Paciente con Diabetes Mellitus Tipo2 Optimización del tratamiento Visión del Endocrinólogo

Maria Jose Goñi

Endocrinología

Complejo Hospitalario de Navarra

COMPLEJO HOSPITALARIO DE NAVARRA

Epidemiología

- Aumento incidencia
- Envejecimiento población

Fármacos

Nuevos tratamientos

- Estudios de seguridad cardiovascular

Tecnología

- Medición de glucosa
- Visualización de los datos
- MCG

Epidemiología

- Aumento incidencia
- Envejecimiento poblacion

International Diabetes Federation

IDF DIABETES ATLAS

Eighth edition 2017

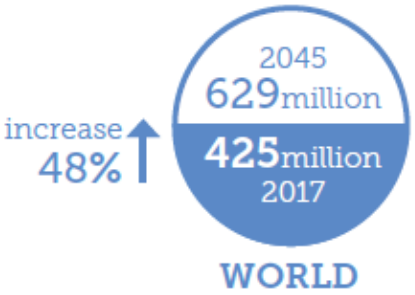
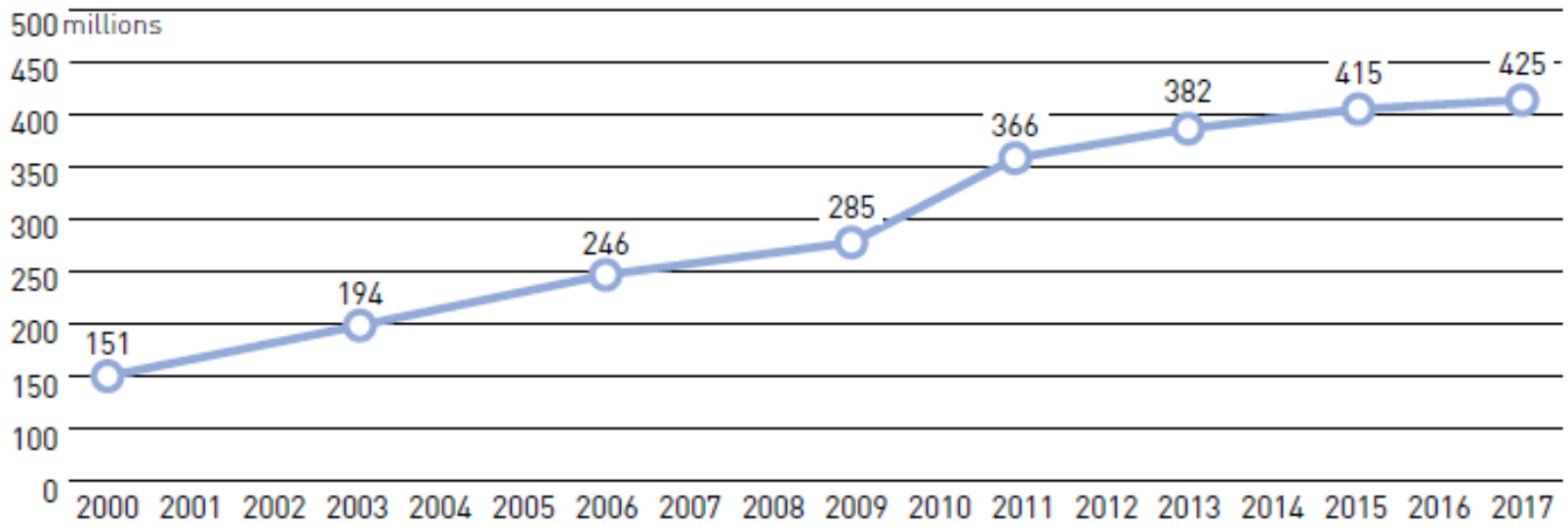
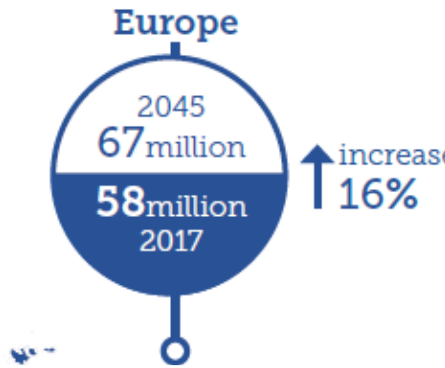


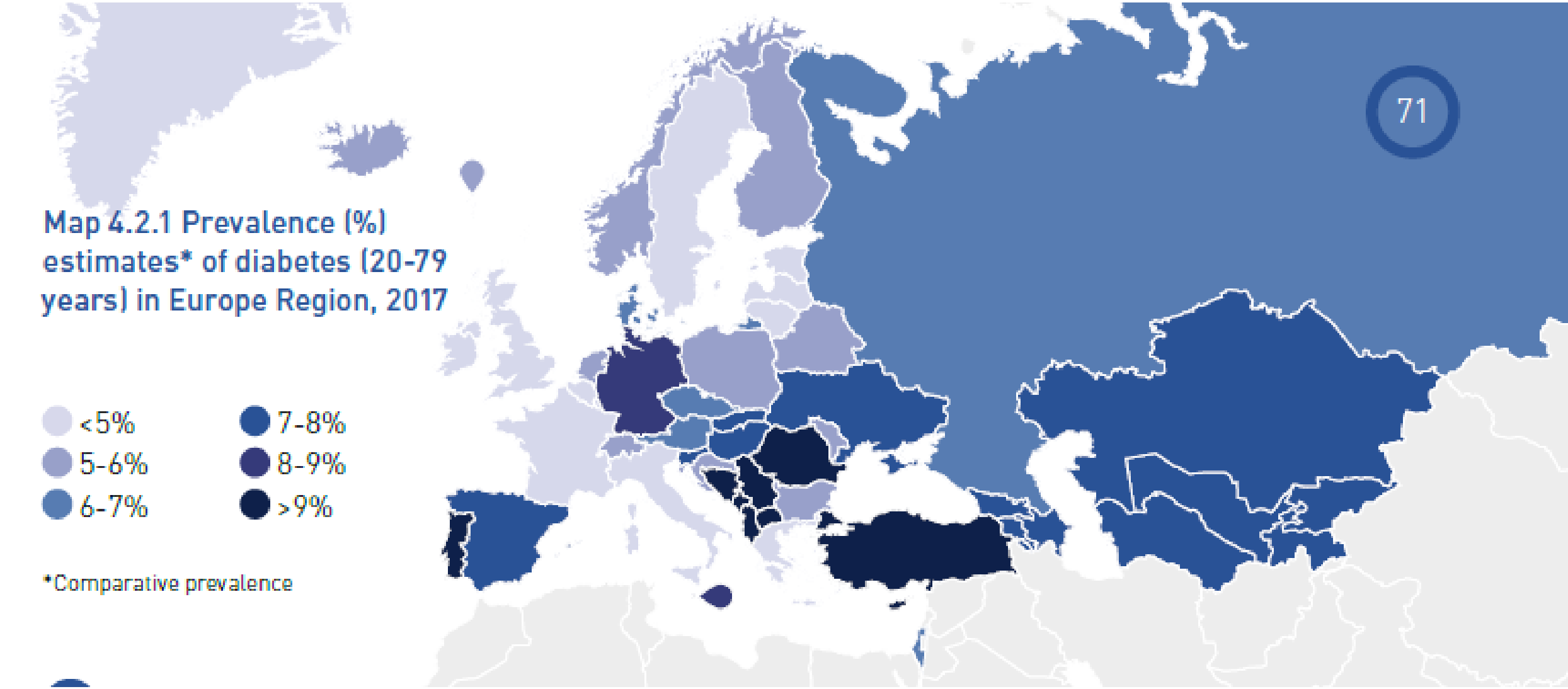
Figure 3.2 Total number of adults with diabetes (20-79 years)





IDF **DIABETES ATLAS**

Eighth edition 2017



Map 4.2.1 Prevalence (%) estimates* of diabetes (20-79 years) in Europe Region, 2017

- <5%
- 5-6%
- 6-7%
- 7-8%
- 8-9%
- >9%

*Comparative prevalence

Table 3.18 IDF regions ranked by diabetes prevalence (%) in people older than in 65 in 2017 and 2045

		2017		2045	
Rank	IDF region	Prevalence	Number of people with diabetes	Prevalence	Number of people with diabetes
1	North America and Caribbean	26.3% (23.4-29.4%)	17.7 million (15.7-19.7)	26.9% (22.7-31.0%)	33.4 million (28.2-38.5)
2	Middle East and North Africa	20.4% (12.6-29.0%)	6.5 million (4.0-9.3)	22.1% (14.0-30.9%)	21.5 million (13.6-30.0)
3	Western Pacific	20.0% (17.8-23.0%)	48.1 million (42.7-55.2)	17.6% (12.4-22.7%)	96.7 million (67.8-123.7)
4	Europe	19.4% (14.9-25.0%)	28.5 million (21.9-36.7)	19.8% (15.2-25.9)	43.9 millon (33.7-57.5)
5	South and Central America	19.0% (15.1–24.4%)	7.9 million (6.3–10.2)	19.3% (15.3-25.1%)	20.4 million (16.1-26.4)
6	South East Asia	13.5% (9.5–18.6%)	12.5 million (8.7–17.1)	13.9% (10.1-19.7%)	33.0 million (24.0-46.8)
7	Africa	5.2% (2.8–12.8%)	1.6 million (0.9–4.0)	5.4% (2.8–14.5%)	4.6 million (2.4-12.2)

di@bet.es

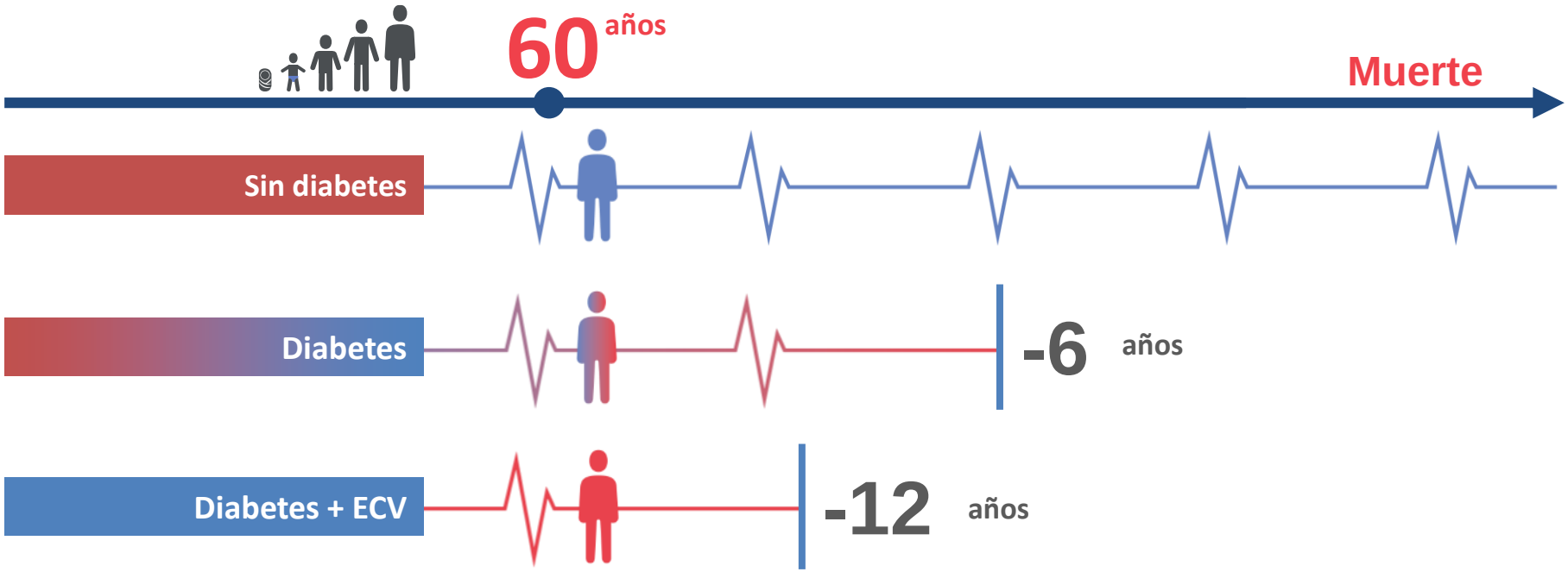
Estudio Epidemiológico de la DIABETES en España

Incidencia de DM2

11,5 casos de DM/1000 personas/año

386.000 nuevos diagnósticos cada año

Esperanza de vida en Pacientes con DM2

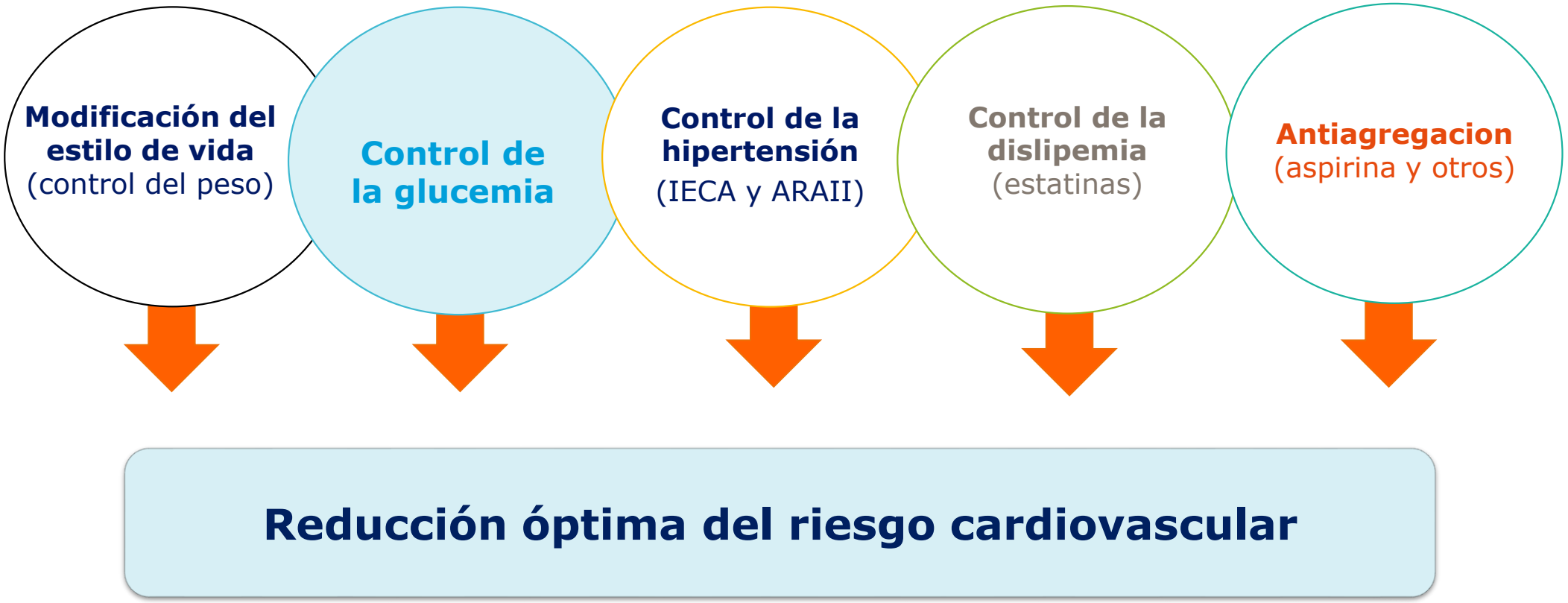


En este caso, la ECV está representada por infarto de miocardio o ictus *Varón, 60 años de edad con antecedentes de infarto de miocardio o ictus. ECV, enfermedad cardiovascular.

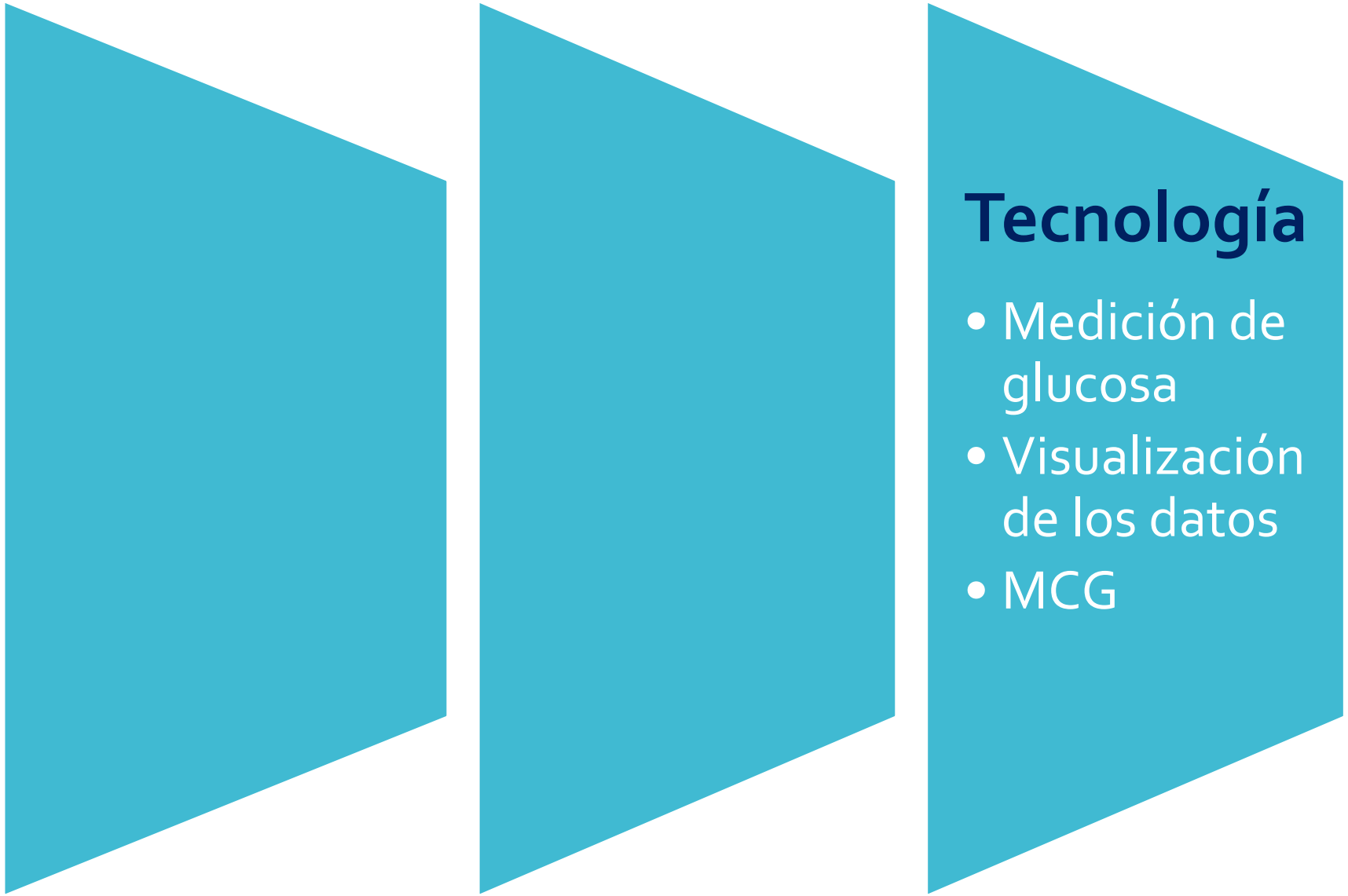
The Emerging Risk Factors Collaboration. JAMA 2015;314:52

COMPLEJO HOSPITALARIO DE NAVARRA

El riesgo cardiovascular en la diabetes tipo 2 solo puede disminuirse utilizando un aproximación multifactorial



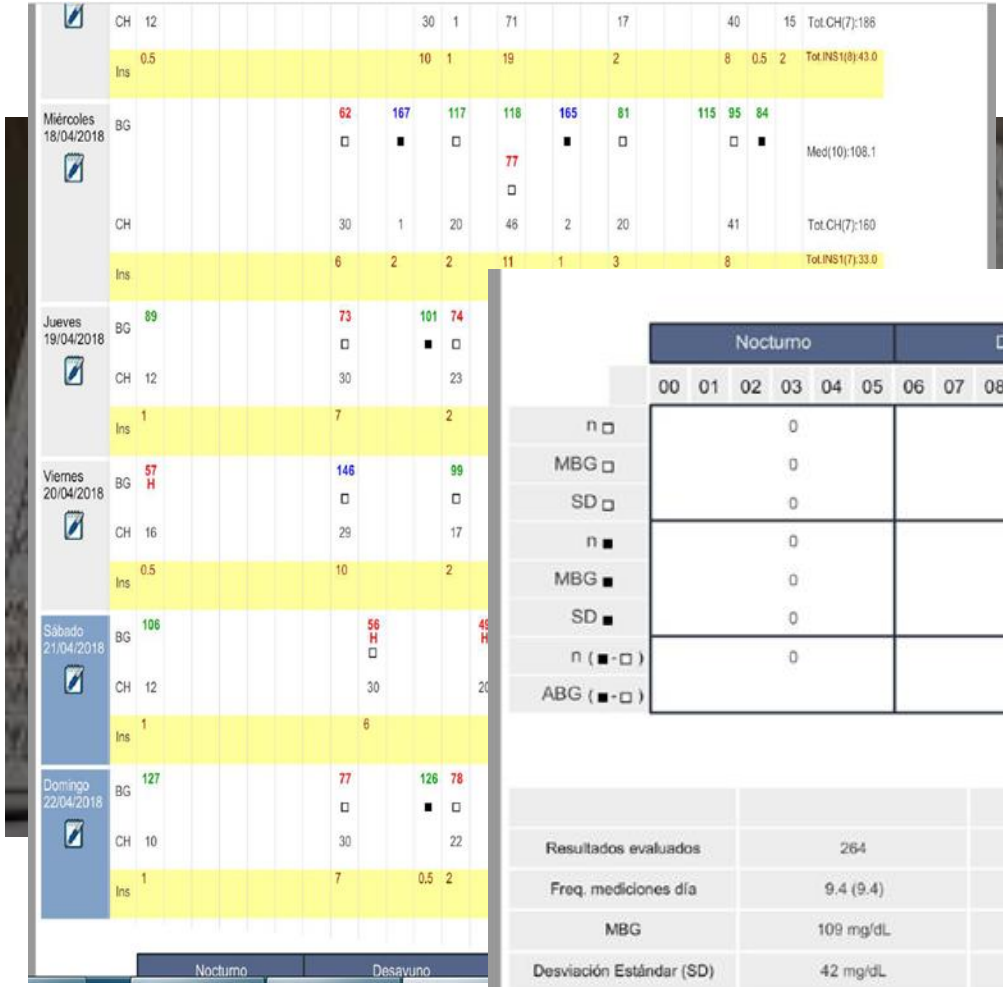
- IECA: Inhibidor de la enzima de conversión de la angiotensina; ARAII: antagonista de los receptores de la angiotensina II.
- Adapted from: Rydén L, et al. *Eur Heart J* 2013;34:3035–87; Fox CS, et al. *Diabetes Care* 2015;38:1777–803; Piepoli MF, et al. *Eur Heart J* 2016;37:2315–81.

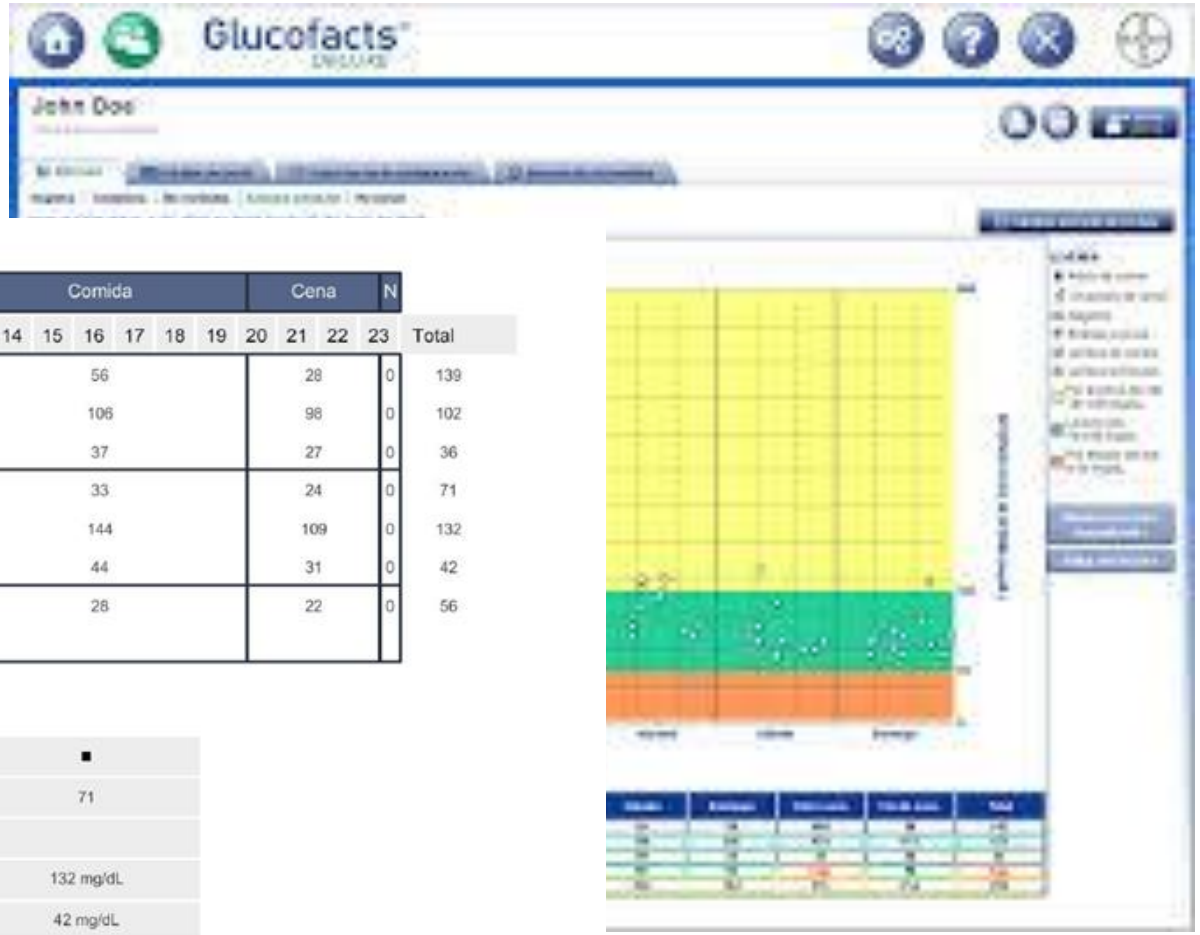

Tecnología
• Medición de glucosa
• Visualización de los datos
• MCG

Tecnología en DM2: Glucómetros y Apps

autonomía paciente
comunicación con
el profesional

Tecnología en DM2: Glucometros y visualización datos





	Nocturno						Desayuno						Comida						Cena				N	Total
	00	01	02	03	04	05	06	07	08	09	10	11	12	13	14	15	16	17	18	19	20	21	22	23		
n □				0						55							56					28			0	139
MBG □				0						101							106					98			0	102
SD □				0						39							37					27			0	36
n ■				0						14							33					24			0	71
MBG ■				0						144							144					109			0	132
SD ■				0						39							44					31			0	42
n (■-□)				0						6							28					22			0	56
ABG (■-□)																										

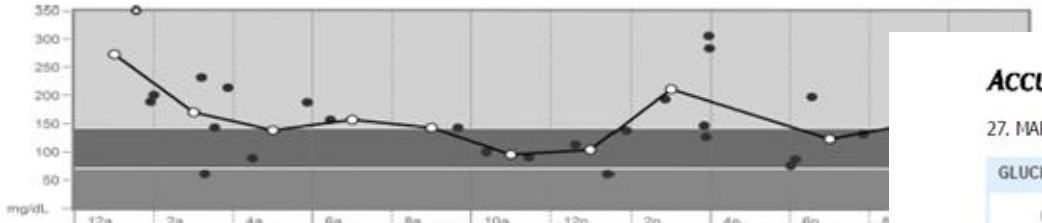
		□	■
Resultados evaluados	264	139	71
Freq. mediciones día	9.4 (9.4)		
MBG	109 mg/dL	102 mg/dL	132 mg/dL
Desviación Estándar (SD)	42 mg/dL	36 mg/dL	42 mg/dL
Máximo	238 mg/dL	219 mg/dL	238 mg/dL
Mínimo	36 mg/dL	42 mg/dL	57 mg/dL
Núm. Hipos	33		

Tecnología en DM2: Glucometros y visualización datos

Día tipo

Abr 10, 2018 - Abr 23, 2018 (14 días)

FreeStyle Auto-Assist



		Noche			Mañana		Mediodía			Tarde	
Glucosa (mg/dL)		PROMEDIO DEL PERIODO									
Promedio	164	273	170	139	157	143	96	104	212	-	123
Alta	357	357	232	188	157	143	100	138	306	-	198
Baja	61	189	61	89	157	143	91	61	127	-	76
Desviación estándar	71,0	84,0	62,2	49,5	-	-	4,5	32,1	71,8	-	48,0
Nº prom. de pruebas	3,5	0,2	0,5	0,2	0,1	0,1	0,2	0,3	0,5	-	0,4
Insulina (unidades) PROM. DIARIO		PROMEDIO DEL PERIODO									
Acción lenta	- -		-		-		-			-	
Comida	- -		-		-		-			-	
Corrección	- -		-		-		-			-	
Promedio total	-		-		-		-			-	
Configuración											
Objetivo de glucemia (mg/dL)			-		-		-			-	
Factor de corrección (mg/dL)			-		-		-			-	

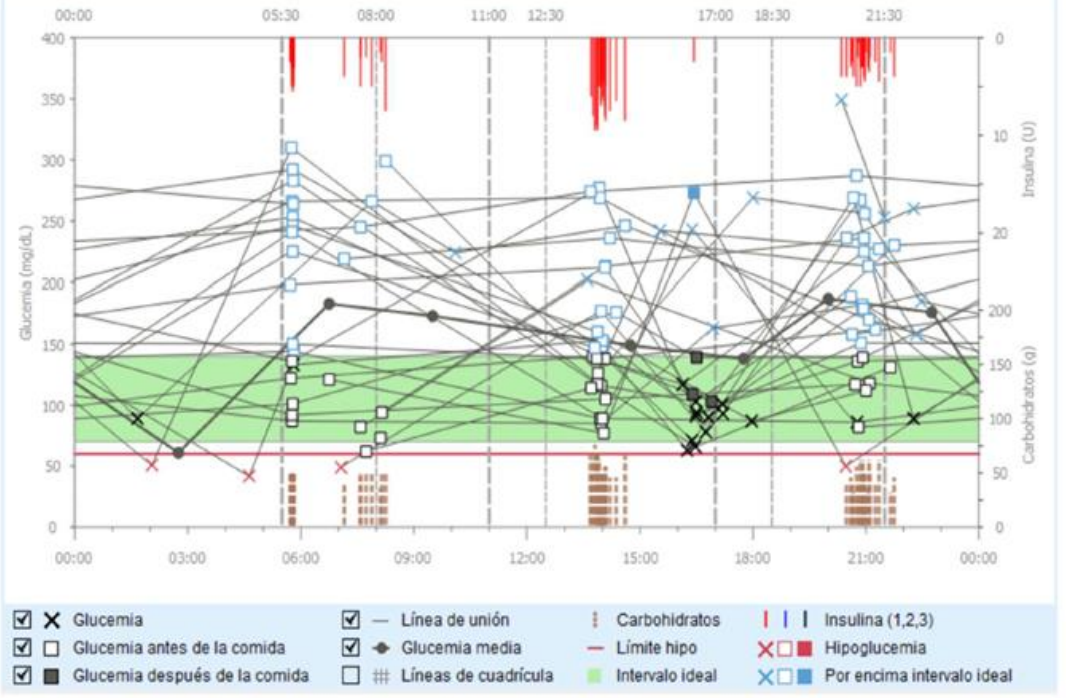
LEYENDA: Rango deseado (70-140) mg/dL · Mayor al objetivo · Menor a valor deseado · Glucemia promedio del periodo · Resultado glucemia (mg/dL) · Resultado glucemia más de 350 mg/dL

ACCU-CHEK Report

Accu-Chek Aviva Expert: 10504322

27. MAR 2018 - 23. ABR 2018

GLUCEMIA - GRÁFICO DÍA



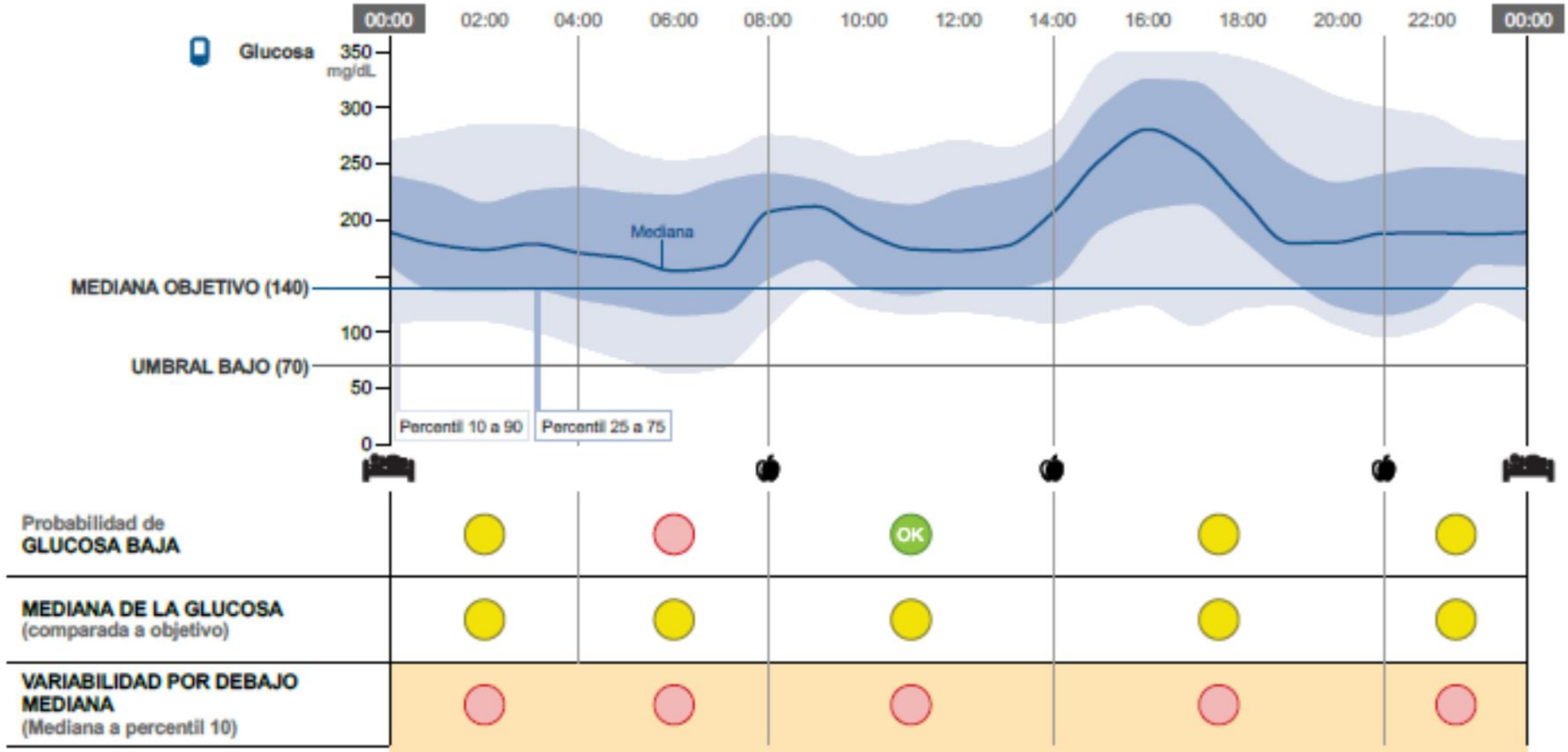
Tecnología en DM2: iMCG

11 de diciembre de 2016 - 23 de diciembre de 2016 (13 días)

CONFIGURACIÓN DE TOLERANCIA DE GLUCOSA BAJA: **Medio**

CONFIGURACIÓN DE MEDIANA OBJETIVO: **140 mg/dL (A1c: 6,5% o 48 mmol/mol)**

A1c estimado 8,5% o 69 mmol/mol



Fármacos

Nuevos tratamientos

- Estudios de seguridad cardiovascular

Tratamiento farmacológico

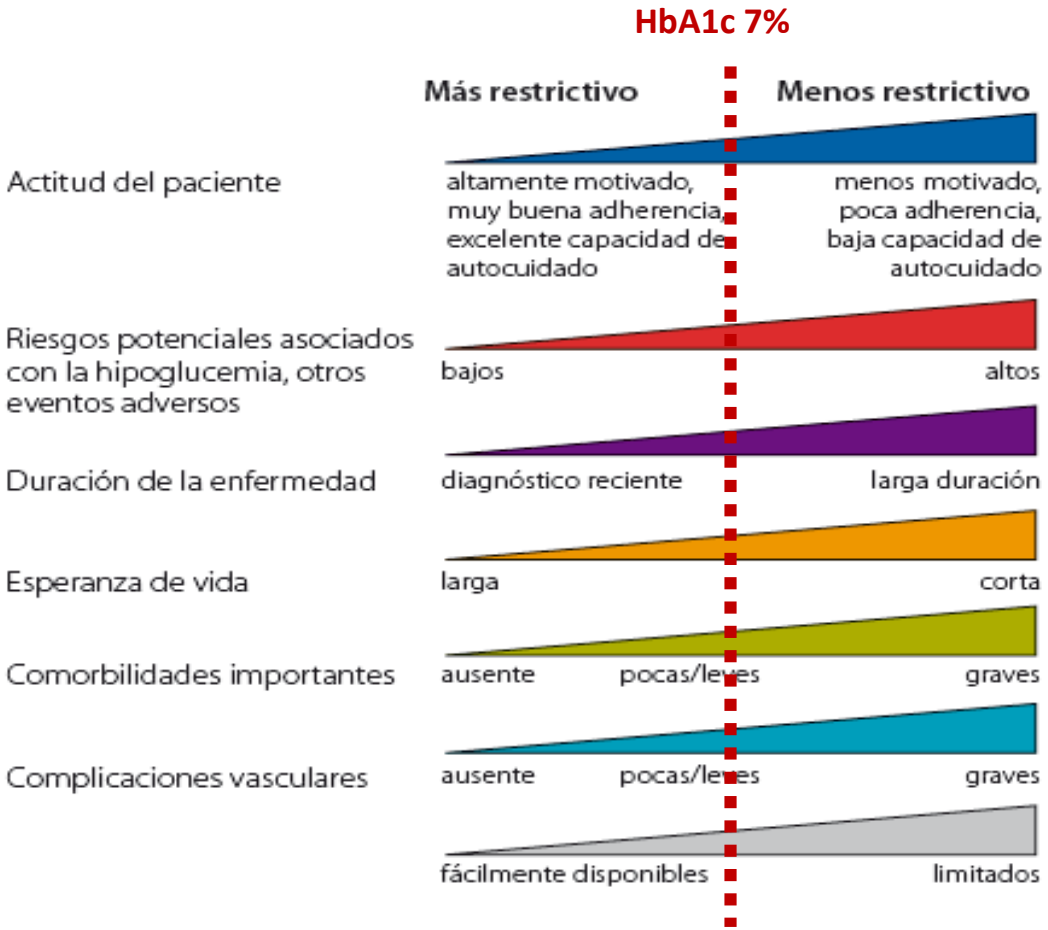
Nuevos fármacos

- **Evidencias de eficacia**
- **Nuevos datos de seguridad**

Guías Práctica Clínica

- **Objetivos individualizados**
- **Estrategia de escalonamiento terapeútico**
- **Priorización de algunos fármacos**

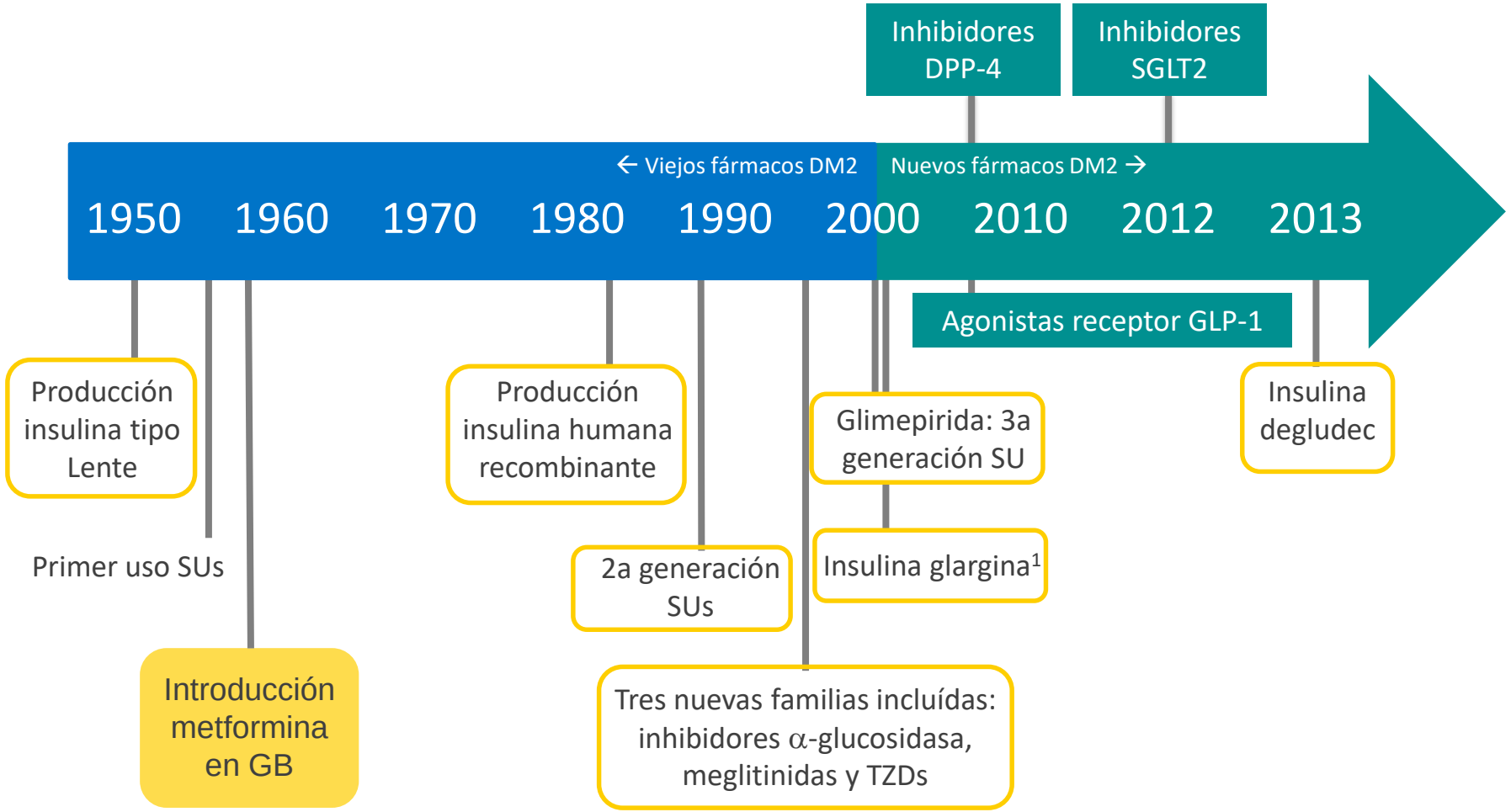
Objetivos de control glucémico



A1c ≤ 6.5%	A1c > 6.5%
Pacientes sin comorbilidad importante y bajo riesgo de hipoglucemia	Pacientes con comorbilidad importante y alto riesgo de hipoglucemia

La Asociación Americana de Endocrinólogos Clínicos (AACE) y el Colegio Americano de Endocrinología (ACE) proponen objetivos más estrictos

ESC/EASD Guidelines. Ryden L et al. Eur Heart J 2013
ADA Standards of medical care in diabetes. Diabetes Care 2018 Jan; 41(Supplement 1): S55-S6
Garber A et al. Endocr Pract 2018;24:91-120



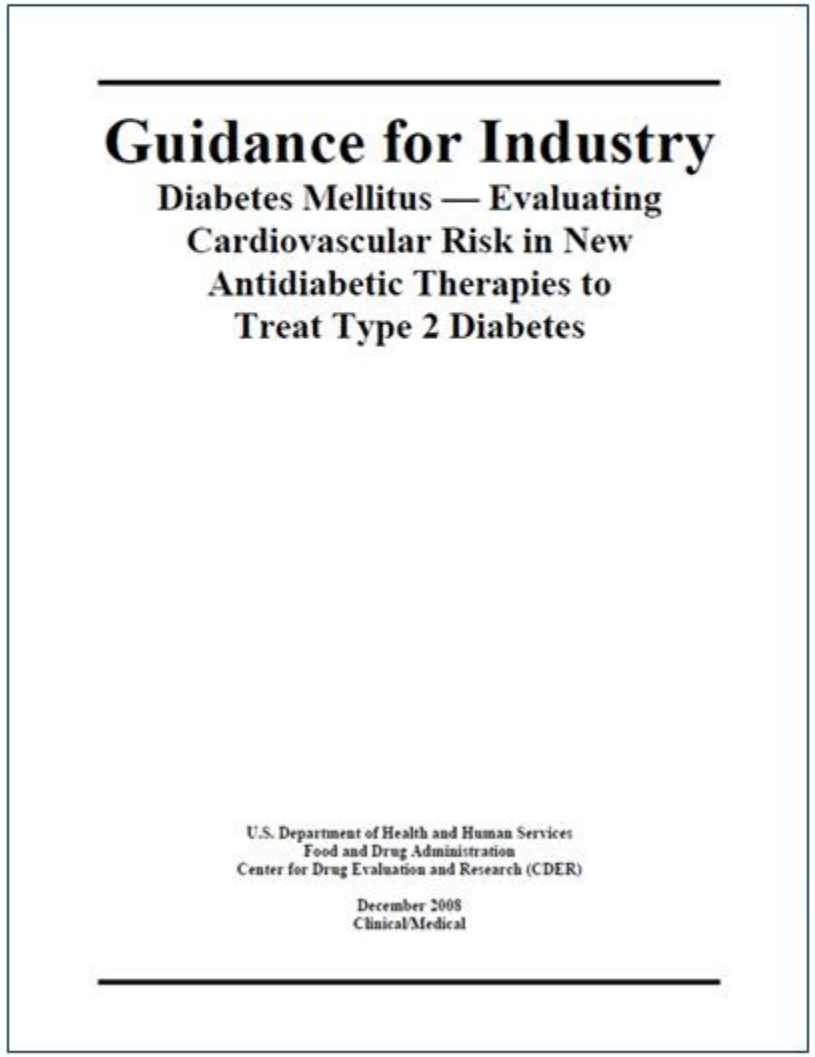
CV, cardiovascular; DM2, diabetes mellitus tipo 2; DPP-4, dipeptidil peptidasa-4; GLP-1, péptido-1 glucagon-like; SGLT2, cotransportador 2 sodio-glucosa; SU, sulfonilurea; TZD, tiazolidindiona.

Adaptado de: Kirby MG. Br J Diabetes Vasc Dis 2012;12:315; 1. Sanofi US. Lantus® (inyección insulina glargina) USPI, 2015

Tratamiento farmacológico

- Metformina
- Sulfonilureas
- Repaglinida
- Acarbosa
- Pioglitazona
- Inhibidores DPP4
- ar-GLP1
- iSGLT2
- insulina

December 2008 FDA Guidance on Evaluating CV Risk in New Antidiabetic Therapies for T2DM



Guidance for Industry

Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes

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

December 2008
Clinical/Medical

III. RECOMMENDATIONS

To establish the safety of a new antidiabetic therapy to treat type 2 diabetes, sponsors should demonstrate that the therapy will not result in an unacceptable increase in cardiovascular risk. To ensure that a new therapy does not increase cardiovascular risk to an unacceptable extent, the development program for a new type 2 antidiabetic therapy should include the following.

For new clinical studies in the planning stage:

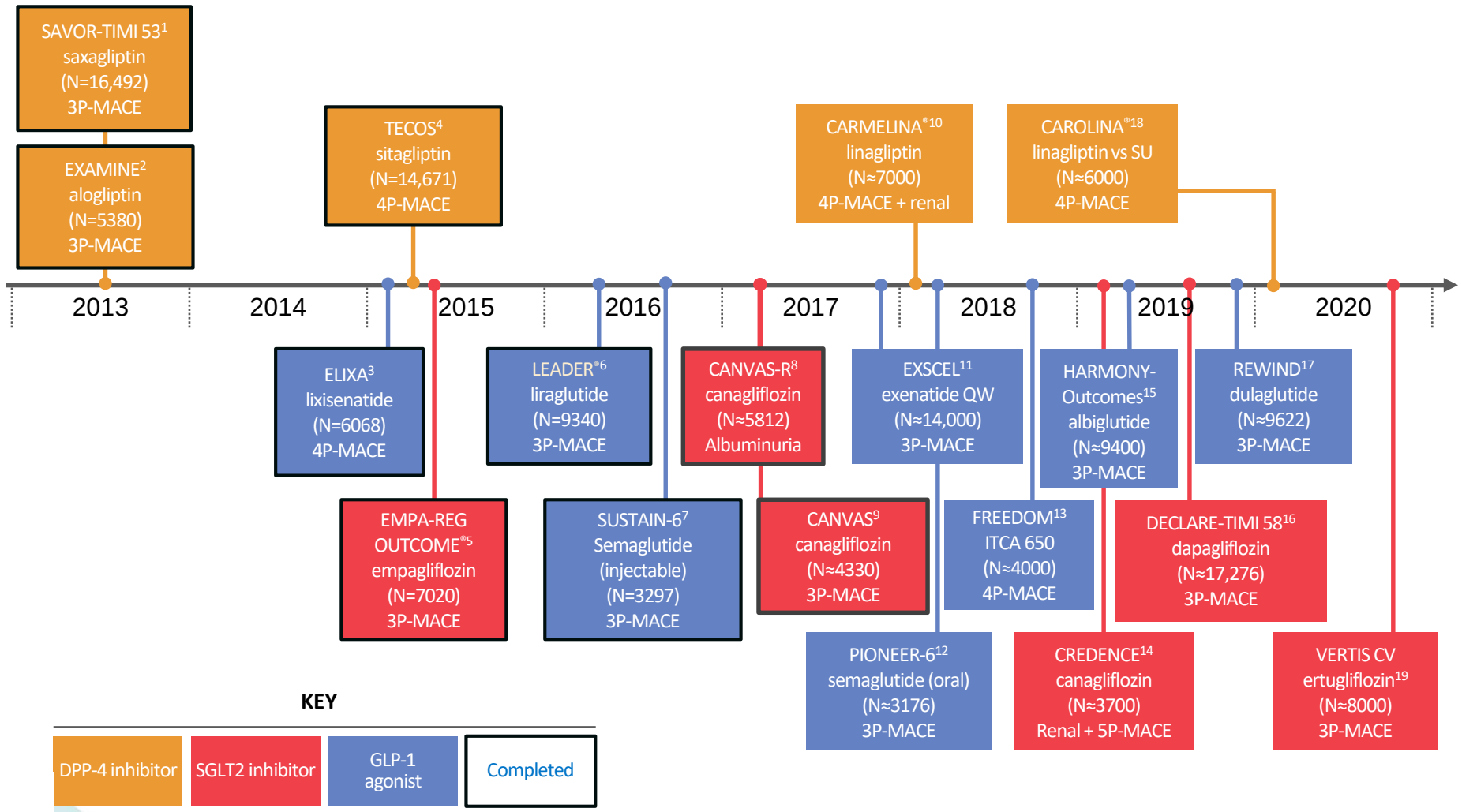
- Sponsors should establish an independent cardiovascular endpoints committee to prospectively adjudicate, in a blinded fashion, cardiovascular events during all phase 2 and phase 3 trials. These events should include cardiovascular mortality, myocardial infarction, and stroke, and can include hospitalization for acute coronary syndrome, urgent revascularization procedures, and possibly other endpoints.

- Sponsors should ensure that phase 2 and phase 3 clinical trials are appropriately designed and conducted so that a meta-analysis can be performed at the time of completion of these studies that appropriately accounts for important study design features and patient or study level covariates. To obtain sufficient endpoints to allow a meaningful estimate of risk, the phase 2 and phase 3 programs should include patients at higher risk of cardiovascular events, such as patients with relatively advanced disease, elderly patients, and patients with some degree of renal impairment. Because these types of patients are likely to be treated with the antidiabetic agent, if approved, this population is more appropriate than a younger and healthier population for assessment of other aspects of the test drug's safety.

- Sponsors also should provide a protocol describing the statistical methods for the proposed meta-analysis, including the endpoints that will be assessed. At this time, we believe it would be reasonable to include in a meta-analysis all placebo-controlled trials, add-on trials (i.e., drug versus placebo, each added to standard therapy), and active-

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071627.pdf

Estudios de seguridad CV



Trial disclosure dates for non-published trials from clinicaltrials.gov
Refer to slide notes for abbreviations
Adapted from Johansen OE. World J Diabetes 2015;6:1092 (references 1–19 expanded in slide notes)

Seguridad Cardiovascular de iDPP4

Molécula	Estudio	Objetivo 1º	Hospitalización IC
Sitagliptina	**TECOS[1]**	√ **No inferioridad** MACE+Hospitalización por angina inestable	√ **No inferioridad**
Vildagliptina	**No realizado**	**No realizado**	**No realizado**
Saxagliptina	**SAVOR-TIMI 53[2]**	√ **No inferioridad** MACE	↑**27%** P=0.007
Linagliptina	**CARMELINA[3]**	Albuminuria (micro /macro) y enfermedad macrovascular previa y/o insuficiencia renal	Pendiente de resultados
Alogliptina	**EXAMINE[4]**	√ **No inferioridad** MACE	↑**19%** P=ns

MACE: Muerte CV, Ictus e Infarto de miocardio no mortal

1.Green JB et al. N Engl J Med 2015;373:232-42

2.Scirica BM, et al. N Engl J Med. 2013.10.1056

3.Marx N, et al. Diab Vasc Dis Res. 2015;12:164-174

4.Scirica BM et al. N Engl J Med 2013;369:1317–1326

Seguridad Cardiovascular de ar-GLP1

ELIXA

lixisenatide

semaglutida

Superioridad

SUSTAIN

SEMAGLUTIDE UNABATED SUSTAINABILITY IN TREATMENT OF TYPE 2 DIABETES

ECV ó alto RCV, 2.1 años, n 3297, MACE3 Nº eventos 254

LEADER®

Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results

liraglutida

REWIND

Dulaglutide

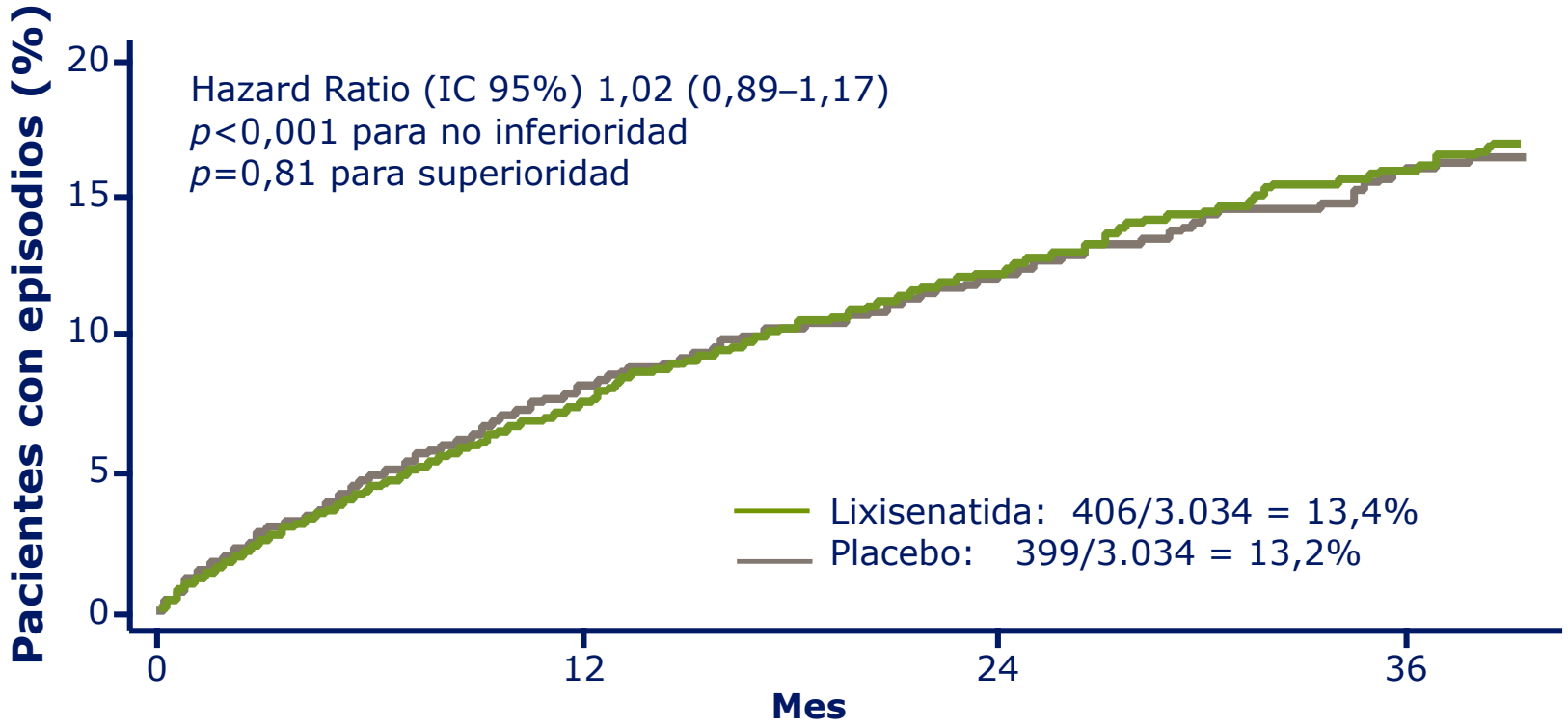
EXSCEL

Exenatide Study of Cardiovascular Event Lowering

Exenatida LAR

No inferioridad

muerte cardiovascular, infarto agudo de miocardio no mortal, ictus no mortal o hospitalización por angina inestable



Número en riesgo				
Placebo	3.034	2.759	1.566	476
Lixisenatida	3.034	2.785	1.558	484

IC: intervalo de confianza.

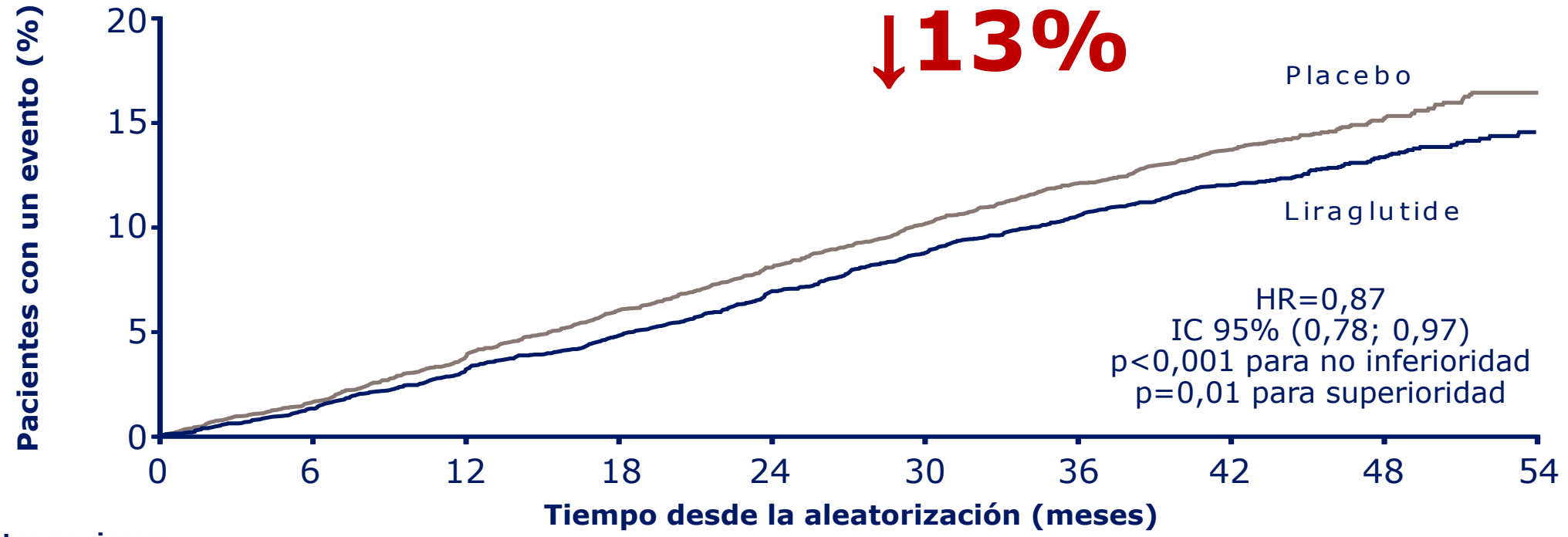
Pfeffer MA et al. *N Engl J Med* 2015;373:2247–2257

LEADER®
Liraglutide Effect and Action in Diabetes:
Evaluation of cardiovascular outcome Results

Superioridad

Criterio de valoración principal

Muerte por causa CV, IM no mortal o ictus no mortal



Pacientes en riesgo

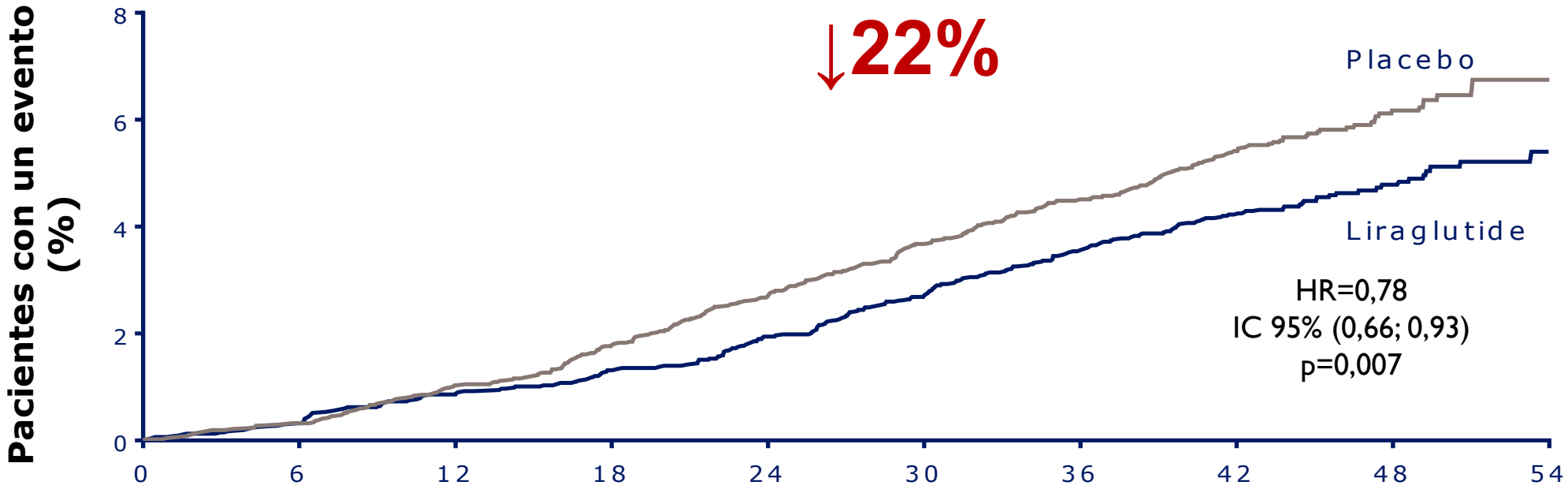
Liraglutida	4668	4593	4496	4400	4280	4172	4072	3982	1562	424
Placebo	4672	4588	4473	4352	4237	4123	4010	3914	1543	407

En el análisis del tiempo hasta el primer evento, el criterio de valoración principal compuesto fue la primera aparición de muerte por causas cardiovasculares, infarto de miocardio no mortal o ictus no mortal. Las incidencias acumuladas se estimaron mediante el método de Kaplan-Meier, y los hazard ratio con el modelo de regresión de riesgos proporcionales de Cox. Los análisis de datos se truncan a los 54 meses, ya que menos del 10% de los pacientes tuvieron un tiempo de observación superior a 54 meses. IC: intervalo de confianza; CV: cardiovascular; HR: hazard ratio.

Marso SP et al. N Engl J Med 2016. DOI: 10,1056/NEJMoa1603827.

LEADER®
Liraglutide Effect and Action in Diabetes:
Evaluation of cardiovascular outcome Results

Muerte por causa cardiovascular



Pacientes en riesgo

Liraglutida	4668	4641	4599	4558	4505	4445	4382	4322	1723	484
Placebo	4672	4648	4601	4546	4479	4407	4338	4267	1709	465

Las incidencias acumuladas se estimaron mediante el método de Kaplan-Meier, y los hazard ratio con el modelo de regresión de riesgos proporcionales de Cox. Los análisis de datos se truncan a los 54 meses, ya que menos del 10% de los pacientes tuvieron un tiempo de observación superior a 54 meses. IC: intervalo de confianza; CV: cardiovascular; HR: hazard ratio.

Marso SP et al. *N Engl J Med* 2016. DOI: 10,1056/NEJMoa1603827.

The NEW ENGLAND JOURNAL of MEDICINE

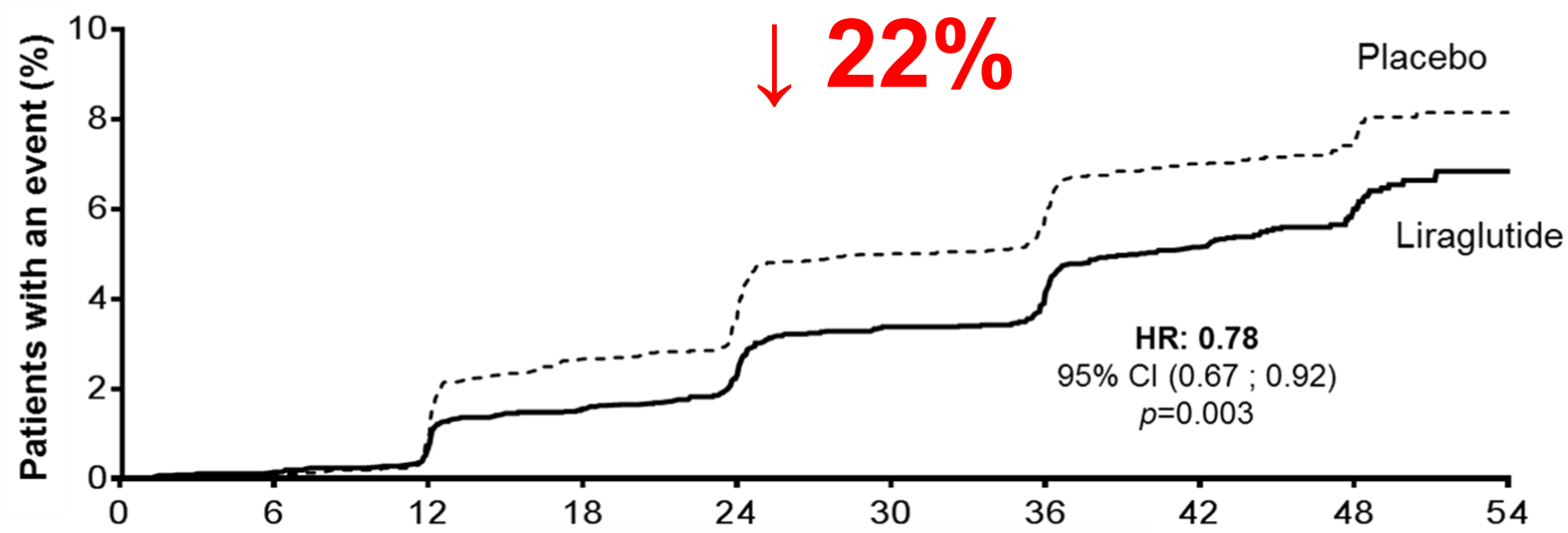
ORIGINAL ARTICLE

Liraglutide and Renal Outcomes in Type 2 Diabetes

Johannes F.E. Mann, M.D., David D. Ørsted, M.D., Ph.D.,
Kirstine Brown-Frandsen, M.D., Steven P. Marso, M.D.,
Neil R. Poulter, F.Med.Sci., Søren Rasmussen, Ph.D., Karen Tornøe, M.D., Ph.D.,
Bernard Zinman, M.D., and John B. Buse, M.D., Ph.D.,
for the LEADER Steering Committee and Investigators*

Time to primary composite nephropathy outcome

Macroalbuminuria, doubling of serum creatinine*, ESRD, renal death (N= 605)



Patients at risk

Liraglutide	4668	4635	4561	4492	4400	4304	4210	4114	1632	454
Placebo	4672	4643	4540	4428	4316	4196	4094	3990	1613	433

*and eGFR ≤45 mL/min/1.73 m² per MDRD. The cumulative incidences were estimated with the use of the Kaplan–Meier method, and the HRs with the use of the Cox proportional-hazard regression model. The data analyses are truncated at 54 months because less than 10% of the patients had an observation time beyond 54 months. CI: confidence interval; eGFR, estimated glomerular filtration rate; ESRD: end-stage renal disease; HR: hazard ratio; MDRD: modification of diet in renal disease. Presented at ASN Kidney week, 19 November 2016, Chicago, USA.

NEJM 8/2017

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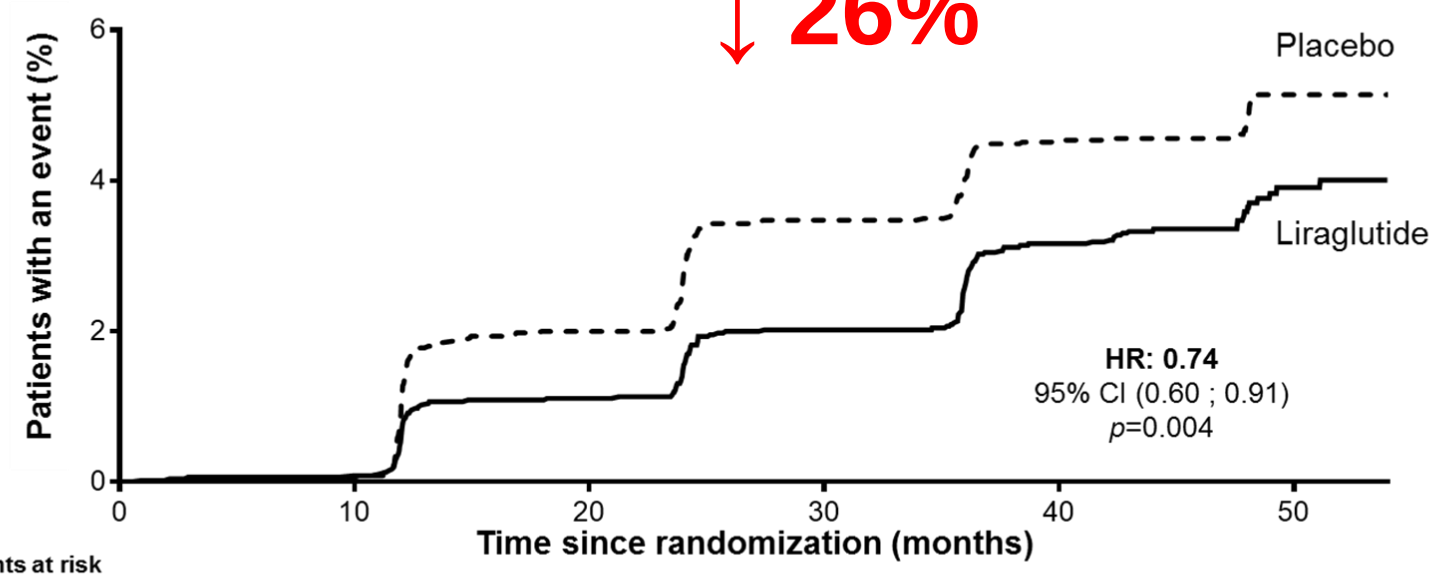
Time to new onset of persistent macroalbuminuria

↓ 26%



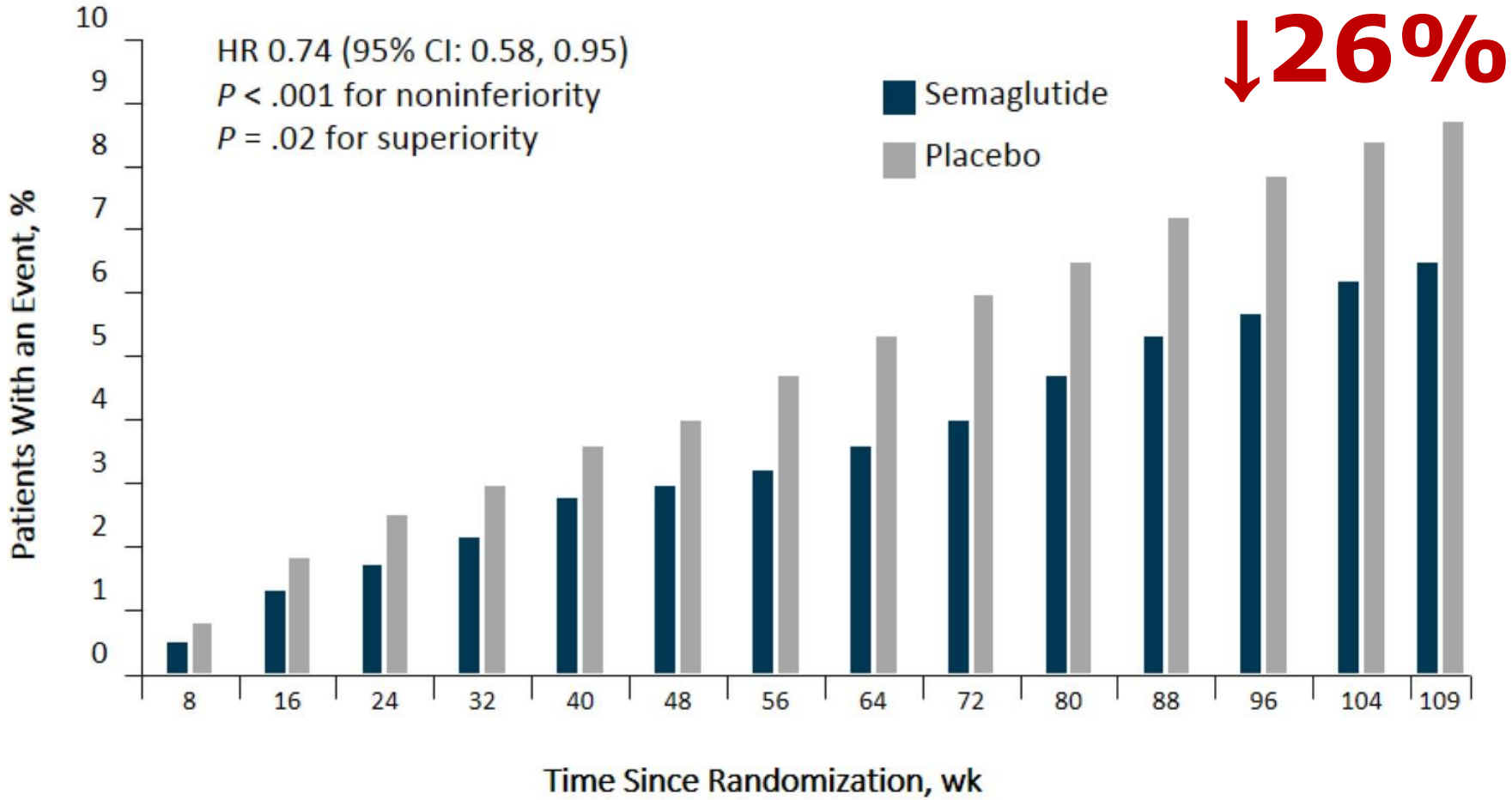
Patients at risk

Liraglutide	4668	4606	4499	4353	4199	1006
Placebo	4672	4615	4433	4252	4094	964

Full analysis set. EAC-confirmed index events from randomization to follow-up. The cumulative incidences were estimated with the use of the Kaplan–Meier method, and the HRs with the use of the Cox proportional-hazard regression model. The data analyses are truncated at 54 months because less than 10% of the patients had an observation time beyond 54 months. Macroalbuminuria defined as urine albumin >300 mg/g creatinine. CI: confidence interval; EAC: event adjudication committee; HR: hazard ratio. Presented at ASN Kidney week, 19 November 2016, Chicago, USA.

NEJM 8/2017

SUSTAIN-6: Primary Outcome Measure*

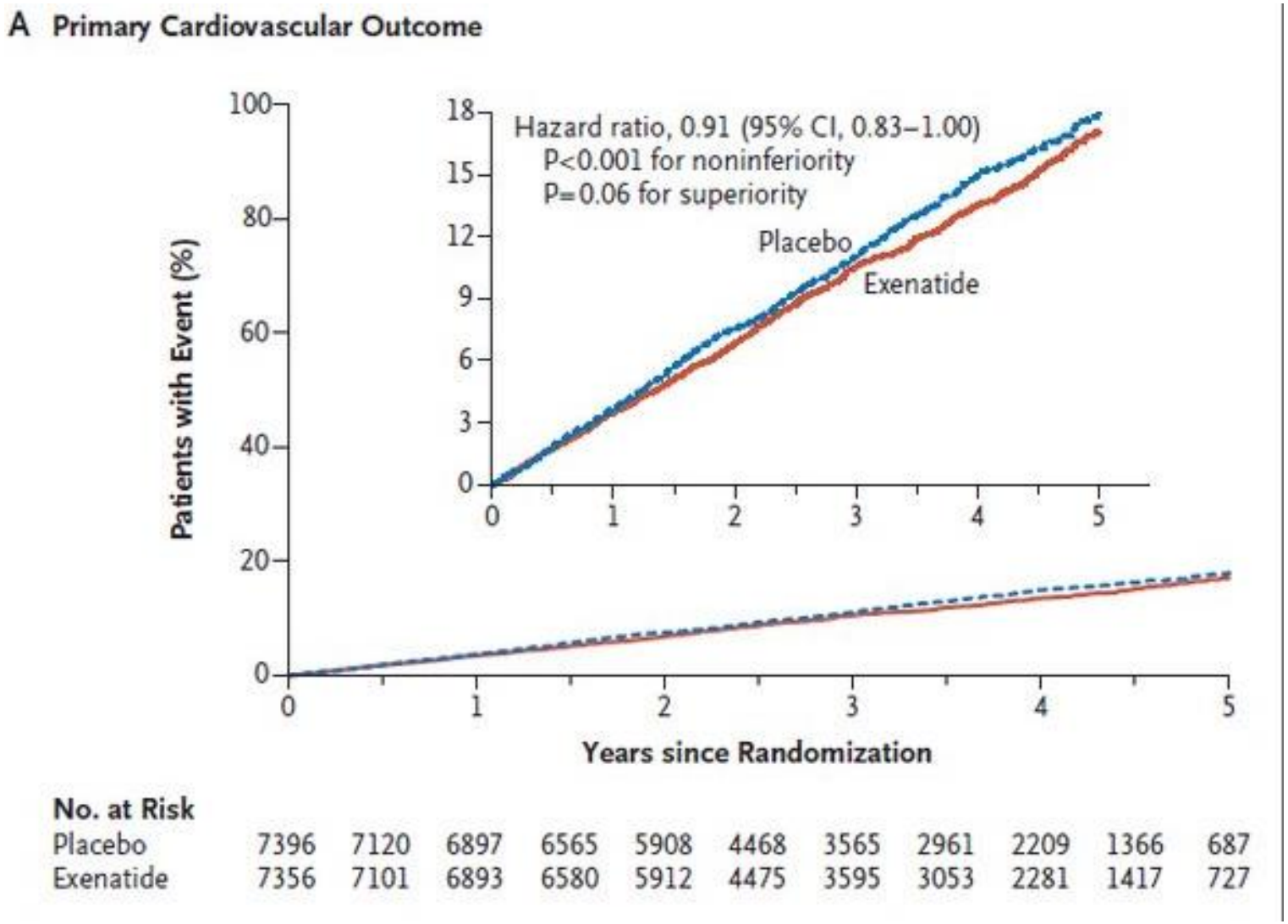


*Composite of CV death, nonfatal MI, or nonfatal stroke

Marso SP, et al. *N Engl J Med*. 2016;375:1834-1844.

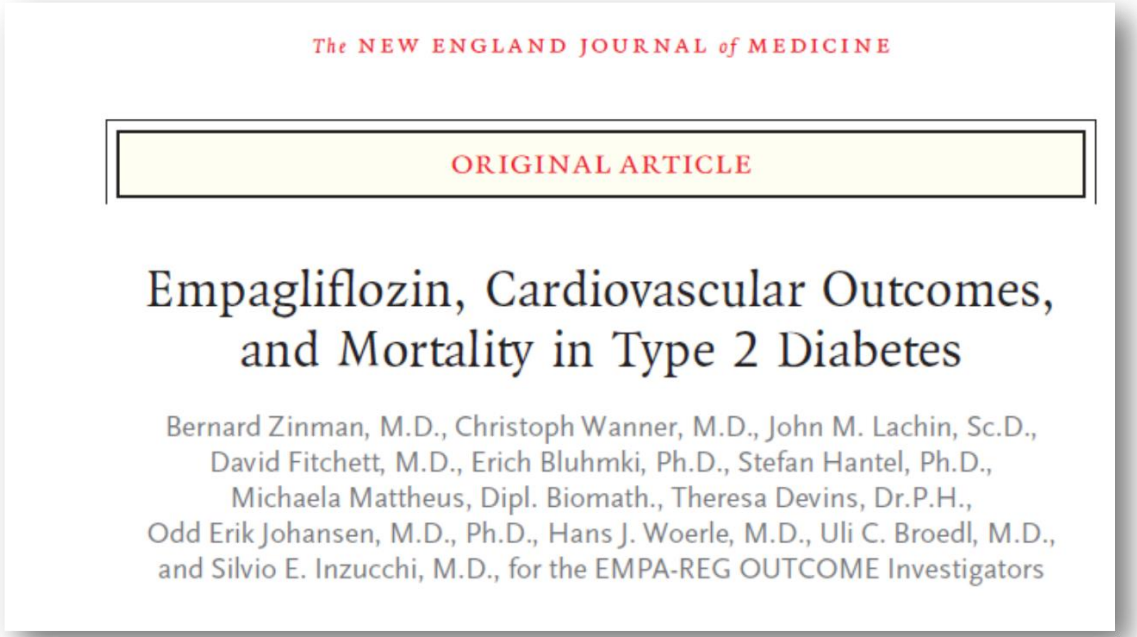
Exenatide LAR

No inferioridad



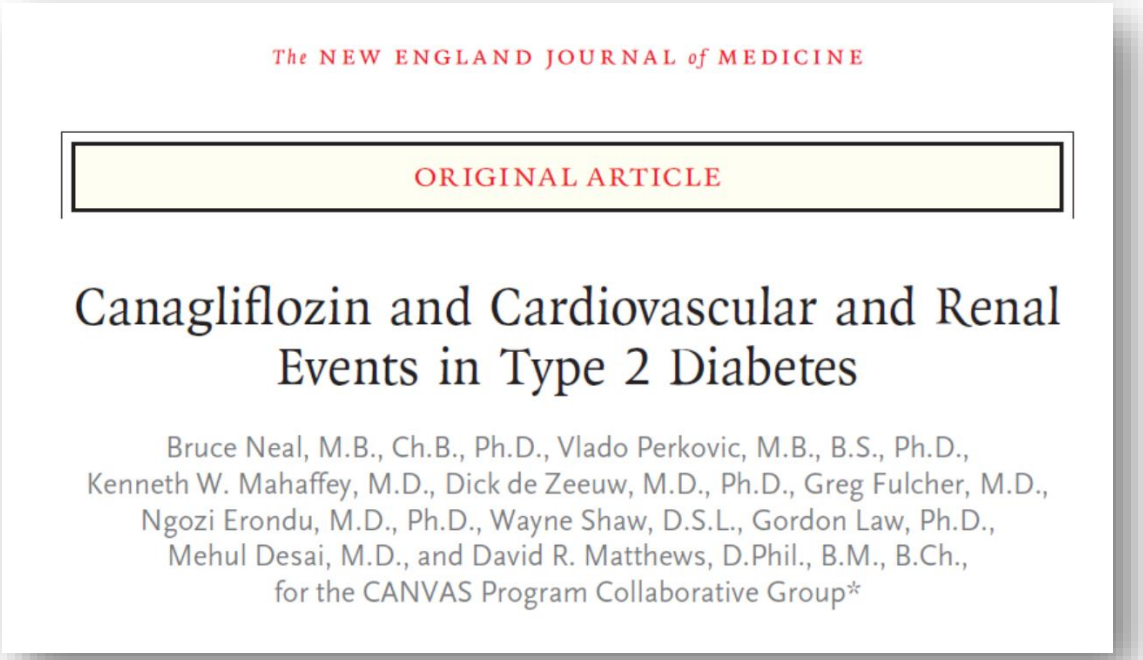
Effects of Once-Weekly Exenatide on Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med 2017; 377:1228-1239. September 28, 2017. DOI: 10.1056/NEJMoa1612917. Rury R. Holman, F.Med.Sci., M. Angelyn Bethel, M.D., Robert J. Mentz, M.D., Vivian P. Thompson, M.P.H., Yuliya Lokhnygina, Ph.D., John B. Buse, M.D.,

Seguridad Cardiovascular de iSGLT2



EMPA-REG OUTCOME

NEJM 9/2015



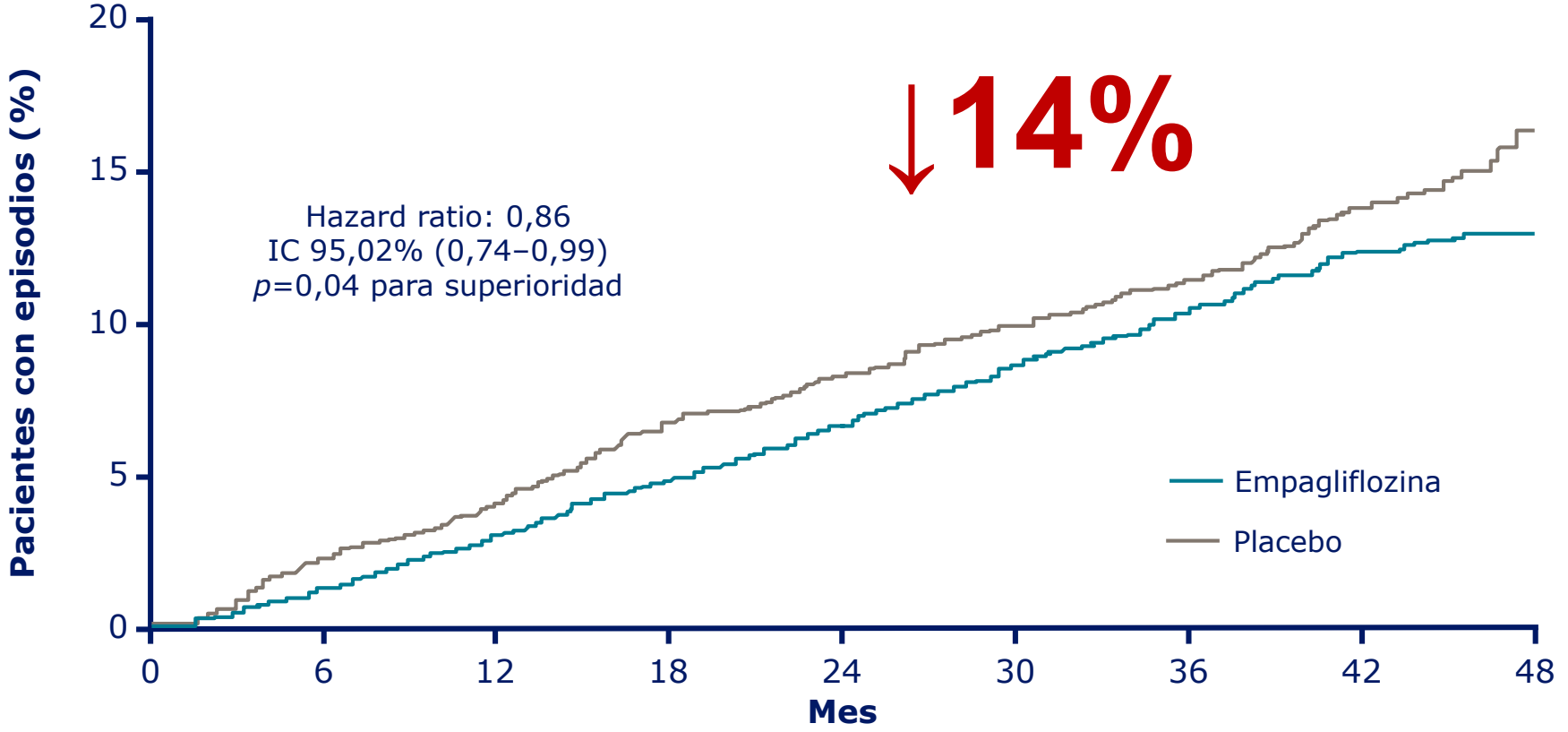
CANVAS Program

NEJM 8/2017

EMPA-REG OUTCOME

Muerte cardiovascular, infarto de miocardio no mortal e ictus no mortal

Superioridad



Número en riesgo

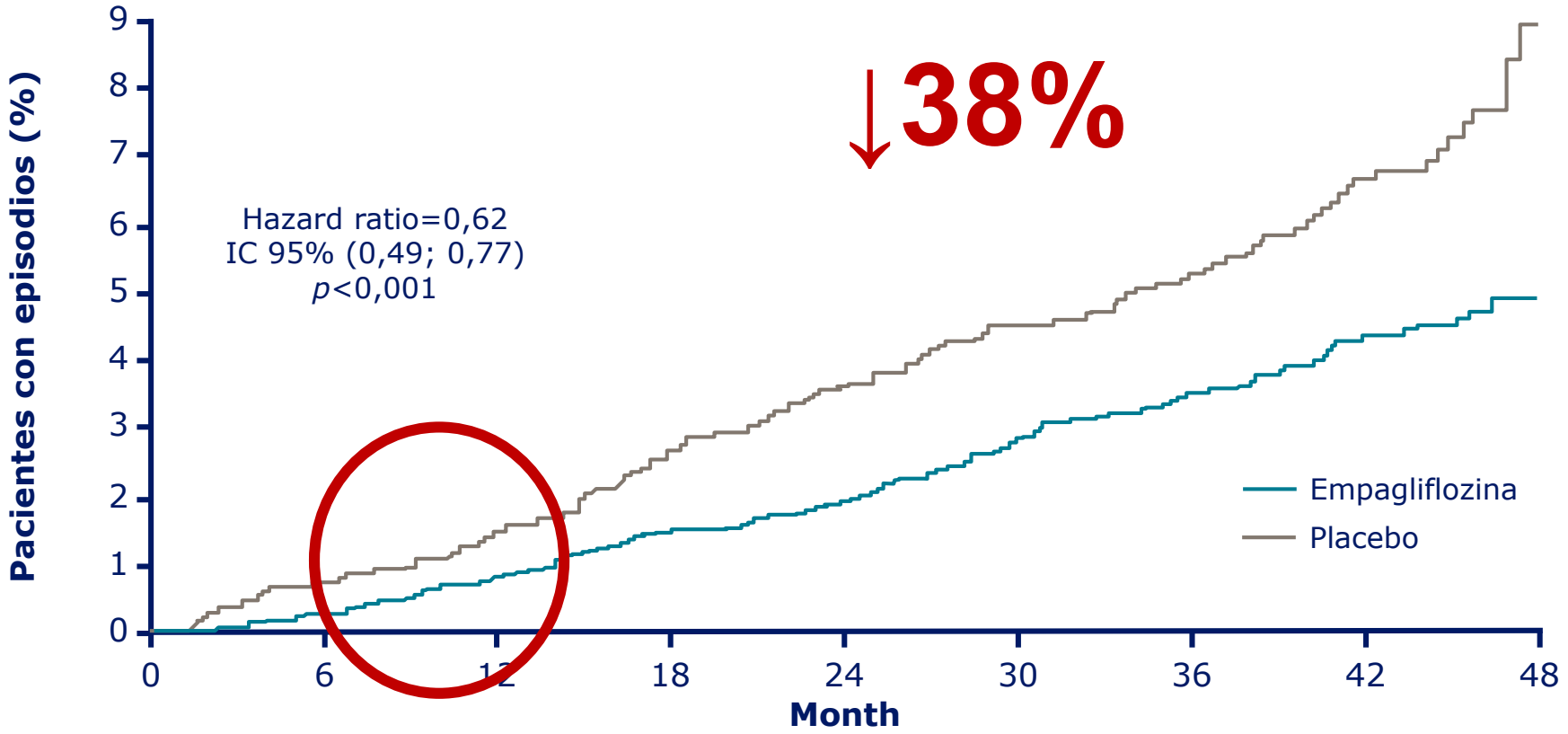
Empagliflozina	4687	4580	4455	4328	3851	2821	2359	1534	370
Placebo	2333	2256	2194	2112	1875	1380	1161	741	166

IC: intervalo de confianza.

Zinman B et al. *N Engl J Med* 2015; 373:2117-28.

EMPA-REG OUTCOME

Muerte por causa cardiovascular



Número en riesgo

Empagliflozina	4687	4651	4608	4556	4128	3079	2617	1722	414
Placebo	2333	2303	2280	2243	2012	1503	1281	825	177

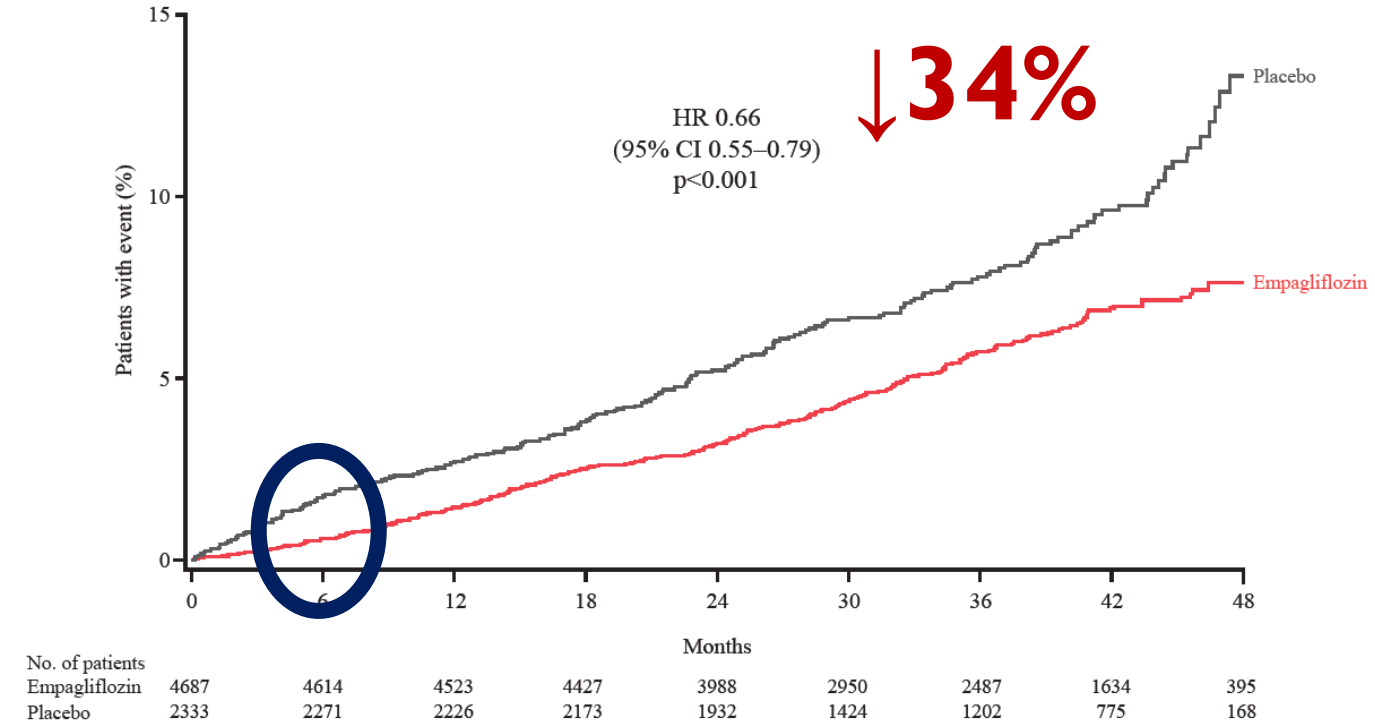
IC: intervalo de confianza.

Zinman B et al. *N Engl J Med* 2015; 373:2117-28.

Heart failure outcomes with empagliflozin in patients with type 2 diabetes at high cardiovascular risk: results of the EMPA-REG OUTCOME® trial

David Fitchett[1*], Bernard Zinman[2,3], Christoph Wanner[4], John M. Lachin[5], Stefan Hantel[6], Afshin Salsali[7], Odd Erik Johansen[8], Hans J. Woerle[9], Uli C. Broedl[9], and Silvio E. Inzucchi[10], on behalf of the EMPA-REG OUTCOME® trial investigators

Hospitalización o muerte por Insuficiencia Cardiaca



- David Fitchett et al. *Eur Heart J* 2016; DOI: http://dx.doi.org/10.1093/eurheartj/ehv728

The NEW ENGLAND JOURNAL of MEDICINE

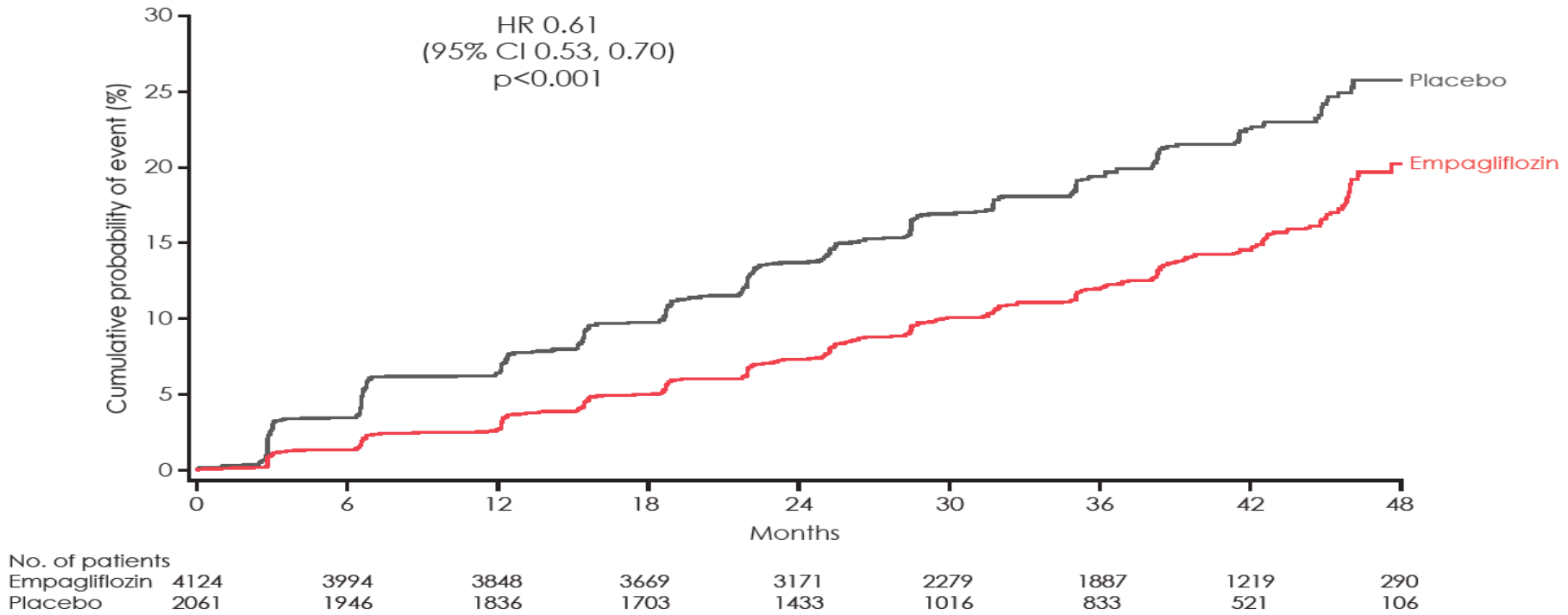
ORIGINAL ARTICLE

Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes

Christoph Wanner, M.D., Silvio E. Inzucchi, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Maximilian von Eynatten, M.D., Michaela Mattheus, Dipl. Biomath., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Bernard Zinman, M.D., for the EMPA-REG OUTCOME Investigators*

New onset or worsening nephropathy

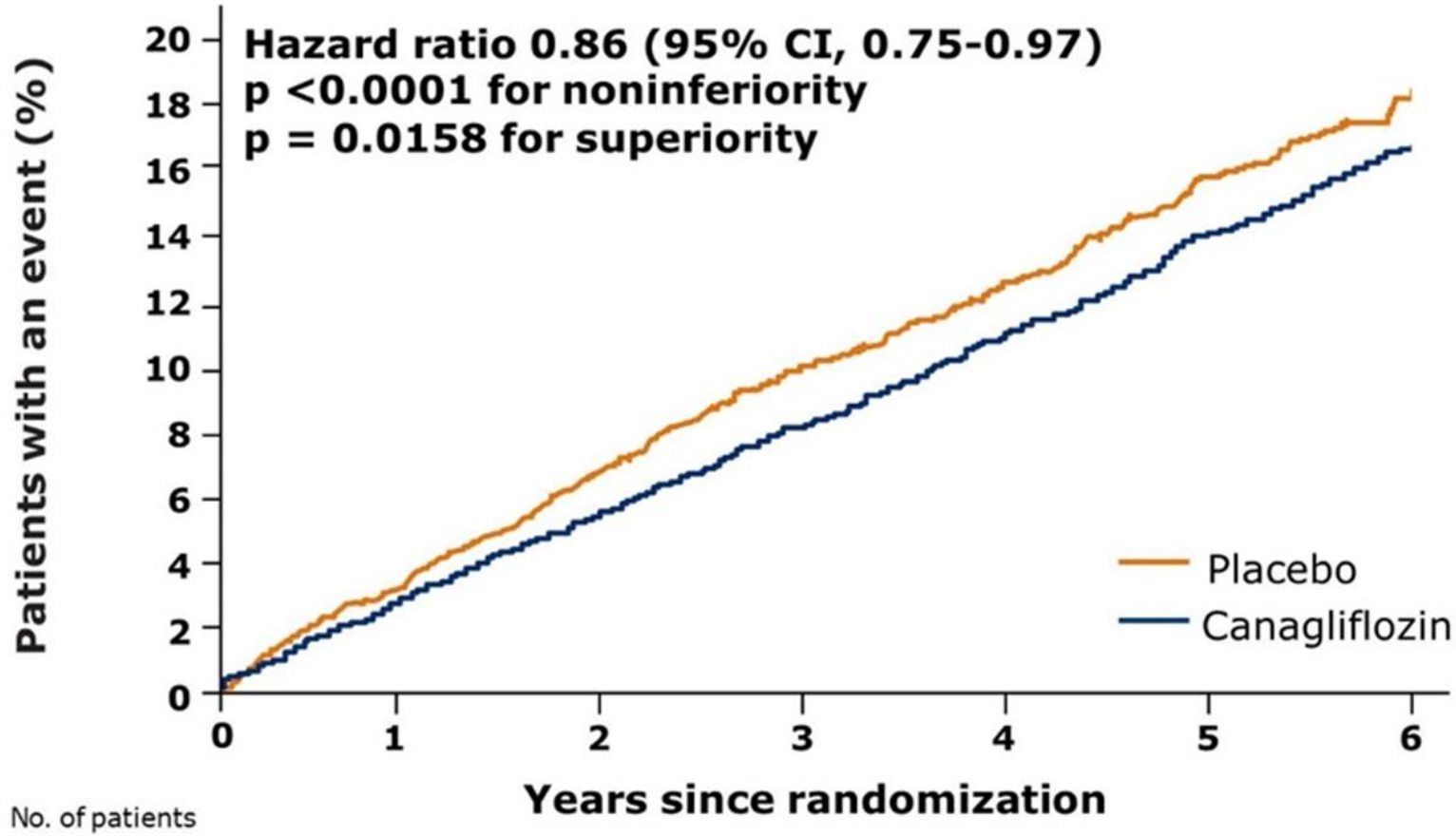
↓39%



NEJM 6-2016

Primary MACE Outcome

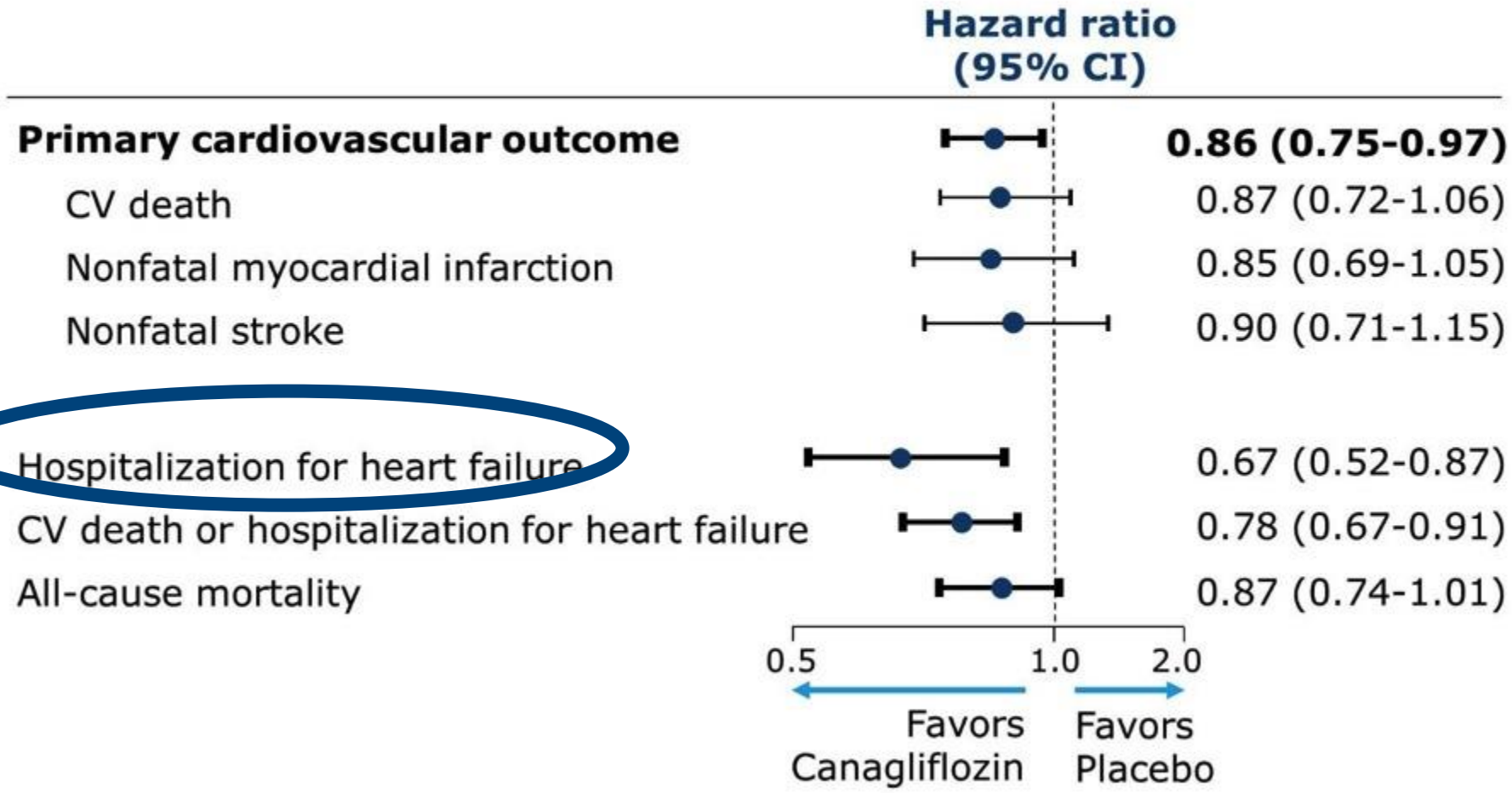
CV Death, Nonfatal Myocardial Infarction or Nonfatal Stroke



No. of patients							
Placebo	4347	4153	2942	1240	1187	1120	789
Canagliflozin	5795	5566	4343	2555	2460	2363	1661

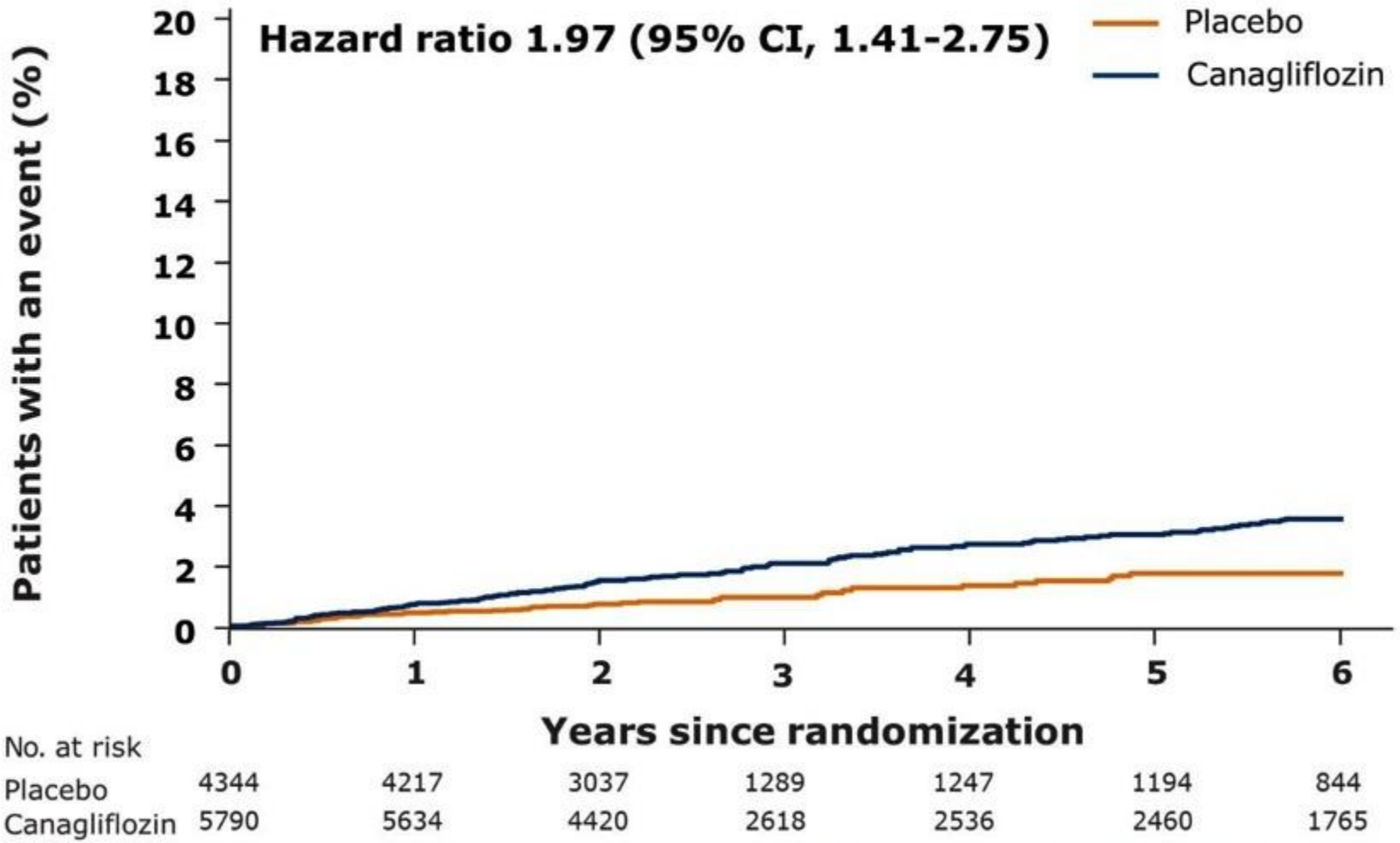
Intent-to-treat analysis

Summary



Intent-to-treat analysis

Lower-extremity Amputations



Increased risk communicated to health authorities, investigators, and providers in 2016 based on IDMC letter.

Presented at the 77th Scientific Sessions of the American Diabetes Association;
June 12, 2017; San Diego, CA.

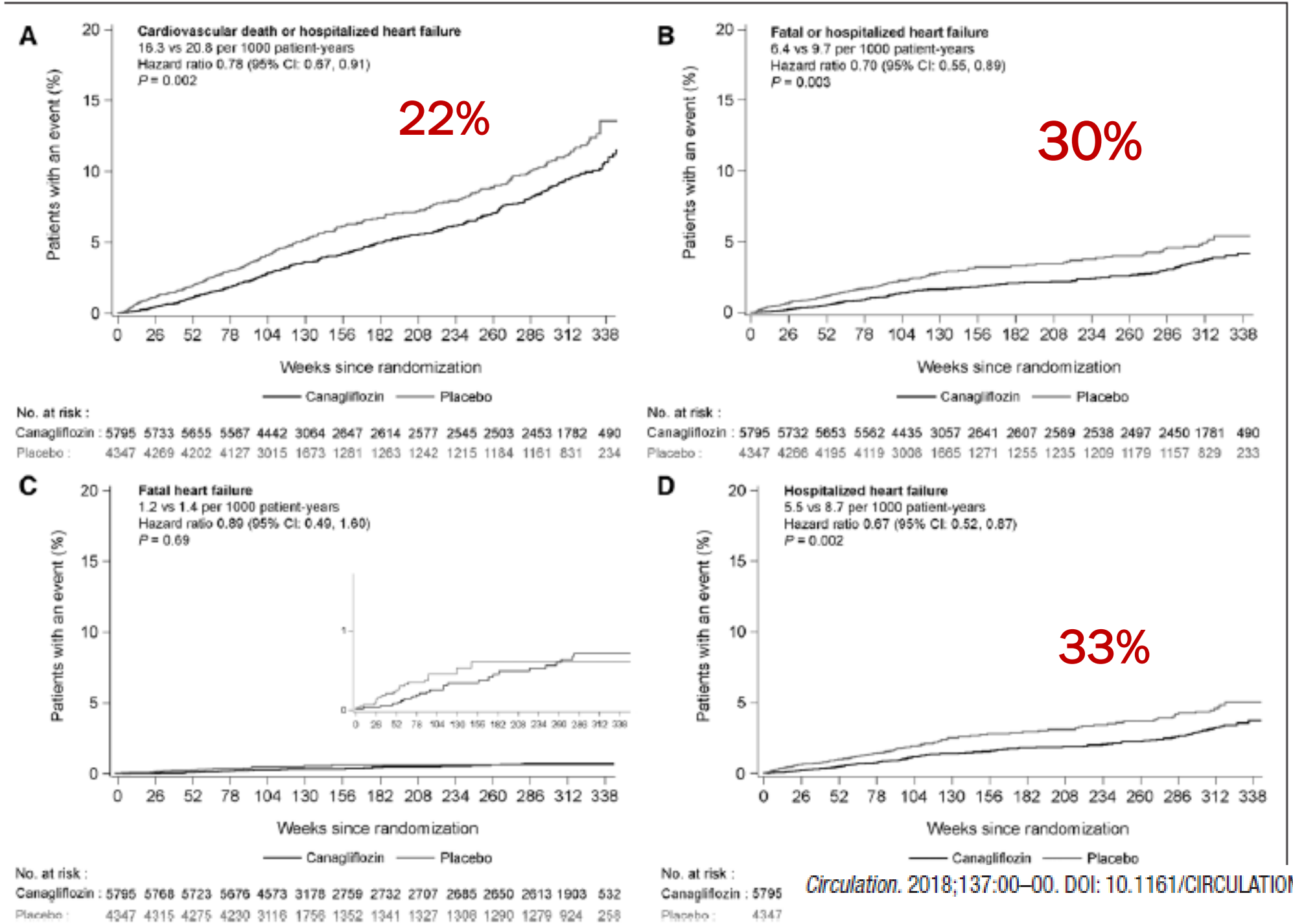
Circulation

ORIGINAL RESEARCH ARTICLE

Canagliflozin and Heart Failure in Type 2 Diabetes Mellitus

Results From the CANVAS Program (Canagliflozin Cardiovascular Assessment Study)

Circulation. 2018;137:00–00. DOI: 10.1161/CIRCULATIONAHA.118.034222



Circulation. 2018;137:00–00. DOI: 10.1161/CIRCULATIONAHA.118.034222

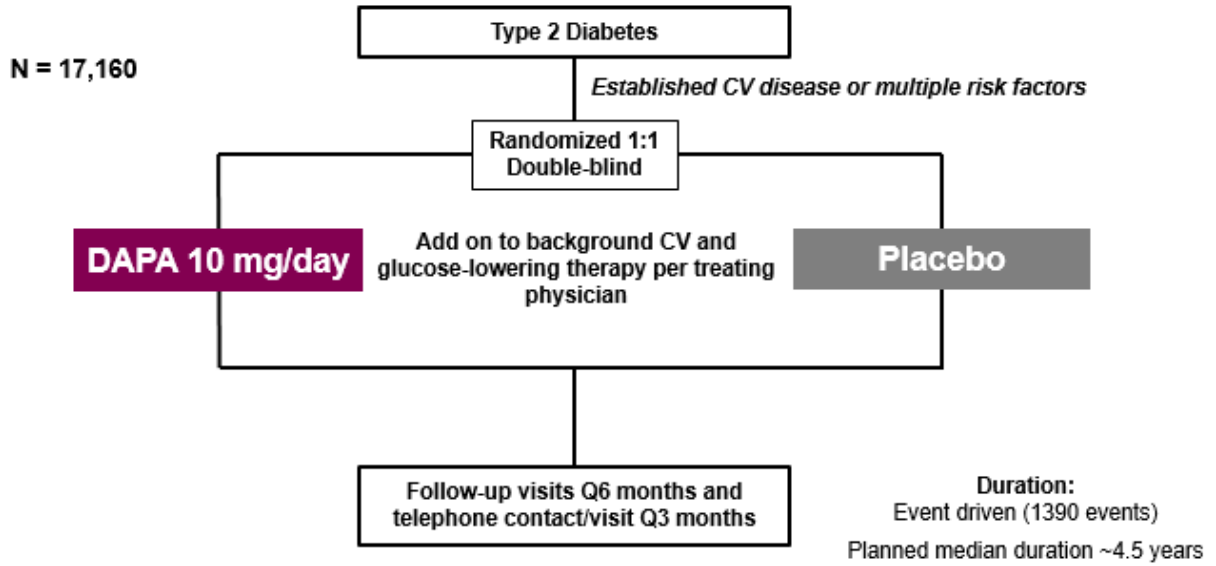
Received: 26 September 2017 | Revised: 24 December 2017 | Accepted: 5 January 2018
DOI: 10.1111/dom.13217

WILEY

CLINICAL TRIAL DESIGN

DECLARE-TIMI 58: Participants' baseline characteristics

Itamar Raz MD[1*] | Ofri Mosenzon MD[1*] | Marc P. Bonaca MD[2] | Avivit Cahn MD[1] | Eri T. Kato MD[3] | Michael G. Silverman MD[2] | Deepak L. Bhatt MD[2] | Lawrence A. Leiter MD[4] | Darren K. McGuire MD[5] | John P. H. Wilding MD[6] | Ingrid A. M. Gause-Nilsson MD[7] | Anna M. Langkilde MD[7] | Peter A. Johansson MSc[7] | Marc S. Sabatine MD[2] | Stephen D. Wiviott MD[2]



Primary endpoint

- Time to first event of a composite of: CV Death, Myocardial Infarction, Ischemic Stroke

Co-primary efficacy endpoint:

- CV Death/MI/Ischemic stroke AND CV Death/ Hospitalization for Heart Failure

Patients with Type 2 Diabetes

Established CV disease:

Age ≥40 years

AND ≥1 additional diagnoses:

- Ischemic heart disease
- Cerebrovascular disease
- Peripheral arterial disease

Multiple risk factors:

Age ≥55 years (men), ≥60 years (women)

AND ≥1 additional risk factors:

- Dyslipidemia
- Hypertension
- Tobacco use

Raz I, et al. ADA 2017 Poster 1245-P.

LOWER RATES OF HOSPITALIZATION FOR HEART FAILURE AND ALL-CAUSE DEATH IN NEW USERS OF SGLT-
LOWE
COUN
THE C

Mikhail K

WAS
FRI
MAR

Circulation

American Heart Association®

Lower Risk of Heart Failure and Death in Patients Initiated on SGLT-2 Inhibitors Versus Other Glucose-Lowering Drugs: The CVD-REAL Study

Mikhail Kosiborod, Matthew A. Cavender, Alex Z. Fu, John P. Wilding, Kamlesh Khunti, Reinhard W. Holl, Anna Norhammar, Kåre I. Birkeland, Marit Jørgensen, Marcus Thuresson, Niki Arya, Johan Bodegård, Niklas Hammar, Peter Fenici and on behalf of the CVD-REAL Investigators and Study Group

on behalf of the CVD-REAL Investigators and Study Group

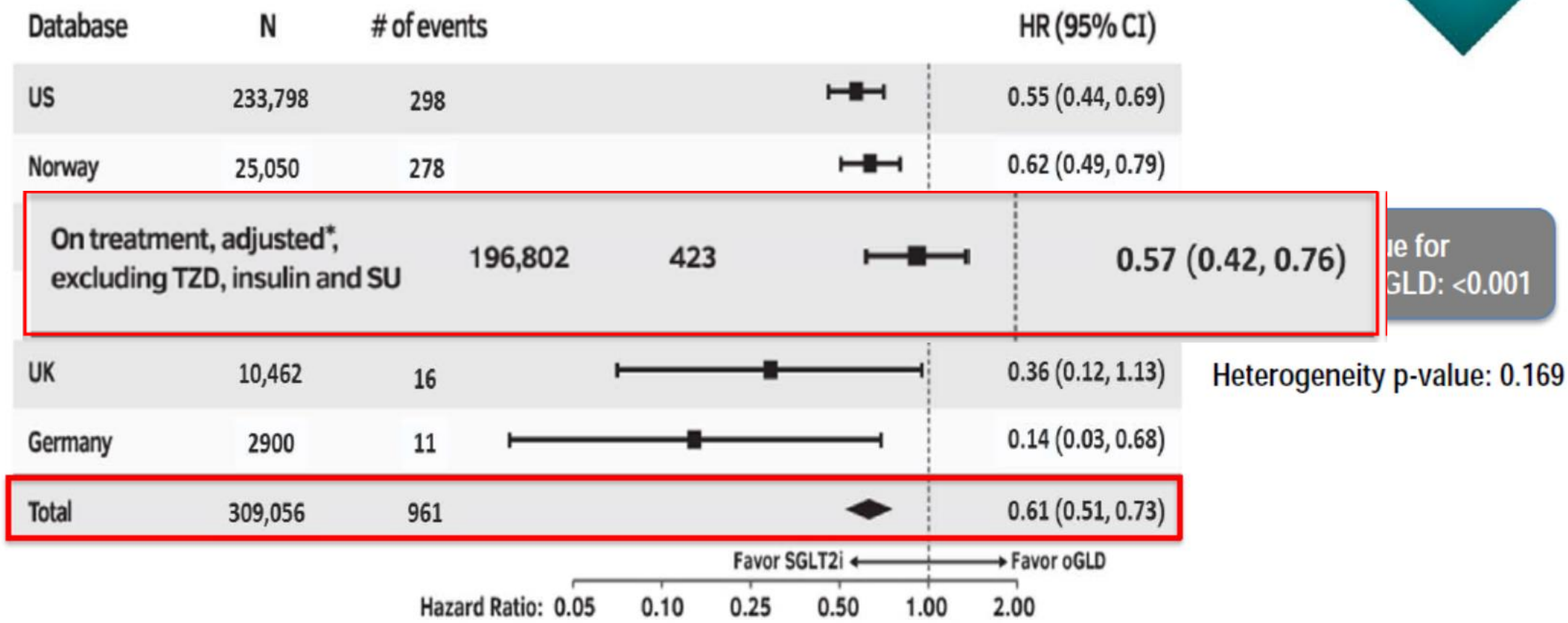
Circulation. published online May 18, 2017;
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0009-7322. Online ISSN: 1524-4539

CVDREAL

HHF Primary Analysis

ACC.17



ue for GLD: <0.001

Heterogeneity p-value: 0.169

Data are on treatment, unadjusted; oGLD=other glucose-lowering drug; HR=hazard ratio

Lower Cardiovascular Risk Associated with SGLT-2i in >400,000 Patients: The CVD-REAL 2 Study

Mikhail Kosiborod MD[a], Carolyn S P Lam MBBS PhD[b], Shun Kohsaka MD[c], Dae Jung Kim MD[d], Avraham Karasik MD[e], Jonathan Shaw MD[f], Navdeep Tangri MD PhD[g], Su-Yen Goh MD[h], Marcus Thuresson PhD[i], Hungta Chen PhD[j], Filip Surmont MD[k], Niklas Hammar PhD[l,m], Peter Fenici MD[n] on behalf of the CVD-REAL Investigators and Study Group.

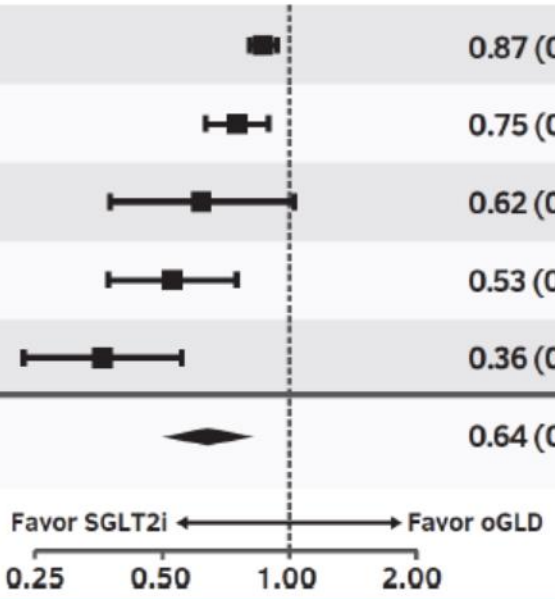
JACC

10.1016/j.jacc.2018.03.009

CVDREAL 2

Hospitalization for Heart Failure

Database	N	# of events	HR (95% CI)
Korea	336,644	5149	0.87 (0.82, 0.92)
Japan	67,780	565	0.75 (0.63, 0.89)
Singapore	2726	67	0.62 (0.38, 1.02)
Israel	19,472	128	0.53 (0.37, 0.75)
Canada	16,064	88	0.36 (0.24, 0.56)
Total	442,686	5997	0.64 (0.50, 0.82)



P-value for SGLT2i vs. oGLD: p<0.001

ITT, unadjusted analysis

Heterogeneity p-value: p<0.001

Lower Cardiovascular Risk Associated with SGLT-2i in >400,000 Patients: The CVD-REAL 2 Study

Mikhail Kosiborod MD[a], Carolyn S P Lam MBBS PhD[b], Shun Kohsaka MD[c], Dae Jung Kim MD[d], Avraham Karasik MD[e], Jonathan Shaw MD[f], Navdeep Tangri MD PhD[g], Su-Yen Goh MD[h], Marcus Thuresson PhD[i], Hungta Chen PhD[j], Filip Surmont MD[k], Niklas Hammar PhD[l,m], Peter Fenici MD[n] on behalf of the CVD-REAL Investigators and Study Group.

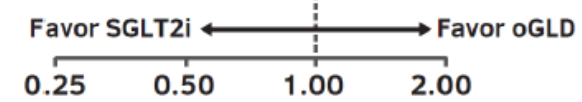
JACC

10.1016/j.jacc.2018.03.009

CVDREAL 2

All-Cause Death

Database	N	# of events	HR (95% CI)
Korea	336,644	3445	0.72 (0.67, 0.77)
Japan	67,780	557	0.56 (0.47, 0.67)
Singapore	2726	36	0.75 (0.38, 1.47)
Israel	19,472	199	0.41 (0.30, 0.55)
Canada	16,064	261	0.51 (0.41, 0.65)
Australia	27,442	718	0.32 (0.27, 0.38)
Total	470,128	5216	0.51 (0.37, 0.70)



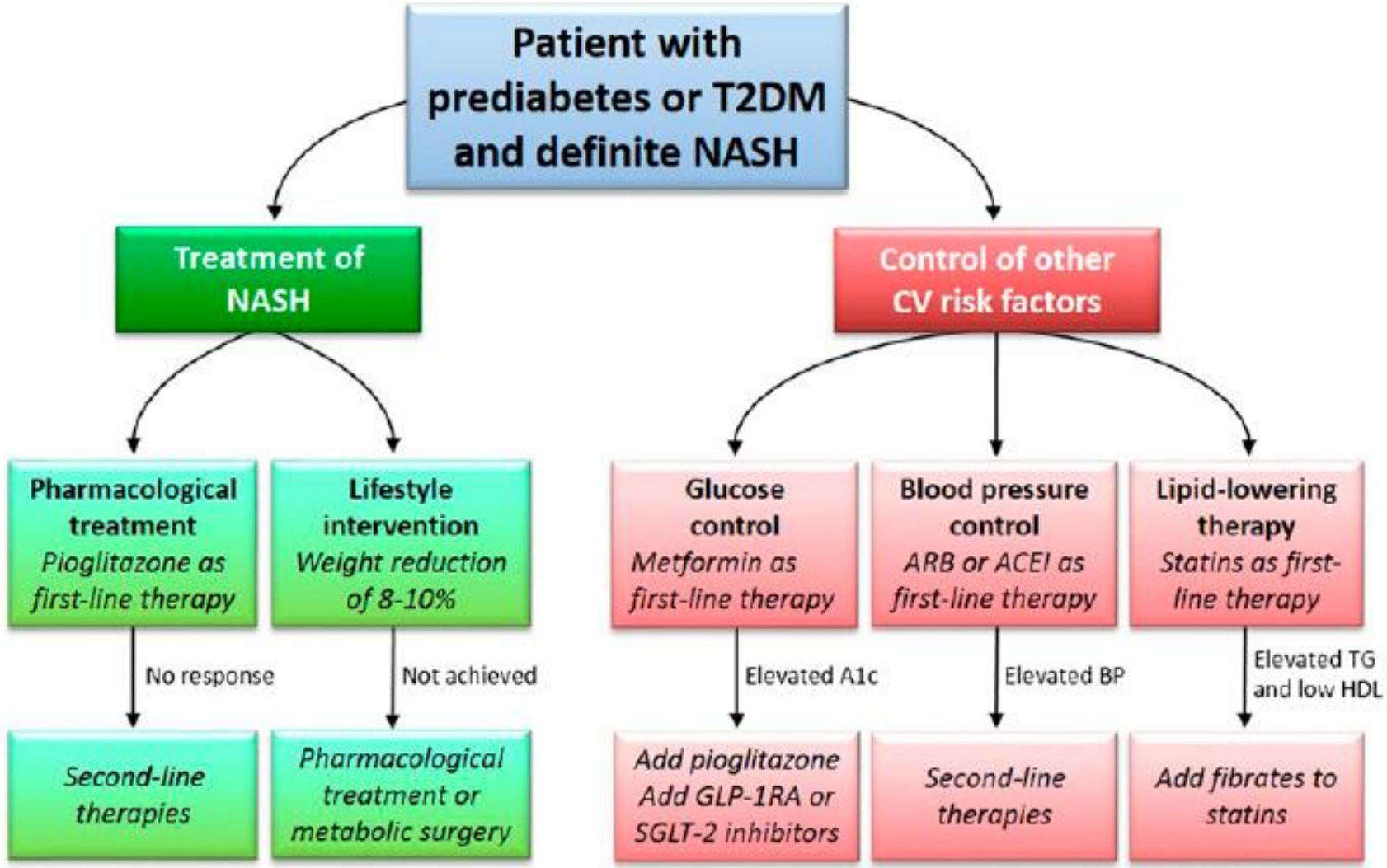
ITT, unadjusted analysis

P-value for SGLT2i vs. oGLD: p<0.001

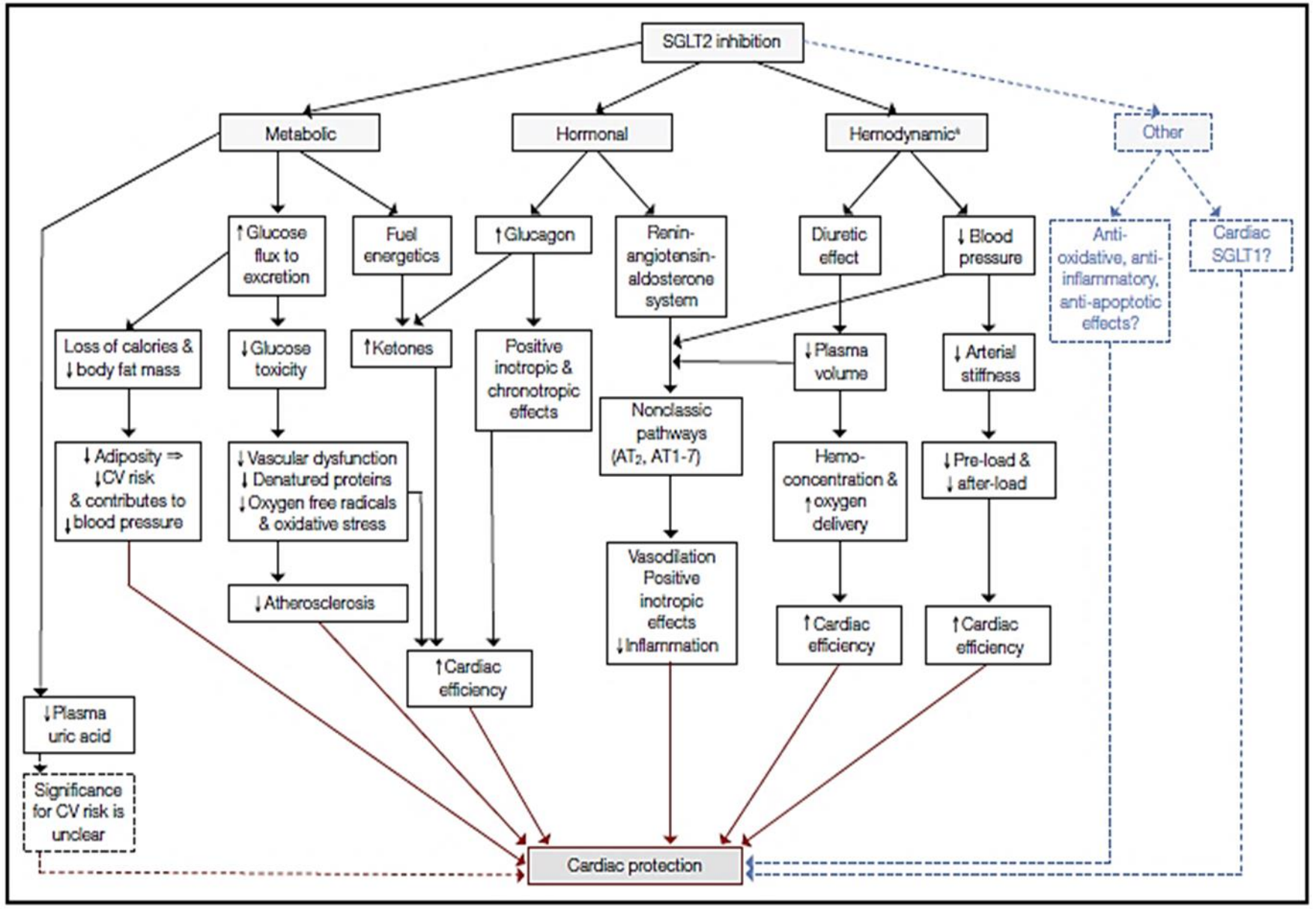
Heterogeneity p-value: p<0.001

futuro

- CREDENCE
- DAPA-CKD
- DAPA-HF
- EMPEROR-Reduced
- EMPEROR -Preserved



Diabetes Care Volume 40, March 2017



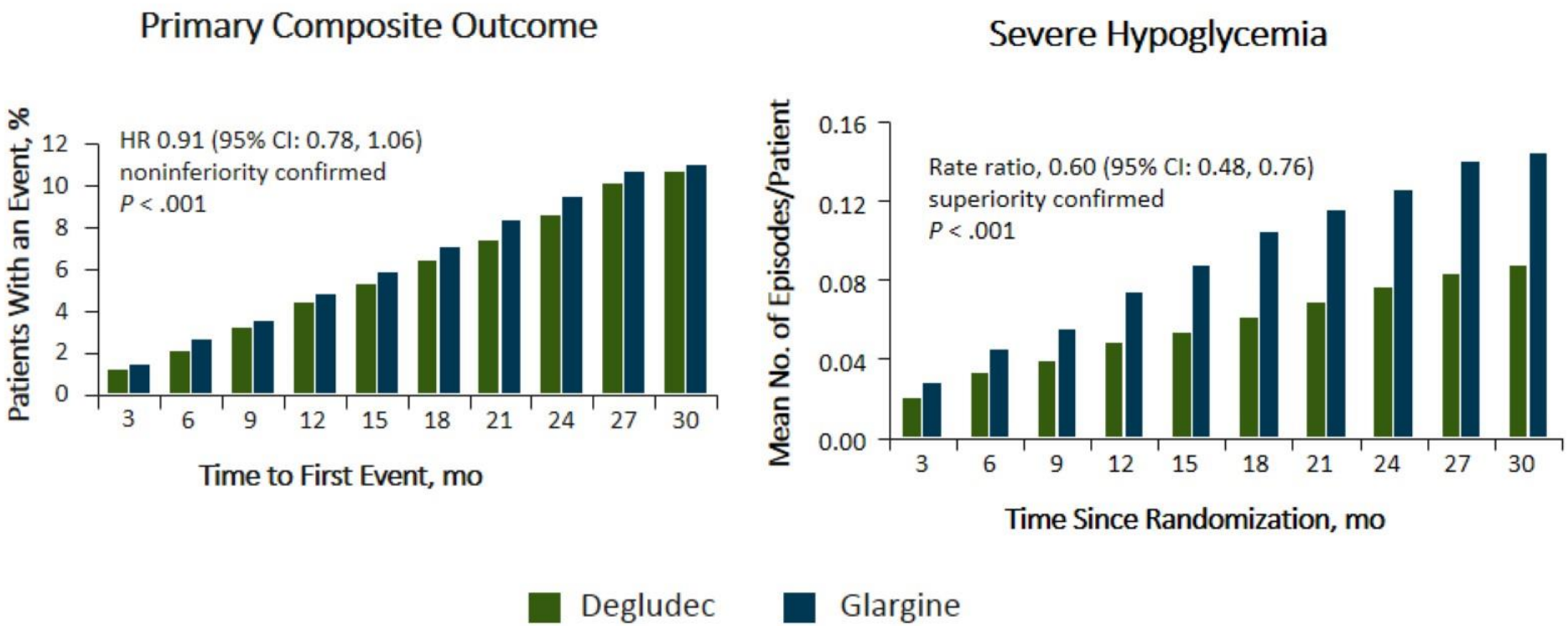
AT2: type 2 angiotensin II receptor pathway
AT1-7: angiotensin 1-7 activation
CV: cardiovascular; SGLT:sodium glucose cotransporter.

Staels B. Am J Cardiol 2017; 120 (suppl): S28-S236
Staels B. The American Journal of Medicine (2017) 130, S30-S39

RESULTADOS DE LOS ESTUDIOS SOBRE EFECTOS VASCULARES DE LOS FÁRMACOS EMPLEADOS EN EL TRATAMIENTO DE LA DIABETES

FÁRMACO	MACE	Muerte CV	IAM	Ictus	Nefro	Insuficiencia Cardiaca
Glargina	↔	↔	↔	↔	↔	↔
Saxagliptina	↔	↔	↔	↔	↔	↑
Alogliptina	↔	↔	↔	↔	↔	↔
Sitagliptina	↔	↔	↔	↔	↔	↔
Lixisenatide	↔	↔	↔	↔	↔	↔
Empaglifozina	↓	↓	↔	↔	↓	↓
Liraglutida	↓	↓	↔	↓	↓	↔
Semaglutida	↓	↔	↔	↔	↓	↔
Canaglifozina	↓	↔	↔	↔	↓	↓
Exenatida L	↔	↔	↔	↔	↔	↔

DEVOTE: Efficacy and Safety Outcomes



Marso SP, et al. *N Engl J Med*. 2017;377:723-732.

¿Que dicen las guías?

2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

Recommendations to prevent or delay the development of overt heart failure or prevent death before the onset of symptoms

Recommendations	Class [a]	Level [b]	Ref [c]
Treatment of hypertension is recommended to prevent or delay the onset of HF and prolong life.	I	A	126, 129, 150, 151
Treatment with statins is recommended in patients with or at high-risk of CAD whether or not they have LV systolic dysfunction, in order to prevent or delay the onset of HF and prolong life.	I	A	137–140, 152
Counselling and treatment for smoking cessation and alcohol intake reduction is recommended for people who smoke or who consume excess alcohol in order to prevent or delay the onset of HF.	I	C	131–134
Treating other risk factors of HF (e.g. obesity, dysglycaemia) should be considered in order to prevent or delay the onset of HF.	IIa	C	130, 141, [illegible]
Empagliflozin should be considered in patients with type 2 diabetes in order to prevent or delay the onset of HF and prolong life.	IIa	B	130
ACE-I is recommended in patients with asymptomatic LV systolic dysfunction and a history of myocardial infarction in order to prevent or delay the onset of HF and prolong life.	I	A	[illegible], 145
ACE-I is recommended in patients with asymptomatic LV systolic dysfunction without a history of myocardial infarction, in order to prevent or delay the onset of HF.	I	B	5

2016 European Guidelines on cardiovascular disease prevention in clinical practice

Recommendations for management of diabetes

Recommendations	Class[a]	Level[b]	Ref[c]
Lifestyle changes including smoking cessation, low fat diet, high fibre diet, aerobic physical activity, and strength training are recommended.	I	A	387
Reduction in energy intake is recommended to patients to help achieve lower weight or prevent weight gain.	I	B	387
A target HbA1c for the reduction in risk of CVD and microvascular complications in DM of <7.0% (<53 mmol/mol) is recommended for the majority of non-pregnant adults with either type 1 or type 2 DM.	I	A	388, 389
For patients with a long duration of DM, the elderly, frail, or those with existing CVD, a relaxing of the HbA1c targets (i.e. less stringent) should be considered.	IIa	B	389
A target HbA1c of ≤6.5% (≤48 mmol/mol) should be considered at diagnosis or early in the course of type 2 DM in patients, who are not frail and do not have CVD.	IIa	B	389
When screening for DM in individuals with or without CVD, assessment of HbA1c (which can be done non-fasting) or fasting blood glucose should be considered. An oral glucose tolerance test can be offered when there is still doubt.	IIa	A	390
Metformin is recommended as first-line therapy, if tolerated and not contra-indicated, following evaluation of renal function.	I	B	391
Avoidance of hypoglycaemia and excessive weight gain should be considered and individual approaches (with respect to both treatment targets and drug choices) should be considered in patients with advanced disease.	IIa	B	389, 392, 393
In patients with type 2 DM and CVD, the use of an SGLT2 inhibitor should be considered early in the course of the disease to reduce CV and total mortality.	IIa	B	394
Lipid lowering agents (principally statins) are recommended to reduce CV risk in all patients with type 2 or type 1 DM above the age of 40 years.	I	A	371, 372

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

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

Monotherapy — Lifestyle Management + Metformin

Dual Therapy — Lifestyle Management + Metformin + Additional Agent

ASCVD?

Yes: - Add agent proven to reduce major adverse cardiovascular events and/or cardiovascular mortality (see recommendations with * on p. 11 and **Table 7**)

No: - Add second agent after consideration of drug-specific effects and patient factors (See Table 7)

A1C at target after 3 months of dual therapy?

Yes: - Monitor A1C every 3–6 months

No: - Assess medication-taking behavior
- Consider Triple Therapy

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

A1C at target after 3 months of triple therapy?

Yes: - Monitor A1C every 3–6 months

No: - Assess medication-taking behavior
- Consider Combination Injectable Therapy (See Figure 8.2)

Combination Injectable Therapy (See Figure 8.2)

Diabetes Care 2018 Jan; 41(Supplement 1): S73-S85.

2018 Clinical Practice Guidelines

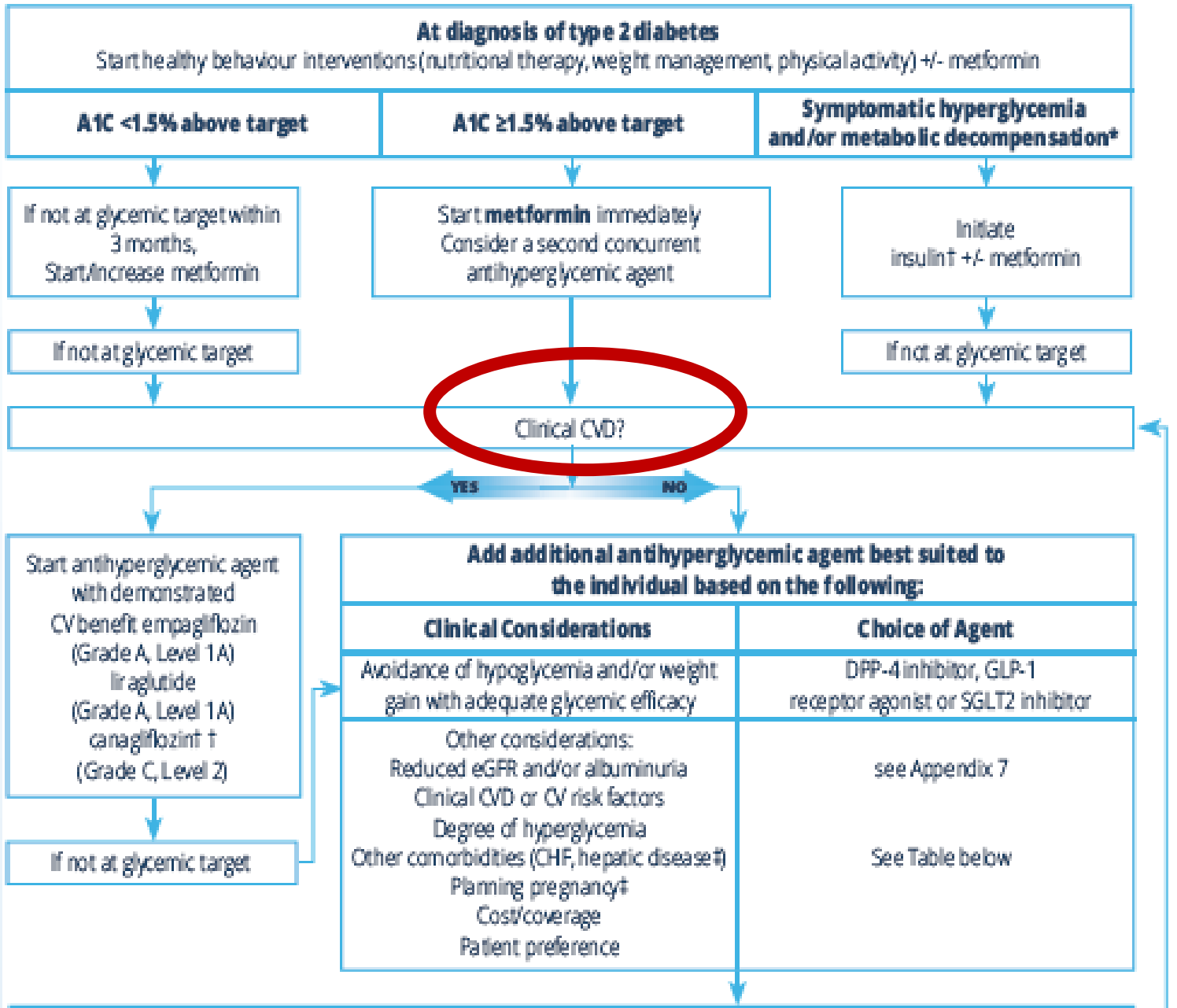
Quick Reference Guide

DIABETES CANADA

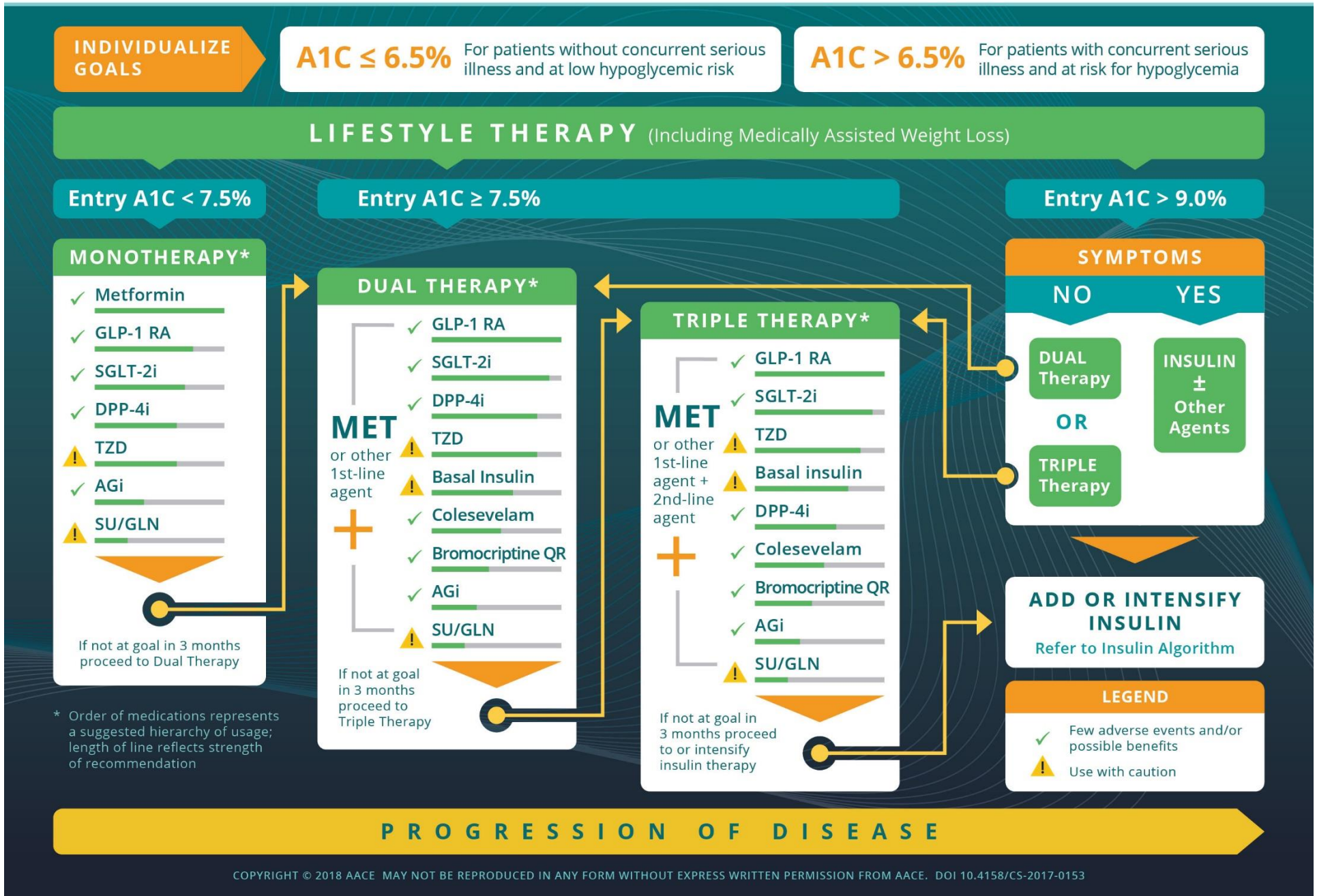
416569-18

guidelines.diabetes.ca
diabetes.ca | 1-800-BANTING (226-8464)

Blood Glucose-lowering Therapies (Type 2 Diabetes)

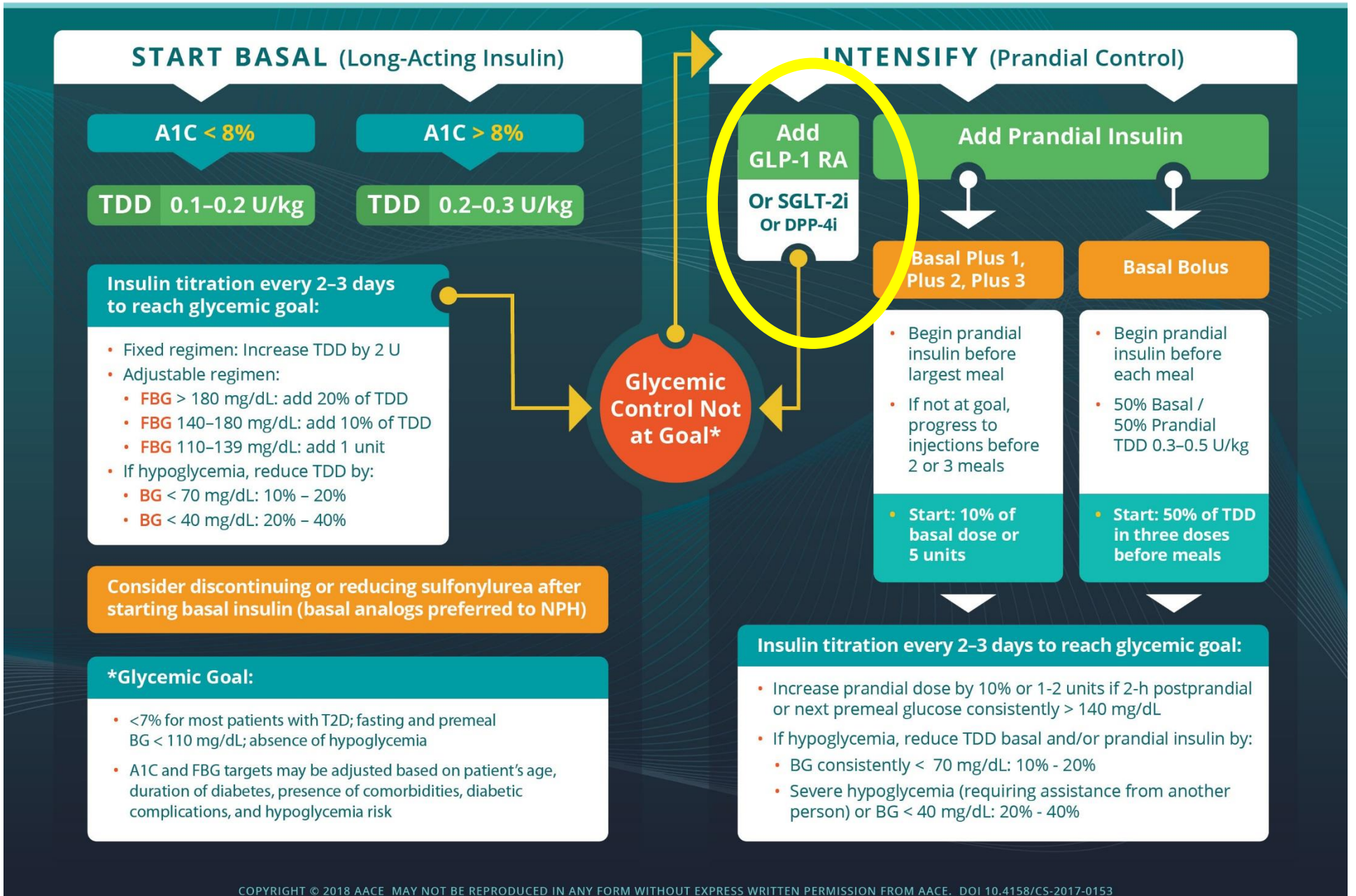


Glycemic Control Algorithm



 DOI 10.4158/CS-2017-0153

Algorithm for Adding/Intensifying Insulin



 DOI 10.4158/CS-2017-0153

Profiles of Antidiabetic Medications

	MET	GLP-1 RA	SGLT-2i	DPP-4i	AGi	TZD (moderate dose)	SU / GLN	COLSVL	BCR-QR	INSULIN	PRAML
HYPO	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Moderate/ Severe / Mild	Neutral	Neutral	Moderate to Severe	Neutral
WEIGHT	Slight Loss	Loss	Loss	Neutral	Neutral	Gain	Gain	Neutral	Neutral	Gain	Loss
RENAL / GU	Contra-indicated if eGFR < 30 mL/min/ 1.73 m^2	Exenatide Not Indicated CrCl < 30 / Possible Benefit of Liraglutide	Not Indicated for eGFR < 45 mL/ min/1.73 m^2 / Genital Mycotic Infections / Possible Benefit of Empagliflozin	Dose Adjustment Necessary (Except Linagliptin) Effective in Reducing Albuminuria	Neutral	Neutral	More Hypo Risk	Neutral	Neutral	More Hypo Risk	Neutral
GI Sx	Moderate	Moderate	Neutral	Neutral	Moderate	Neutral	Neutral	Mild	Moderate	Neutral	Moderate
CHF	Neutral	See #1	See #2	See #3	Neutral	Moderate	Neutral	Neutral	Neutral	CHF Risk	Neutral
CARDIAC											
ASCVD						May Reduce Stroke Risk	Possible ASCVD Risk	Benefit	Safe	Neutral	
BONE	Neutral	Neutral	Mild Fracture Risk	Neutral	Neutral	Moderate Fracture Risk	Neutral	Neutral	Neutral	Neutral	Neutral
KETOACIDOSIS	Neutral	Neutral	DKA Can Occur in Various Stress Settings	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral

Few adverse events or possible benefits

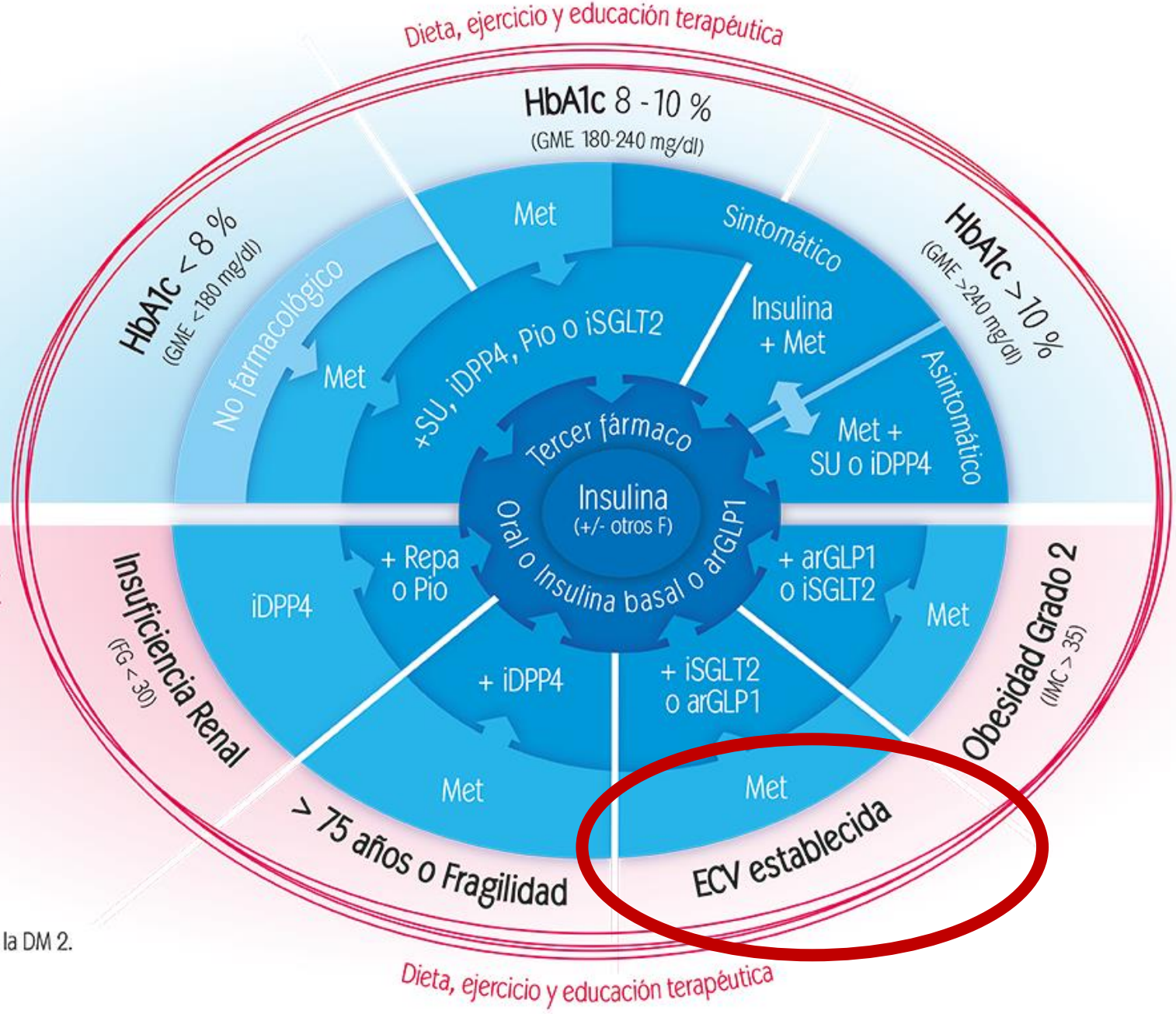
Likelihood of adverse effects

Use with caution

1. Liraglutide—FDA approved for prevention of MACE events.
2. Empagliflozin—FDA approved to reduce CV mortality. Canagliflozin shown to reduce MACE events.
3. Possible increased hospitalizations for heart failure with alogliptin and saxagliptin.

 DOI 10.4158/CS-2017-0153

Fundación redGDPS
Comprometidos con la DIABETES



Algoritmo de tratamiento de la DM 2.
redGDPS 2017

conclusiones

- La **prevalencia** de DM es alta y se prevee un aumento en los próximos años
- La **tecnología** se esta incorporando a la atención del paciente con Dm2
- Los **nuevos fármacos** para el tratamiento de la diabetes:
  beneficios adicionales al control glucémico
  estudios de seguridad cardiovascular muestran beneficios con algunos fármacos
- **GPC: priorizar** aquellos fármacos que muestran beneficio a nivel CV