Tratamiento de la DM2 en Prevención Secundaria

DM 2 en P 2ª

Posicionamiento

SOCIEDAD ESPAÑOLA DE CARDIOLOGÍA

Sección de Riesgo Vascular y Rehabilitación Cardiaca

Grupo de Trabajo de Diabetes

DM2 Control multifactorial p2ª

* Especialmente en DM1 o jóvenes con DM2 o con albuminuria o retinopatía

* * Sin riesgo hipoglucemias

* ** Riesgo extremo

European Heart Journal (2016) 37, 2315–2381
Endocr Pract. 2017 Apr 2;23(4):479-497

DYSLIPIDEMIA

LIFESTYLE THERAPY (Including Medically Assisted Weight Loss)

LIPID PANEL: Assess ASCVD Risk

STATIN THERAPY
If TG > 500 mg/dL, fibrates, Rx-grade omega-3 fatty acids, niacin

If statin-intolerant

Try alternate statin, lower statin dose or frequency, or add nonstatin LDL-C- lowering therapies

Repeat lipid panel; assess adequacy, tolerance of therapy

Intensify therapies to attain goals according to risk levels

RISK LEVELS	HIGH	VERY HIGH	EXTREME
	DESIRABLE LEVELS	DESIRABLE LEVELS	DESIRABLE LEVELS
LDL-C (mg/dL)	<100	<70	<55
Non-HDL-C (mg/dL)	<130	<100	<80
TG (mg/dL)	<150	<150	<150
Apo B (mg/dL)	<90	<80	<70

RISK LEVELS:

- **HIGH:** DM but no other major risk and/or age <40
- **VERY HIGH:** DM + major ASCVD risk(s) (HTN, Fam Hx, low HDL-C, smoking, CKD3,4)*
- **EXTREME:** DM plus established clinical CVD

If not at desirable levels: Intensify lifestyle therapy (weight loss, physical activity, dietary changes) and glycemic control; consider additional therapy

To lower LDL-C:	Intensify statin, add ezetimibe, PCSK9i, colesevelam, or niacin
To lower Non-HDL-C, TG:	Intensify statin and/or add Rx-grade OM3 fatty acid, fibrate, and/or niacin
To lower Apo B, LDL-P:	Intensify statin and/or add ezetimibe, PCSK9i, colesevelam, and/or niacin
To lower LDL-C in FH:**	Statin + PCSK9i

Assess adequacy & tolerance of therapy with focused laboratory evaluations and patient follow-up

HYPERTENSION

GOAL: SYSTOLIC <130, DIASTOLIC <80 mm Hg

ACEi or ARB

For initial blood pressure >150/100 mm Hg:

DUAL THERAPY

ACEi or ARB + Calcium Channel Blocker ✓ / ß-blocker ✓ / Thiazide ✓

If not at goal (2–3 months)

Add calcium channel blocker, ß-blocker or thiazide diuretic

If not at goal (2–3 months)

Add next agent from the above group, repeat

If not at goal (2–3 months)

Additional choices (α-blockers, central agents, vasodilators, aldosterone antagonist)

Achievement of target blood pressure is critical

* EVEN MORE INTENSIVE THERAPY MIGHT BE WARRANTED ** FAMILIAL HYPERCHOLESTEROLEMIA

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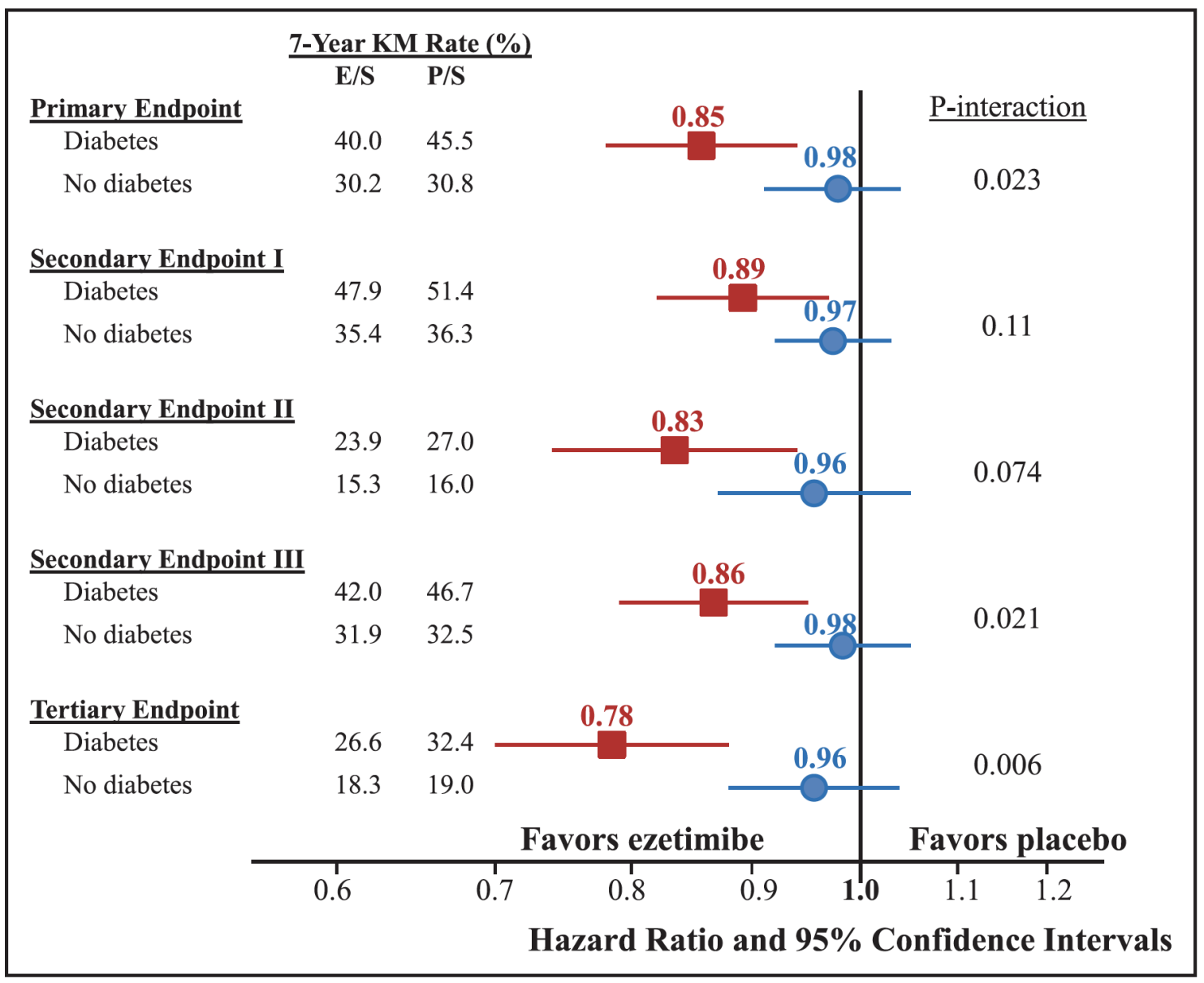
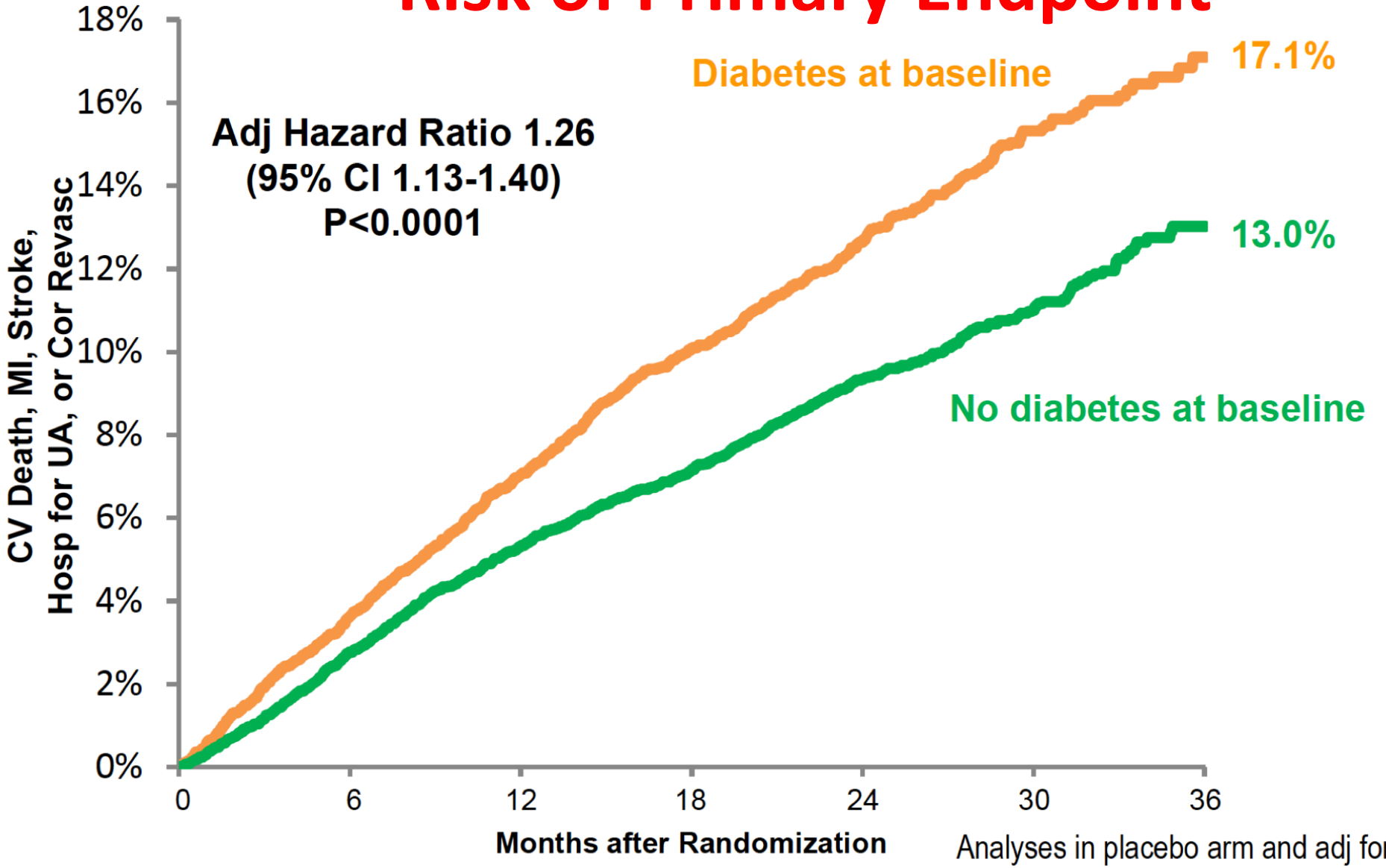
Mayor beneficio en DM2



Reducción 14% End point 1º
Reducción 21% IAM
Reducción 42% ICTUS

Circulation. 2018;137:1571–1582

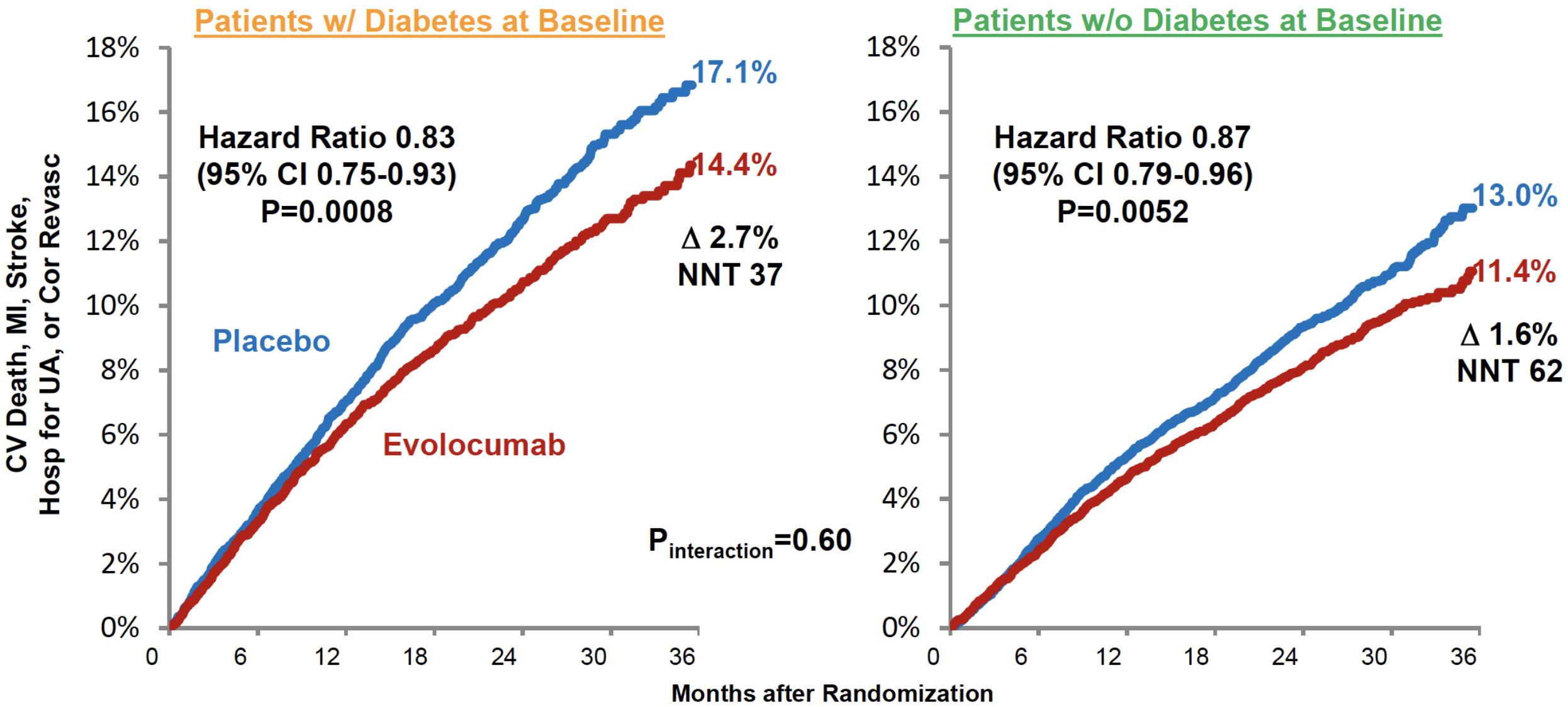
Risk of Primary Endpoint



Analyses in placebo arm and adj for age, sex, BMI, race, region, history of MI, stroke, PAD, HTN, smoking, HF, eGFR, lipids, statin.

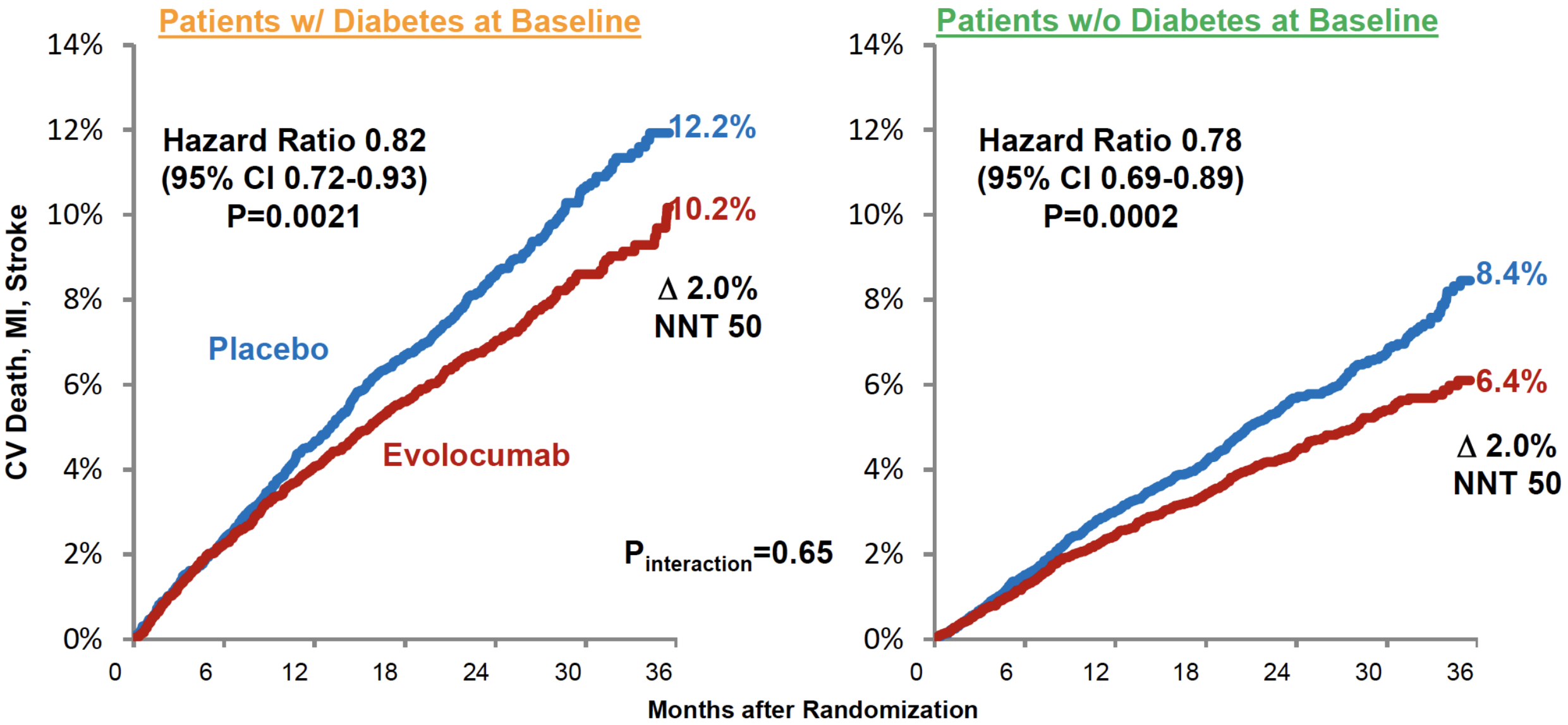
Sabatine, Marc S et al. The Lancet Diabetes & Endocrinology , 2017:12 , 941 - 950

Primary Endpoint



Sabatine, Marc S et al. The Lancet Diabetes & Endocrinology , 2017:12 , 941 - 950

Secondary Endpoint



Sabatine, Marc S et al. The Lancet Diabetes & Endocrinology , 2017:12 , 941 - 950

2016 European Guidelines on cardiovascular disease prevention in clinical practice

The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts)

BP targets in type 2 DM are generally recommended to be <140/85 mmHg, but a lower target of <130/80 mmHg is recommended in selected patients (e.g. younger patients at elevated risk for specific complications) for additional gains on stroke, retinopathy and albuminuria risk. Renin-angiotensin-aldosterone system blocker is recommended in the treatment of hypertension in DM, particularly in the presence of proteinuria or micro- albuminuria. Recommended BP target in patients with type 1 DM is <130/80 mmHg.	I	B

European Heart Journal (2016) 37, 2315–2381

2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults

A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines

Paul K. Whelton, Robert M. Carey, Wilbert S. Aronow, Donald E. Casey Jr., Karen J. Collins, Cheryl Dennison Himmelfarb, Sondra M. DePalma, Samuel Gidding, Kenneth A. Jamerson, Daniel W. Jones, Eric J. MacLaughlin, Paul Muntner, Bruce Ovbiagele, Sidney C. Smith Jr., Crystal C. Spencer, Randall S. Stafford, Sandra J. Taler, Randal J. Thomas, Kim A. Williams Sr., Jeff D. Williamson and Jackson T. Wright Jr.

Recommendations for Treatment of Hypertension in Patients With DM

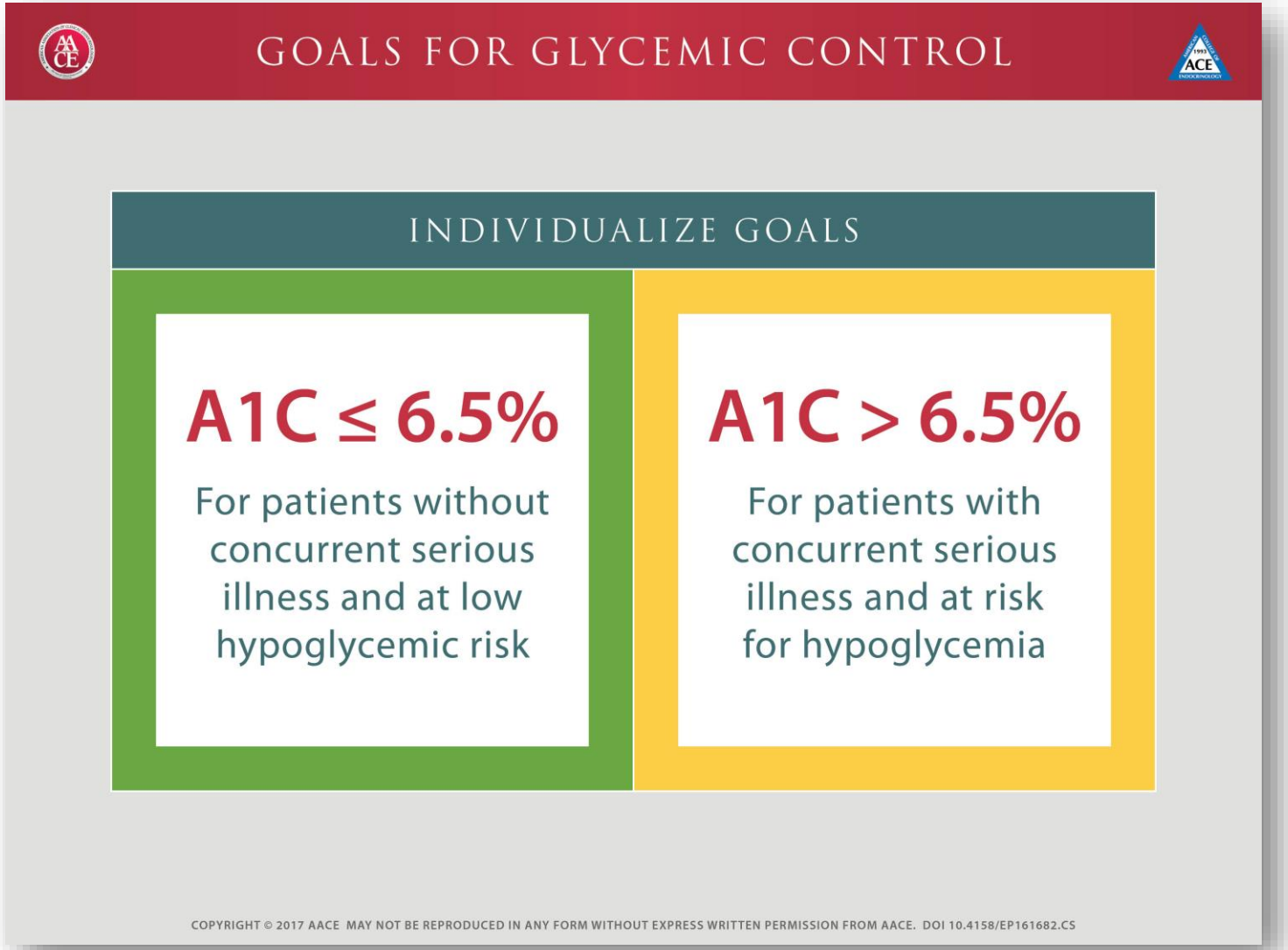
References that support recommendations are summarized in Online Data Supplements 46 and 47 and Systematic Review Report.

COR	LOE	Recommendations
I	SBP: B-R[SR] DBP: C-EO	1. In adults with DM and hypertension, antihypertensive drug treatment should be initiated at a BP of 130/80 mm Hg or higher with a treatment goal of less than 130/80 mm Hg (1-8).
I	A[SR]	2. In adults with DM and hypertension, all first-line classes of antihypertensive agents (i.e., diuretics, ACE inhibitors, ARBs, and CCBs) are useful and effective (1, 9, 10).
IIb	B-NR	3. In adults with DM and hypertension, ACE inhibitors or ARBs may be considered in the presence of albuminuria (11, 12).

ACCEPTED

JACC (2017), doi: 10.1016/j.jacc.2017.11.006.

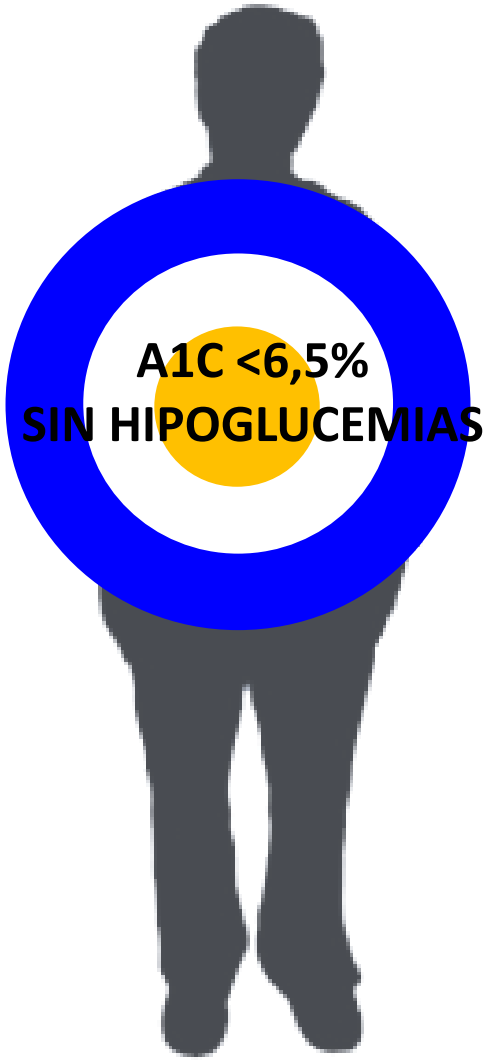
A1C: Lo más baja posible SIN hipoglucemias



Endocr Pract.2017,doi:10.4158/EP161682.CS

Objetivos del tratamiento en la DM2

ADA/EASD 2017, AACE 2017
Tras estudios de seguridad CV



Objetivos Individualizados

<7% >7%

6,5% 7% 8-8,5%

- Diabetes de corta duración
-Esperanza de vida larga
-Sin ECV significativa
-Se puede lograr sin riesgo significativo de hipoglucemia u otros efectos adversos

La mayoría de los pacientes con diabetes

-Expectativa de vida limitada
-Alto nivel de dependencia fc
-EC extensa con ↑ riesgo de eventos isquémicos
-Múltiples comorbilidades
-Hipoglucemias graves recurrentes
-Hipoglucemias inadvertidas
-Dificultad para alcanzar A1c ≤ 7% pese a múltiples fármacos.

Toma de las decisiones conjuntamente con el paciente

Adaptado de: Inzucchi SE, et al. Diabetes Care 2012;35:1364–79.

¿ Por qué no nos fijamos en la A1C en primer escalón ?

EMPA-REG OUTCOME®

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

SUSTAIN
SEMAGLUTIDE UNABATED SUSTAINABILITY IN TREATMENT OF TYPE 2 DIABETES

CANVAS Program

14% MACE 3 años

N Engl J Med 2015; 373:2117-2128

13% MACE 3 años

N Engl J Med 2016; 375:311-322

26% MACE 2 años

N Engl J Med 2016;375:1834-44.

14% MACE 5 años

N Engl J Med 2017; 377:644-657

Castro A, Marzal D et al.. SEC Monogr. 2018;6 (2):19-23

	Subgrupos según A1C	P interacción (activo placebo)
EMPA-REG OUTCOME®	<8,5% - ≥8,5%	0.01 (1º) 0.51 (muerte)
N Engl J Med 2015; 373:2117-2128		
LEADER® Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results	<8,3% - ≥8,3%	0.58 (1º)
N Engl J Med 2016; 375:311-322		
SUSTAIN SEMAGLUTIDE UNABATED SUSTAINABILITY IN TREATMENT OF TYPE 2 DIABETES	<8,5% - ≥8,5%	0.94 (1º)
N Engl J Med 2016;375:1834-44.		
CANVAS Program	<8,0% - ≥8,0%	0.29 (1º)
N Engl J Med 2017; 377:644-657		

Beneficio independiente de A1C

Beneficio independiente de los fármacos asociados

EMPA-REG OUTCOME®

Table S7. Hazard ratios for the primary outcome in subgroups.

	Patients with event/ patients analyzed		Hazard ratio	(95% CI)	p-value for interaction
	Empagliflozin	Placebo			
Metformin					0.14
No	146/1228	93/599	0.72	(0.56, 0.94)	
Yes	344/3459	189/1734	0.92	(0.77, 1.10)	

Table S8. Hazard ratios for cardiovascular death in subgroups.

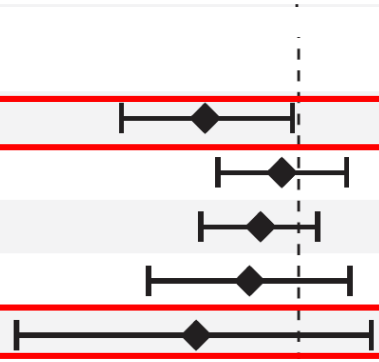
	Patients with event/ patients analyzed		Hazard ratio	(95% CI)	p-value for interaction
	Empagliflozin	Placebo			
All patients	172/4687	137/2333	0.62	(0.49, 0.77)	
Metformin					0.07
No	54/1228	53/599	0.46	(0.32, 0.68)	
Yes	118/3459	84/1734	0.71	(0.54, 0.94)	

N Engl J Med. DOI: 10.1056/NEJMoa1504720

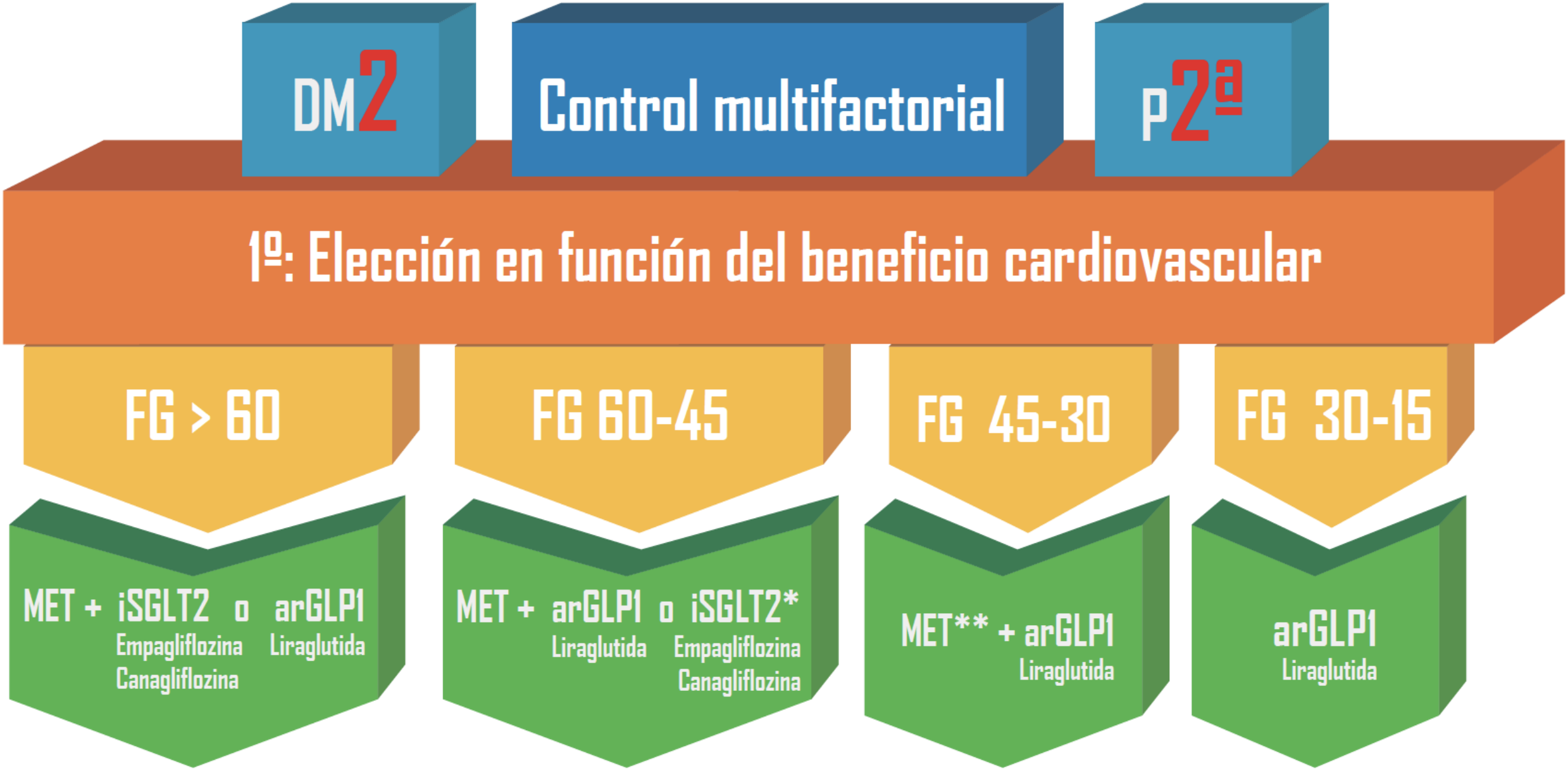
LEADER®
Liraglutide Effect and Action in Diabetes:
Evaluation of cardiovascular outcome Results

Beneficio independiente de los fármacos asociados

Subgroup	No. of Patients	Liraglutide	Placebo	Hazard Ratio (95% CI)	P Value for Interaction
		no. of events/no. of patients (%)			
Antidiabetic therapy					0.73
1 Oral antidiabetic agent	1818	99/922 (10.7)	125/896 (14.0)	0.75 (0.58–0.98)	
>1 Oral antidiabetic agent	2997	191/1515 (12.6)	196/1482 (13.2)	0.95 (0.78–1.16)	
Insulin with oral antidiabetic agent	3422	223/1674 (13.3)	259/1748 (14.8)	0.89 (0.74–1.06)	
Insulin without oral antidiabetic agent	737	71/361 (19.7)	86/376 (22.9)	0.86 (0.63–1.17)	
None	366	24/196 (12.2)	28/170 (16.5)	0.73 (0.42–1.25)	



N Engl J Med 2016; 375:311-322



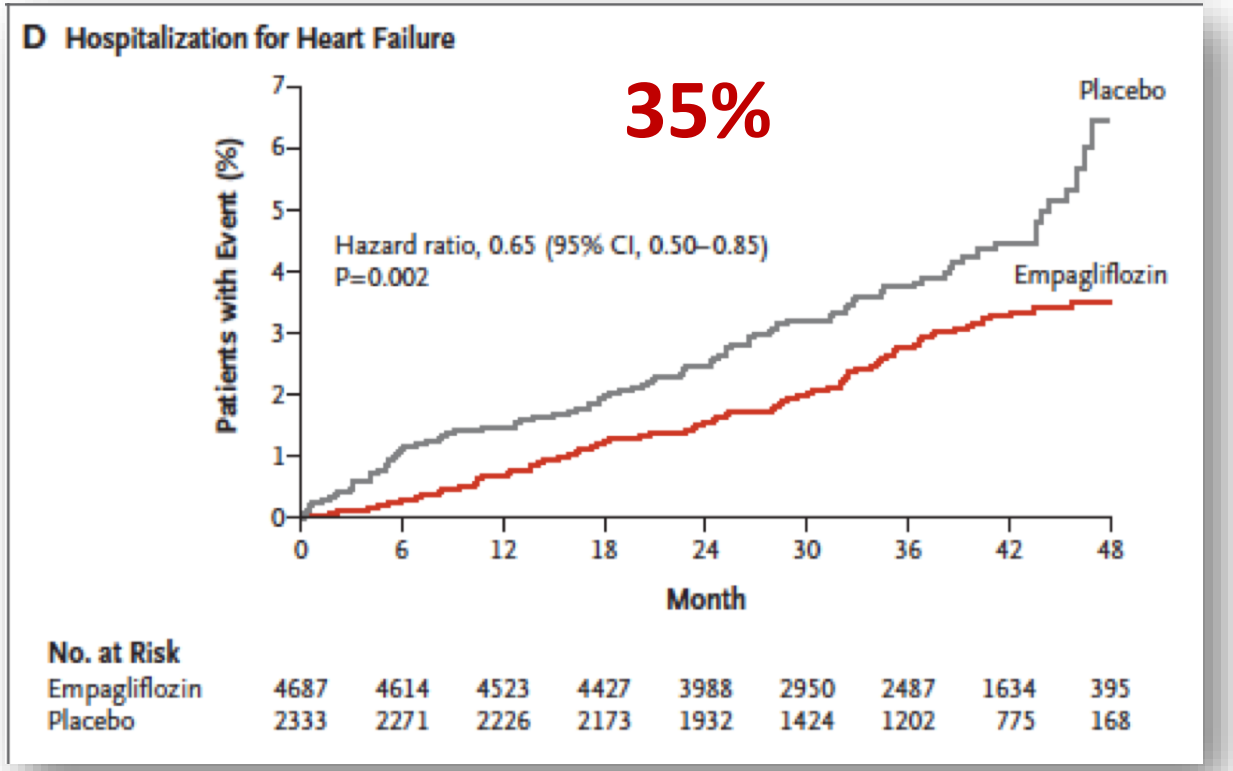
*** No iniciar. Sí mantener: Empa 10 mg o Cana 100 mg**

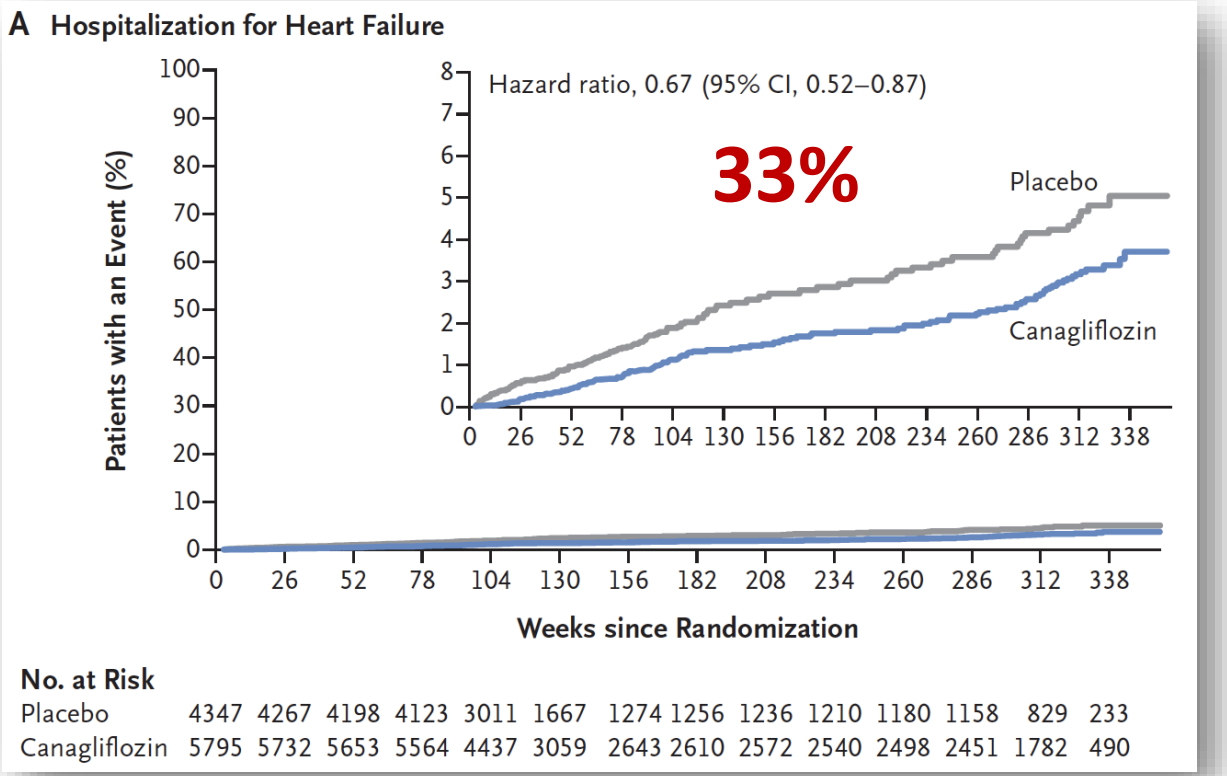
**** No iniciar MET. Sí mantener.**

Castro A, Marzal D et al.. SEC Monogr. 2018;6 (2):19-23

EMPA-REG OUTCOME®

CANVAS Program

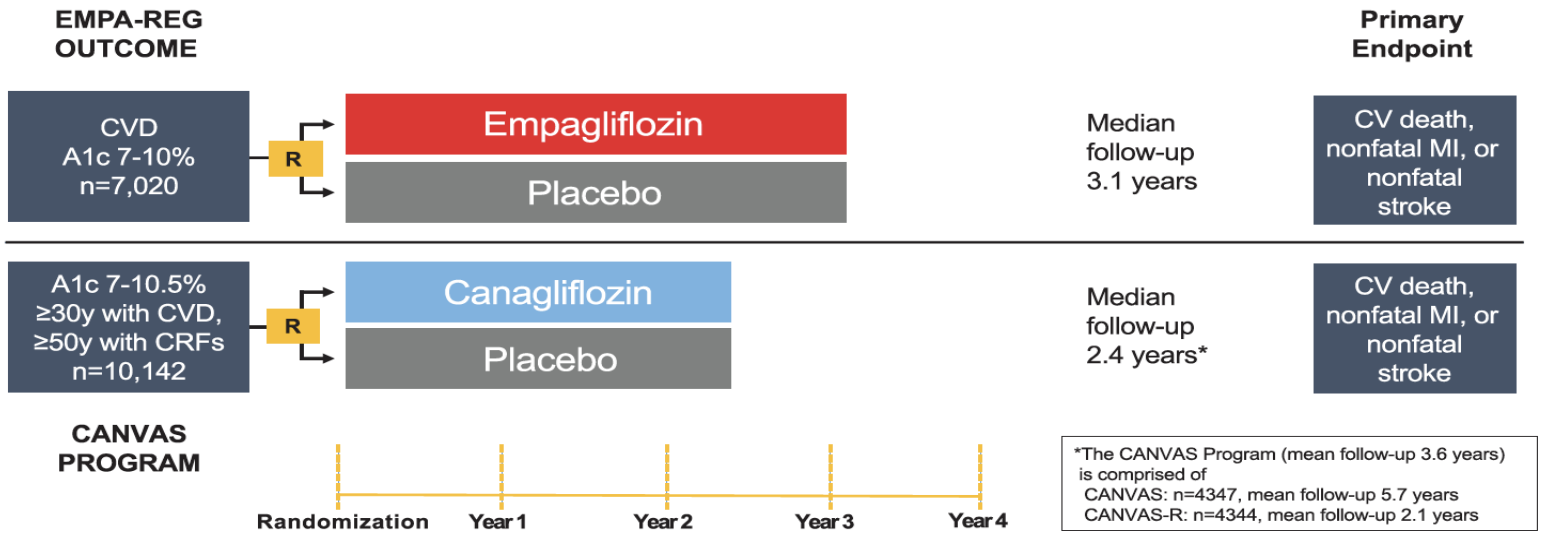




N Engl J Med 2015; 373:2117-2128

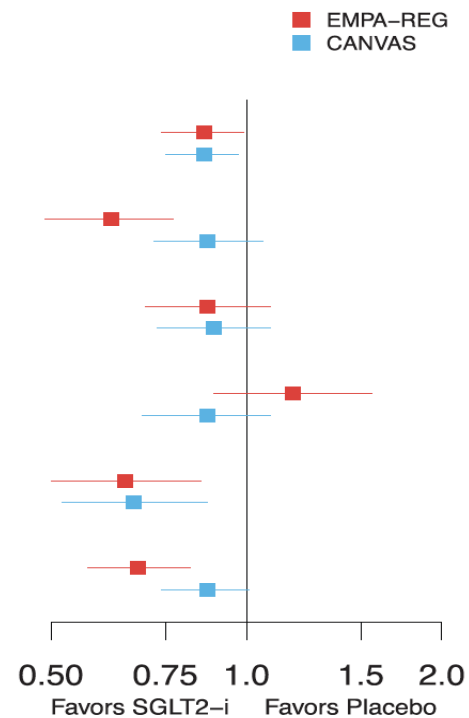
N Engl J Med 2017; 377:644-657

A Trial Design Summary



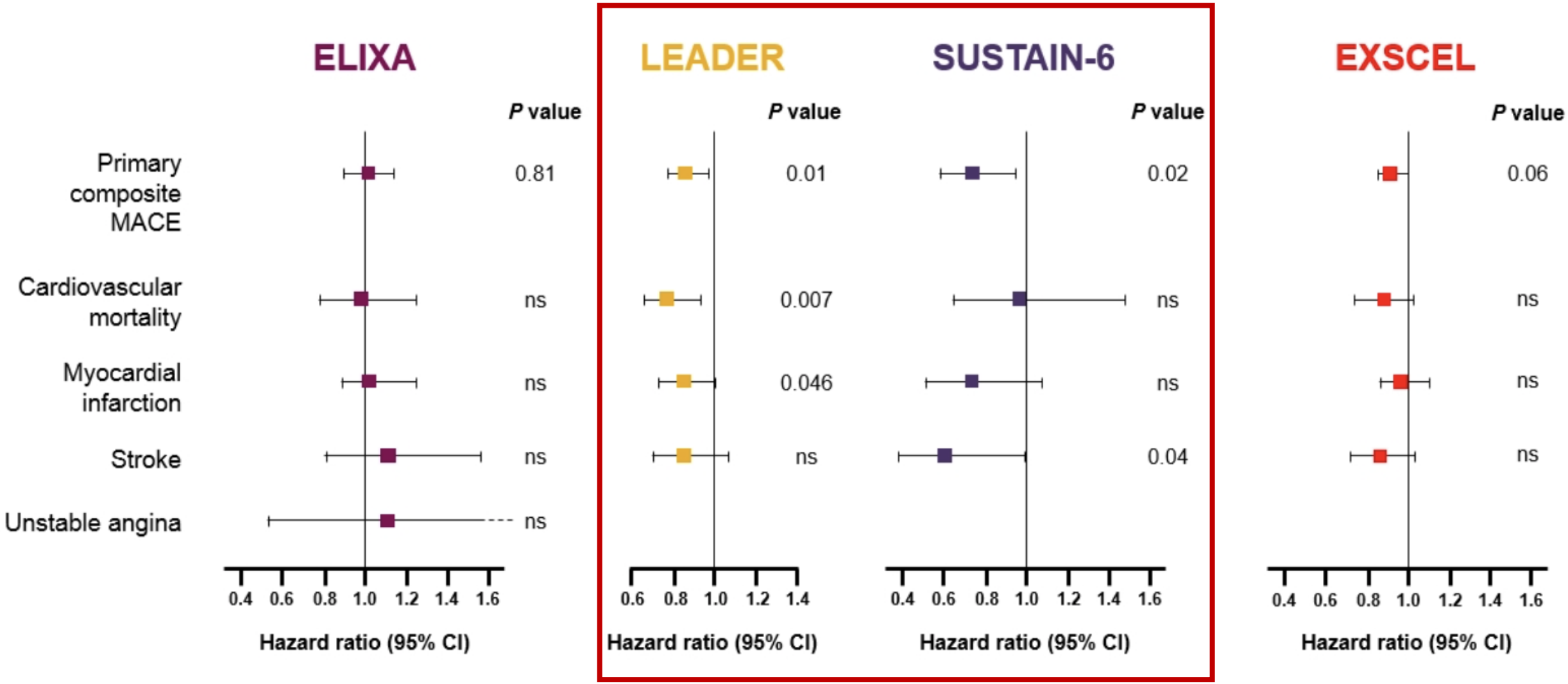
B Summary of key cardiovascular outcomes

	Active Rate per 1000 patient-years	Placebo Rate per 1000 patient-years	Hazard Ratio (95% CI)
MACE-3	37.4	43.9	0.86 (0.74 – 0.99)
	26.9	31.5	0.86 (0.75 – 0.97)
CV Death	12.4	20.2	0.62 (0.49 – 0.77)
	11.6	12.8	0.87 (0.72 – 1.06)
Fatal and nonfatal MI	16.8	19.3	0.87 (0.70 – 1.09)
	11.2	12.6	0.89 (0.73 – 1.09)
Fatal and nonfatal stroke	12.3	10.5	1.18 (0.89 – 1.56)
	7.9	9.6	0.87 (0.69 – 1.09)
Heart failure hospitalization	19.4	14.5	0.65 (0.50 – 0.85)
	5.5	8.7	0.67 (0.52 – 0.87)
All cause mortality	19.4	28.6	0.68 (0.57 – 0.82)
	17.3	19.5	0.87 (0.74 – 1.01)



Circulation. 2018;137:1218–1220

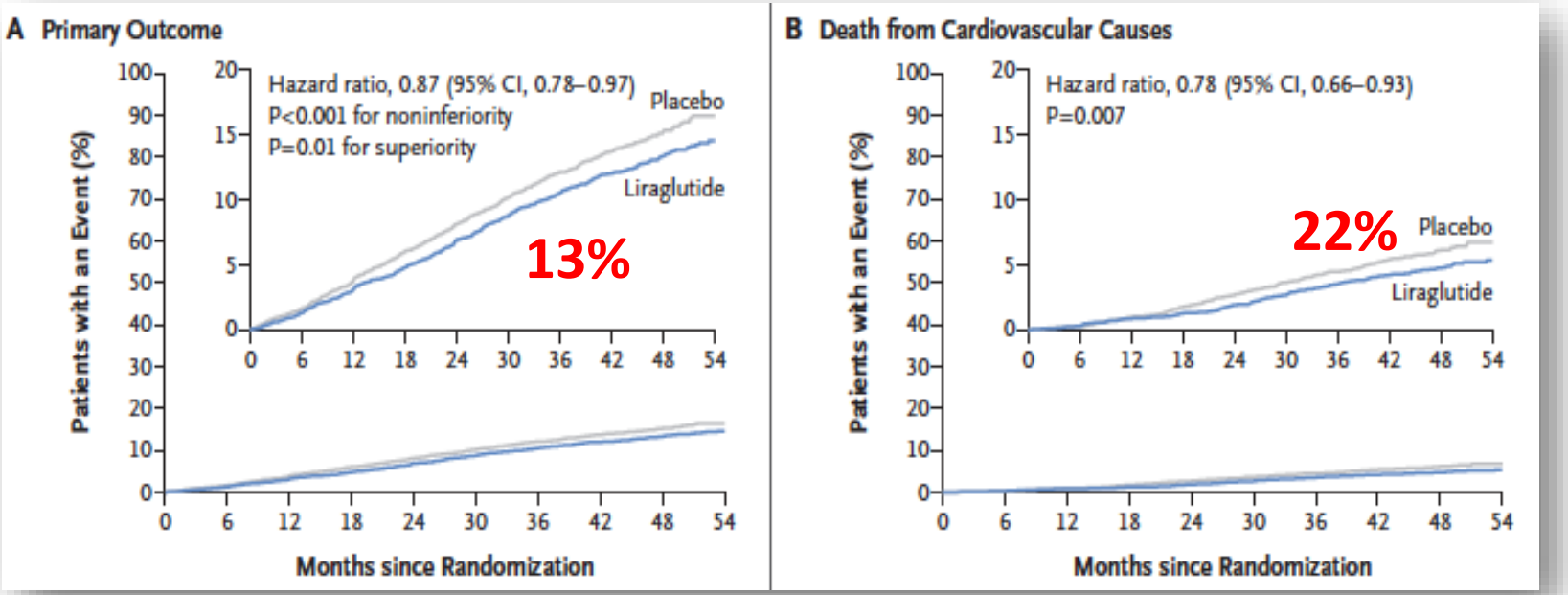
Primary Endpoint and Its Individual Components in ELIXA, LEADER, SUSTAIN-6 and EXSCEL

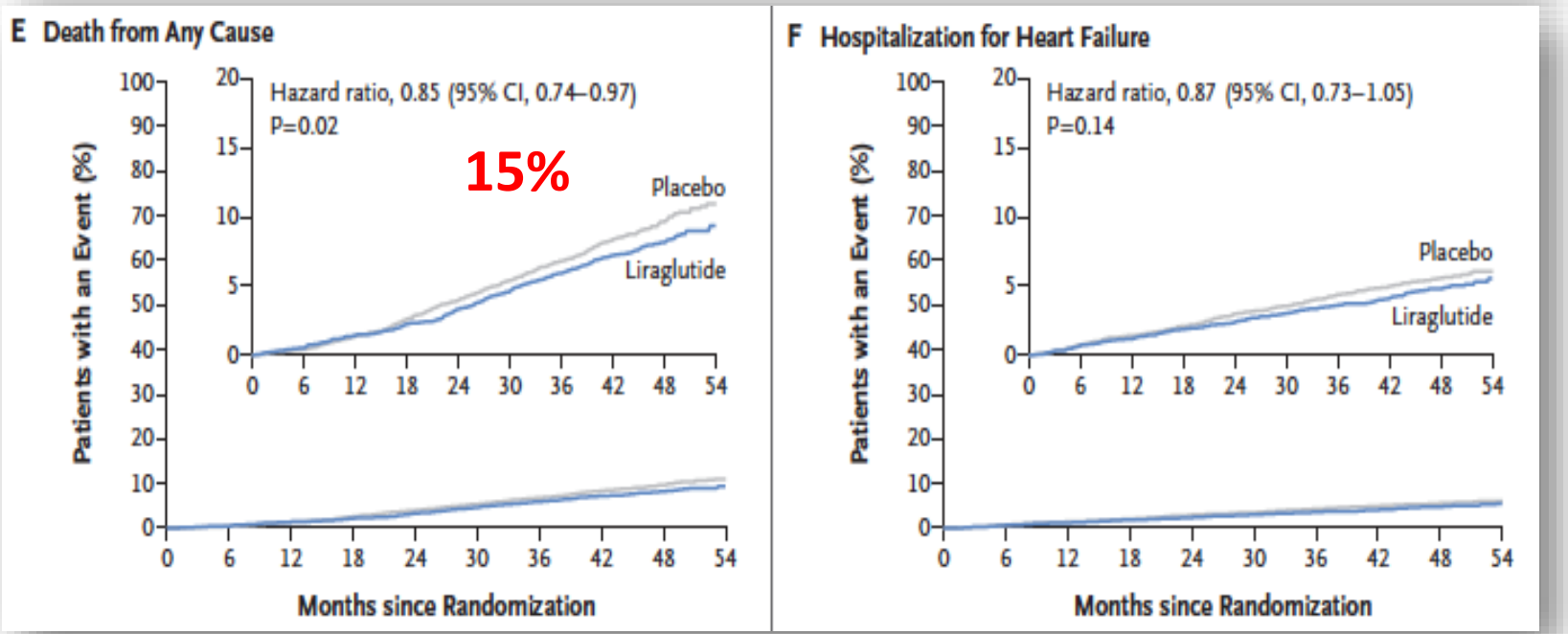


CI, confidence interval; MACE, major adverse cardiovascular event; ns, not significant.
Adapted from Pfeffer MA, et al. *N Engl J Med* 2015;373:2247–2257; Marso SP, et al., *N Engl J Med* 2016;375:311-22; Marso SP, et al., *N Engl J Med* 2016 375:1834-1844; Holman RR et al., *N Engl J Med,* in press.

LEADER®

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





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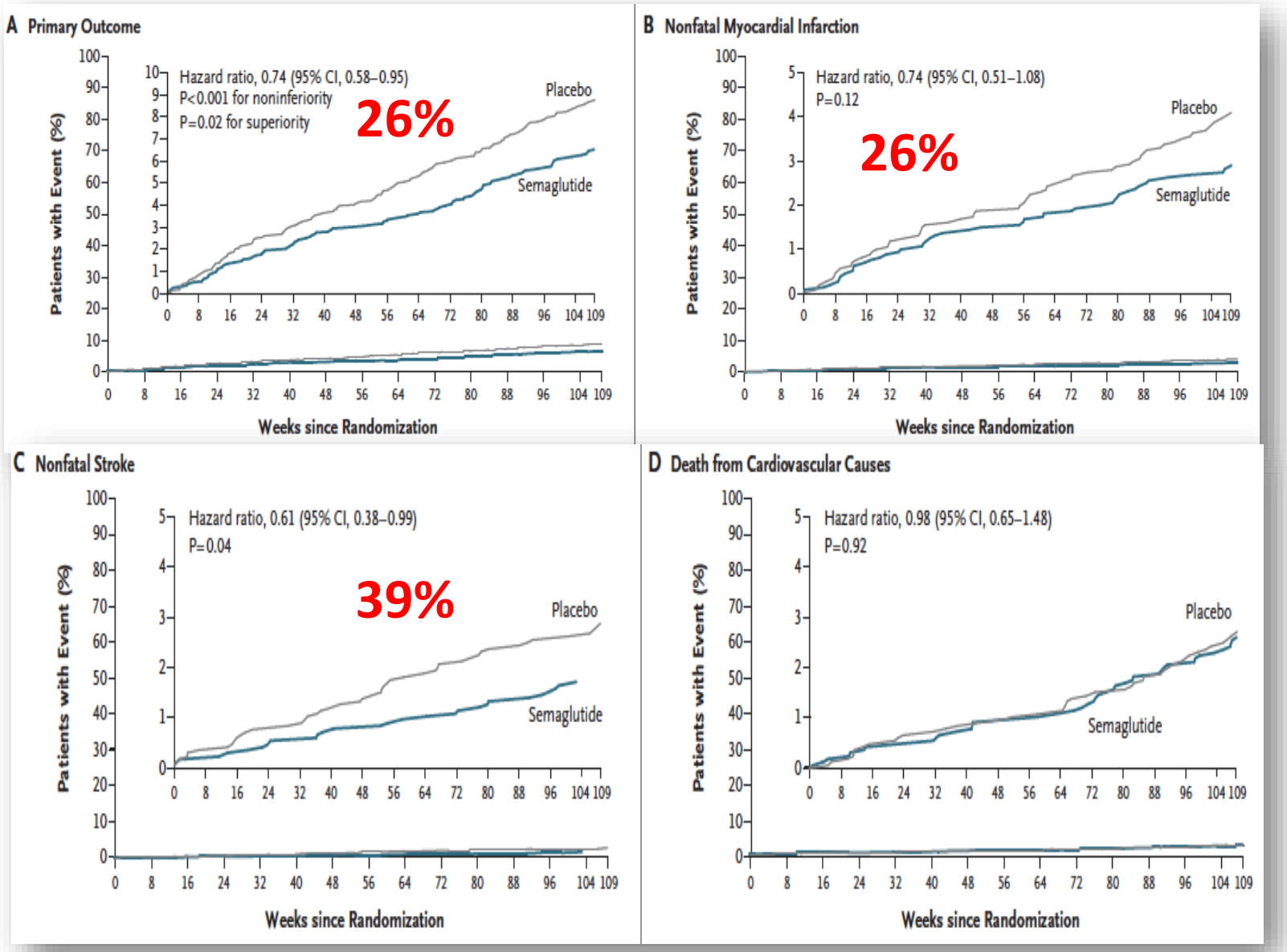
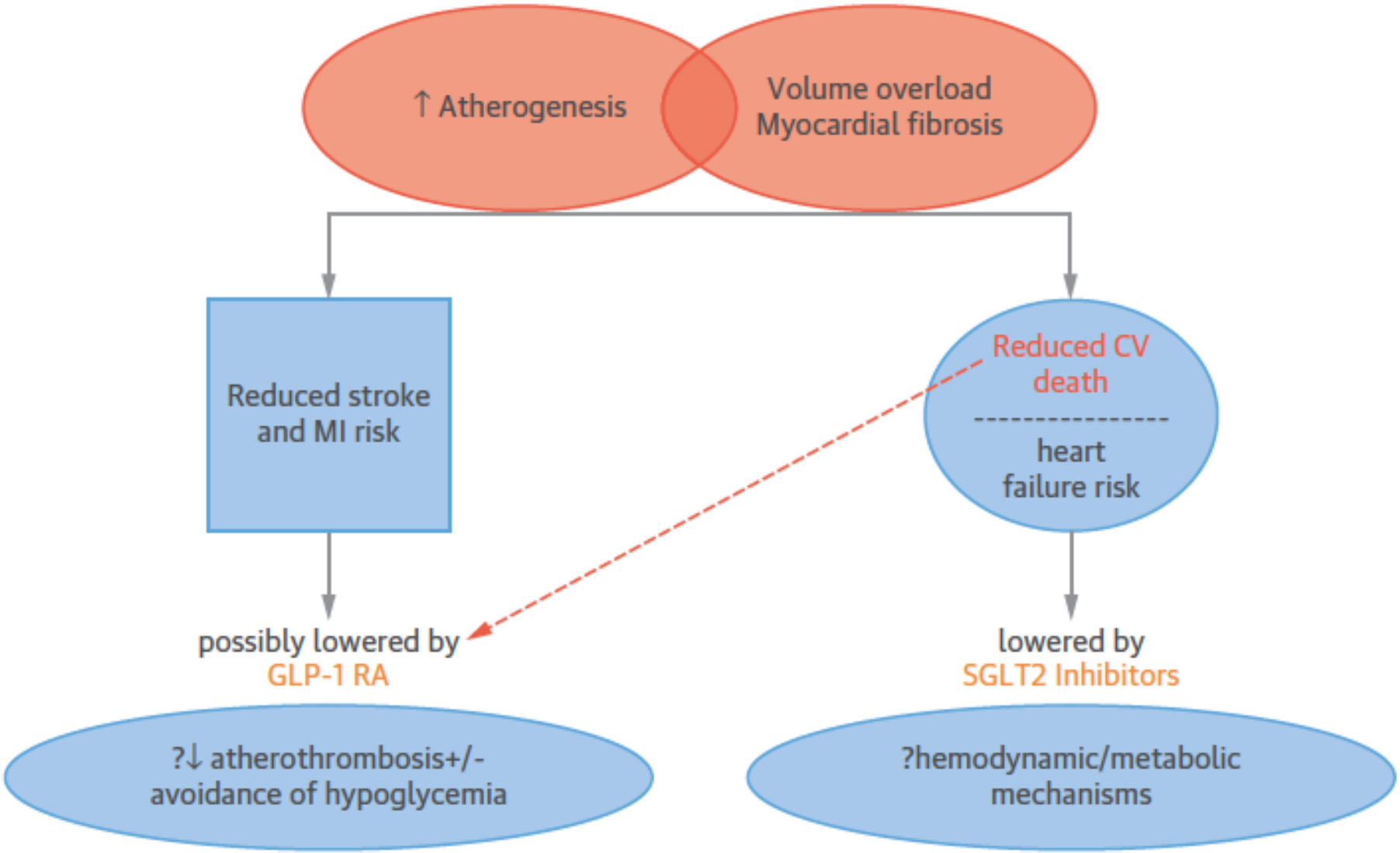
SUSTAIN

SEMAGLUTIDE UNABATED SUSTAINABILITY IN TREATMENT OF TYPE 2 DIABETES

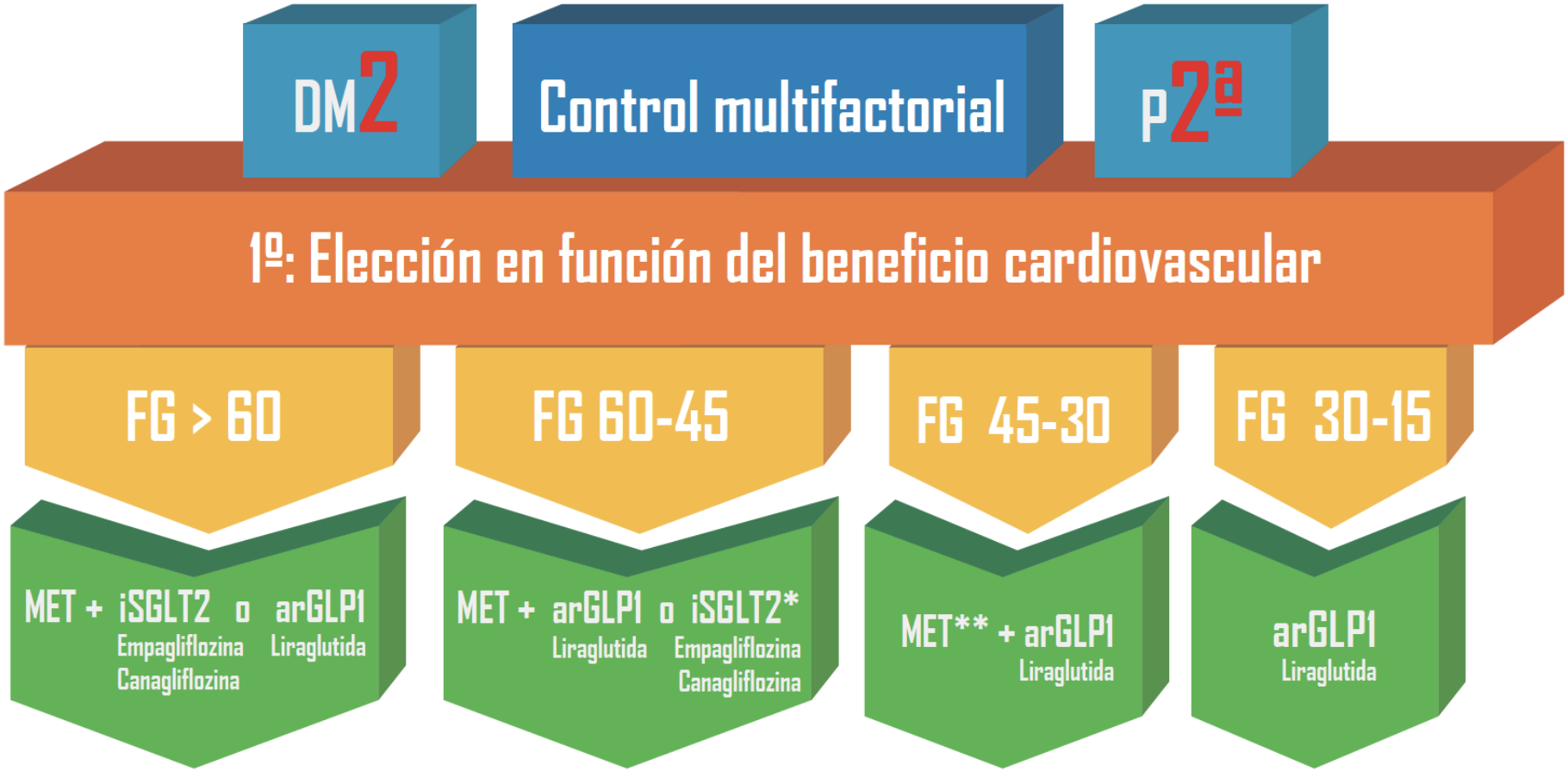


N Engl J Med 2016;375:1834-44.

FIGURE 3 Summary of New Diabetes Drugs and Patterns of CV Benefits in Patients With T2DM and CV Disease



Sattar et al. JACC. 6 9 , N O. 2 1 , 2 0 1 7 M AY 3 0 , 2 0 1 7 : 2 6 4 6 – 5 6



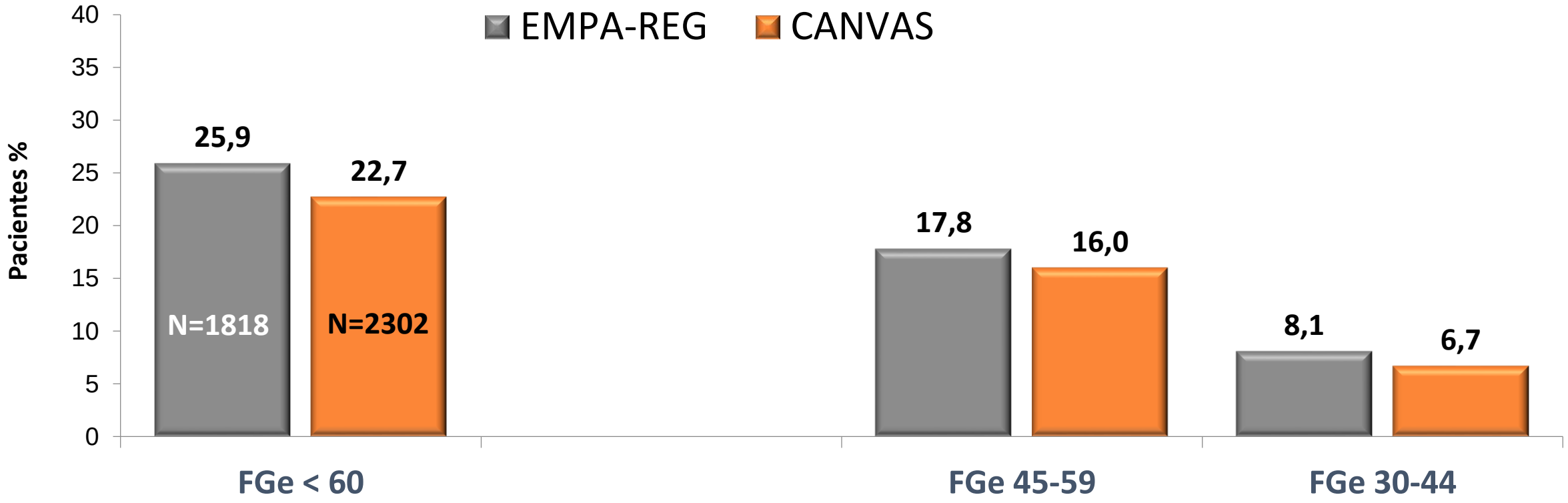
¿ FG ?

*** No iniciar. Sí mantener: Empa 10 mg o Cana 100 mg**

**** No iniciar MET. Sí mantener.**

Castro A, Marzal D et al.. SEC Monogr. 2018;6 (2):19-23

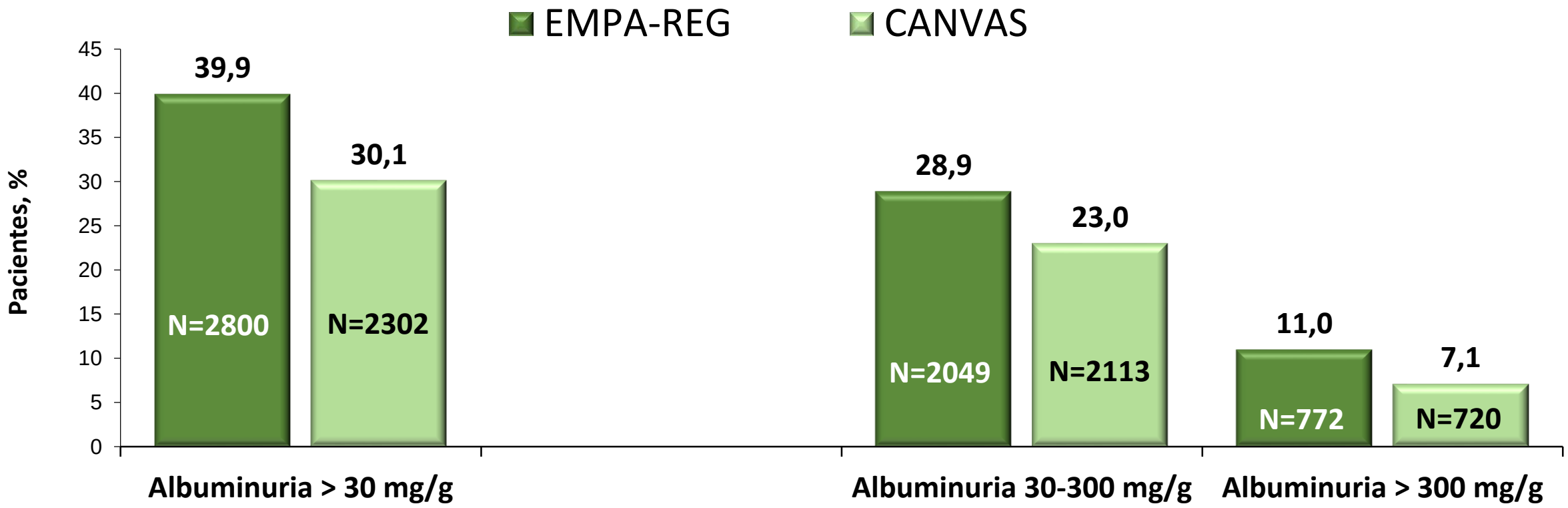
Porcentaje de pacientes con FGe< 60 ml/min/1,73 m^2 en los estudios EMPA-REG OUTCOME Y CANVAS



FGe: ml/min/1,73 m^2

Wanner C. New Engl J Med 2016, June 14
Neal B. New Engl J Med 2017, 377(7):644-657
Perkovic V. Poster FR-PO 1058. ASN New Orleans. Novbre 2017

Porcentaje de pacientes con ALBUMINURIA en los estudios EMPA-REG OUTCOME Y CANVAS

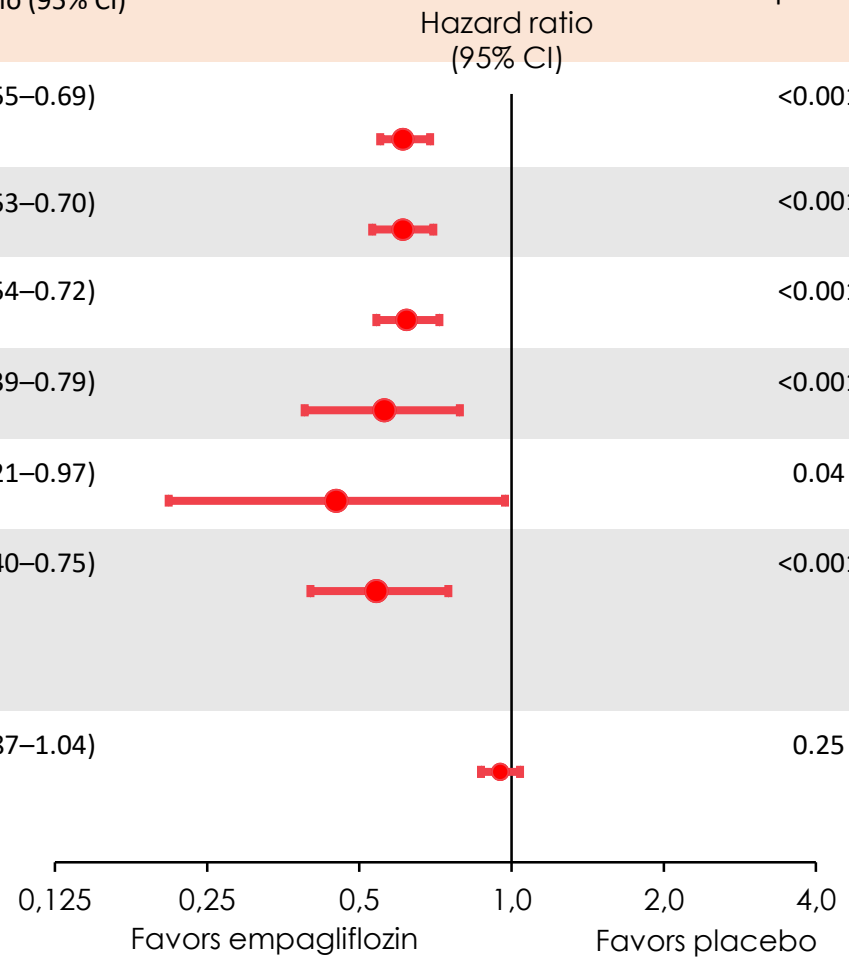


IRMA 2: 950 pacientes
RENAAL: 1513 pacientes
IDNT: 1715 pacientes

Wanner C. New Engl J Med 2016, June 14
Neal B. New Engl J Med 2017, 377(7):644-657
Perkovic V. Poster FR-PO 1058. ASN New Orleans. Novbre 2017

EMPA-REG OUTCOME: Renal outcomes (todos los pacientes)

	Empagliflozin		Placebo				
	no. with event /analyzed (%)	rate/ 1000 pt-yr	no. with event/ analyzed (%)	rate/ 1000 pt-yr	Hazard Ratio (95% CI)	Hazard ratio (95% CI)	p-value
Incident or worsening nephropathy or CV death	675/4170 (16.2)	60.7	497/2102 (23.6)	95.9	0.61 (0.55–0.69)		<0.001
Incident or worsening nephropathy	525/4124 (12.7)	47.8	388/2061 (18.8)	76.0	0.61 (0.53–0.70)		<0.001
Progression to macroalbuminuria	459/4091 (11.2)	41.8	330/2033 (16.2)	64.9	0.62 (0.54–0.72)		<0.001
Doubling of serum creatinine*	70/4645 (1.5)	5.5	60/2323 (2.6)	9.7	0.56 (0.39–0.79)		<0.001
Initiation of renal replacement therapy	13/4687 (0.3)	1.0	14/2333 (0.6)	2.1	0.45 (0.21–0.97)		0.04
Doubling of serum creatinine*, initiation of renal replacement therapy, or death due to renal disease	81/4645 (1.7)	6.3	71/2323 (3.1)	11.5	0.54 (0.40–0.75)		<0.001
Incident albuminuria in patients with normoalbuminuria at baseline	1430/2779 (51.5)	252.5	703/1374 (51.2)	266.0	0.95 (0.87–1.04)		0.25

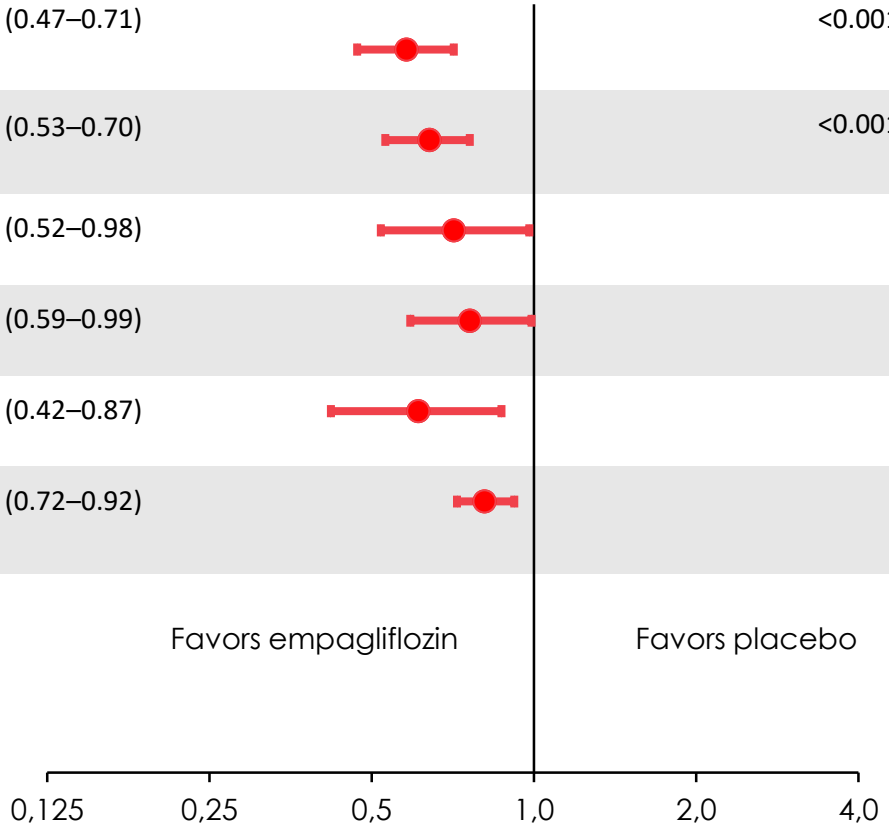


Analyses were prespecified except for the composite of doubling of serum creatinine, initiation of renal replacement therapy, or death due to renal disease.
*Accompanied by eGFR [MDRD] ≤45 ml/min/1.73m^2.

Wanner C., N Engl J Med, 2016: 375: 323-334

EMPA-REG OUTCOME: Renal outcomes **in prevalent kidney disease***

N= 2250 (32 %)	Empagliflozin no. with event /analyzed (%)	Empagliflozin rate/ 1000 pt-yr	Placebo no. with event/ analyzed (%)	Placebo rate/ 1000 pt-yr	Hazard Ratio (95% CI)	p-value
Incident or worsening nephropathy or CV	207/998 (20.7)	82.0	161/507 (31.8)	141.7	0.58 (0.47–0.71)	<0.001
Incident or worsening nephropathy or CV death	290/1039 (27,9)	110.6	213/539 (39,5)	178,8	0.64 (0.53–0.70)	<0.001
CV death					0.71 (0.52–0.98)	
All cause mortality					0.76 (0.59–0.99)	
Hospitalization for heart failure					0.61 (0.42–0.87)	
All cause of hospitalization					0.81 (0.72–0.92)	



***prevalent kidney disease**: eGFR <60 mL/min/1.73m2 and/or urine albumin-creatinine ratio [UACR] >300 mg/g) at baseline

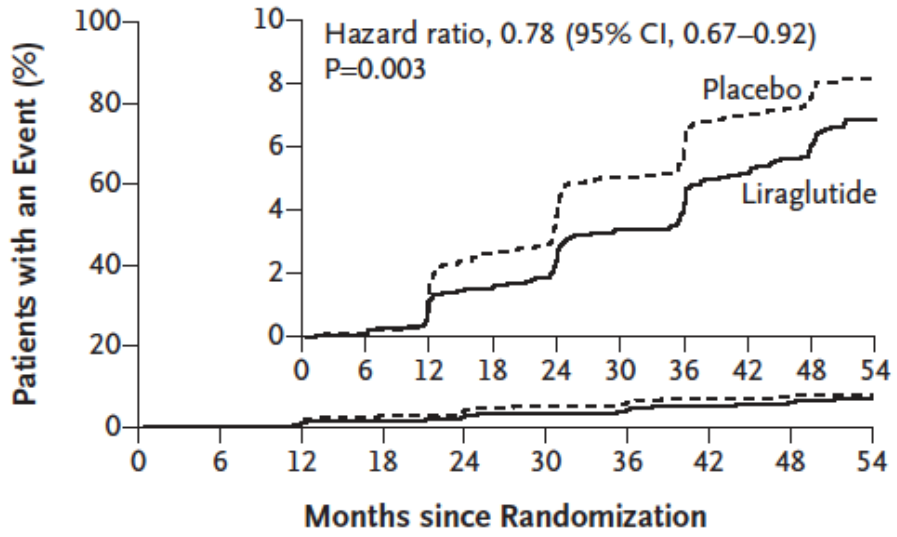
N= 2250 (32 %)

Wanner C. Circulation. 2017 Sep 13. pii: CIRCULATIONAHA.117.028268.

Liraglutide: efecto en nefropatía*

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

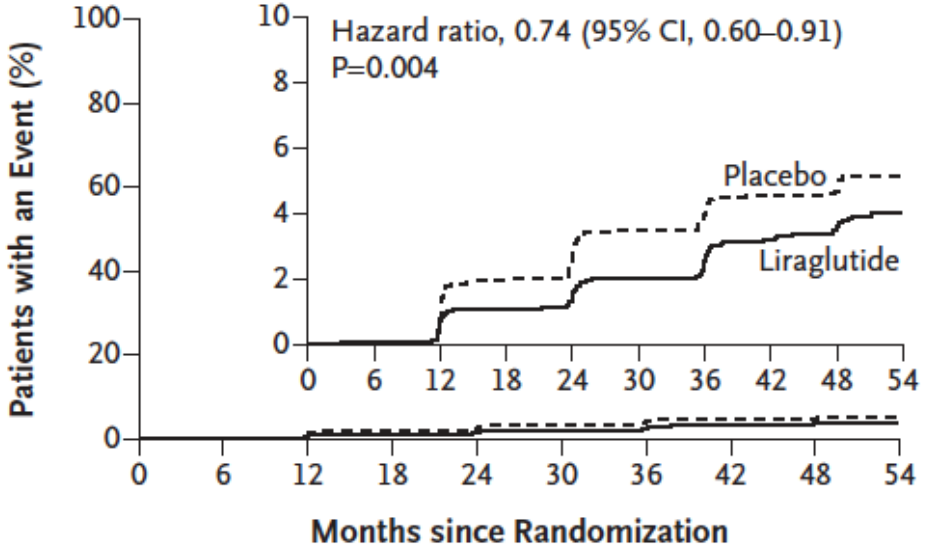
A Composite Renal Outcome



No. at Risk

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

B New Onset of Persistent Macroalbuminuria



No. at Risk

Placebo	4672	4646	4551	4455	4359	4252	4162	4073	1642	442
Liraglutide	4668	4638	4570	4508	4437	4353	4268	4182	1662	461

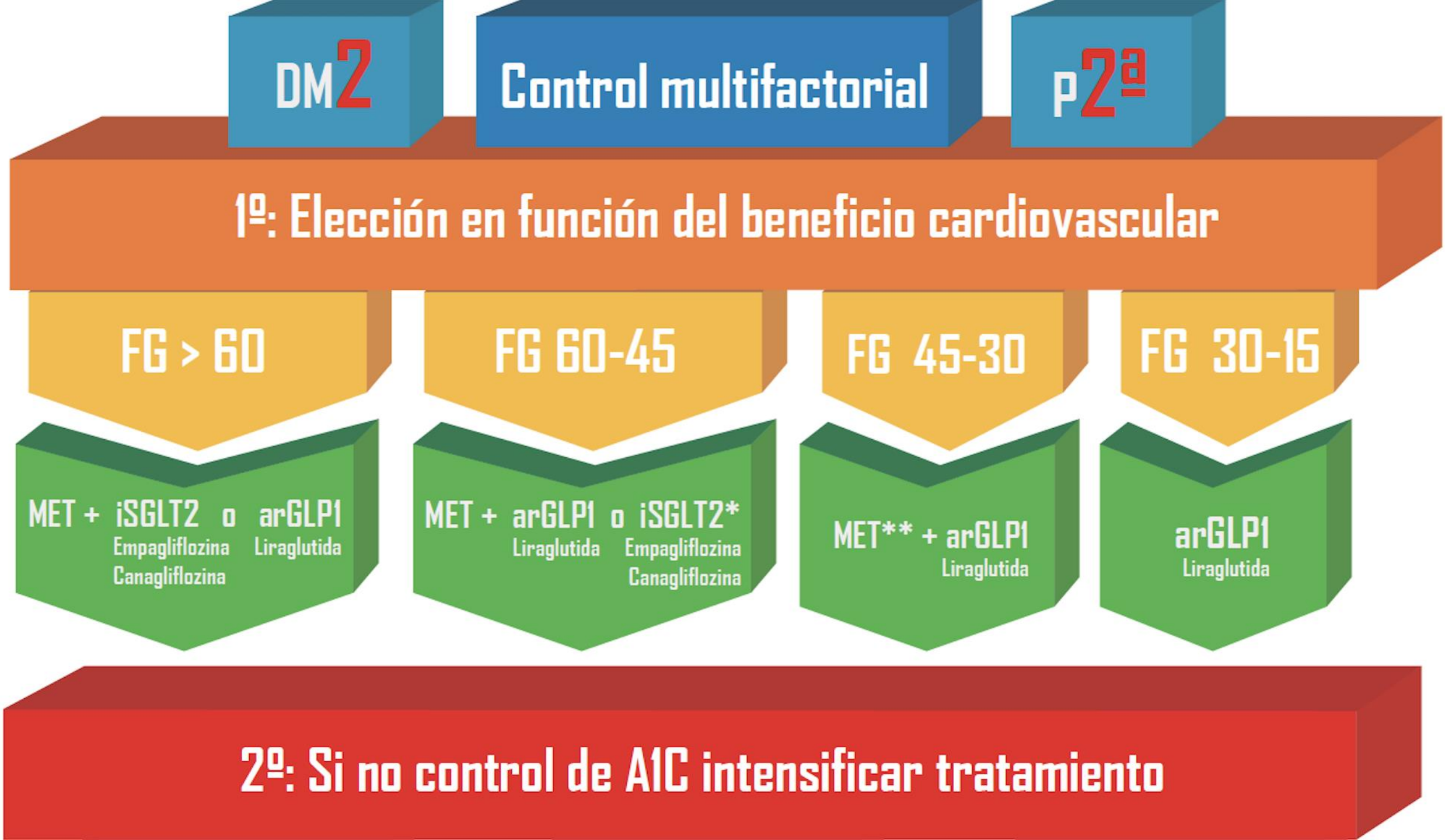
No beneficio en duplicación de creatinina ni IRCT

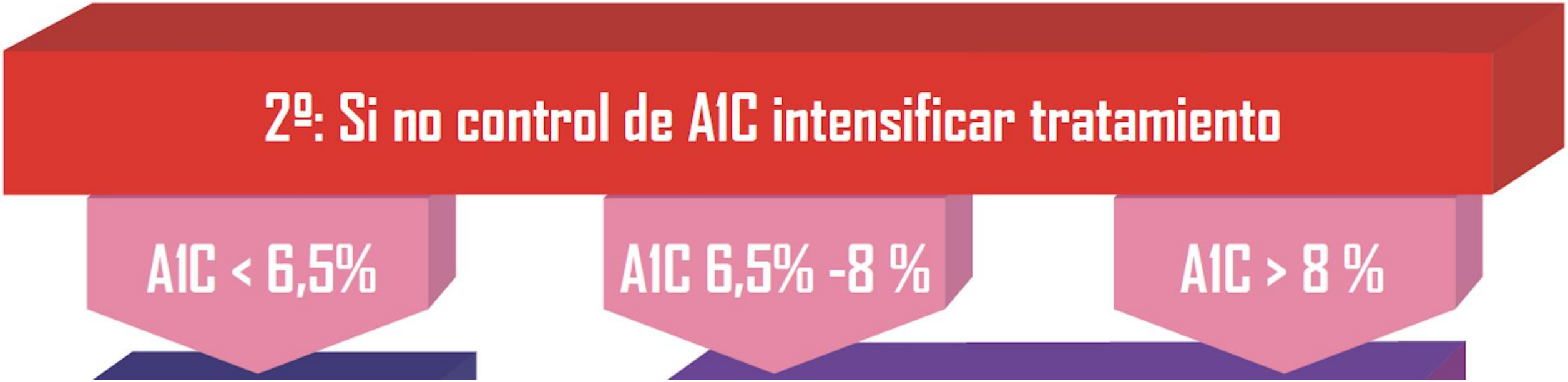
	%	Nº
FGe 30-59 ml/min/1,73 m^2	20.7 %	1934
Microalbuminuria	26.1 %	244
Macroalbuminuria	10.3 %	966

	Hazard Ratio (95% CI)	P Value
Microvascular event	0.84 (0.73–0.97)	0.02
Retinopathy	1.15 (0.87–1.52)	0.33
Nephropathy ↓ 22%	0.78 (0.67–0.92)	0.003

*Macroalbuminuria, doubling of serum creatinine, ESRD, renal death

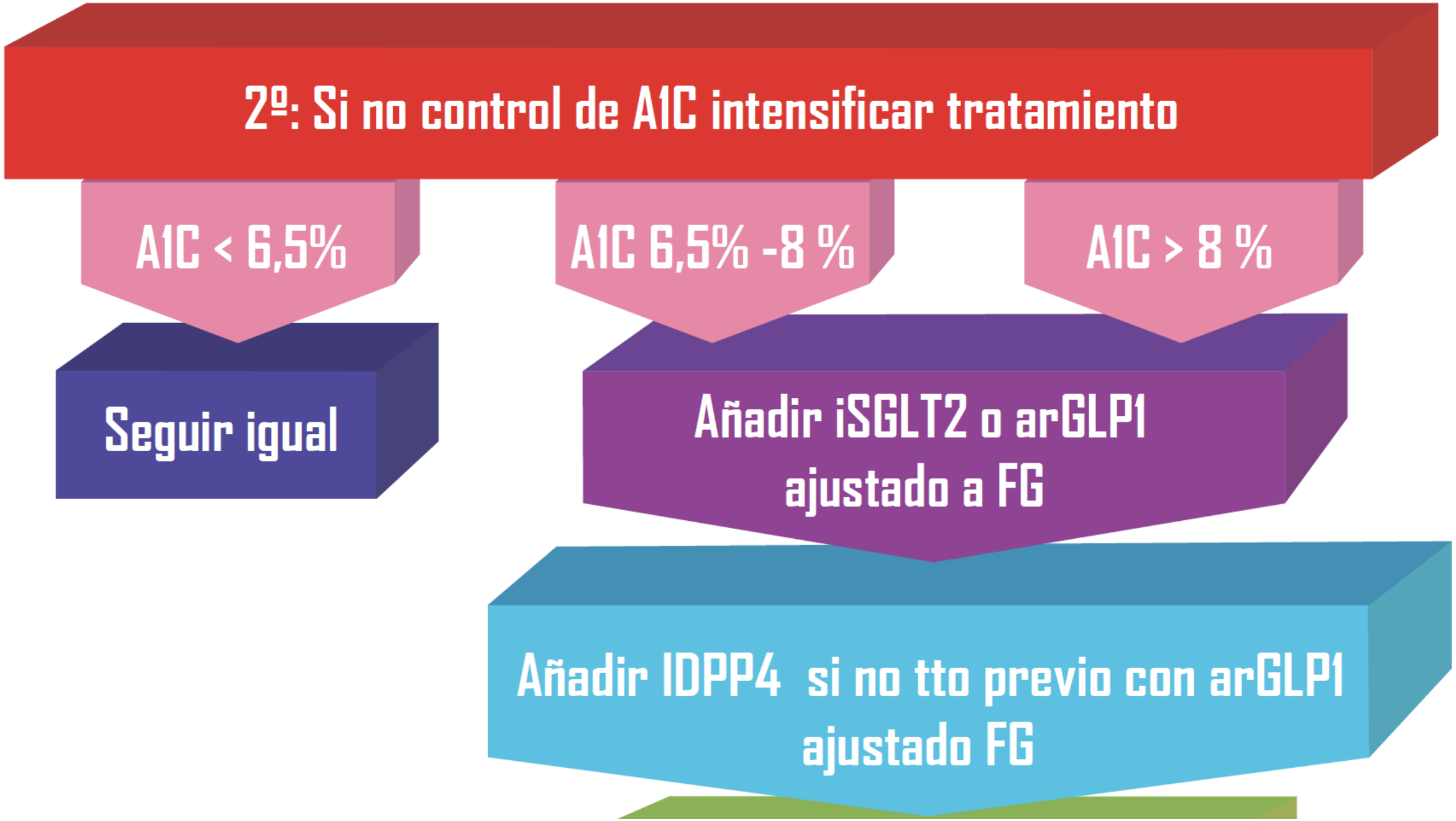
Mann JFE. N Engl J Med 2017;377:839-48
Marso SP. N Engl J Med 2016; 375(4):311-22


DM2
Control multifactorial
p2ª
1º: Elección en función del beneficio cardiovascular
FG > 60
MET + iSGLT2 o arGLP1
Empagliflozina Liraglutida
Canagliflozina
FG 60-45
MET + arGLP1 o iSGLT2*
Liraglutida Empagliflozina
Canagliflozina
FG 45-30
MET** + arGLP1
Liraglutida
FG 30-15
arGLP1
Liraglutida
2º: Si no control de A1C intensificar tratamiento

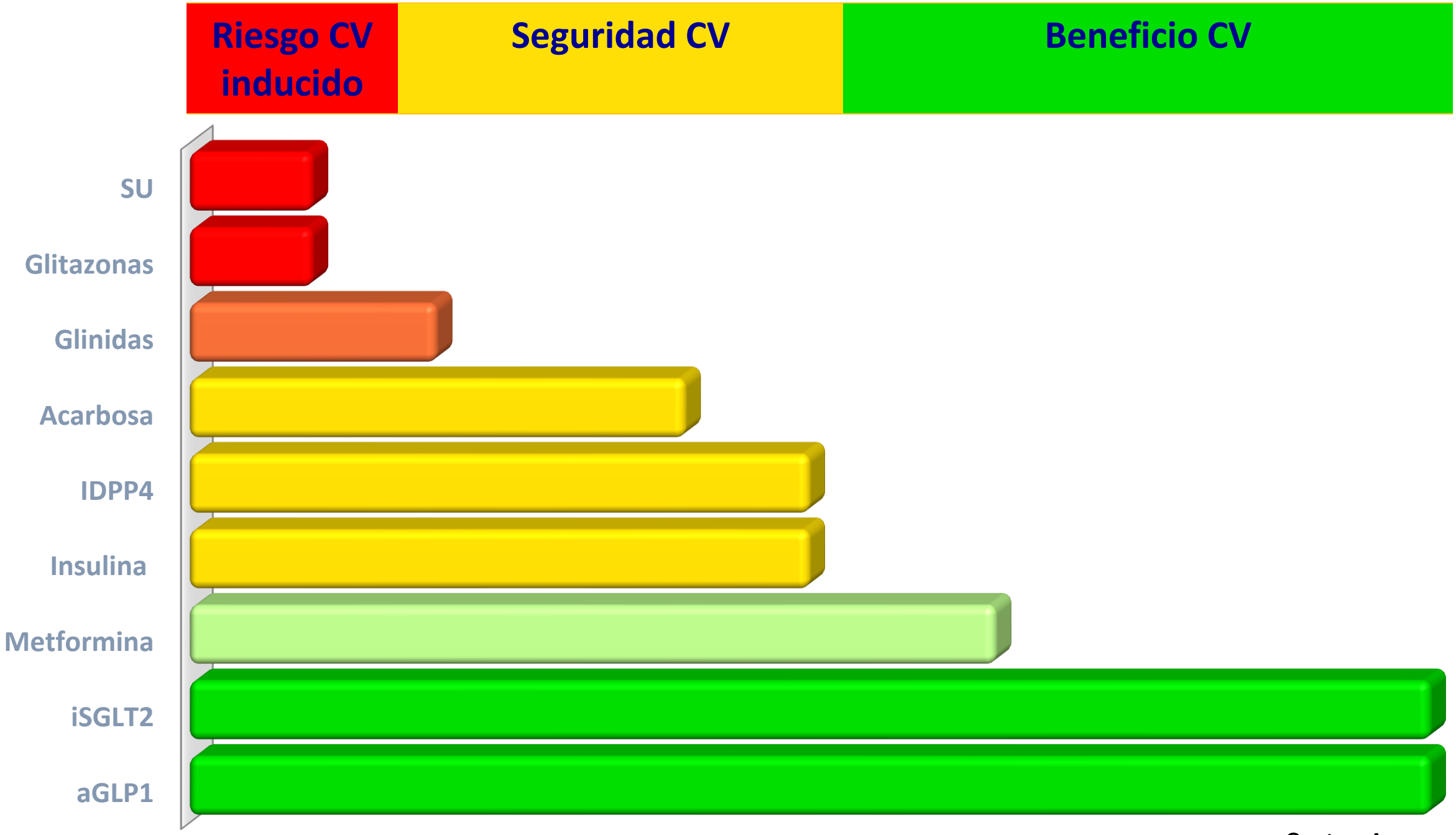


¿ Qué asociamos?

Castro A, Marzal D et al.. SEC Monogr. 2018;6 (2):19-23



Castro A, Marzal D et al.. SEC Monogr. 2018;6 (2):19-23


Riesgo CV inducido
Seguridad CV
Beneficio CV
SU
Glitazonas
Glinidas
Acarbosa
IDPP4
Insulina
Metformina
iSGLT2
aGLP1

Castro A.

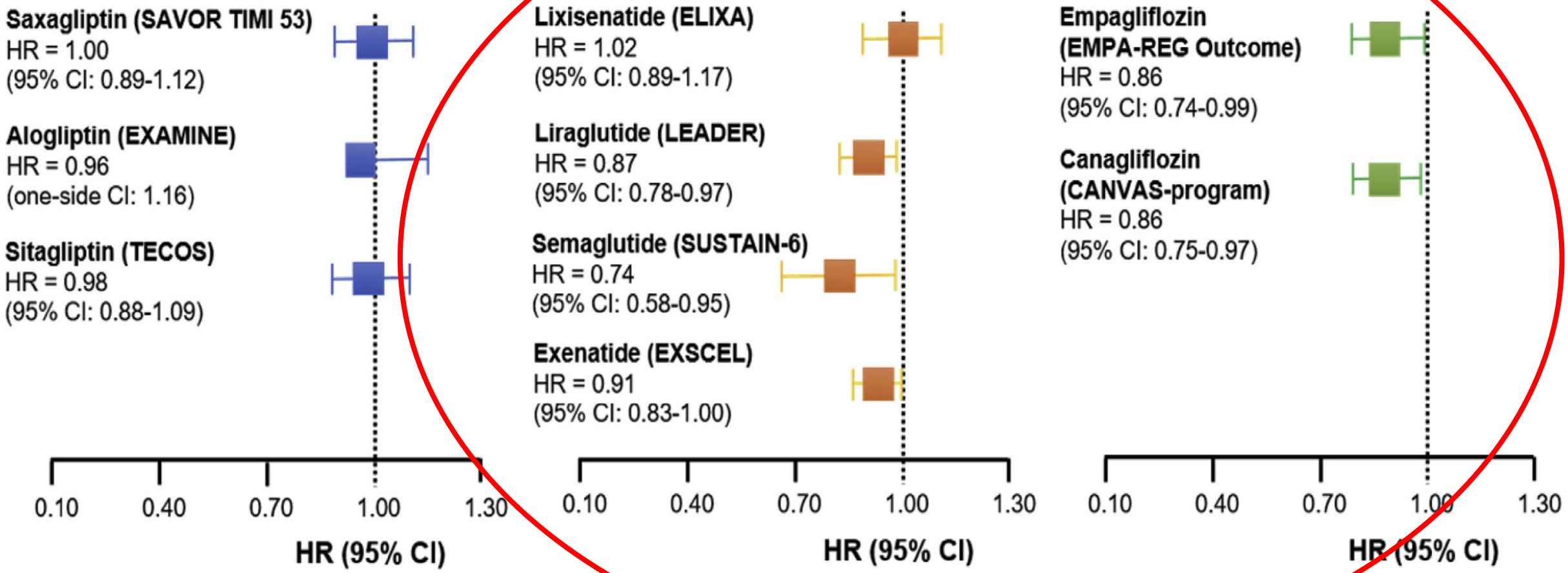
Resultados CV de los últimos estudios en antidiabéticos no-insulínicos

	Inhibidores del SGLT-2		Agonistas del receptor GLP-1			Inhibidores de la DPP-4		
Estudio	EMPA-REG OUTCOME	Programa CANVAS	ELIXA	LEADER	SUSTAIN	SAVOIR	EXAMINE	TECOS
Fármaco	Empagliflozina	Canagliflozina	Lixisenatide	Liraglutide	Semaglutide	Saxagliptina	Alogliptina	Sitagliptina
3P-MACE	0,86* 0,74-0,99	0,86* 0,75-0,97	1.02 0,89-1.17	0,87* 0,78-0,97	0,74* 0,58-0,95	1,0 0,89-1,08	0,96 Sobre 1,16	0,98^ 0,89-1,08
Muerte CV	0,62* 0,70-0,77	0,87 0,72-1,06	0,98 0,78-1,22	0,78* 0,66-0,93	0,98 0,65-1,48	1,03 0,87-1,22	0,79 0,60-1,04	1,03 0,89-1,19
Infarto no fatal	0.67* 0,70-1,09	0,85 0,69-1,05	1,03+ 0,87-1,22	0,88 0,75-1,03	0,74 0,51-1,08	1,95 0,80-1,12	1,08 0,88-1,33	0,95+ 0,81-1,11
ACV no fatal	1.24 0,92-1,67	0,90 0,71-1,15	1,12+ 0,79-1,58	0,89 0,72-1,11	0,61* 0,38-0,99	1,11 0,88-1,39	0,91 0,55-1,50	0,97+ 0,89-1,08
Hospitalización por IC	0.65* 0,50-0,85	0,67 0,52-0,87	0,96 0,75-1,23	0,87 0,73-1,05	1,11 0,77-1,61	1,27* 1,07-1,51	1,07 0,78-1,15	1,00 0,83-1,20
Muerte por todas las causas	0,68* 0,57-0,82	0,87 0,74-1,01	0,94 0,78-1,13	0,85* 0,74-0,97	1,05 0,74-1,50	1,11 0,96-1,27	0,88 0,71-1,09	1,01 0,90-1,14

* Estadísticamente significativo, + ACV e infarto fatal y no fatal, ^ TECOS tuvo análisis 4P-MACE. Scirica BM et al. N Engl J Med 2013;369:1317; White WB et al. N Engl J Med 2013;369:1327; Pfeffer MA et al. N Engl J Med 2015;373:2247; Green JB et al. N Engl J Med 2015;373:232; Zinman B et al. N Engl J Med 2015;373:2117; Marso SP, et al. N Engl J Med. 2016;375(4):311–22; Marso SP, et al. N Engl J Med. 2016;375(19):1834–44. Buse N, et al. M Engl J Med. DOI: 10.1056/NEJMoa1611925

IDPP4	Estudio	Publicado	Seguridad CV	Eficacia CV
Alogliptina	EXAMINE	2013	Sí	Neutro
Saxagliptina	SAVOR	2013	Sí en MACES No en IC	Neutro
Sitagliptina	TECOS	2015	Sí	Neutro
Linagliptina	CAROLINA CARMELINA	En marcha En marcha		
Vildagliptina	META-ANÁLISIS	2015	Sí	Neutro
Omarigliptina	OMARIGLIPTINA	2017	Sí	Neutro

Posicionamiento DM2 en P2ª; 2017



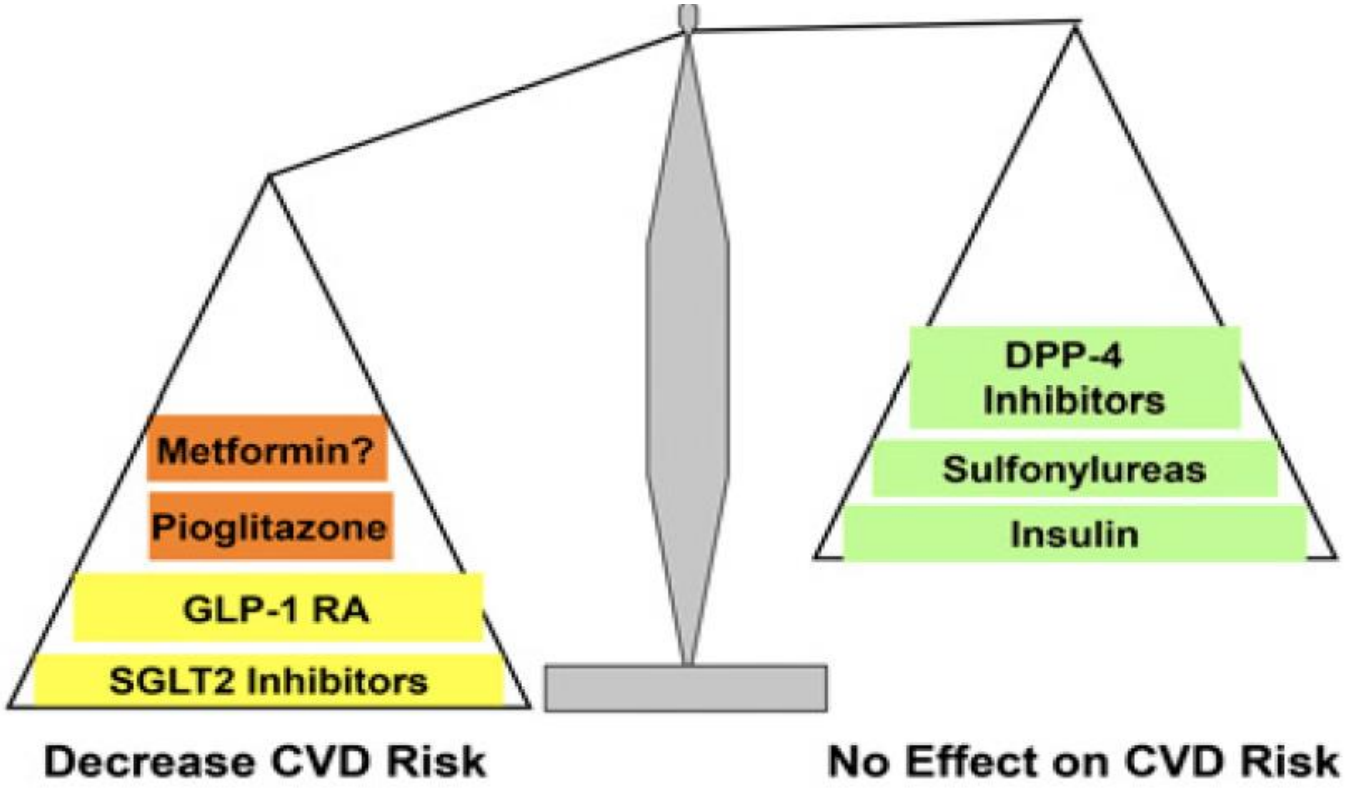
¿La combinación razonable?

Atherosclerosis 272 (2018) 33e40

Cardiovascular Disease and Type 2 Diabetes: Has the Dawn of a New Era Arrived?

Diabetes Care 2017;40:813–820 | https://doi.org/10.2337/dc16-2736

Muhammad Abdul-Ghani,[1,2] Ralph A. DeFronzo,[1] Stefano Del Prato,[3] Robert Chilton,[4] Rajvir Singh,[2] and Robert E.J. Ryder[5]



"…there emerges the intriguing possibility that, if used in combination, the effects of these antidiabetes agents may be additive or even multiplicative with regard to cardiovascular benefit."

Strategies for Diabetes Management: Using Newer Oral Combination Therapies Early in the Disease

Results: New oral agents have made it possible to improve glycemic control to near-normal levels with a low risk of hypoglycemia and without weight gain, and sometimes with weight loss. Early combination therapy is effective and has been shown to have a favorable legacy effect. A number of agents are

Diabetes Ther (2016) 7:621–639

GLP-1 receptor agonists and SGLT2 inhibitors: a couple at last?

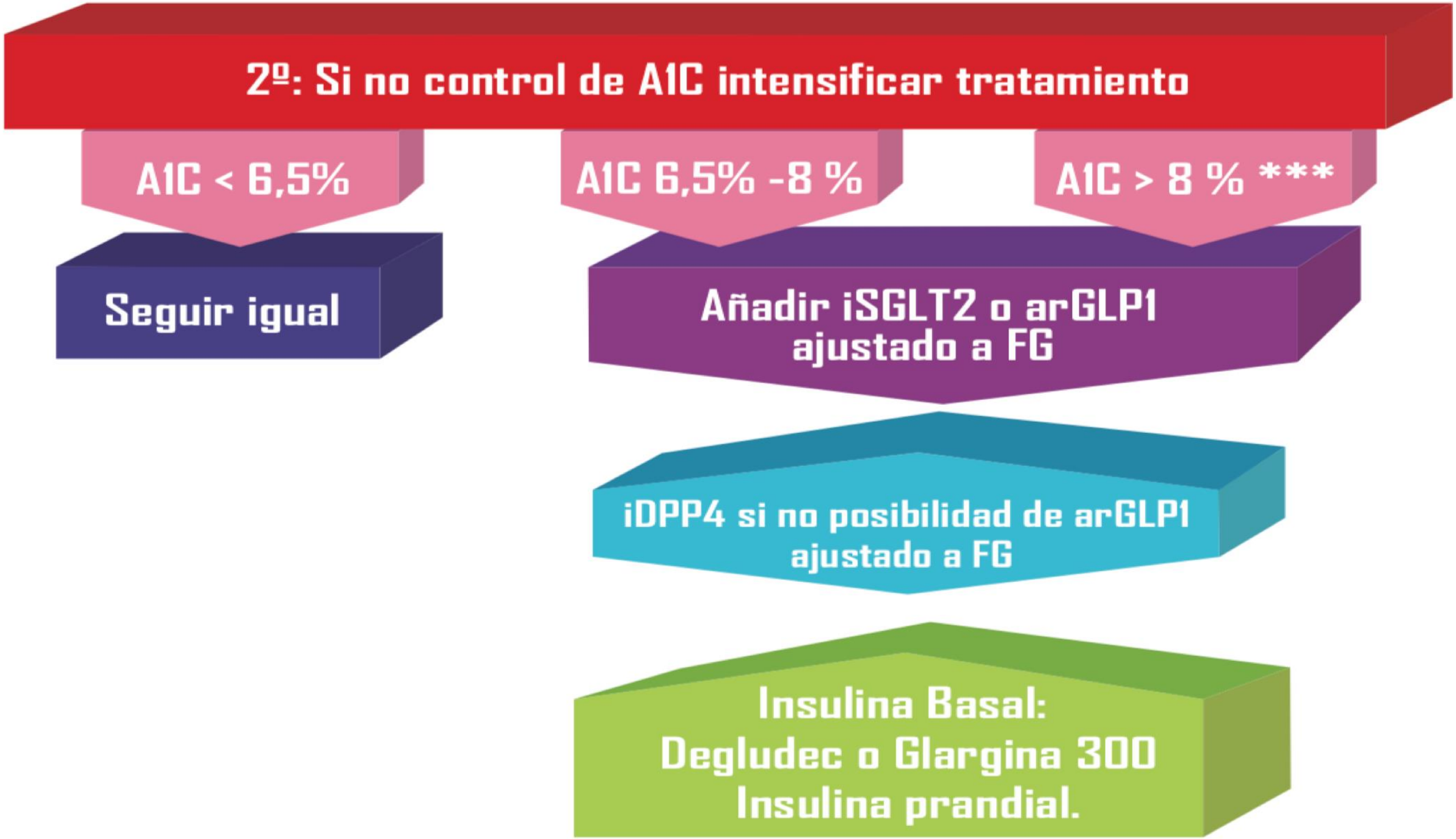
risk for such events. A question for future trials will be whether a combination of GLP-1 receptor agonists and SGLT2 inhibitors, the two classes that have shown cardiovascular benefit in large outcomes trials, can increase the benefit over and above what the individual drugs can provide. Importantly, the GLP-1 receptor

http://dx.doi.org/10.1016/ S2213-8587(16)30263-7

GLP-1 receptor agonists and SGLT2 inhibitors: a couple at last?

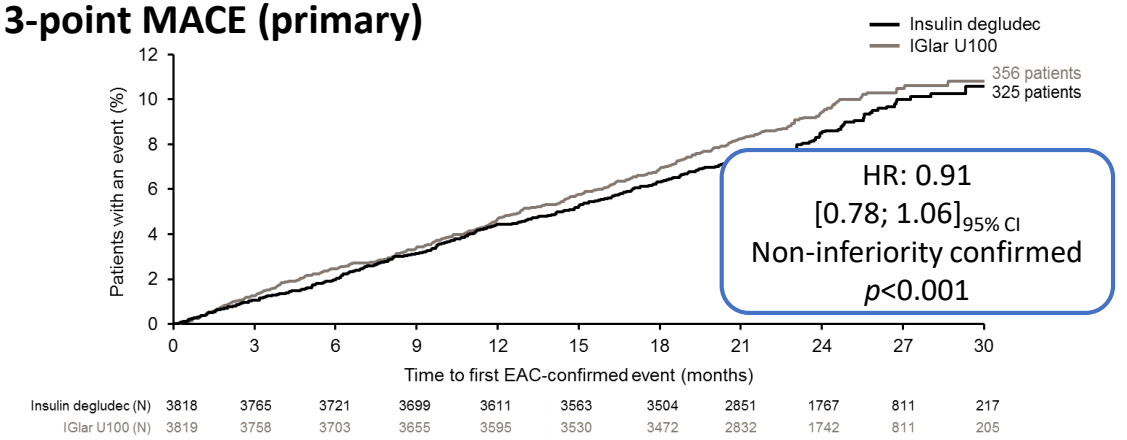
.doi.org/10.1016/ S2213-8587(16)30263-7

	GLP-1 receptor agonist		SGLT2 inhibitor	Combination therapy
Appetite	↓		↑ (?)	↓
Bodyweight	↓		↓	↓↓
Ischaemic cardiovascular events	↓		↓	↓↓
Heart failure events	↔		↓	↓
Insulin secretion	↑		↓	↑
Glucagon secretion	↓		↑	↔
Hepatic glucose output	↓		↑	↔
Ketone body production	↓ (?)		↑	↔
Glucose uptake (insulin-mediated)	↑ (?)		↑	↑↑
Diuresis, natiruresis	↑ (acutely)		↑	↑
Urinary glucose excretion	↔		↑	↑
Renoprotection	↔		↑	↑

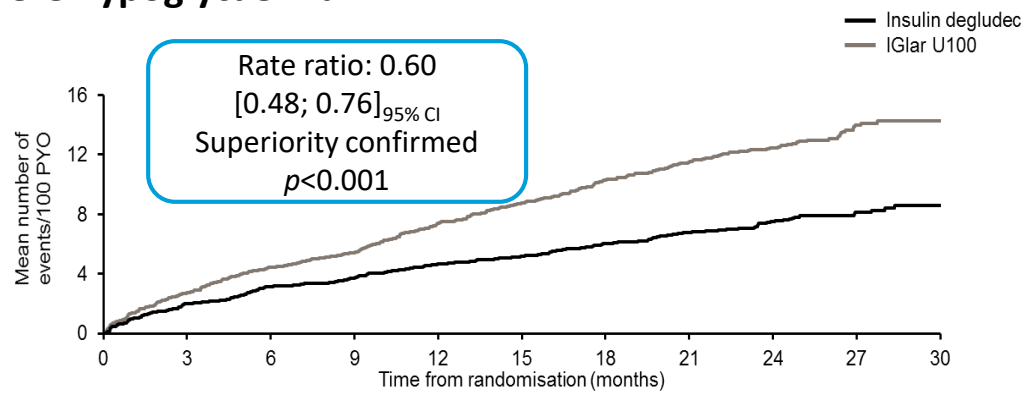

2º: Si no control de A1C intensificar tratamiento
A1C < 6,5%
A1C 6,5% -8 %
A1C > 8 % ***
Seguir igual
Añadir iSGLT2 o arGLP1
ajustado a FG
iDPP4 si no posibilidad de arGLP1
ajustado a FG
Insulina Basal:
Degludec o Glargina 300
Insulina prandial.

DEVOTE (degludec vs glargine100)

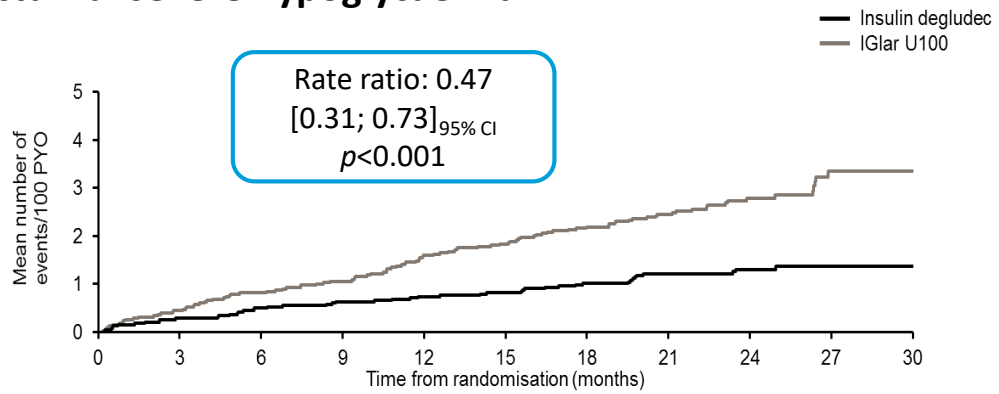
3-point MACE (primary)



Severe hypoglycaemia



Nocturnal severe hypoglycaemia

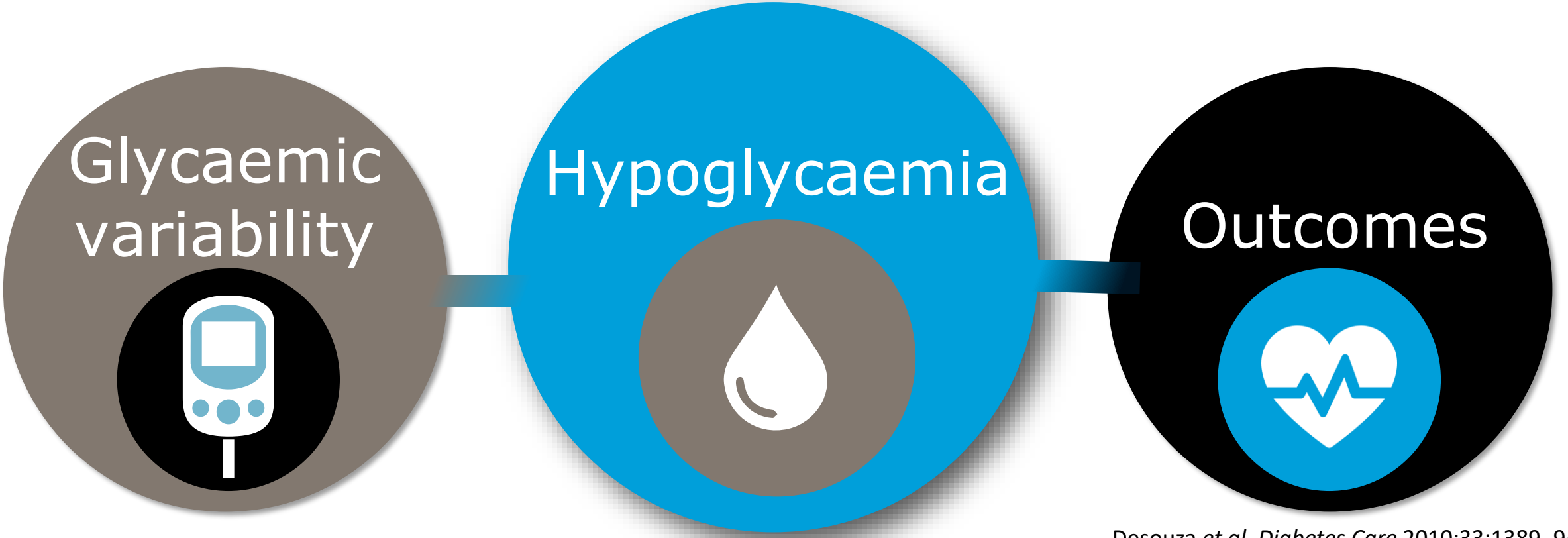


- DEVOTE confirmed the cardiovascular safety of insulin degludec in comparison with insulin glargine (both U100)
- DEVOTE reported 752 adjudication-confirmed severe hypoglycaemic events in a blinded head-to-head trial
- A 40% lower rate of severe hypoglycaemia was confirmed at similar levels of HbA_{1c}
- A 53% lower rate of nocturnal severe hypoglycaemia was confirmed at a lower fasting plasma glucose

CI, confidence interval; EAC, Event Adjudication Committee; HR, hazard ratio; IGlar U100, insulin glargine U100; MACE, major adverse cardiovascular events; N, number of patients at risk; PYO, patient-years of observation

Marso *et al. N Engl J Med* 2017;377:723–32

Association between glycaemic variability, hypoglycaemia and outcomes



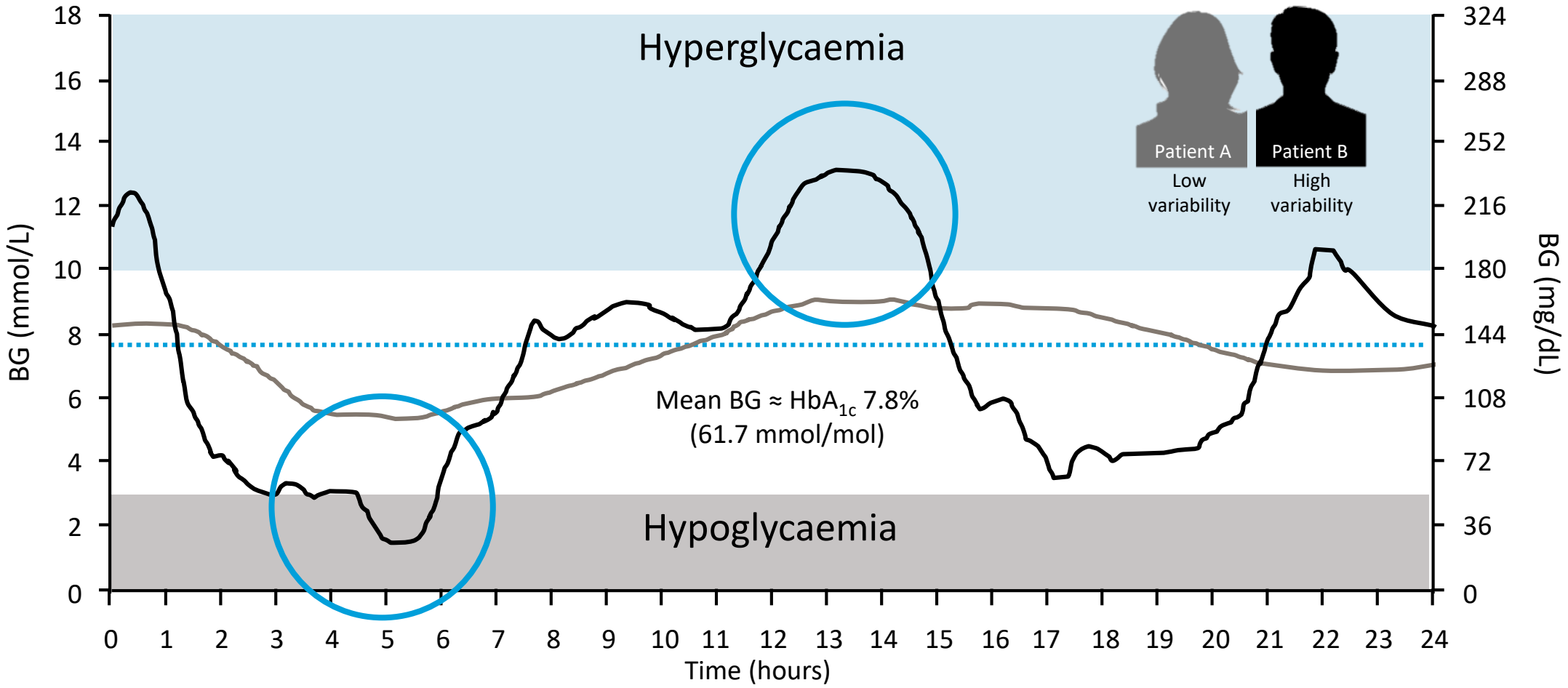
Desouza *et al. Diabetes Care* 2010;33:1389–94;

Driesen *et al. J Neurosci Res* 2007;85:575–82;

Mooradian. *Brain Res Brain Res Rev* 1997;23:210–8;

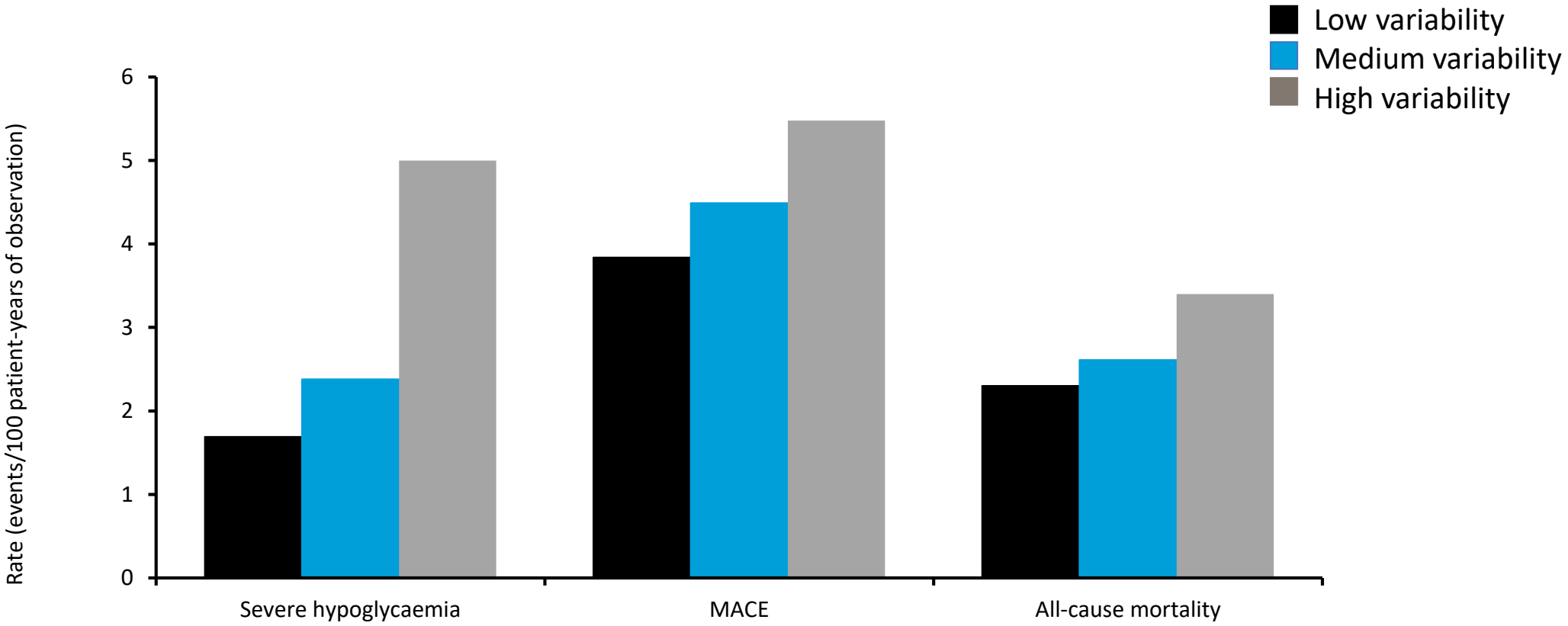
Sanon *et al. Clin Cardiol* 2014;37:499–504; Dhalla *et al. J Hypertens* 2000;18:655–73

Glycaemic control: similar A_{1c}, different profile



Diabetes Technol Ther 2012;14:303–10; Vora & Heise. *Diabetes Obes Metab* 2013;15:701–12

Outcomes by variability tertile



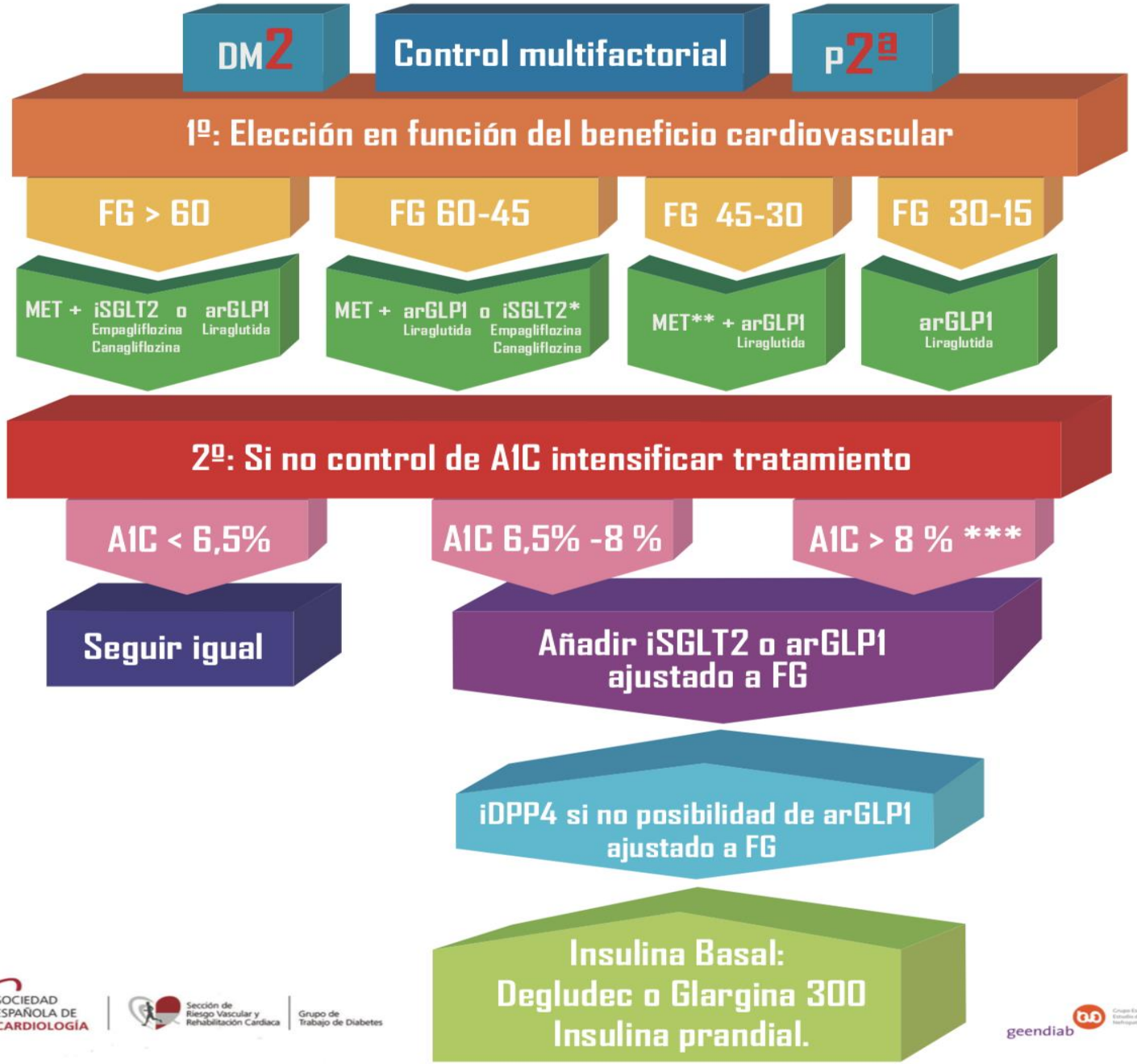
MACE, major adverse cardiovascular events

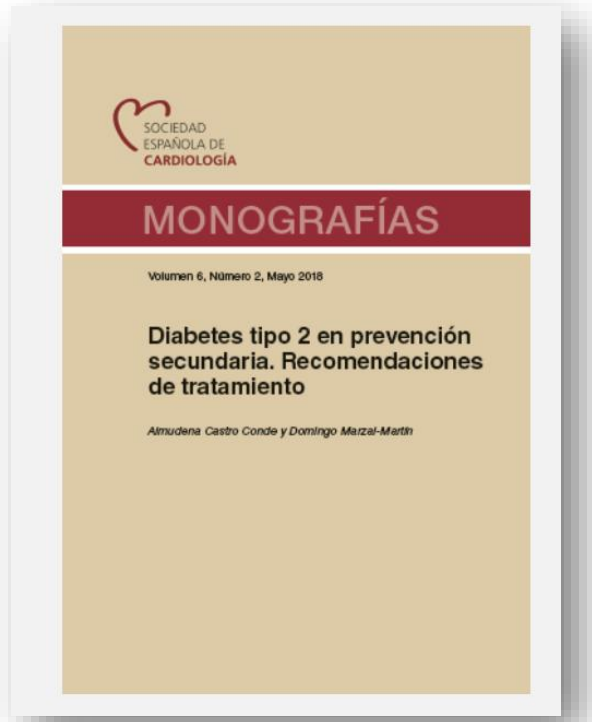
Diabetologia. 2017 Sep 15. doi.org/10.1007/s00125-017-4423-z

	Reducción de mortalidad en cardiopatía isquémica
Aspirina	15%
IECA	23 %
BB	23 %
Estatinas	29 %
Dejar de fumar	**36%**
Empagliflozina	**38%**
Liraglutida	**22%**

Critchley JA, Capewell S. *JAMA*; 2003 ; 290: 86-97.

Zinman B N Engl J Med 2015; 373:2117-2128
Marso S et al; N Engl J Med 2016; 375:311-322





Castro A, Marzal D et al.. SEC Monogr. 2018;6 (2):19-23