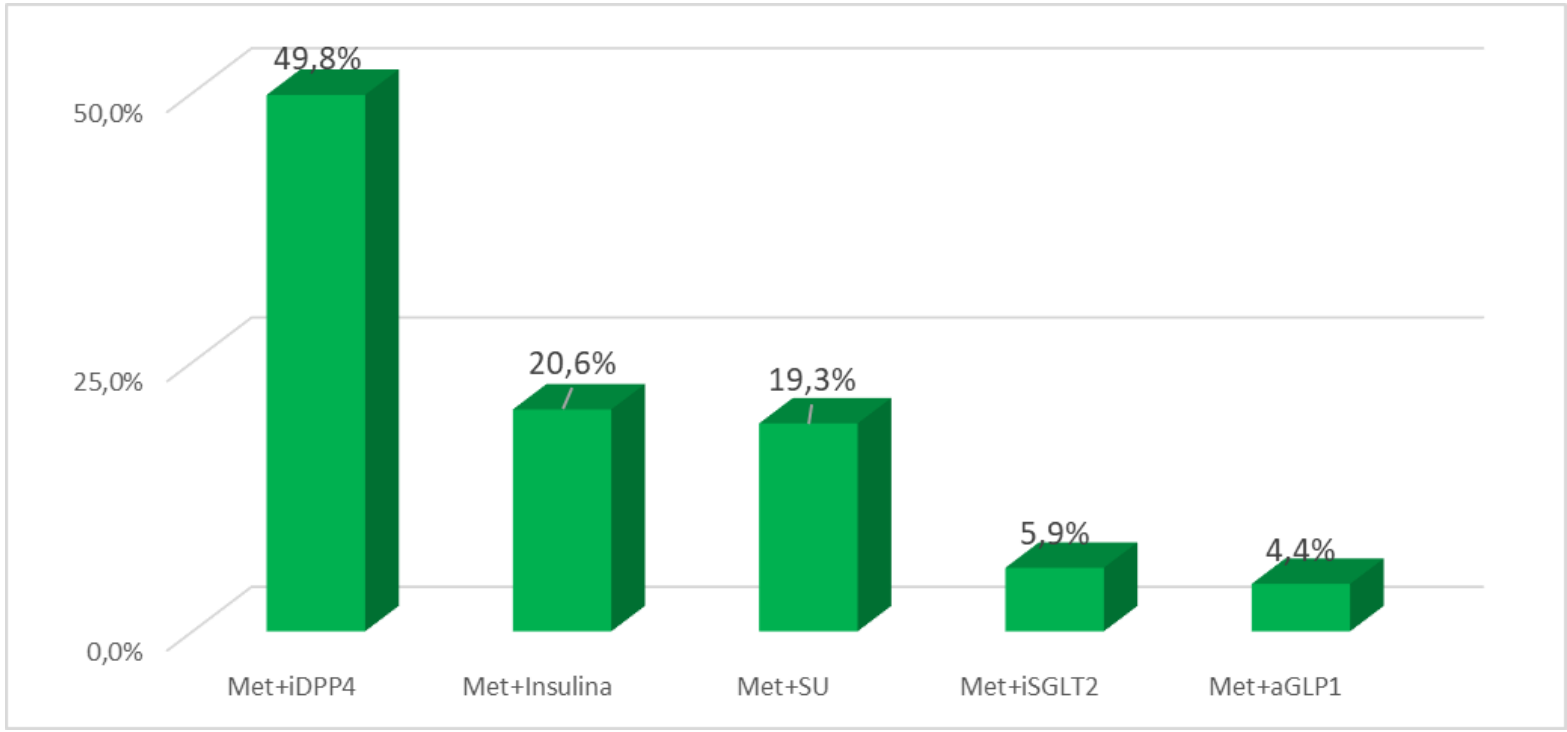
N=6.007



ESTUDIO IBERICAN

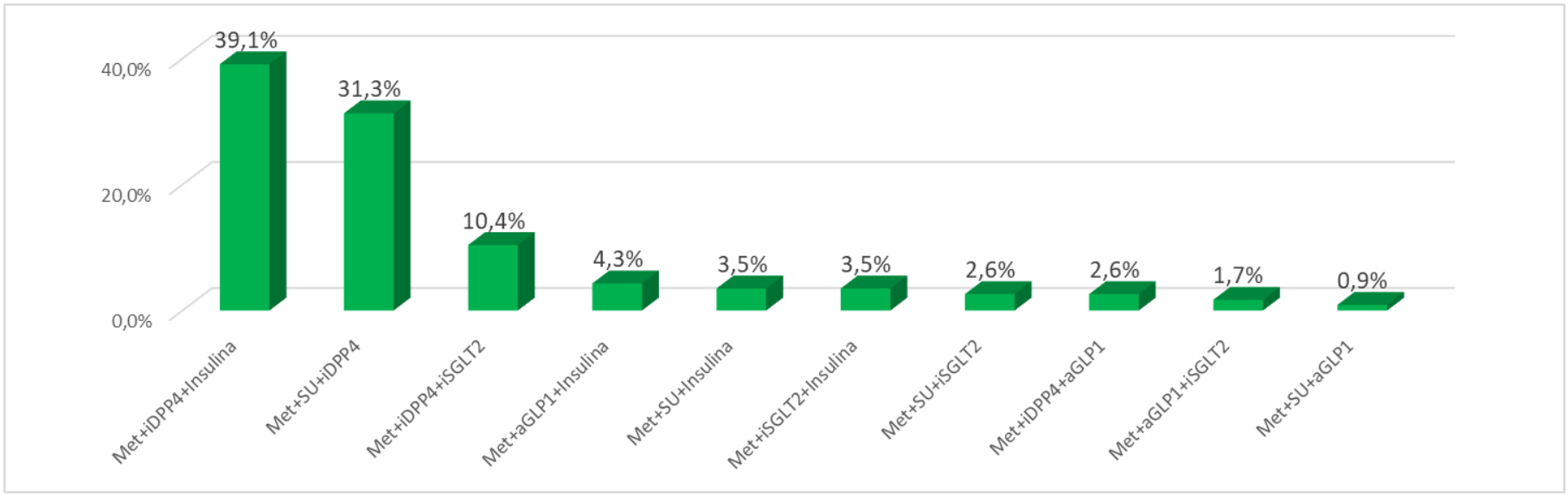
Terapia combinada en DMt2

N=6.007



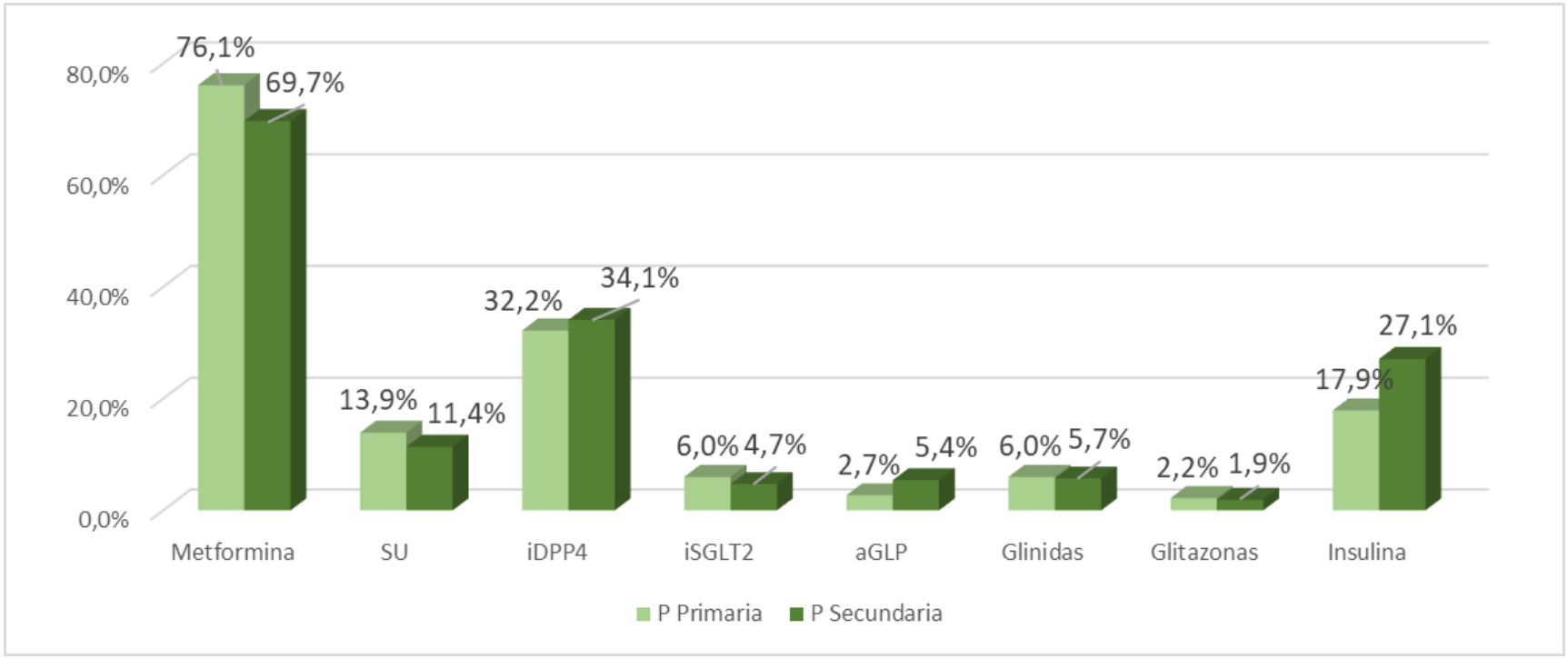
Terapia combinada en DMt2

N=6.007



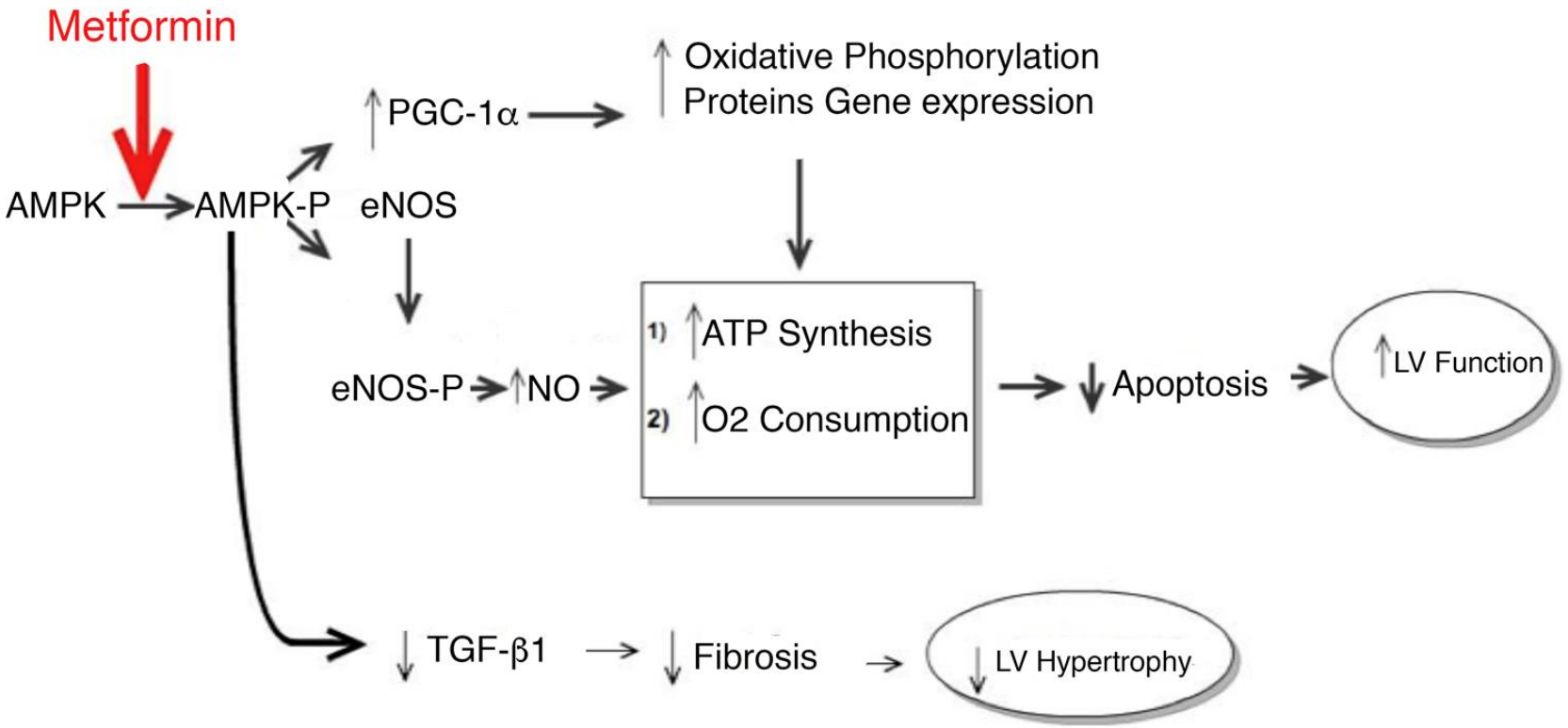
Tratamiento DMt2 en pacientes con enfermedad CV

N=6.007



¿Qué más podemos hacer ante un paciente diabético?

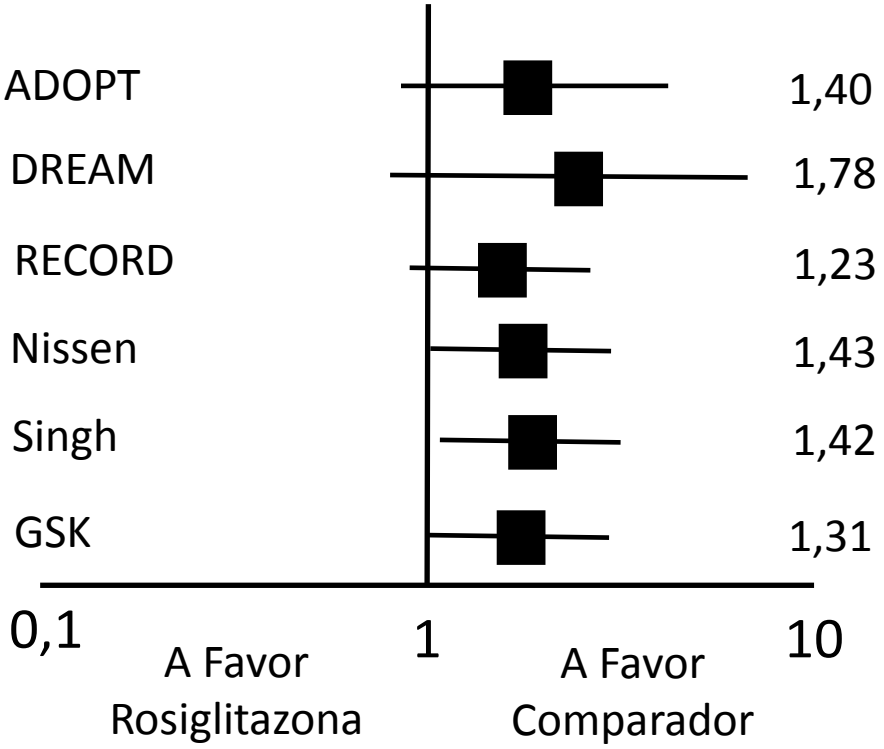
Efecto cardioprotector de Metformina



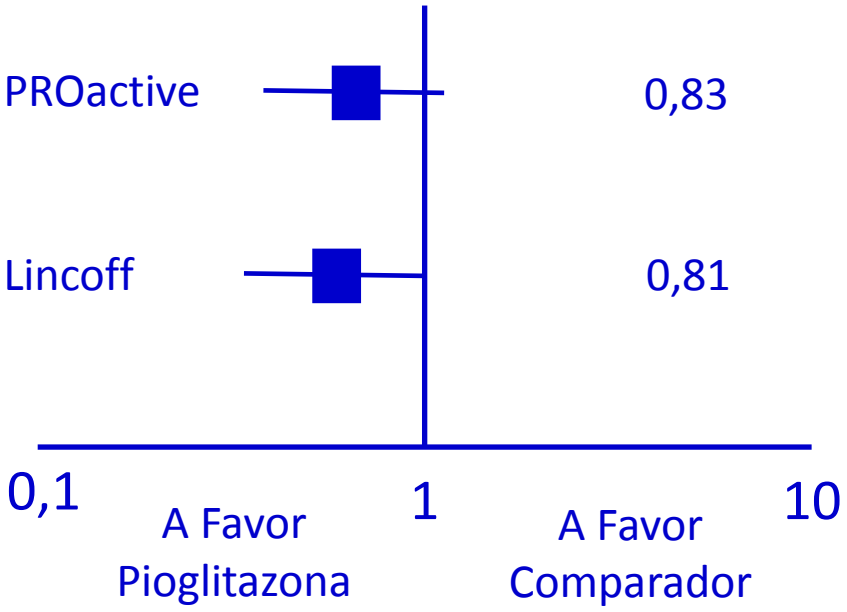
Varjabedian et al. Cardioprotection by Metformin: Beneficial Effects Beyond Glucose Reduction. Am J Cardiovasc Drugs 2018

RCV de la Glitazonas

Rosiglitazona



Pioglitazona



Rohatgi A et al. Cardiovasc Drugs Ther 2008; 22: 233-240

Guías de la FDA para los ensayos sobre seguridad cardiovascular de los fármacos antidiabéticos

Guidance for Industry

Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

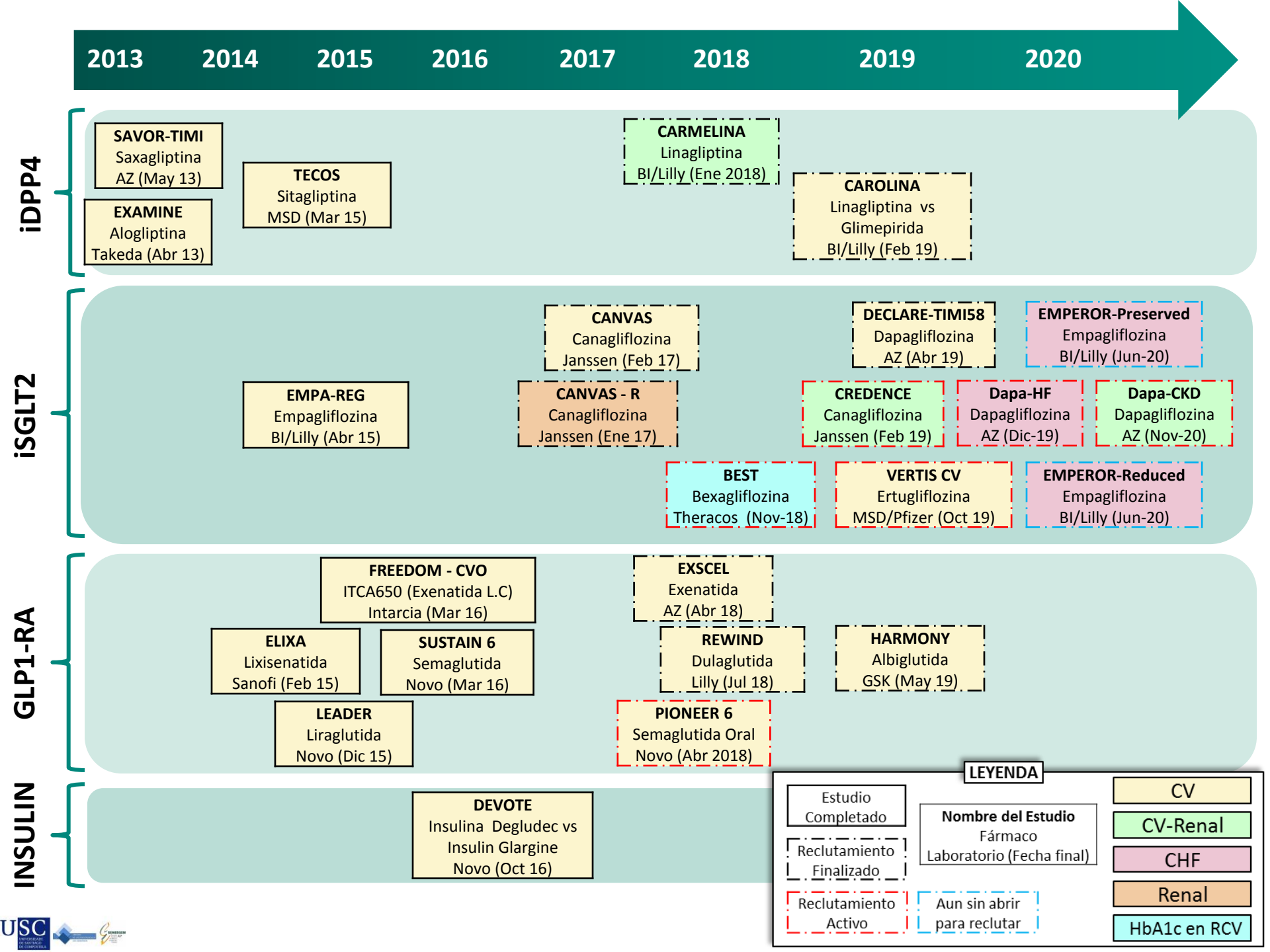
Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact Ilan Irony at 301-796-2290.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

February 2008
Clinical/Medical

1:\76350dft.doc
02/13/08

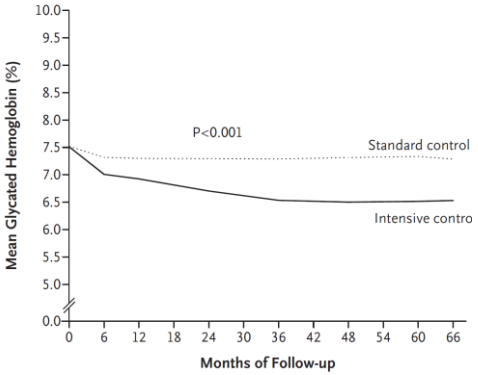

2013
2014
2015
2016
2017
2018
2019
2020
iDPP4
SAVOR-TIMI
Saxagliptina
AZ (May 13)
EXAMINE
Alogliptina
Takeda (Abr 13)
TECOS
Sitagliptina
MSD (Mar 15)
CARMELINA
Linagliptina
BI/Lilly (Ene 2018)
CAROLINA
Linagliptina vs
Glimepirida
BI/Lilly (Feb 19)
iSGLT2
EMPA-REG
Empagliflozina
BI/Lilly (Abr 15)
CANVAS
Canagliflozina
Janssen (Feb 17)
CANVAS - R
Canagliflozina
Janssen (Ene 17)
DECLARE-TIMI58
Dapagliflozina
AZ (Abr 19)
EMPEROR-Preserved
Empagliflozina
BI/Lilly (Jun-20)
CREDENCE
Canagliflozina
Janssen (Feb 19)
Dapa-HF
Dapagliflozina
AZ (Dic-19)
Dapa-CKD
Dapagliflozina
AZ (Nov-20)
BEST
Bexagliflozina
Theracos (Nov-18)
VERTIS CV
Ertugliflozina
MSD/Pfizer (Oct 19)
EMPEROR-Reduced
Empagliflozina
BI/Lilly (Jun-20)
GLP1-RA
FREEDOM - CVO
ITCA650 (Exenatida L.C)
Intarcia (Mar 16)
ELIXA
Lixisenatida
Sanofi (Feb 15)
SUSTAIN 6
Semaglutida
Novo (Mar 16)
LEADER
Liraglutida
Novo (Dic 15)
EXSCEL
Exenatida
AZ (Abr 18)
REWIND
Dulaglutida
Lilly (Jul 18)
PIONEER 6
Semaglutida Oral
Novo (Abr 2018)
HARMONY
Albiglutida
GSK (May 19)
INSULIN
DEVOTE
Insulina Degludec vs
Insulin Glargine
Novo (Oct 16)
LEYENDA
Estudio Completado
Reclutamiento Finalizado
Reclutamiento Activo
Nombre del Estudio
Fármaco
Laboratorio (Fecha final)
Aun sin abrir para reclutar
CV
CV-Renal
CHF
Renal
HbA1c en RCV

Ensayos de eficacia CV tradicionales frente a ensayos de seguridad CV con iDPP-4

Ensayos de resultados CV tradicionales (p. ej., ADVANCE)

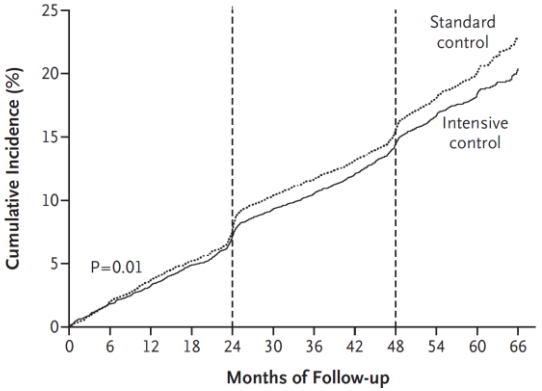
Inicio de tratamiento enmascarado o placebo

Ningún aju
para mant
los niveles de
iguales en a
grupos



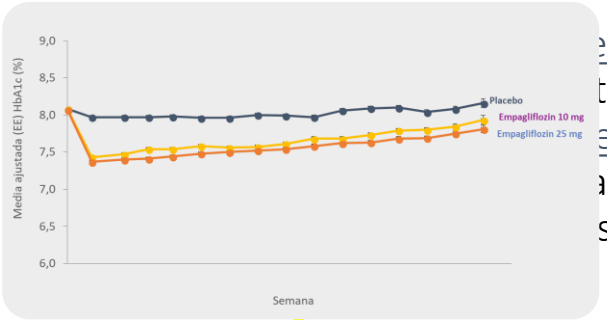
Diferencia de HbA1c
entre tratamiento y placebo

Benefi
una red
do por
dos CV



Ensayos de seguridad CV con antidiabéticos

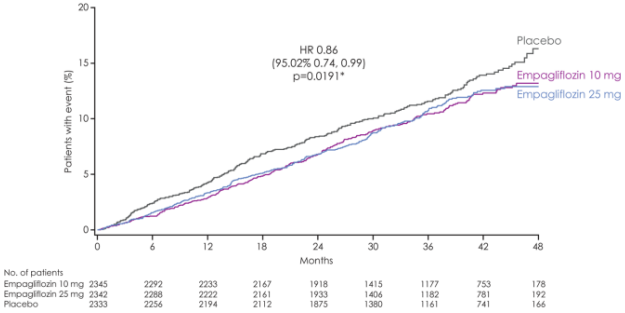
Inicio de tratamiento enmascarado o placebo



tener
e HbA_{1c}
ambos
s

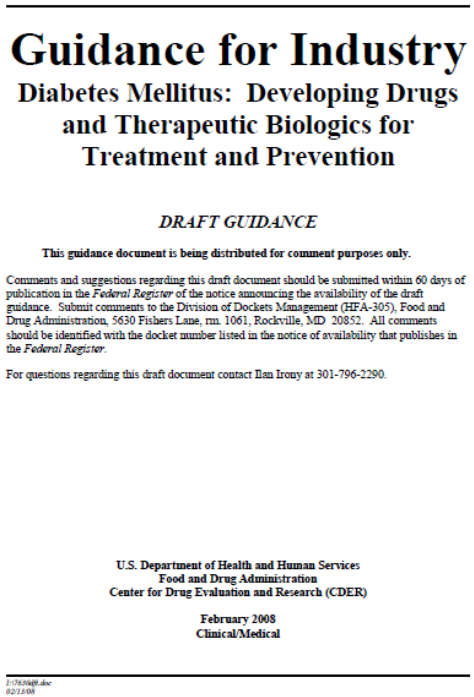
Diferencia de HbA_{1c}
pequeña o nula entre tratamiento y placebo

No h
cor
CV)
o



Guías de la FDA para los ensayos sobre seguridad cardiovascular de los fármacos antidiabéticos

to the active control. Typically, we accept a noninferiority margin of 0.3 or 0.4 HbA1c percentage units provided this is no greater than a suitably conservative estimate of the magnitude of the treatment effect of the active control in previous placebo-controlled trials. For additional guidance on noninferiority studies, refer to ICH E9 and ICH E10.



Guidance for Industry

Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

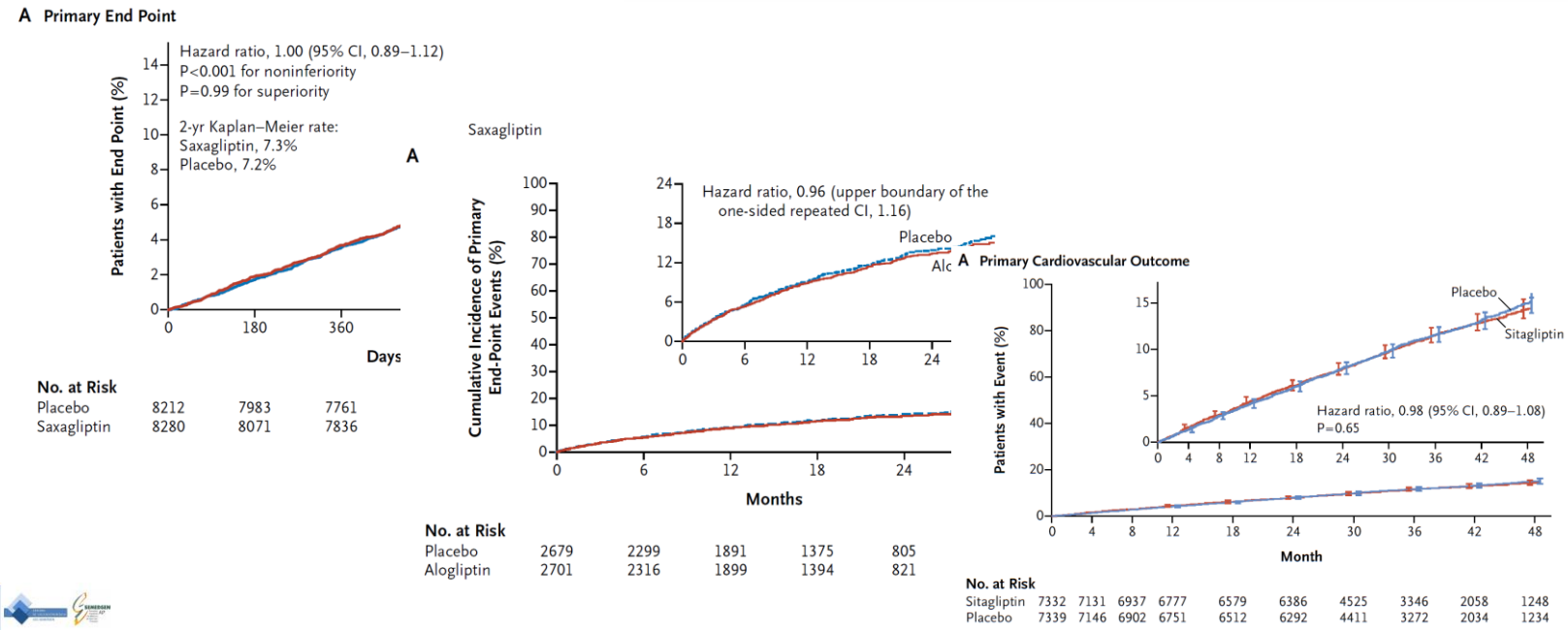
For questions regarding this draft document contact Ilan Irony at 301-796-2290.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

February 2008
Clinical/Medical

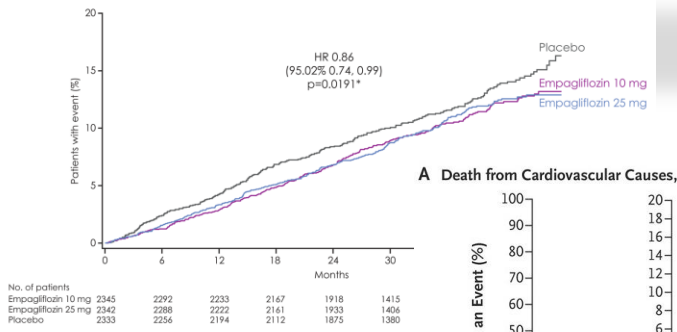
RCV de i-DPP4

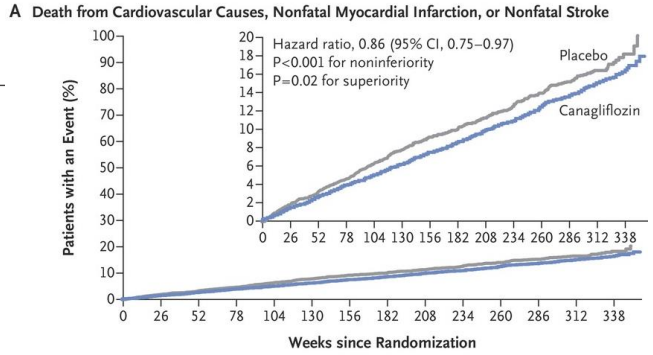
	SAVOR	EXAMINE	TECOS	CAROLINA	CARMELINA
IDPP-4	Saxagliptina	Alogliptina	Sitagliptina	Linagliptina	Linagliptina
Comparador	Placebo	Placebo	Placebo	SU	Placebo
N	16500	5400	14000	6000	8300
Resultados	2013	2013	Junio 2015	2017	2017



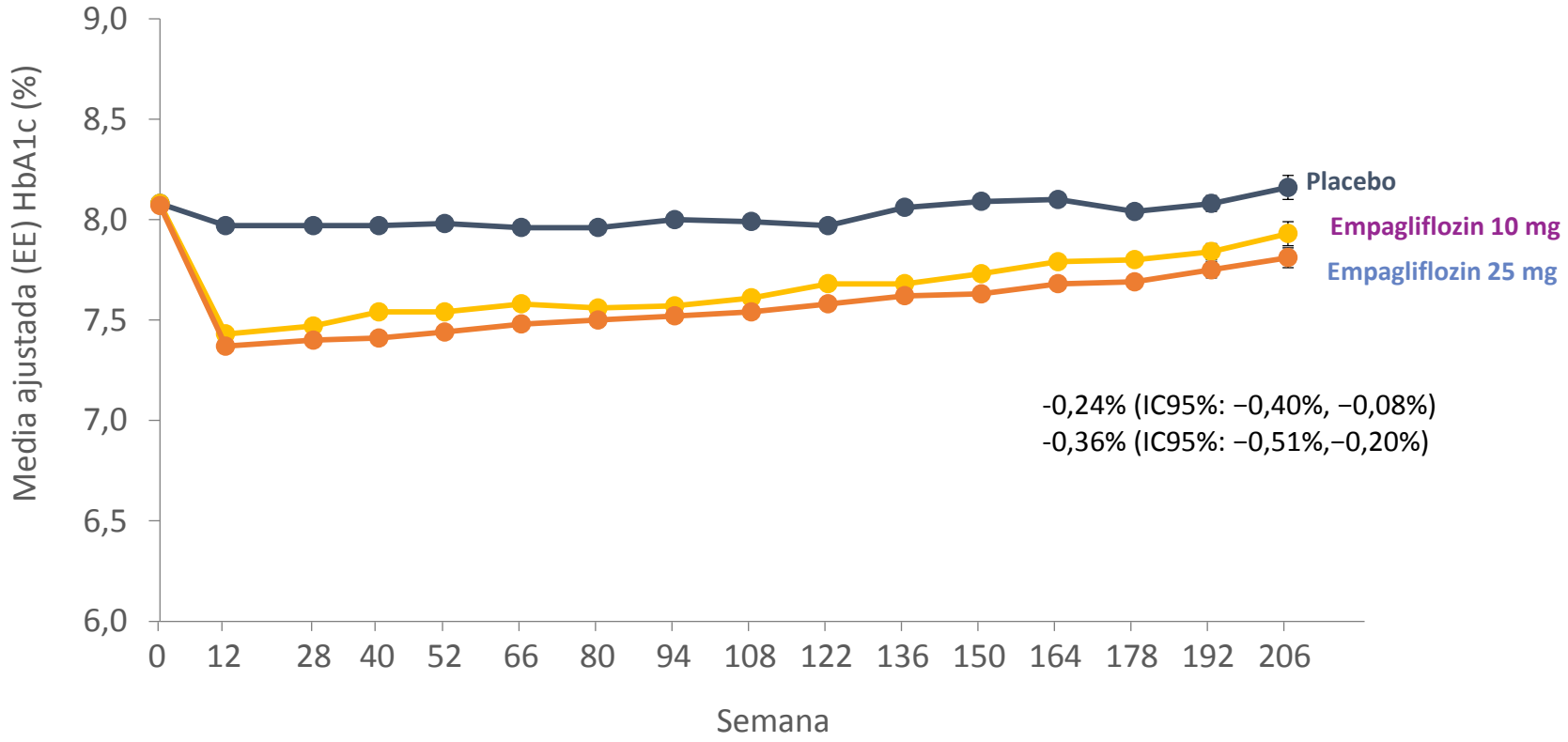
RCV de i-SGLT2

	EMPA-REG	CANVAS	DECLARE	NCT01986881
SGLT-2	Empagliflozina	Canagliflozina	Dapagliflozina	Ertugliflozina
Comparador	Placebo	Placebo	Placebo	Placebo
N	7.300	4.300	22.200	3.900
Resultados	2015	2017	2018	2020





Reducción significativa de la Hba1c

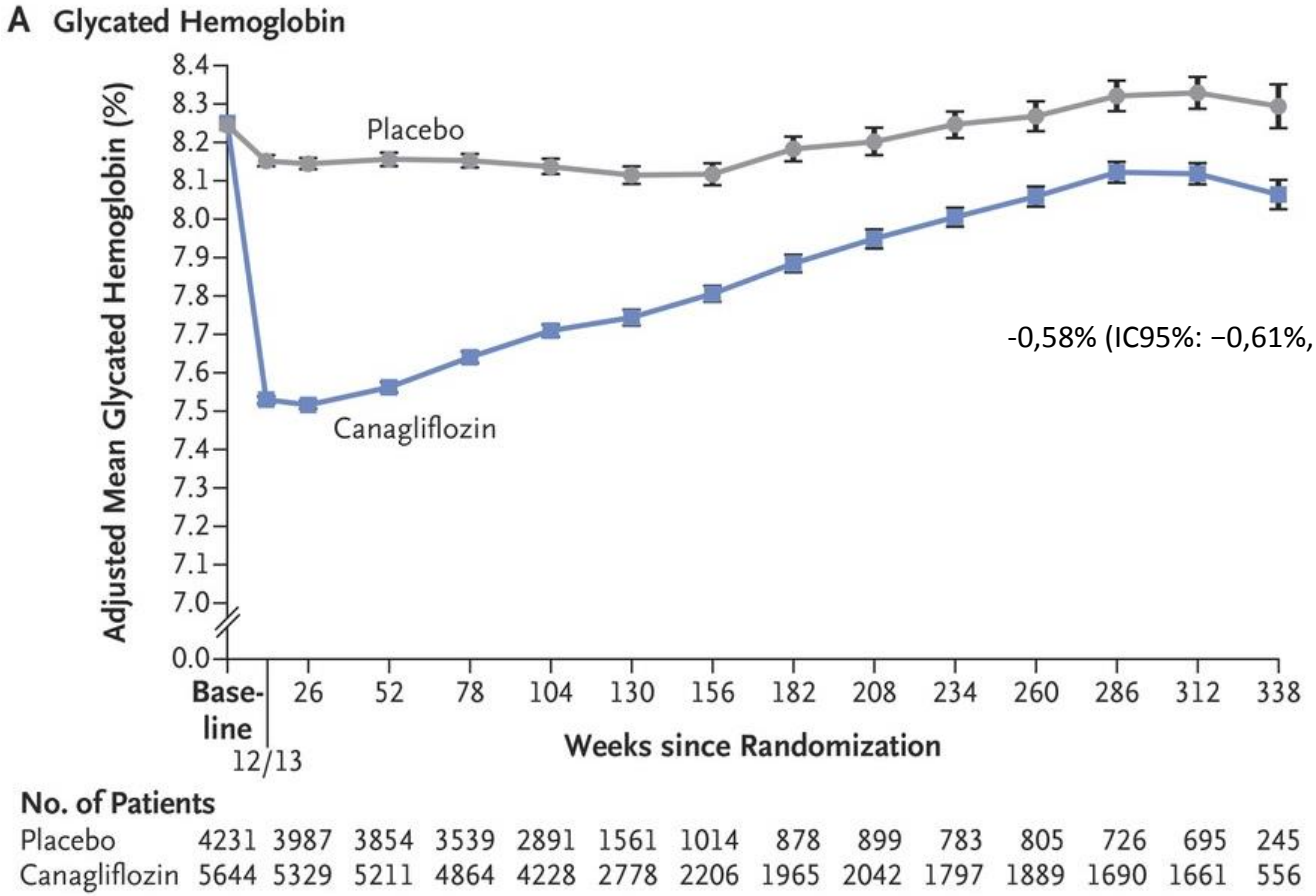


Placebo	2294	2272	2188	2133	2113	2063	2008	1967	1741	1456	1241	1109	962	705	420	151
Empagliflozina 10 mg	2296	2272	2218	2150	2155	2108	2072	2058	1805	1520	1297	1164	1006	749	488	170
Empagliflozina 25 mg	2296	2280	2212	2152	2150	2115	2080	2044	1842	1540	1327	1190	1043	795	498	195

Todos los pacientes (incluidos los que interrumpieron el tratamiento con el fármaco de estudio o iniciaron otros tratamientos) fueron incluidos en este modelo mixto de análisis para medidas repetidas (intención de tratar)

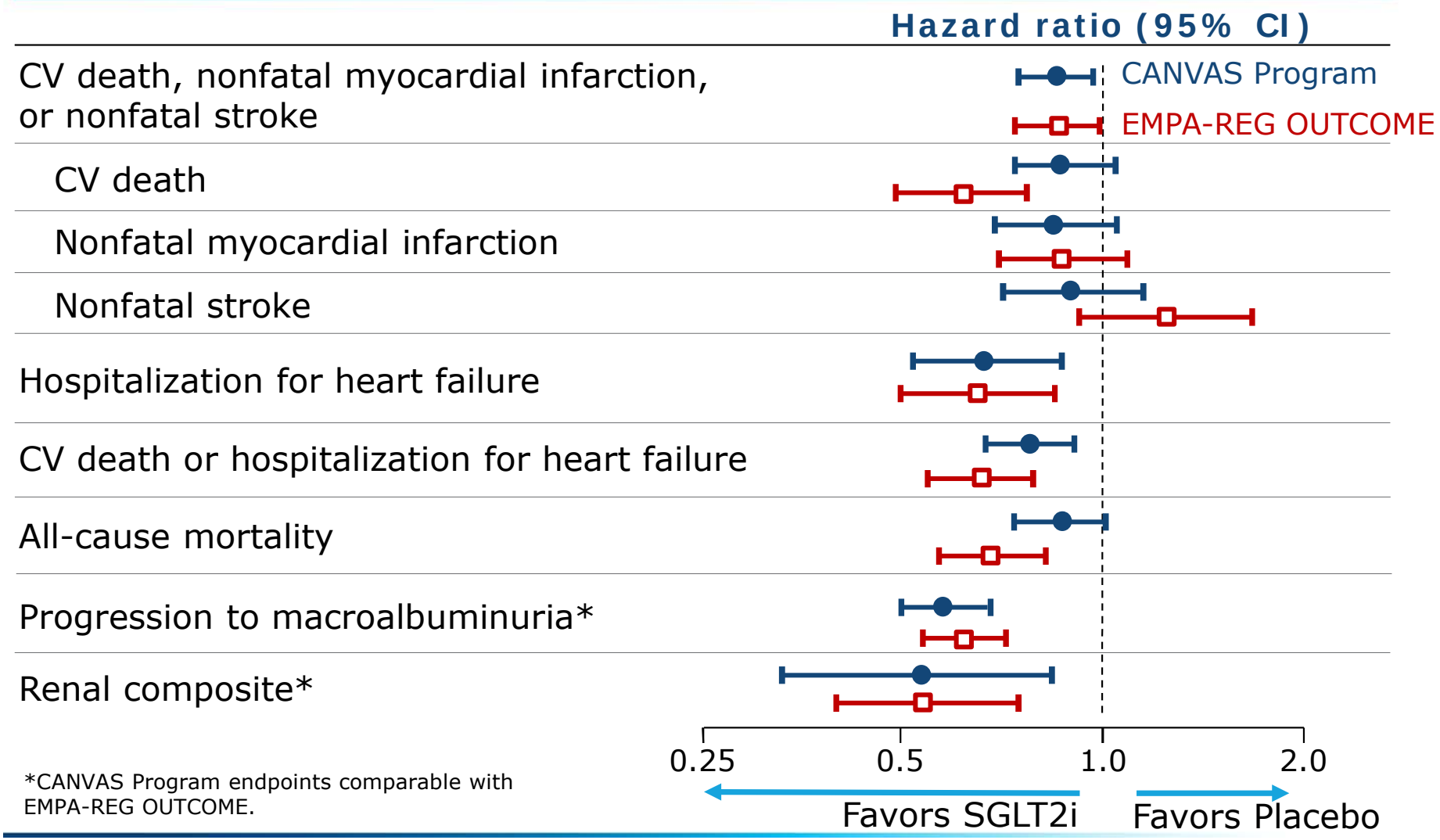
Zinman B, et al. N Engl J Med. 2015

Cambios de HbA1c en CANVAS Study



Neil, et al. N Engl J Med. 2017

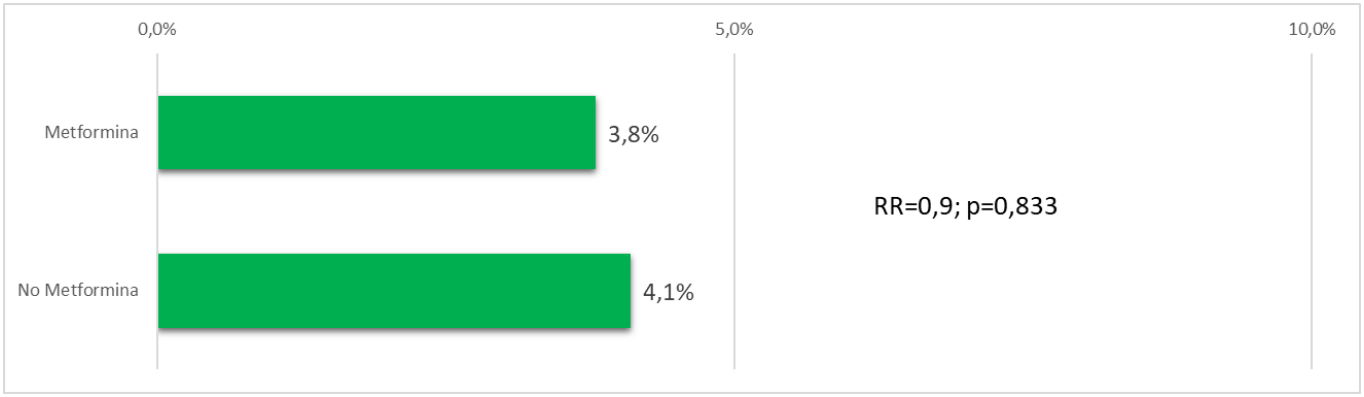
Comparativa entre EMPA-REG Y CANVAS

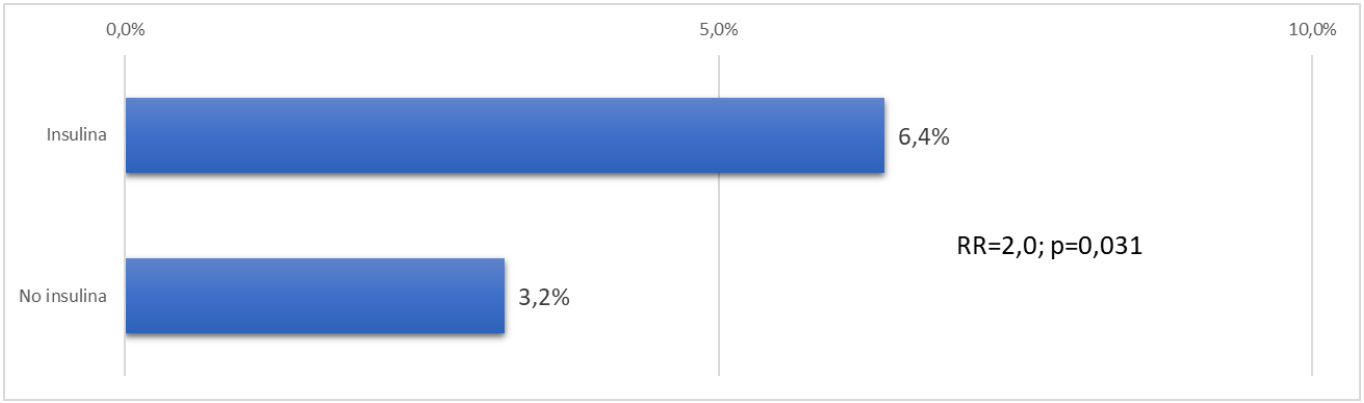


*CANVAS Program endpoints comparable with EMPA-REG OUTCOME.

Eventos CV asociados a fármaco

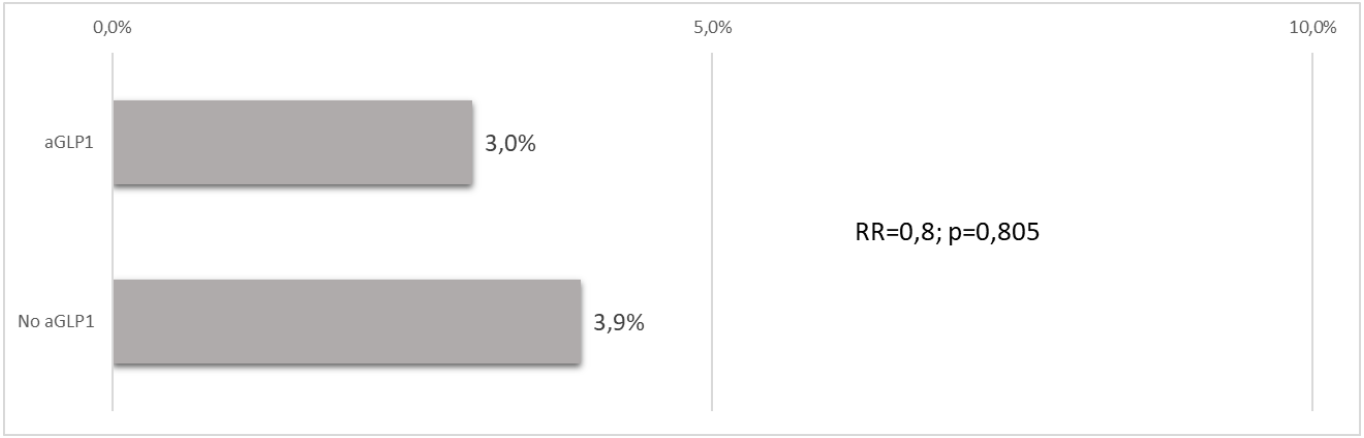
N=6.007

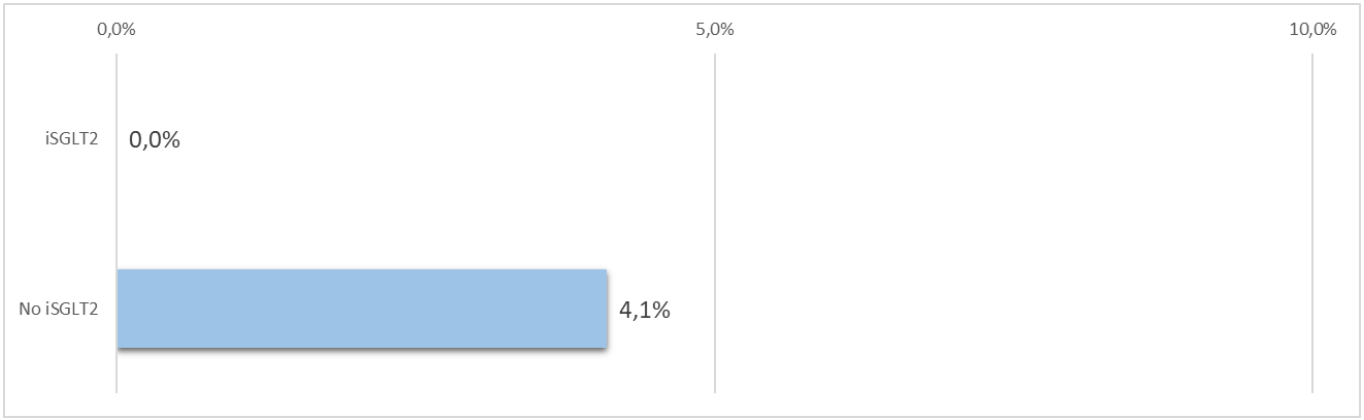




Eventos CV asociados a fármaco

N=6.007





Conclusiones

1. Existe una estrecha relación entre DMt2 y ECV
2. El objetivo principal del tratamiento de la DMt2 debe orientarse a prevenir eventos CV
3. El tratamiento de los diferentes FRCV asociados a la DMt2 ayuda a reducir el RCV
   - Solamente la reducción intensiva del LDL aporta beneficio pronóstico
4. Más allá del control de HbA1c debemos aprovechar el beneficio demostrado de ciertas moléculas en la reducción del RCV