“Aportación de los agonistas del receptor de GLP-1 más allá del control glucémico”

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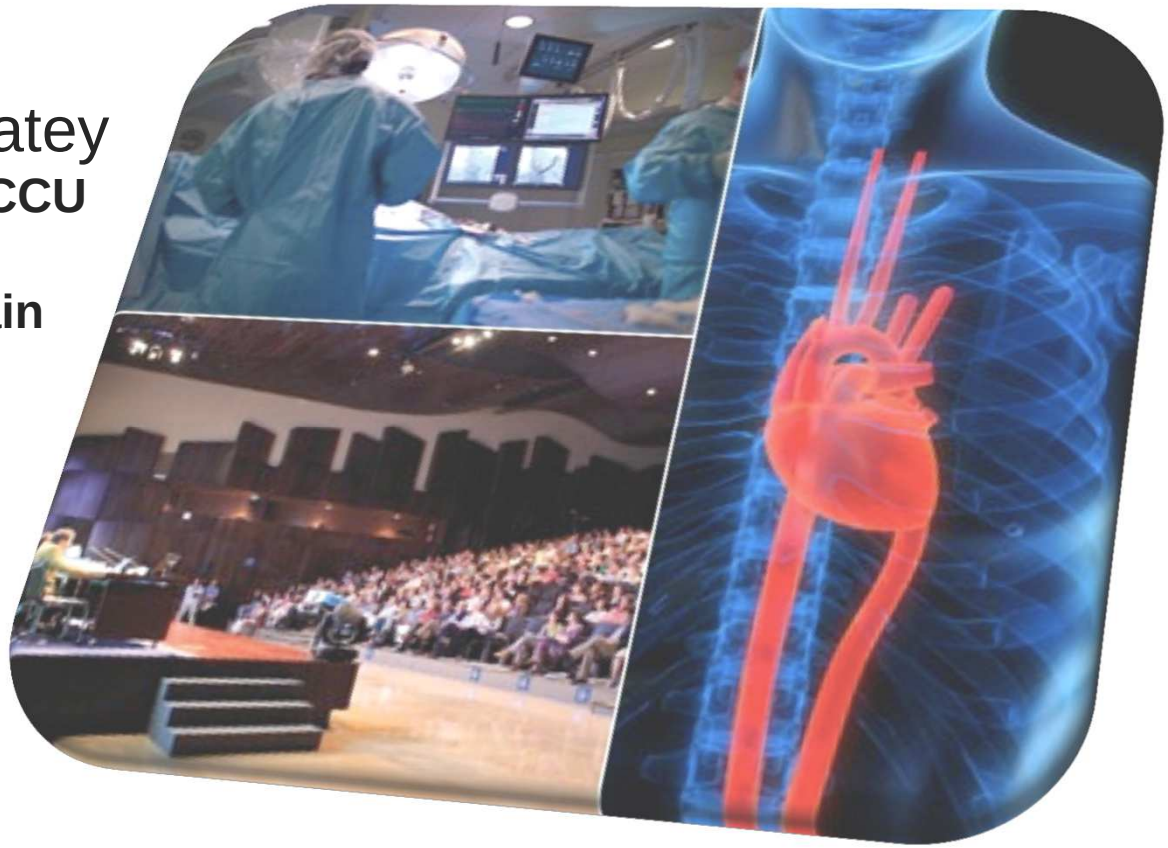


Disclosures:

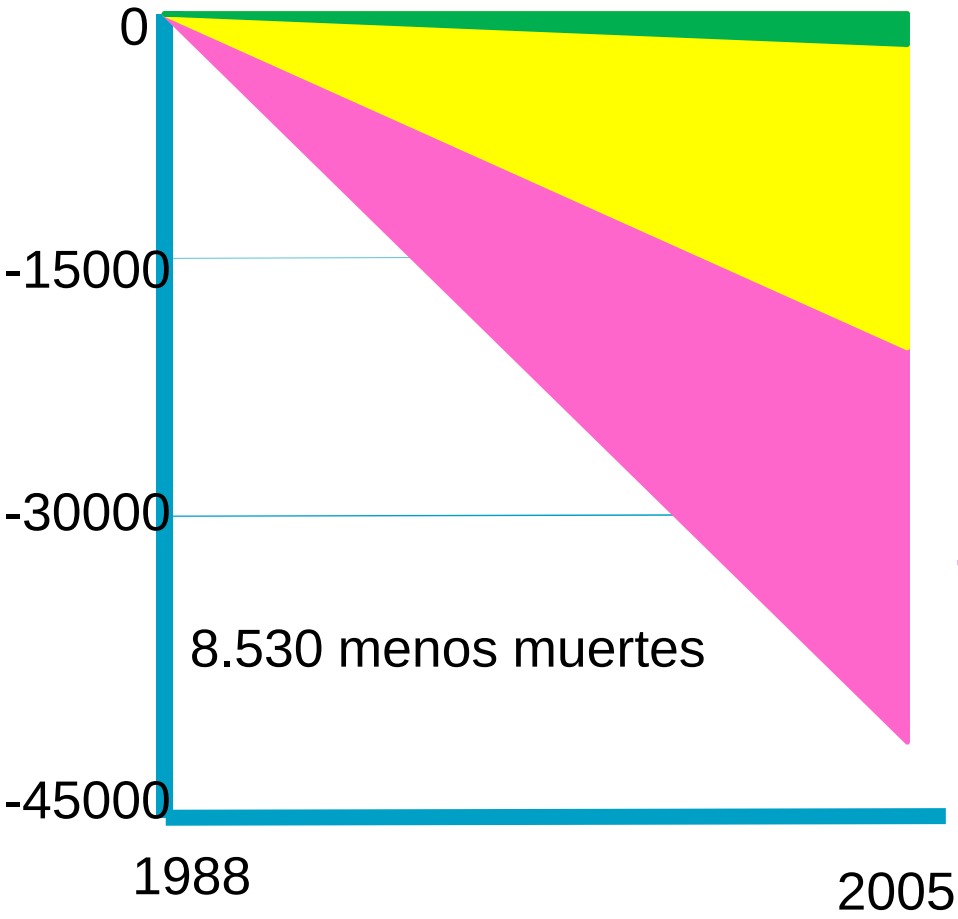
Research Grants: AZ, Boehringer Ingelheim, Pfizer, Novartis, Daichii-Sankyo, Sanofi, Bayer, MSD, Servier, Ferrer

Consultant/Honorarium. AZ, Boehringer-Ingelheim, Bayer, Pfizer, BMS, MSD, Daichii-Sankyo, Servier, Menarini; Ferrer

GLP1-Agonistas. Efectos Extraglucemicos

- Antidiabéticos y enfermedad CV
- Agonistas GLP1 y Riesgo CV
- Agonistas GLP1, Frecuencia cardíaca y Riesgo CV

Explicación de la caída en muerte CV en España: 1988-210



Empeoramiento factores de riesgo +13%

•Aumento de obesidad +6%

•Aumento de diabetes +7%

Mejora de factores de riesgo -54%

•Mejora en la PA -19%

•Reducción del tabaco -16%

•Mejora colesterol -27%

•Actividad física -2%

Tratamientos farmacológico -48%

•Para IAM -10%

•Prevención secundaria -10%

•Insuficiencia cardiaca -10%

•Revascularización -2%

•Antihipertensivos -5%

•Estatinas (p. primaria) -2%

Inexplicables -2%

Estudio IMPACT -2014 (datos presentados en el congreso ESC 2014)

Tratamiento de la Diabetes

¿Qué esperamos de un NUEVO antidiabético?

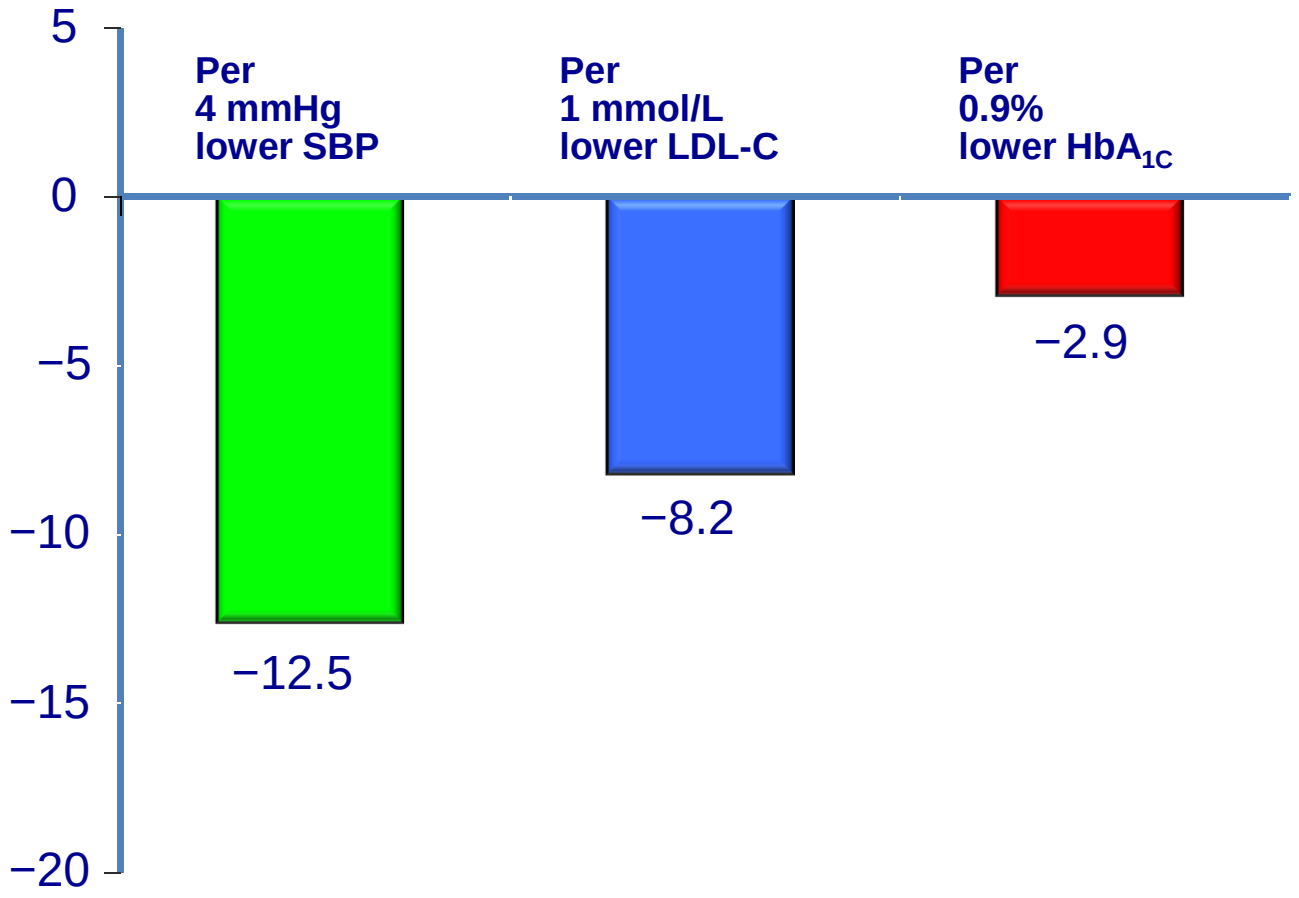
Eficacia:

- Mecanismo “fisiológico” de redución de la glucemia
- Preservar la función pancreatica
- Efectos “extra-glucémicos” / Peso (grasa)
- Protección frente:
  1. Enf. Macrovascular
  2. Enf. Microvascular
  3. Nefropatía
  4. Neuropatía

Seguridad:

- Hipoglucemias
- Pancreatitis
- Insuficiencia cardíaca
- MACE, …

Benefit of different interventions on CV risk per 1000 diabetic patients treated for 5 years



Adapted from: Preiss D, Ray KK. *BMJ* 2011;343:d4243.

ADA/EASD 2012 Position Statement: 2-Drug Combinations

Metformin +	SU*	TZD	DPP-4 Inhibitor	GLP-1 RA	Insulin (usually basal)
Efficacy (↓ HbA1c)	High	High	Intermediate	High	Highest
Hypoglycemia	Moderate risk	Low risk	Low risk	Low risk	High risk
Weight	Gain	Gain	Neutral	Loss	Gain
Major side effect	Hypoglycemia	Edema, CHF, fractures	Rare	GI	Hypoglycemia
Costs	Low	High	High	High	Variable
If needed to reach individualized HbA1c target after ~3 months, proceed to 3-drug combination (order not meant to denote any specific preference)					

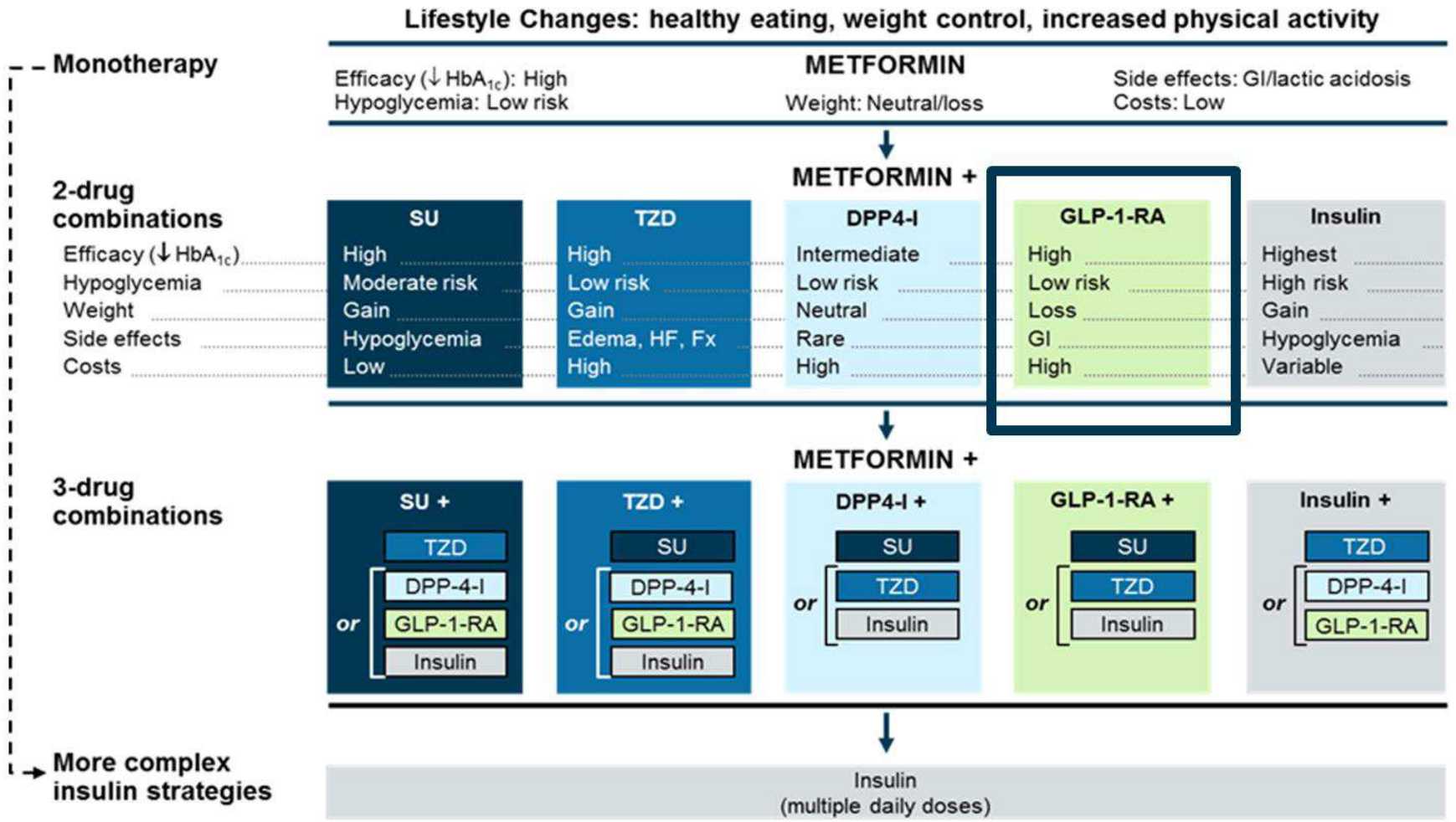
Appropriate class selection is based on specific patient requirements.

*Consider glinides as alternative

CHF = congestive heart failure; GI = gastrointestinal; GLP-1RA = glucagon-like peptide-1 receptor agonist; SU = sulfonylurea; TZD = thiazolidinedione

Adapted from Inzucchi SE, et al. *Diabetologia*. 2012;55(6):1577-1596.

ADA/EASD 2012 Recommendations for Antihyperclycemic Therapy



Inzucchi SE, et al. Diabetes Care. 2012;35:1364-1379.[4] Copyright and all rights reserved. Material from this publication has been used with the permission of American Diabetes Association.[4]

Consequences of the new guidelines. Ongoing trials with CV outcomes

Class	Trial	Drug	n
GLP-1 RA	T-emerge*	Taspoglutide	2,118
	REWIND	Dalaglutide	9,622
	AWARD 1,3,5	Dalaglutide (non CV data)	≈3,000
	LEADER	Liraglutide	9,340
	ELIXA	Lixixenatide	6,000
	EXSCEL	Exenatide LAR	9,500
SGLT2 inh	DECLARE	Dapaglifozin	17,150
	CANVAS	Canaglifozin	4,330
	C-CASCADE	Empagliflozin	7,000

*In September 2010 Roche halted Phase III clinical trials due to incidences of serious hypersensitivity reactions and gastrointestinal side effects

Class	Trial	Drug	n
DPP4 inh	SAVOR Timi	Saxagliptin	16,500
	TECOS	Sitagliptin	14,000
	EXAMINE	Alogliptin	5,400
	CAROLINA	Linagliptin	6,000
	CARMELINA	Linagliptin	8,300
Dual PPAr inh	AleCardio*[2]	Aleglitazar	7,244
	AlePrevent	Aleglitazar	1,915
α glucosidase inh	ACE**	Acarbose	7,500
Insulin analog	ORIGIN***	Insulin Gar	12,500

*AleCardio trial and all other trials involving aleglitazar were recently stopped because of safety and lack of efficacy
** Impaired glucose tolerance patients

Adapted from www.clinicaltrials.gov; 2. Aleglitazar: http://www.medicalnewstoday.com/articles/263167.php

** *With results

Persistent Dilemmas in Diabetes Therapy

- No diabetic medication has demonstrated benefit in reducing major CV events
- Continued concern about safety in for diabetic agents in patients at high risk for CV events

GLP1-Agonistas. Efectos Extraglucemicos

- Antidiabéticos y enfermedad CV
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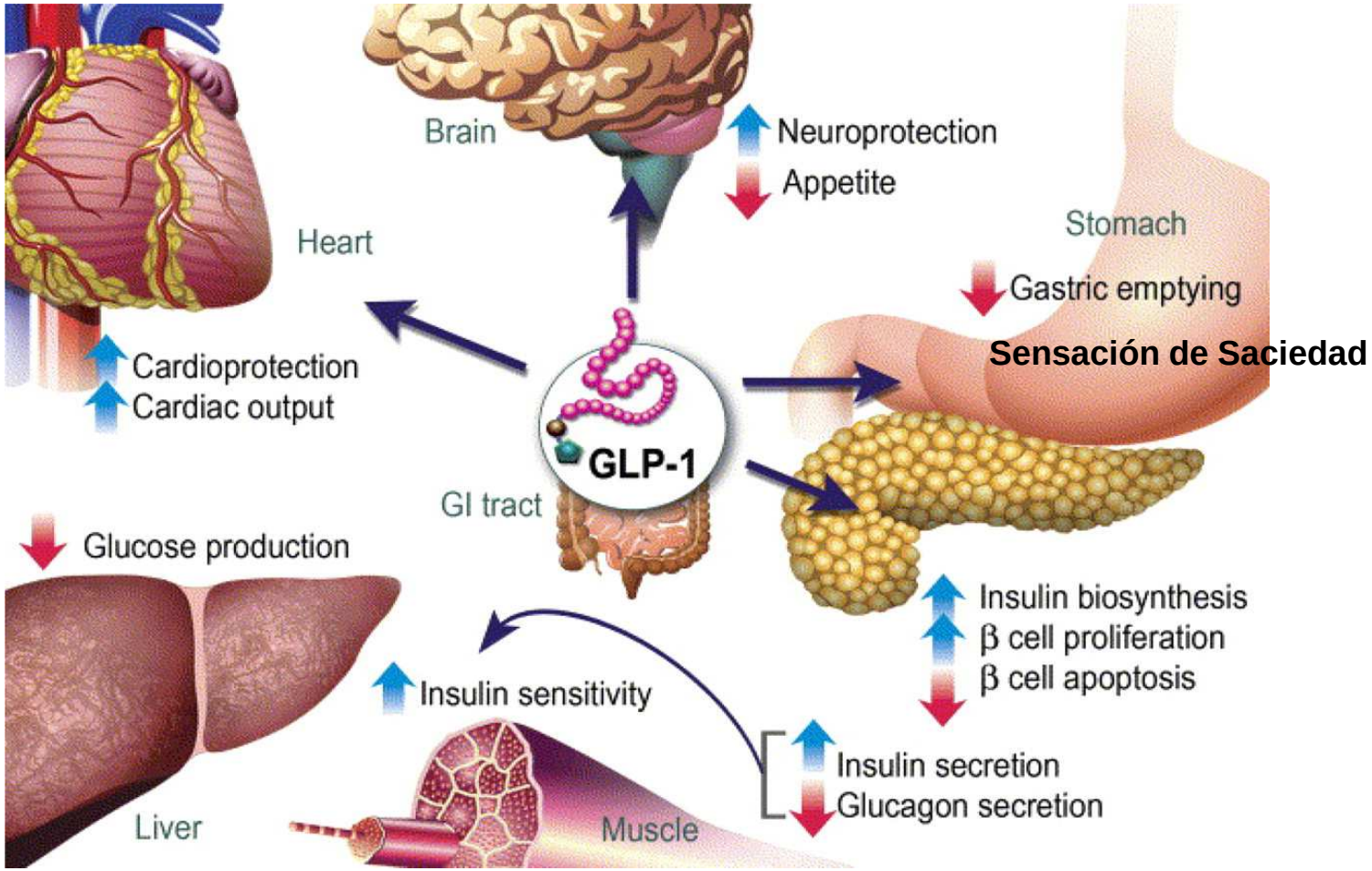
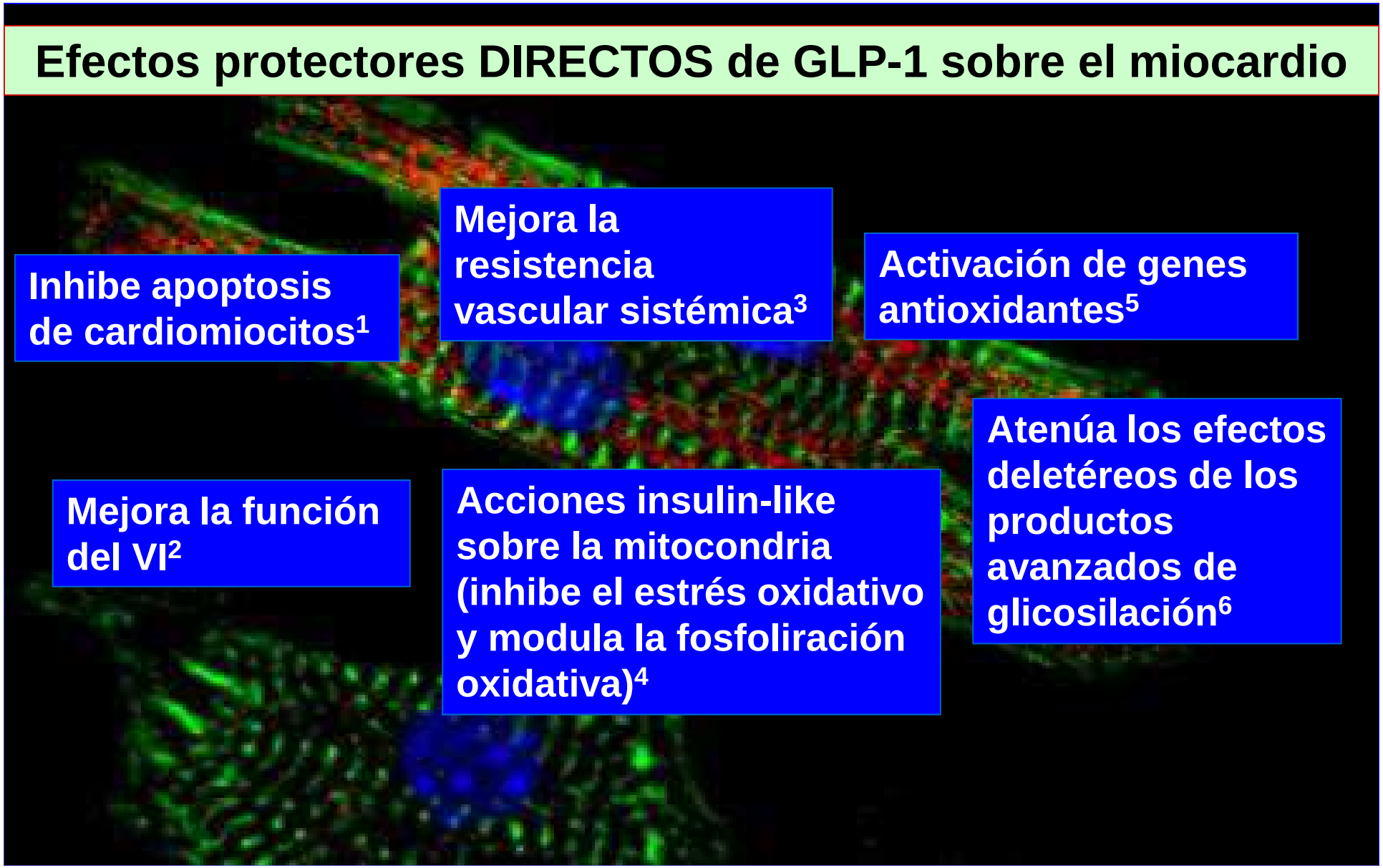
GLP1 Y RIESGO CARDIOVASCULAR

Efectos extrapancreáticos:



La mayoría de éstos efectos se han comprobado con GLP1r, exenatide o liraglutide.

Nuevos Anti-diabéticos y Enfermedad CV



Approved Antidiabetic Medications

Oral	Injectable (Subcutaneous)
Sulfonylureas Glimepiride, glipizide, glyburide	Insulins Rapid-acting, intermediate-acting, long-acting
Meglitinides Nateglinide, repaglinide	Amylin analog Pramlintide
Biguanides Metformin	GLP-1 receptor agonists/incretin mimetics **Exenatide, Liraglutide, Lixisenatide**
Thiazolidinediones Pioglitazone, rosiglitazone	
α-glucosidase inhibitors Acarbose, meglitol, voglibose	
DPP-4 inhibitors Alogliptin (Japan), linagliptin, saxagliptin, sitagliptin, vildagliptin (EU, LA)	
SGLT2 inhibitors Canagliflozin, dapagliflozin (EU)	

Putative CV Effects of Incretin-based Therapies

DPP-4 inhibitors

- Reduce glycemia including MAGE
- Have anti-inflammatory and antioxidant effects
- Reduce postprandial hyperlipidemia triglycerides, free fatty acids, apolipoprotein B-48
- Produce modest reduction in blood pressure
- Improve endothelial function (increase in flow-mediated vasodilation and number of endothelial progenitor cells)

GLP-1 Agonists

- Reduce size of myocardial infarction in animal models
- Have anti-inflammatory and antioxidant effects
- Are associated with some improvement in myocardial function
- Improve endothelial function (reduce intimal hyperplasia, platelet-derived growth factor-induced vascular smooth muscle cell proliferation; improve endothelium-dependent vasodilation)
- Produce modest reduction in blood pressure
- Reduce triglycerides, total cholesterol, low-density lipoprotein cholesterol

a. Jialal I, et al. *Atherosclerosis*. 2013;227:224-225[14]; b. Deacon CF, et al. *Cardiovasc Ther*. 2012;10:337-351.[15]

SAVOR-TIMI 53 and EXAMINE: Effect on CV Risk Factors

	Saxagliptin	Alogliptin E
Lipids	Not yet analyzed	No change
HR	No change	Not yet analyzed
SBP/DBP	No change	Not yet analyzed
Weight	No change	No change

CV Neutral

Scirica BM, et al. *N Engl J Med.* 2013;369:1317-1326.[7]
White WB, et al. *N Engl J Med.* 2013;369:1327-1335.[11]

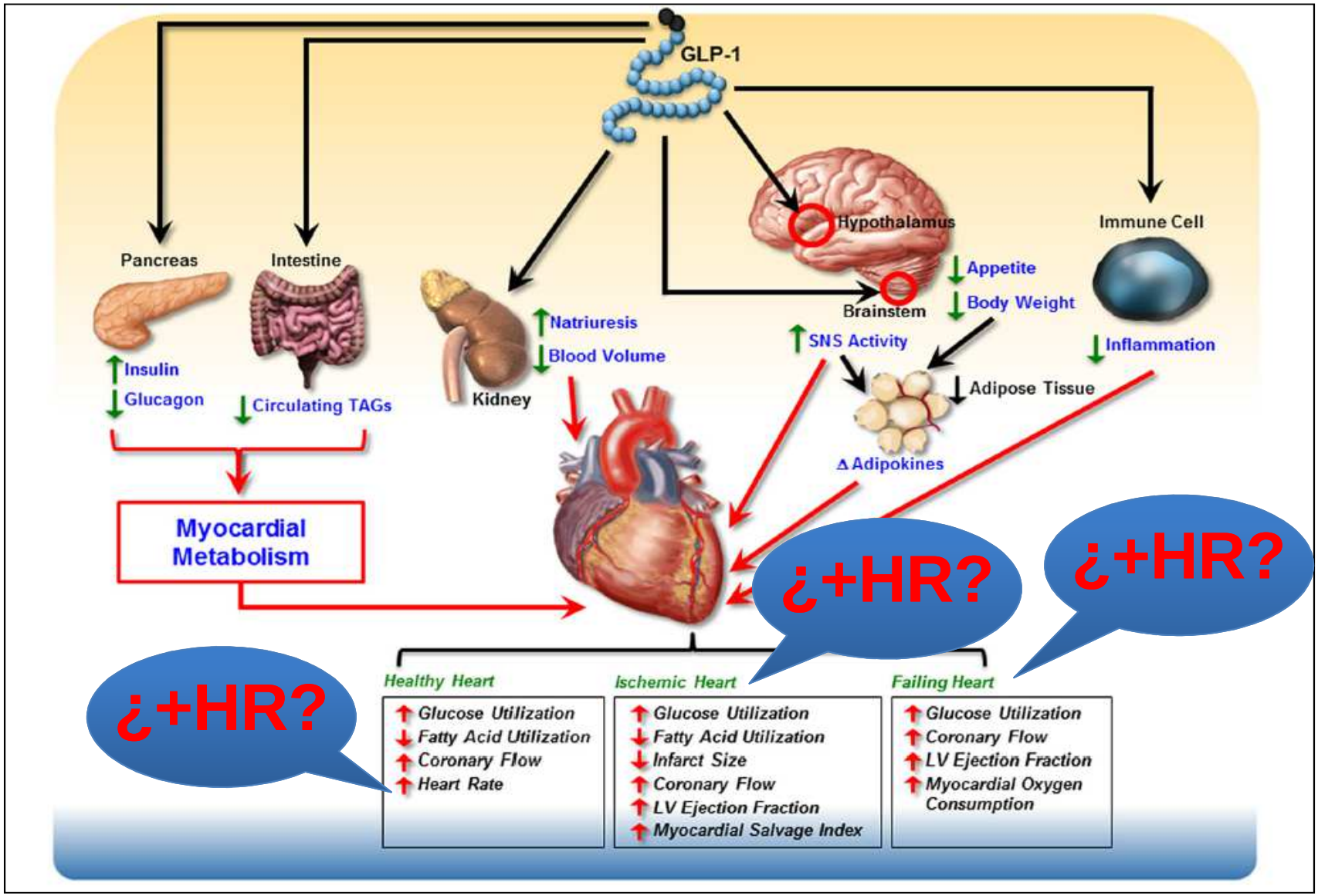
TZDs: Effects on CV Risk Factors in Patientes with T2D

- Improvement of dyslipidemia[a]
- Lowering of blood pressure[a]
- Reduction of microalbuminuria[b]
- Increase of adiponectin[a]
- Reduction of C-reactive protein[c]
- Reduction of visceral fact[a]
- Reduction of PAI-1[a]
- Reduction of matrix metalloproteinases[a]
- Reduction of carotid intima-media thickness[a]
- Reduction of coronary stent restenosis[d]

Increased Risk of:
Heart Failure
Myocardial Infarction

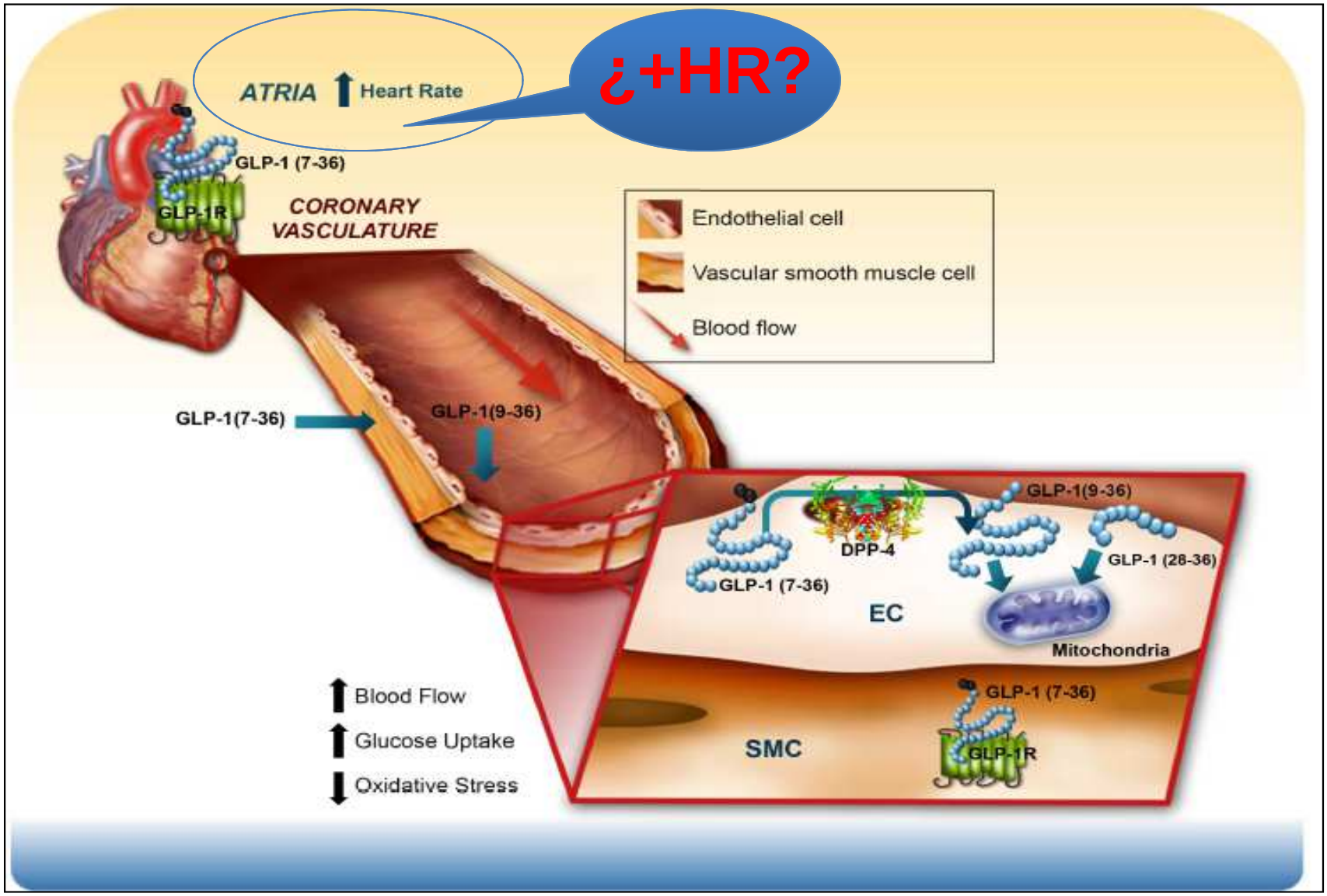
a. Martens F, et al. *Drugs*. 2002;62:1463-1480.[12]
b. Sarafidis PA, et al. *Am J Kidney Dis*. 2010;55:835-847.[13]
c. Kahn SE, et al. *Diabetes Care*. 2010;33:177-183.[14]
d. Geng D, et al. *Atherosclerosis*. 2009;202:521-528.[15]

Potential indirect cardiovascular effects of glucagon-like-1 receptor (GLP-1) agonists



Ussher J., et al. **Cardiovascular Actions of Incretin-Based Therapies.** Circ Res. 2014 May 23;114(11):1788-803

Actions of glucagon-like peptide-1 (GLP-1) and GLP-1 receptor (GLP-1R) agonists on the atria and vasculature



Ussher J., et al. **Cardiovascular Actions of Incretin-Based Therapies.** Circ Res. 2014 May 23;114(11):1788-803

GLP1-Agonistas. Efectos Extraglucemicos

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- Agonistas GLP1, Frecuencia cardíaca y Riesgo CV

Seguridad y tolerabilidad entre lixisenatida y liraglutida
Diferencias en la variación de la frecuencia cardíaca

- La **frecuencia cardiaca** se midió en decúbito supino a las 24h tras la última administración del estudio (día 29)
  - Con *lixisenatida disminuyó 3,6 lpm* frente a un *aumento de 5,3 lpm con liraglutida*, con una **diferencia neta de 8,9 lpm que fue estadísticamente significativa**.

	Lixisenatide (n = 77)	Liraglutide (n = 71)
Adverse event (AE), n (%)		
Any AE	45 (58.4)	52 (73.2)
Any AE (excluding decreased appetite)	42 (54.5)	46 (64.8)
Serious AE	0	0
AE leading to death	0	0
AE leading to discontinuation	2 (2.6)	2 (2.8)
Any symptomatic hypoglycaemia*	0	0
Gastrointestinal disorders (any)	28 (36.4)	33 (46.5)
Nausea	17 (22.1)	16 (22.5)
Dyspepsia	6 (7.8)	12 (16.9)
Diarrhoea	2 (2.6)	11 (15.5)
Abdominal distension	5 (6.5)	9 (12.7)
Vomiting	8 (10.4)	5 (7.0)
Vital sign measurements		
Δ heart rate, bpm [mean (95% CI)]†	−3.6 (−5.8, −1.3)	5.3 (2.9, 7.7)
Treatment difference, mmHg (95% CI)	−8.9 (−12.2, −5.6)	
Δ ECG heart rate, bpm [mean (95% CI)]†	−3.4 (−5.6, −1.2)	5.9 (3.6, 8.2)
Treatment difference, mmHg (95% CI)	−9.3 (−12.5, −6.1)	
Δ SBP, mmHg [mean (95% CI)]†	−2.0 (−4.9, 0.8)	−2.8 (−5.9, 0.2)
Treatment difference, mmHg (95% CI)	0.8 (−3.3, 5.0)	
Δ DBP, mmHg [mean (95% CI)]†	−0.6 (−2.2, 1.1)	1.1 (−0.7, 2.8)
Treatment difference, mmHg (95% CI)	−1.7 (−4.1, 0.7)	

Christoph Kapitza et cols. DOI: 10.1111/dom.12076. *Diabetes, Obesity and Metabolism* 2013.

PDY10931 – Resumen de las modificaciones de parámetros CV

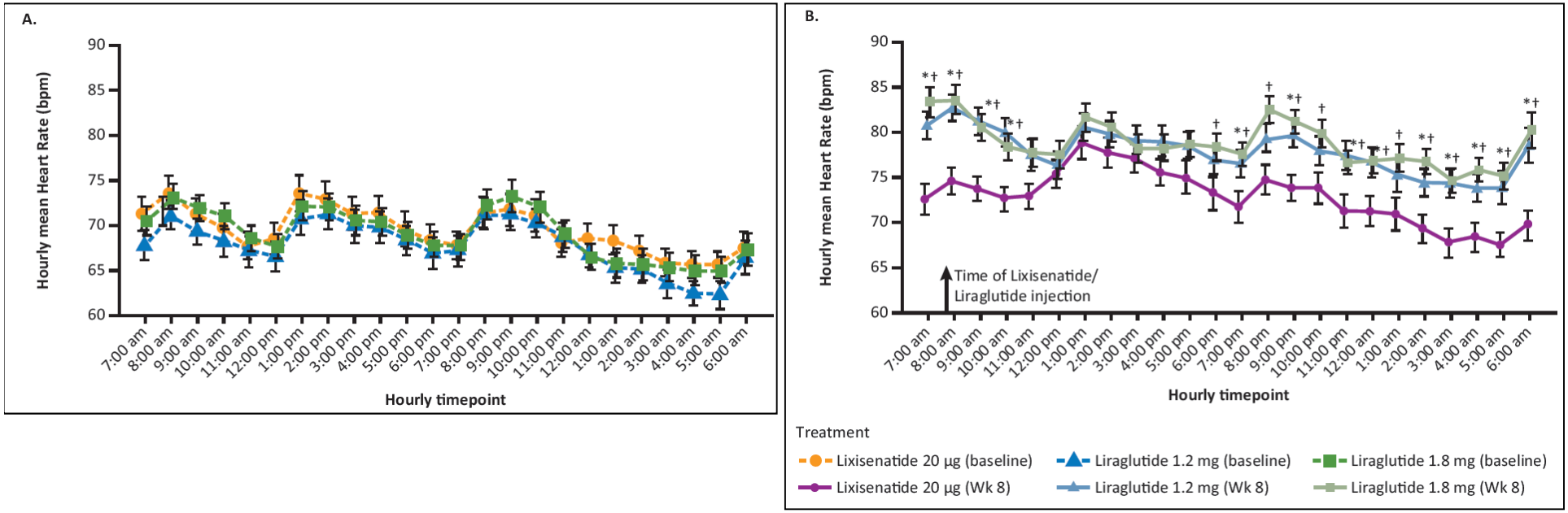
	Lixisenatide			Liraglutide			Lixisenatide vs. liraglutide	
	N	Cambio medio	95% CI	N	Cambio medio	95% CI	Diferencia media	95% CI
Frecuencia cardíaca (lpm)	76	-3.57	(-5.81 to -1.32)	68	5.31	(2.93 to 7.69)	-8.87	(-12.15 to -5.60)
PAS (mmHg)	76	-2.01	(-1.87 to 0.84)	68	-2.84	(-5.86 to 0.18)	0.83	(-3.33 to 4.98)
PAD (mmHg)	76	-0.58	(-2.22 to 1.07)	68	1.07	(-0.67 to 2.81)	-1.65	(-4.05 to 0.74)

	Lixisenatide			Liraglutide			Lixisenatide vs. liraglutide	
	N	Cambio medio	95% CI	N	Cambio medio	95% CI	Diferencia media	95% CI
Frec. Cardíaca por ECG	76	-3.41	(-5.59 to 1.22)	68	5.91	(3.60 to 8.22)	-9.32	(-12.50 to -6.14)

Source: www.clinicaltrial.gov NCT01175473, IDF 2011 D-0740, Sanofi-confidential data

GLP1: safety and tolerability – *CV (safety population)*

Secondary Endpoints: Heart Rate and Blood Pressure (mITT Population)



- **Increases in Heart Rate from baseline were significantly greater with Liraglutide 1.2 and 1.8 mg than with Lixisenatide (9.3 and 9.2 bpm vs 3.3 bpm, respectively; p<0.0001)**
- **At Week 8, SBP was slightly decreased from baseline with Liraglutide 1.8 mg and DBP was slightly increased with Liraglutide 1.2 and 1.8 mg**

Statistical tests compared treatment arms at each timepoint at Week 8
*p<0.05 for Liraglutide 1.2 mg versus Lixisenatide 20 µg; †p<0.05 for Liraglutide 1.8 mg versus Lixisenatide 20 µg
bpm=beats per minute; mITT=modified intent-to-treat; SEM=standard error of the mean

GLP1: safety and tolerability – *CV (safety population)*

Nighttime mean Heart Rate

Mean 24hr Heart Rate (bpm)	Lixisenatide (n=42)	liraglutide 1.2 mg (n=43)	liraglutide 1.8 mg (n=44)
At baseline	**67.1**	**65.1**	**66.2**
At Week 8	**69.7**	**75.7**	**76.7**
LS Change from baseline (Mean, SE)	**2.20 (1.47)**	**9.97 (1.37)**	**10.12 (1.45)**
LS mean difference (SE) vs lixisenatide		**7.78 (1.26)**	**7.92 (1.24)**
Difference vs lixisenatide: p-value		**<0.0001**	**<0.0001**

- Treatment difference was more pronounced during nighttime vs daytime (+ 2 bpm)

GLP1: safety and tolerability – *CV (safety population)*

- Supine heart rate (measured 24 hours after the last study drug administration on Day 29) had decreased from baseline for lixisentide *vs* an increase for liraglutide (mean = -3.6 beats/min *vs* mean = 5.3 beats/min respectively) resulting in a mean difference of 8.9 beats/min
- Mean changes in SBP and DPB were comparable between the two groups

Vital sign measurements	Lixisenatide (n=77)	Liraglutide (n=71)
Δ Heart rate, bpm (mean [95% CI])†	-3.6 [5.8, -1.3]	5.3 [2.9, 7.7]
Treatment difference, mmHg [95% CI]	-8.9 [-12.2, -5.6]	
Δ ECG heart rate, bpm (mean [95% CI])†	-3.4 [5.6, -1.2]	5.9 [3.6, 8.2]
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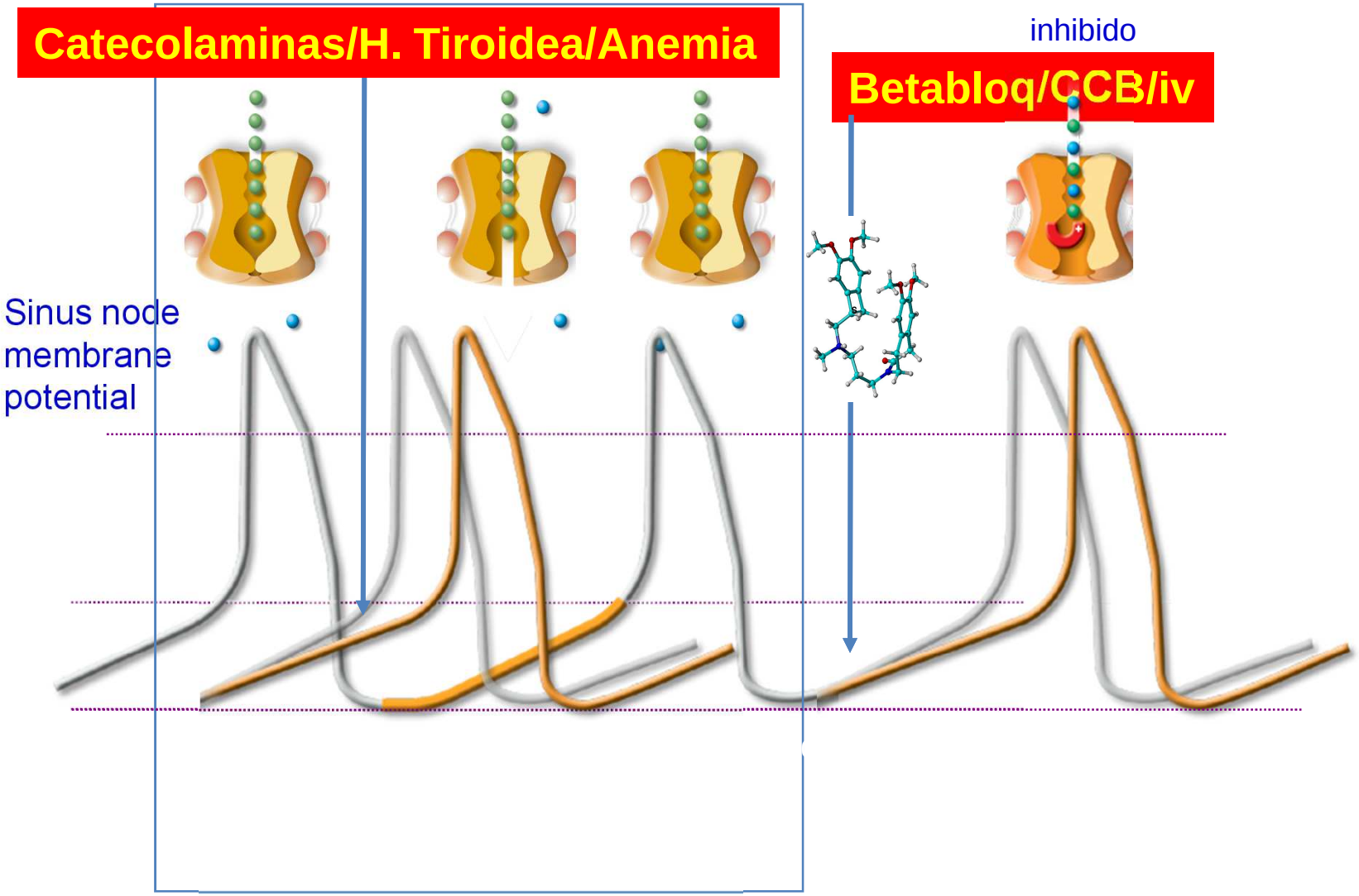
Treatment difference, mmHg [95% CI]	0.8 [-3.3, 5.0]	
Δ DBP, mmHg (mean [95% CI])†	-0.6 [-2.2, 1.1]	1.1 [-0.7, 2.8]
Treatment difference, mmHg [95% CI]	-1.7 [-4.1, 0.7]	

SBP = systolic blood pressure; DBP = Diastolic blood pressure; bpm = beats per minute;
ECG = electrocardiogram
†All measurements taken in the supine position (n=76 for lixisenatide; n=68 for liraglutide)
Δ = change from Day -2 (baseline) to Day 29

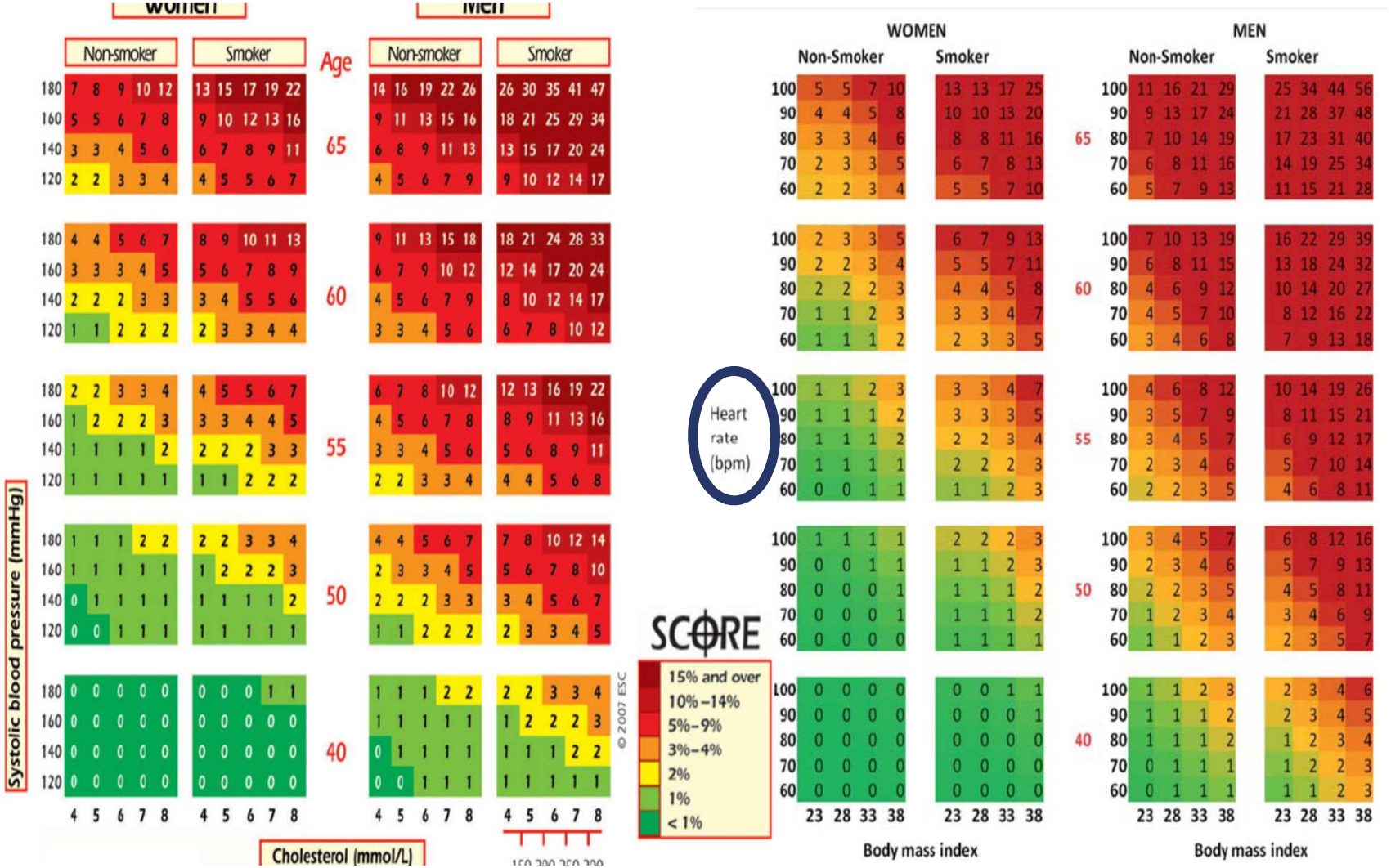
Automatismo Sinusal determinante de la FC



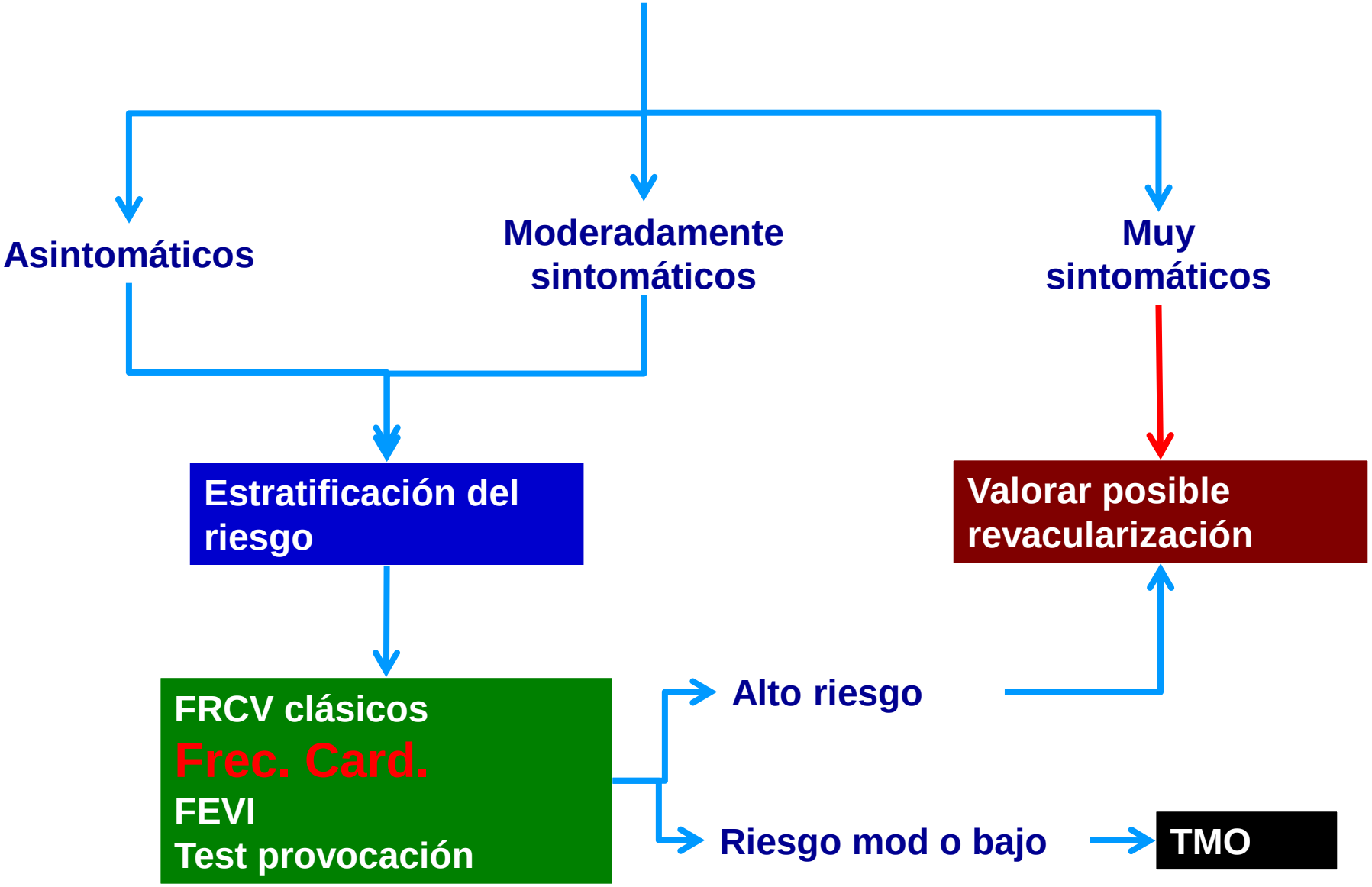
Partening with the Patient

Inzucchi SE, et al. *Diabetes Care*. 2012;35:1364-1379.[4]

Simplifying cardiovascular risk estimation using *resting heart rate*



Pacientes con AE y CI crónica



Prognostic importance of resting heart rate: epidemiological evidence (in general population and hypertensives)

Study	Population	Follow-up	Cardiovascular mortality	RR
Chicago Gas Company '80	1 233 M	15 y	>94 vs. ≤60 bpm	2.3
Chicago Heart Ass. Project '80	33 781 M&W	22 y	≥90 vs. <70 bpm	M: 1.6 W: 1.1 (ns)
Framingham '93	4 530 M&W HTN	36 y	>100 vs. <60 bpm	M: 1.5 W: 1.4 (ns)
British Regional Heart '93	735 M	8 y	>90 vs. ≤ 90 bpm	IHD death 3.3
Spandau '97	4 756 M&W	12 y	Sudden death	5.2 per 20 bpm
Benetos '99	19 386 M&W	18.2 y	>100 vs. <60 bpm	M: 2.2 W: 1.1 (ns)
Castel '99	1 938 M&W	12 y	5th vs. 3rd quintile	M: 1.6 W: 1.1
Cordis '00	3 257 M	8 y	≥90 vs. <70 bpm	2.0
Reunanen '00	10 717 M&W	23 y	M: 1.4 (>84 vs. <60)	W: 1.5 (>94 vs.<66)
Thomas '01	60 343 M HTN	14 y	>80 vs. ≤ 80 bpm	<55 y:1.5 >55 y:1.3
Matiss '01	2 533 M	9 y	per 20 bpm: 1.5	≥90 vs. <60 bpm: 2.7
Ohasama '04	1 780 M&W	10 y	M: 1.2 W: 1.1 (ns) per 5 bpm	
Okamura '04	8 800 M&W	16.5 y	per 11 bpm (1 SD) M: 1.3 W: 1.2	
Jouven '05	5 713 M	23 y	Sudden death from AMI	3.92 (>75 bpm)

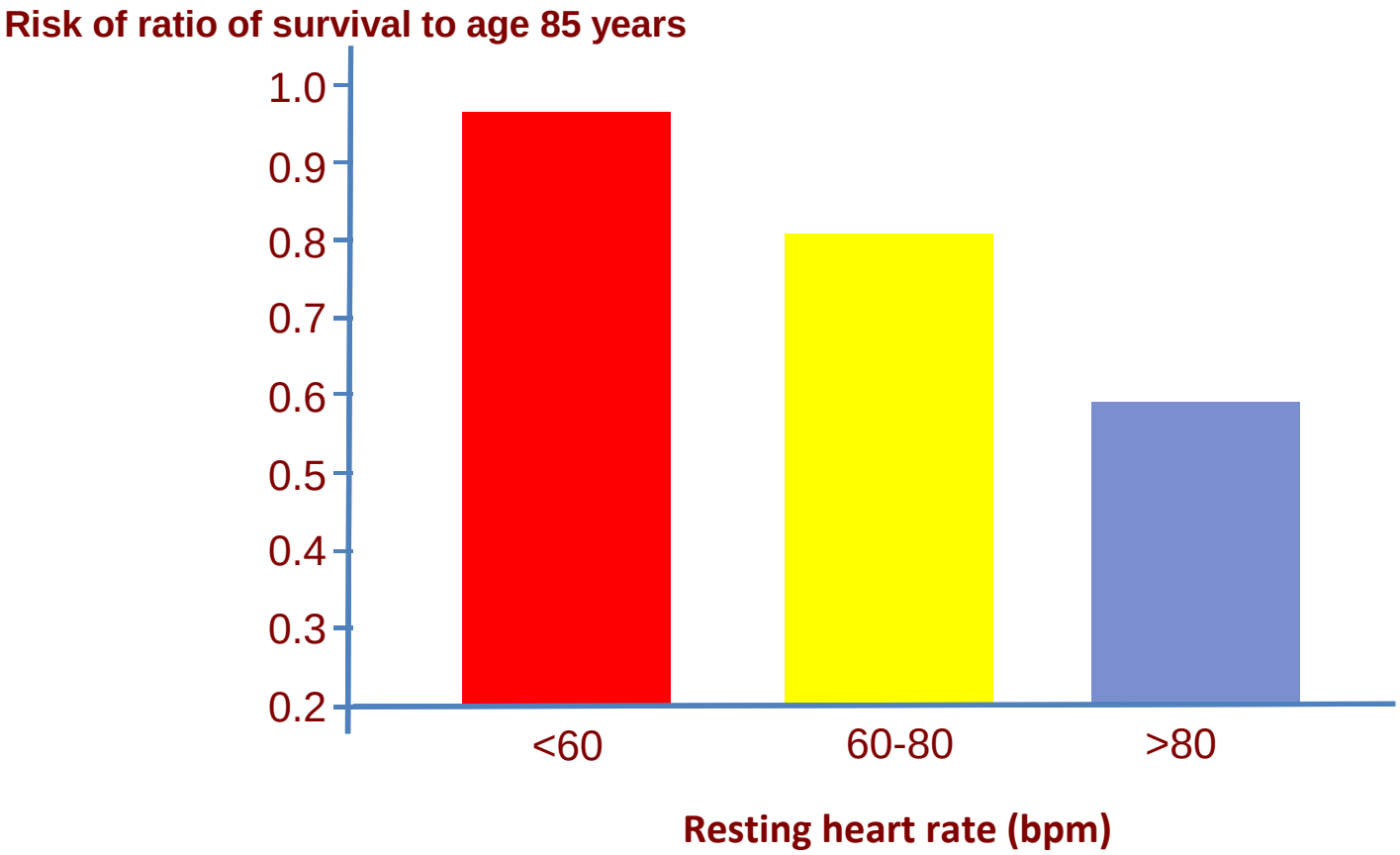
During 25 years - more than 155 000 patients, follow-up 8-36 years

Adapted from Aboyans V, et al. *J Clin Epidemiol*. 2006;59:547-558.

J.R.G. JUANATEY C.H.U.Santiago

Resting heart rate predicts survival in people aged over 65 years

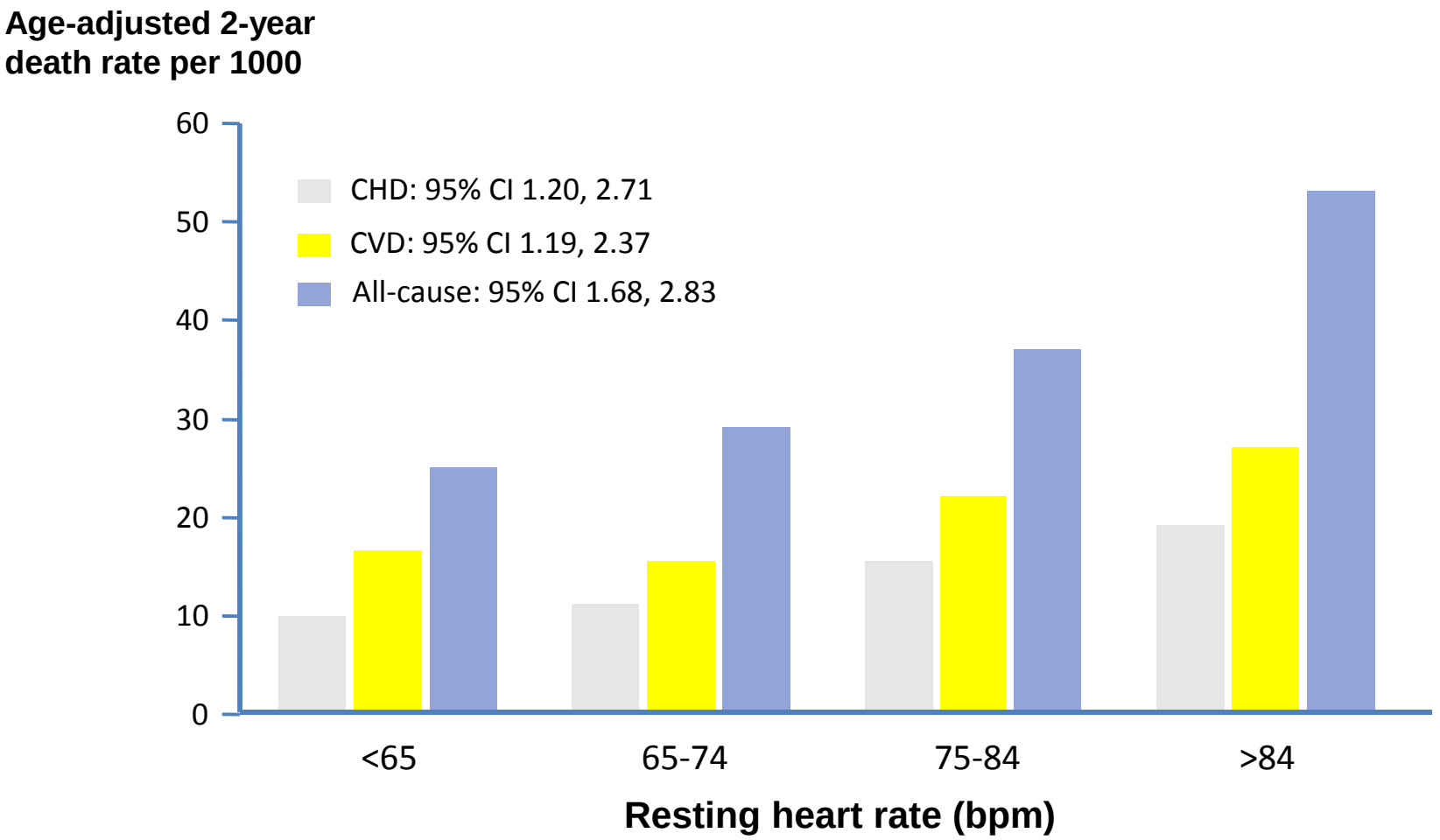
The Cohort study (n=1407)



Benetos A, et al. *J Am Geriatr Soc.* 2003;51:284-285.

All-cause mortality increases progressively with resting heart rate in men with hypertension

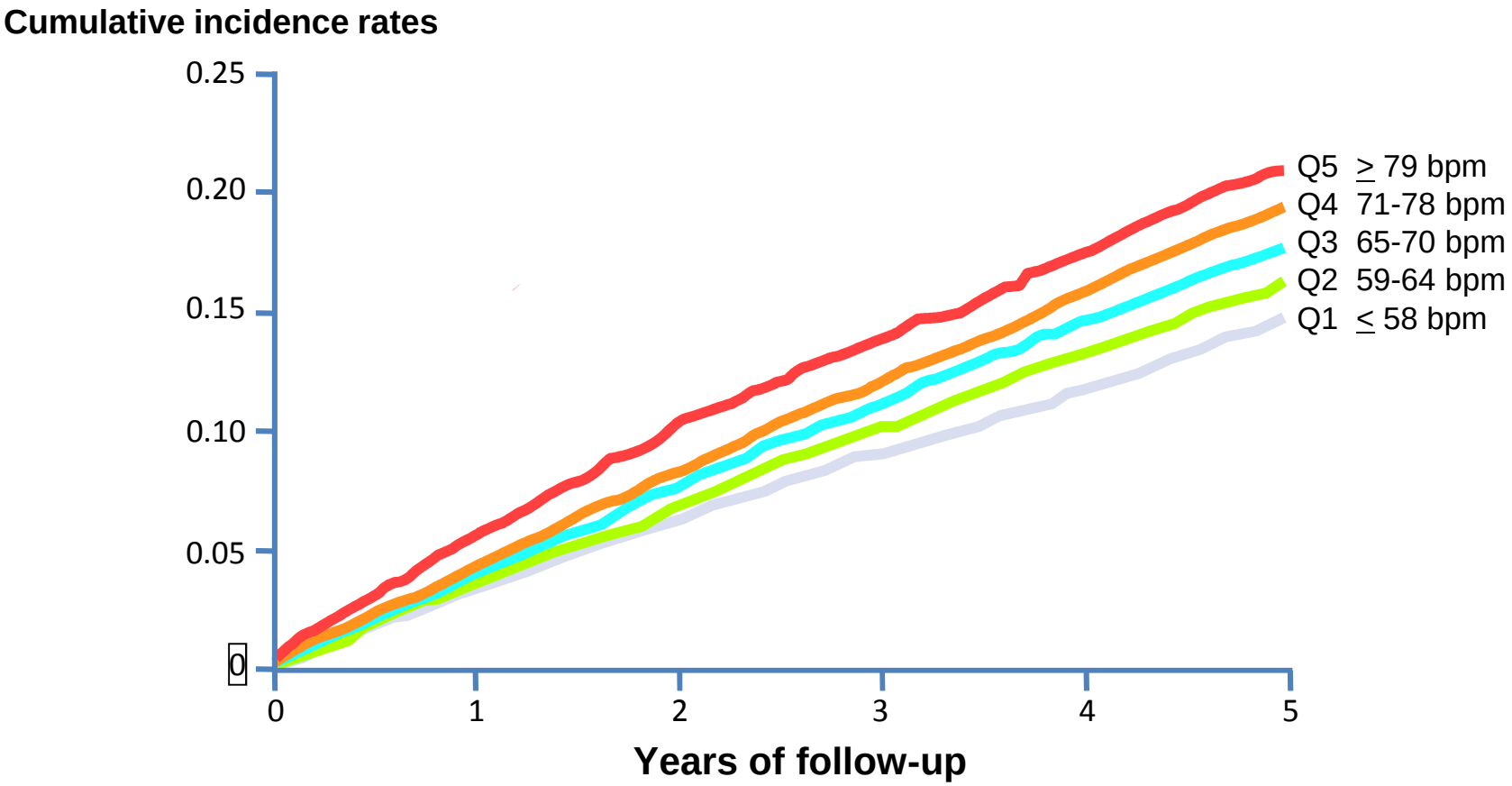
The Framingham Study (n=2037)



Gillman MW, et al. *Am Heart J.* 1993;125:1148-1154.

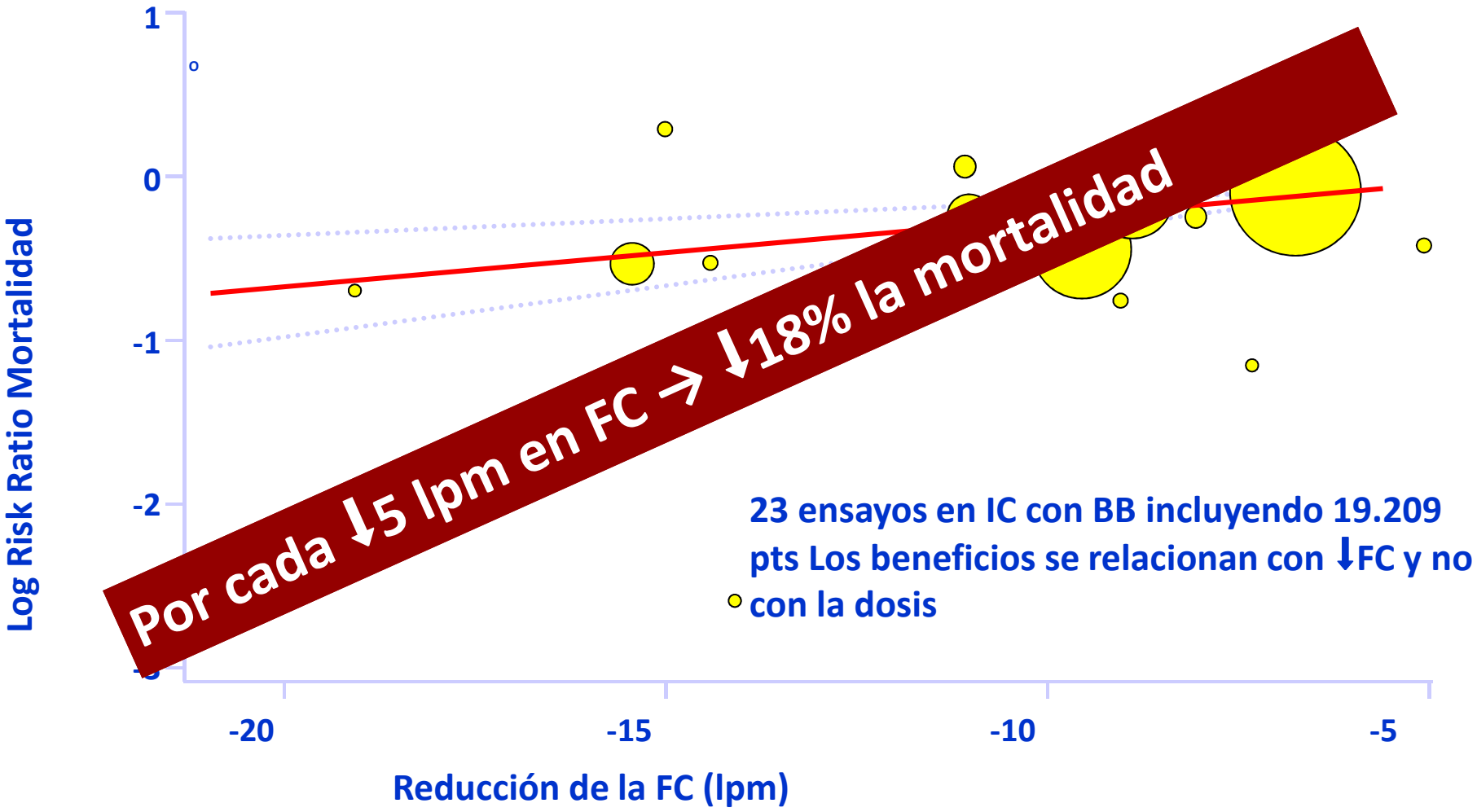
Heart rate is associated with increased risk of major CV events in Diabetes and stable CAD

The ONTARGET/TRANSCEND trial (n=31531)



Rambihar S, et al. *Circulation*. 2010;122(suppl. 21): abstract12667

Metaanálisis de ß-bloq. en ICC



McAlister et al Ann Intern Med 2009;150:784-794

El papel de la FC en la enfermedad CV

↑ Frecuencia cardiaca

Isquemia

Consumo de O_2 ↑

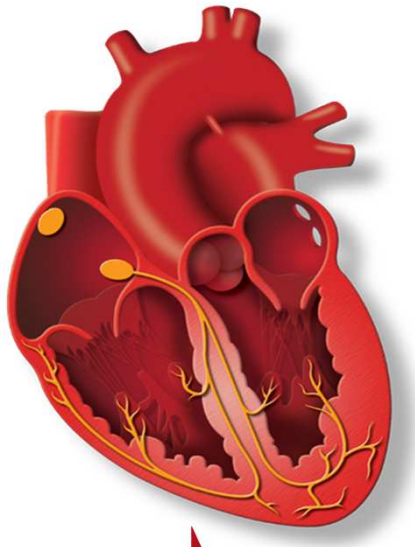
Duración diástole ↓

Perfusión coronaria ↓

Aterosclerosis

Disfunción endotelial ↑

Rotura de placa



Insuficiencia cardiaca

Demanda de O_2 ↑

Eficiencia ventricular ↓

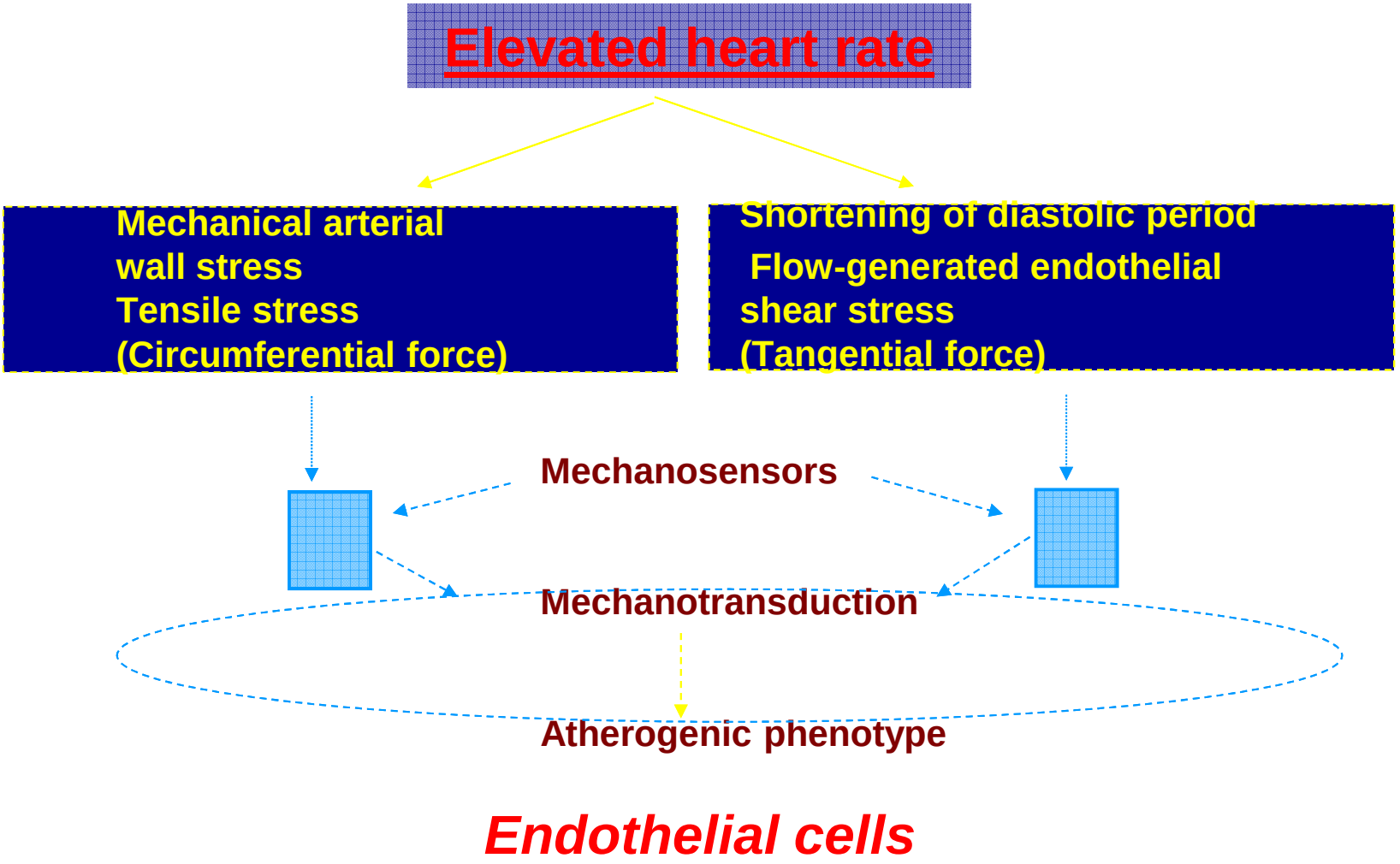
Relajación ventricular ↑

Hipertrofia cardiaca ↑

Isquemia → **Morbi-Mortalidad CV**

Corto plazo — **Largo plazo**

Putative mechanisms underlying pro-atherosclerotic effect of increasing heart rate



Adapted from Giannoglou G, et al. *Int J Cardiol*. 2008;126:302-312.

In Summary

Maximum benefit

- Treat early
- Short duration of diabetes
- Long life expectancy

Treat safely

- Avoid hypoglycemia
  - Especially severe hypoglycemia
- Agent used less impotant than goal achieved
- Individualize therapy
  - HbA1c goal

Defining a clinically relevant composite endpoint

HbA_{1c} <7.0%

+

No weight gain

+

No confirmed hypoglycaemia (minor or major)

+

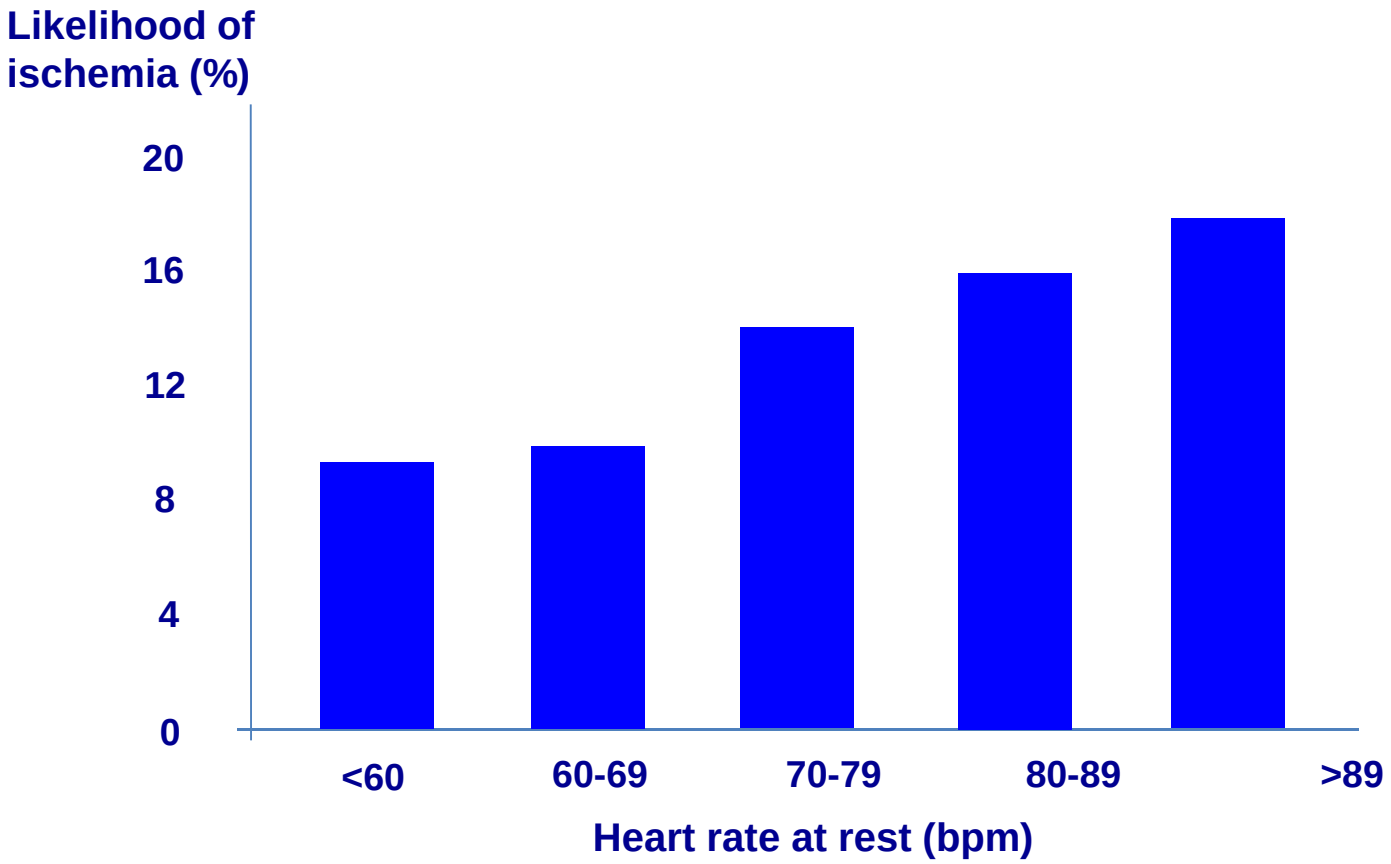
No Increase CV Risk (HR, BP, Lipids, etc)

J.R.G. JUANATEY
C.H.U.Santiago

GLP1-Agonistas. Efectos Extraglucemicos

- Antidiabéticos y enfermedad CV
- Agonistas GLP1 y Riesgo CV
- Agonistas GLP1, Frecuencia cardíaca y Riesgo CV

Heart rate as a major determinant of ischemia



Andrews TC, et al. *Circulation*. 1993;88:92-100.