8th CHALLENGES in CARDIOLOGY

Gliptins, an unquestioned role in the clinical management of patients with diabetes

Miguel Melo

Serviço de Endocrinologia, Diabetes e Metabolismo

Centro Hospitalar e Universitário de Coimbra

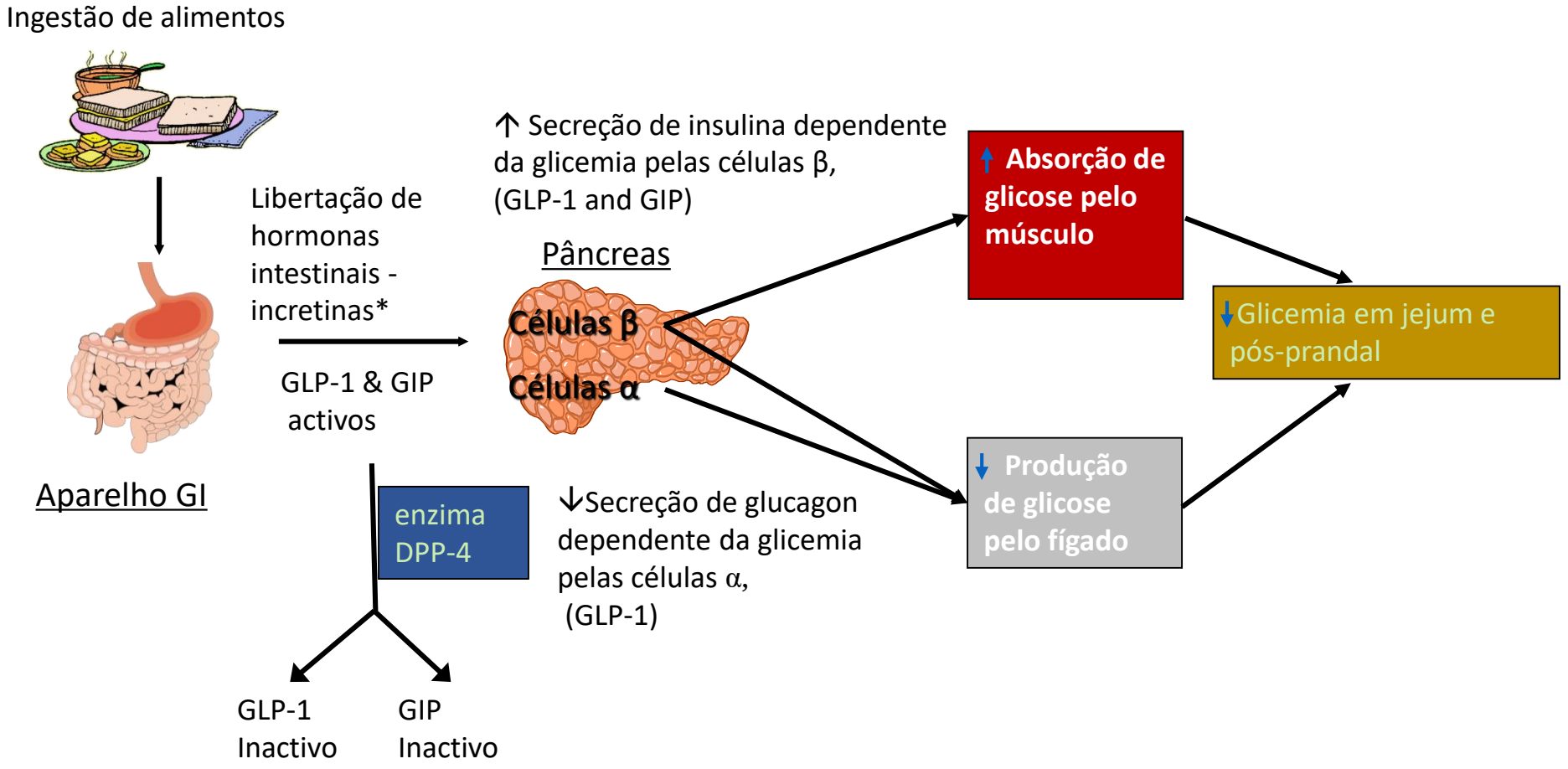
Faculdade de Medicina da Universidade de Coimbra

Overview

8th CHALLENGES in CARDIOLOGY

- Gliptins/DPP-4 inhibitors: mechanism of action
- Efficacy, tolerability and safety of Gliptins
- Role in current Guidelines
- Cardiovascular outcome trials (CVOTs)
- Special populations
- Conclusions

Incretins modulate insulin and glucagon secretion after meals



* As hormonas incretinas GLP-1 e GIP são libertadas pelo intestino ao longo do dia; os seus níveis aumentam como resposta à ingestão de uma refeição.

GLP-1=peptídeo-1 semelhante ao glucagon; GIP=peptídeo insulinotrópico dependente da glicose.

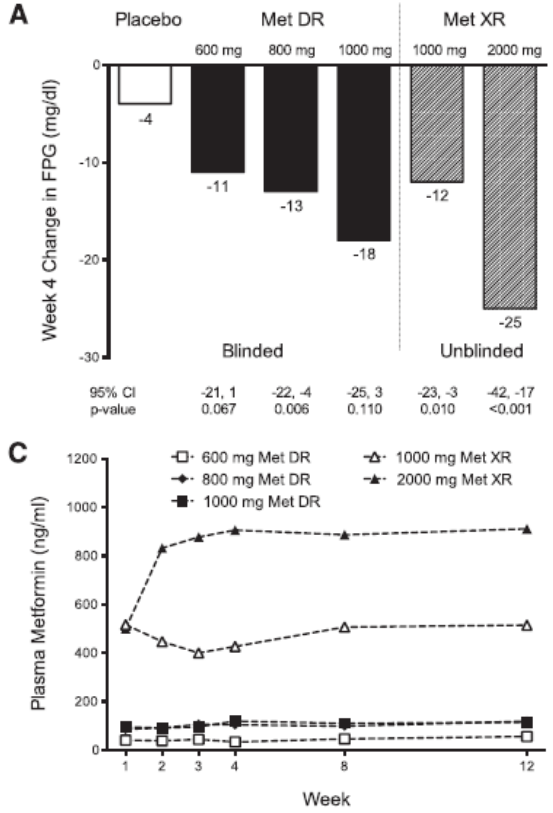
Brubaker PL et al. *Endocrinology* 2004;145:2653–2659; Zander M et al. *Lancet* 2002;359:824–930; Ahren B. *Curr Diab Rep* 2003;3:365–372; Buse JB et al. In *Williams Textbook of Endocrinology*. 10th ed. Philadelphia, Saunders, 2003:1427–1483; Drucker DJ. *Diabetes Care* 2003;26:2929–2940.

The primary glucose-lowering effect of metformin resides in the gut, not in the circulation

8th CHALLENGES in CARDIOLOGY

The Primary Glucose-Lowering Effect of Metformin Resides in the Gut, Not the Circulation. Results From Short-term Pharmacokinetic and 12-Week Dose-Ranging Studies

John B. Buse,[1] Ralph A. DeFronzo,[2] Julio Rosenstock,[3] Terri Kim,[4] Colleen Burns,[4] Sharon Skare,[4] Alain Baron,[4] and Mark Fineman[4]

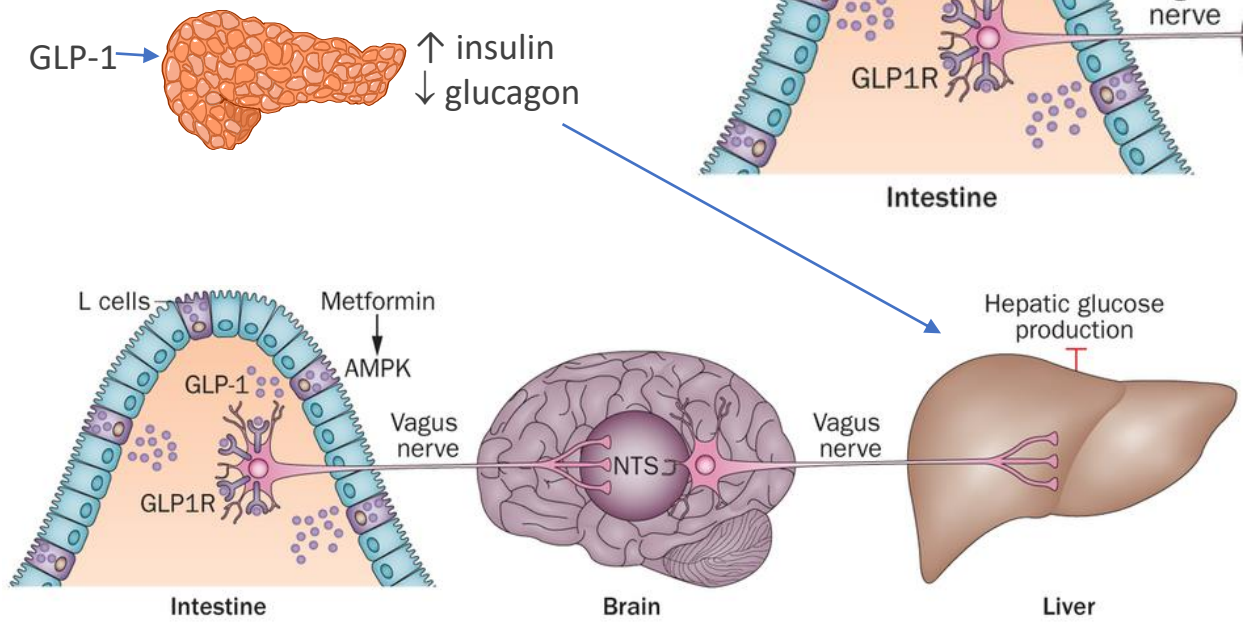


Diabetes Care. 2015 Aug 18. pii: dc150488

THERAPY

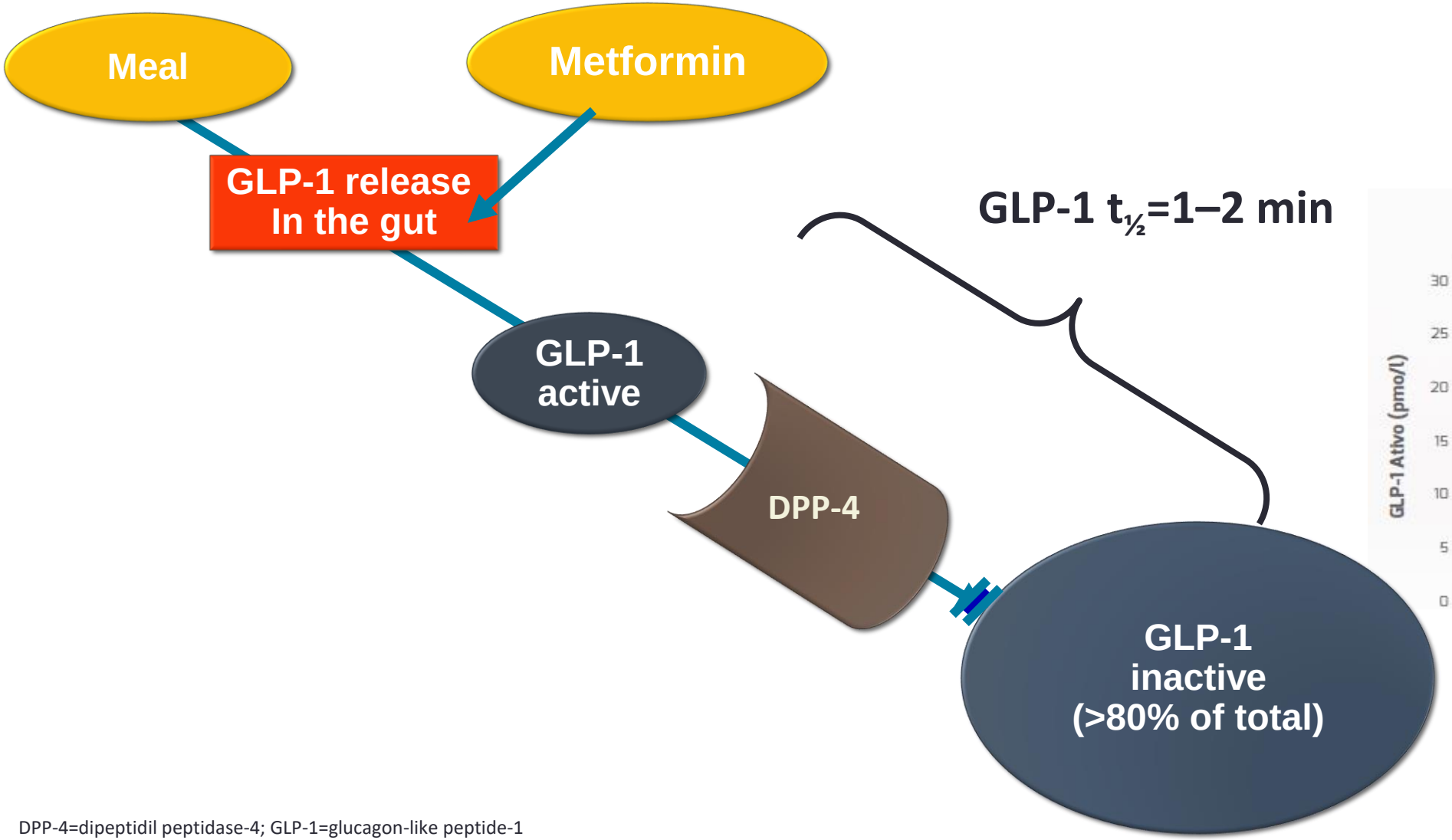
Metformin takes a new route to clinical efficacy

Marc Foretz and Benoit Viollet

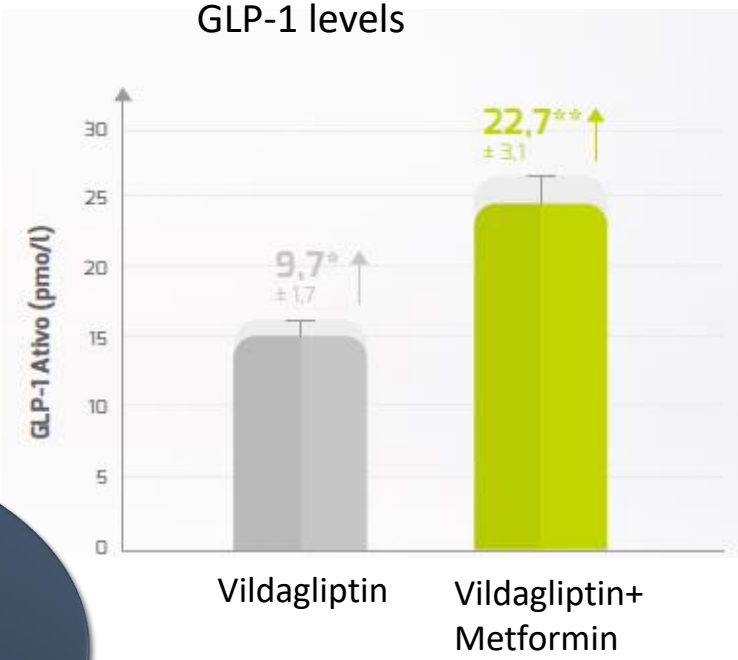


Nat. Med. 21, 506–511 (2015)
Nat Rev Endocrinol. 2015 Jul;11(7):390-2.

Sinergistic effect metformin-gliptin



Effect of vildagliptin on GLP-1 levels



DPP-4=dipeptidil peptidase-4; GLP-1=glucagon-like peptide-1

Adaptado de Rothenberg P, et al. *Diabetes*. 2000; 49(suppl 1): A39. Abstract 160-OR.

Adaptado de Deacon CF, et al. Diabetes. 1995; 44: 1126-1131.

Recomendações Nacionais da SPD para o Tratamento da Hiperglicemia na Diabetes Tipo 2 – Proposta de Actualização

(adaptação do recente "Update" 2015 da Declaração de Posição Conjunta ADA/EASD)*

8th CHALLENGES in CARDIOLOGY

ALIMENTAÇÃO SAUDÁVEL, CONTROLO DO PESO CORPORAL, AUMENTO DA ATIVIDADE FÍSICA, EDUCAÇÃO TERAPÊUTICA

Monoterapia farmacológica inicial: Metformina

Eficácia (↓HbA1c)	alta
Hipoglicemia	baixo risco
Peso	neutro/perda
Efeitos secundários	GI/acidose láctica
Custos	baixos

Caso não seja atingido um **valor alvo de HbA1c** individualizado decorridos 3 meses, prosseguir para associação de 2 fármacos (ordem não denota qualquer preferência específica – escolha do 2º fármaco dependente de fatores específicos da pessoa com diabetes e/ou da doença)

Terapêutica dupla	Metformina + Sulfonilureia	Metformina + Glitazona	Metformina + Inibidor DPP4	Metformina + Inibidor SGLT2	Metformina + Agonistas GLP-1	Metformina + Insulina (basal)
Eficácia (↓HbA1c)	alta	alta	intermédia	intermédia	alta	muito alta
Hipoglicemia	risco moderado	baixo risco	baixo risco	baixo risco	baixo risco	risco alto
Peso	ganho	ganho	neutro	perda	perda	ganho
Efeitos secundários	hipoglicemia	edema, IC, Fx's	raros	GU, desidratação	GI	hipoglicemia
Custos	baixos	baixos	altos	altos	altos	variáveis

Caso não seja atingido um **valor alvo de HbA1c** individualizado decorridos 3 meses, prosseguir para associação de 3 fármacos (ordem não denota qualquer preferência específica – escolha do 2º fármaco dependente de fatores específicos da pessoa com diabetes e/ou da doença)

Na ausência de estudos comparativos que demonstrem a superior eficácia a longo prazo, não é possível fazer uma recomendação uniforme sobre o melhor fármaco a associar à metformina.

Terapê

ou Insulina *ou* Insulina

Caso não seja atingido um **valor alvo de HbA1c** individualizado decorridos 3 meses, com a terapêutica tripla: 1) nas pessoas tratadas com uma associação tripla oral, passar à terapêutica injetável (GLP-1 ou insulina); 2) nas pessoas tratadas com GLP-1, adicionar insulina basal; 3) nas pessoas tratadas com insulina basal em titulação ótima, adicionar GLP-1 ou insulina prandial. Nas pessoas refratárias considerar adicionar glitazona ou i-SGLT2.

Terapêutica injetável em associação: Metformina + **Insulina Basal + Insulina Prandial *ou* Agonistas GLP-1**

Rui Duarte, Miguel Melo, José Silva Nunes. Revista Portuguesa de Diabetes. 2015; 10 (1): 40-48

Gliptins/DPP-4 inhibitors

	DPP-4 inhibitor
Efficacy	Intermediate
Hypoglycaemia risk	Low risk
Weight	Neutral
Side effects	Rare
Costs	High

Efficacy – Intermediate (?)

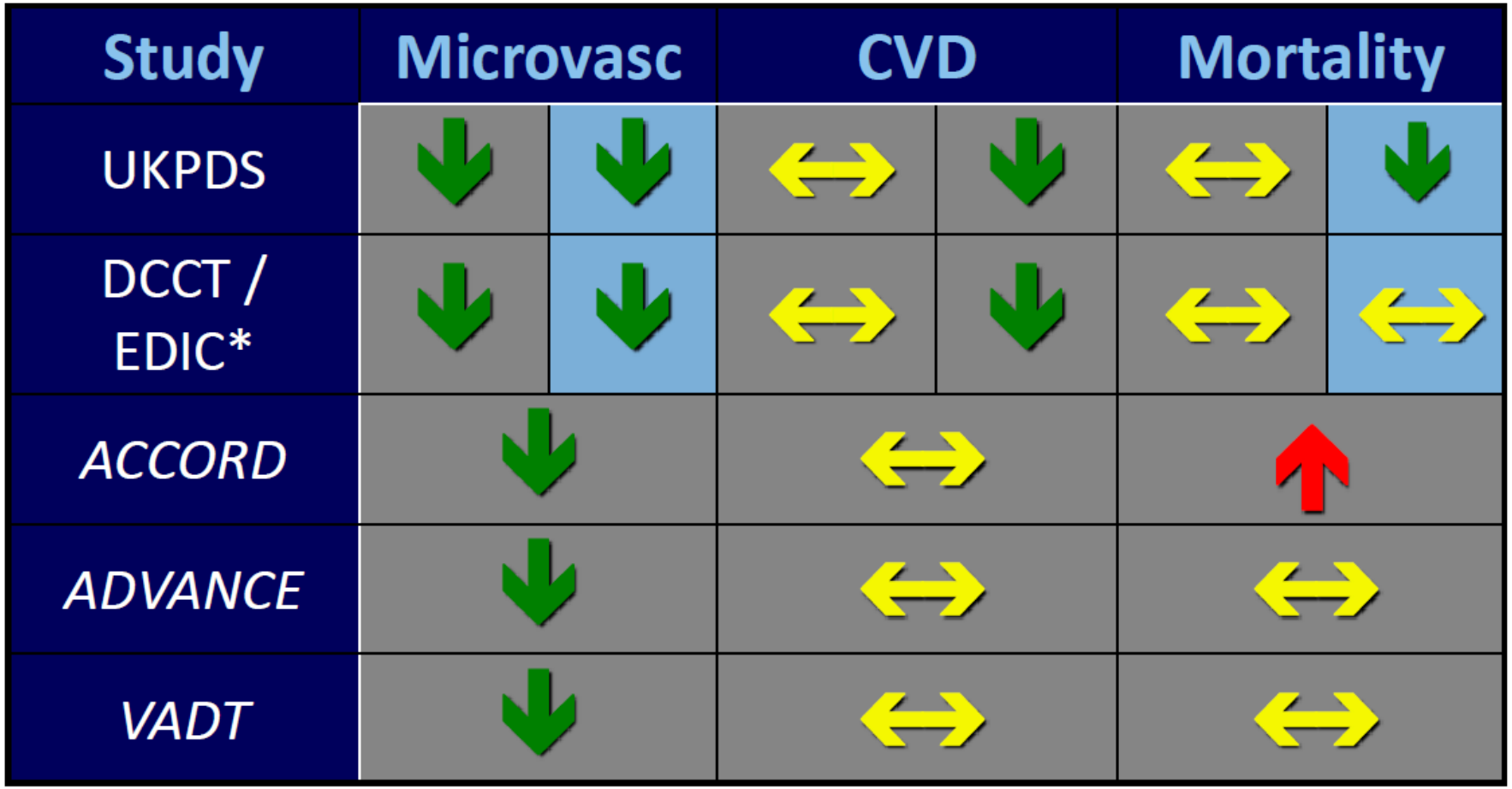
- **Similar to other oral drugs when comparisons are made using the same baseline A1C (↓ 0,7-0,8%)**
- **Lower when compared with GLP-1R agonists or insulin**

Side effects - rare

- **Excellent profile of tolerability and safety**
  - **Elderly patients**

May be used at any stage of Chronic Kidney Disease

Impact of intensive treatment of glycemia: summary of major clinical trials



UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998;352:854.
Holman RR et al. *N Engl J Med*. 2008;359:1577. DCCT Research Group. N Engl J Med 1993;329;977.
Nathan DM et al. *N Engl J Med*. 2005;353:2643. Gerstein HC et al. *N Engl J Med*. 2008;358:2545.
Patel A et al. N Engl J Med 2008;358:2560. Duckworth W et al. N Engl J Med 2009;360:129. (erratum: Moritz T. *N Engl J Med* 2009;361:1024)

Summary (UKPDS, ACCORD, VADT)

8th CHALLENGES in CARDIOLOGY

- **An intensive approach to hyperglycemiais always effective in preventing microvascular complications (retinopathy and nephropathy) or its progression.**
- **Intensive treatment of hyperglycemia for the prevention of macrovascular complications is only proven to be effective in younger patients, with short duration of disease and without established cardiovascular disease.**
  - **Long-term follow-up was necessary to show benefit!**

Antidiabetic therapies and cardiovascular risk

8th CHALLENGES in CARDIOLOGY

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 14, 2007 VOL. 356 NO. 24

Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes

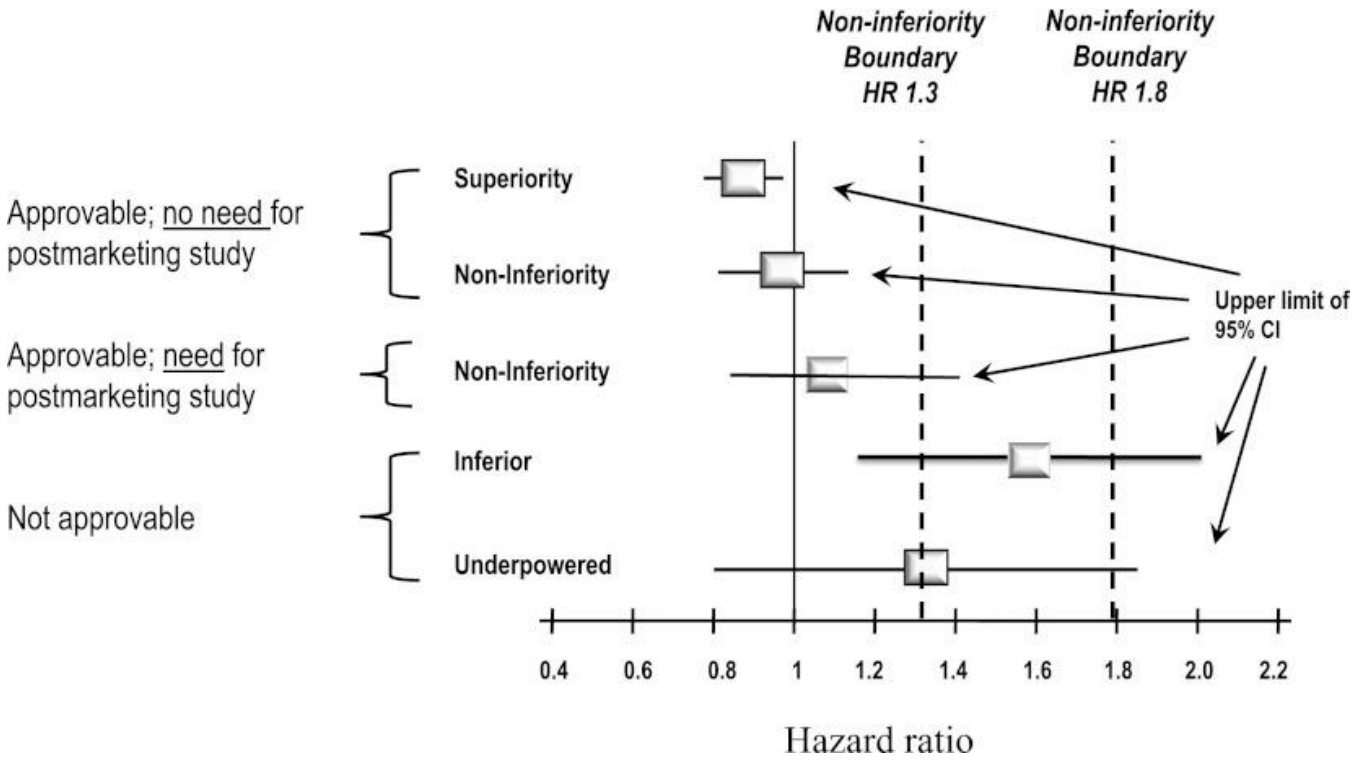
Steven E. Nissen, M.D., and Kathy Wolski, M.P.H.

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)

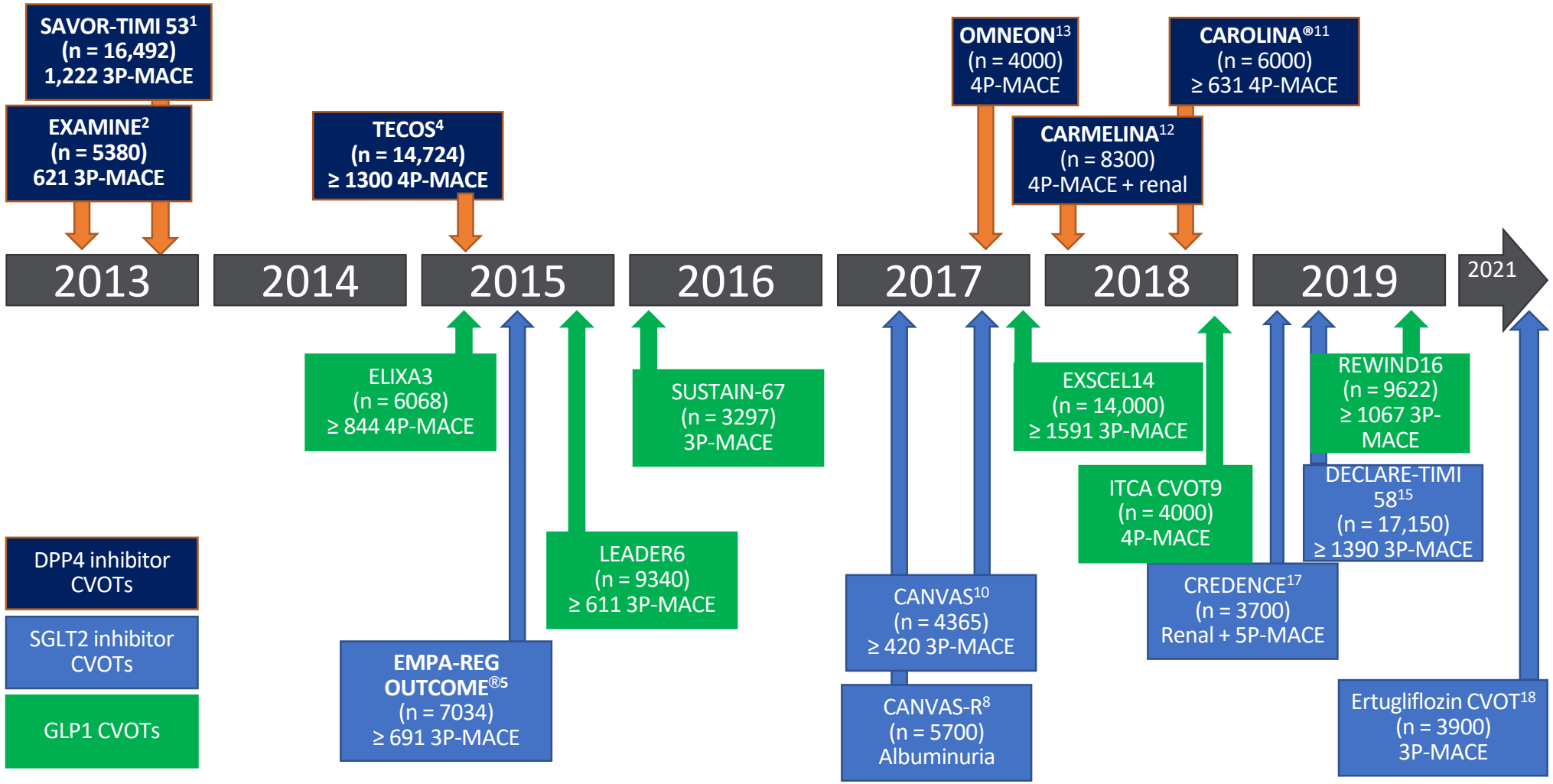
December 2008
Clinical/Medical



Studies should include older patients, with long duration of diabetes and established cardiovascular disease.

Overview of Cardiovascular Outcomes Trials with antidiabetic agents

8th CHALLENGES in CARDIOLOGY

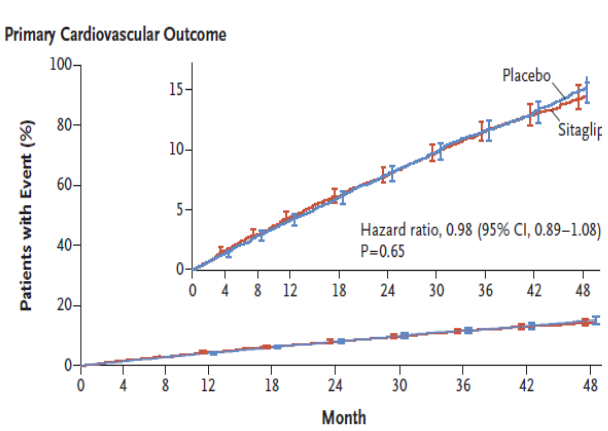


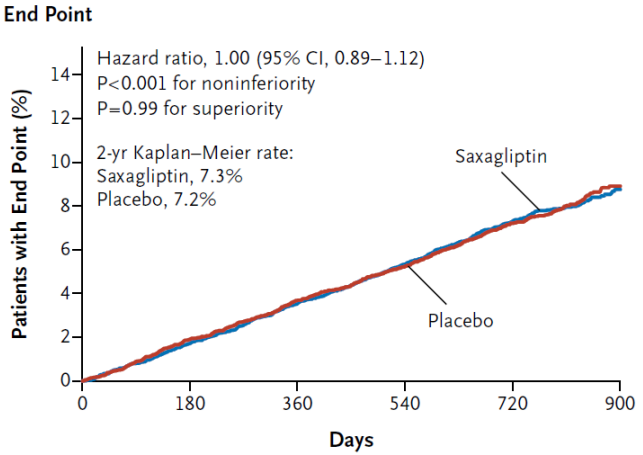
Timings and study details consulted at ClinicalTrials.gov.

CVOTs with gliptins

8th CHALLENGES in CARDIOLOGY

	SAVOR[1]	TECOS*[2]	EXAMINE[3]
Primary end-point	3-p MACE (cardiovascular death, nonfatal myocardial infarction, or nonfatal ischemic stroke) *hospitalization for unstable angina.		
Design	Multicenter, double blind and randomized		
Treatment	Saxagliptin vs placebo	Sitagliptin vs placebo	Alogliptin vs placebo
Patients	16 492 Established CVD or high risk	14 671 Established CVD	5380 Established CVD (ACS in the previous 15-90 days)
Median follow-up	2.1 years	3 years	1.5 years





	SAVOR[1]	TECOS[2]	EXAMINE[3]
Primary end-points (MACE)	HR=1,00 (0,89-1,12)	HR=0,98 (0,88-1,09)	HR=0,96 (≤1,16)
Heart failure	HR=1,27 (1,07-1,51)	HR=1,00 (0,83-1,20)	HR= 1,19 (0,89-1,58)
Hypoglycemia	1,16 (1,08-1,25)	1,12 (0,89-1,40)	6,7% (A) vs 6,5% (P)

1. *N Engl J Med* 2013 Oct 3;369(14):1317-26.
2. *N Engl J Med* 2015 Jul 16;373(3):232-42
3. *N Engl J Med*. 2013; 369:1327-35

EDITORIAL

The Safety of Dipeptidyl Peptidase 4 Inhibitors and the Risk for Heart Failure

Benjamin M. Scirica, MD, MPH

Putative explanations for the differences in HF outcomes

- Different population?
  - The populations were more similar than different
- Different adjudication of Hospitalization for HF?
  - all 3 studies used a similar well-defined HF end point, adjudicated by a blinded committee.
- Different pharmacological properties between gliptins?
  - No reported differences regarding non-GLP-1 substrates (BNP)

Observational studies and meta-analyzes did not find any association between gliptins and increased risk of hospitalization for HF.

JAMA Cardiol. 2016;1(2):123-125

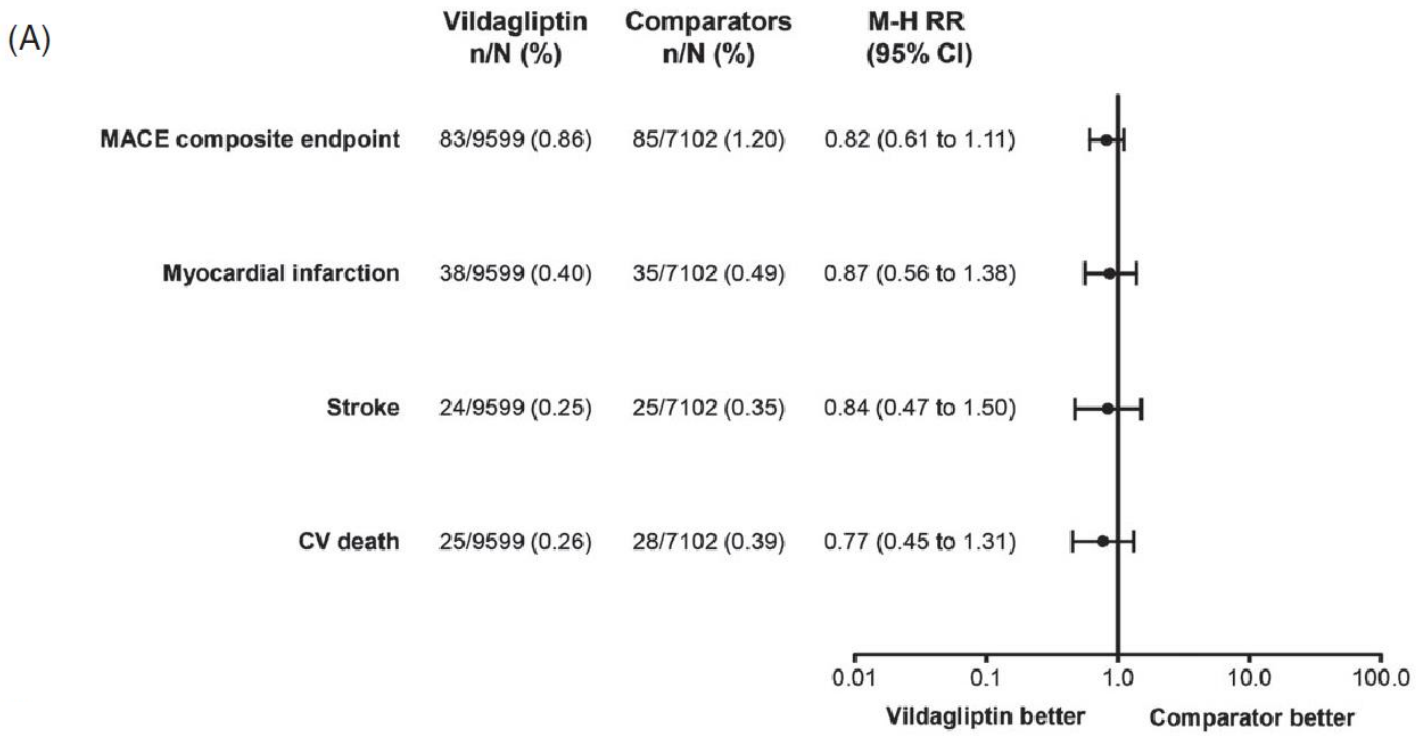
original article

Diabetes, Obesity and Metabolism 17: 1085–1092, 2015.

Cardiovascular and heart failure safety profile of vildagliptin: a meta-analysis of 17 000 patients

G. McInnes[1], M. Evans[2], S. Del Prato[3], M. Stumvoll[4], A. Schweizer[5], V. Lukashevich[6], Q. Shao[6] & W. Kothny[5]

8th CHALLENGES in CARDIOLOGY



Heart Failure (HF) events

- 0,43% (vilda) *vs* 0,45% (placebo)
- RR = 1,08 (95% CI 0,68-1,70)

<u>Conclusions</u> –Vildagliptin is not associated with an increased risk of adjudicated MACE relative to comparators.

CLINICAL RESEARCH

Effects of Vildagliptin on Ventricular Function in Patients With Type 2 Diabetes Mellitus and Heart Failure

A Randomized Placebo-Controlled Trial

8th CHALLENGES in CARDIOLOGY

Methods

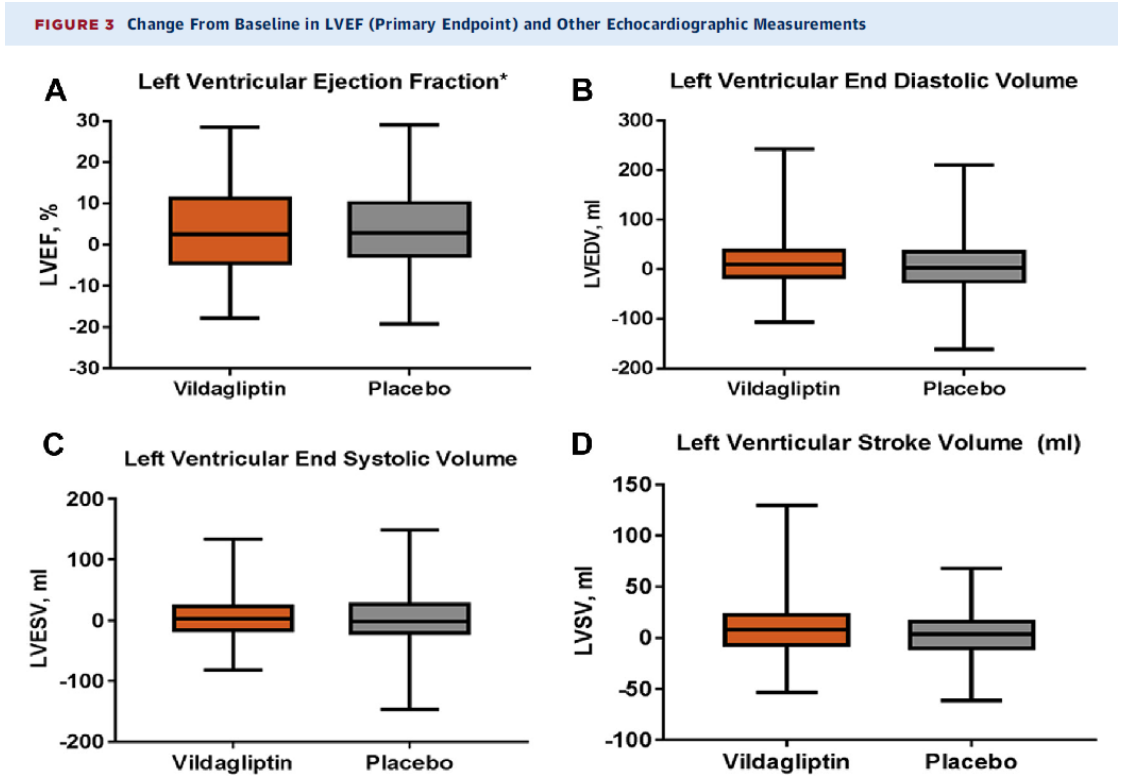
- 254 patients with T2DM and heart failure (class I-III) and LVEF <0.40
- Vildagliptin *vs* placebo

Results

- Mean change LVEF = 4.95±1.25% (vildagliptin) *vs* 4.33±1.23% (ns)
- LVED and LVES volumes increased more in the vildagliptin group

Conclusions

- Vildagliptin had no major effect on LVEF



JACC Heart Fail. 2018 Jan;6(1):8-17

Design of major positive CVOTs

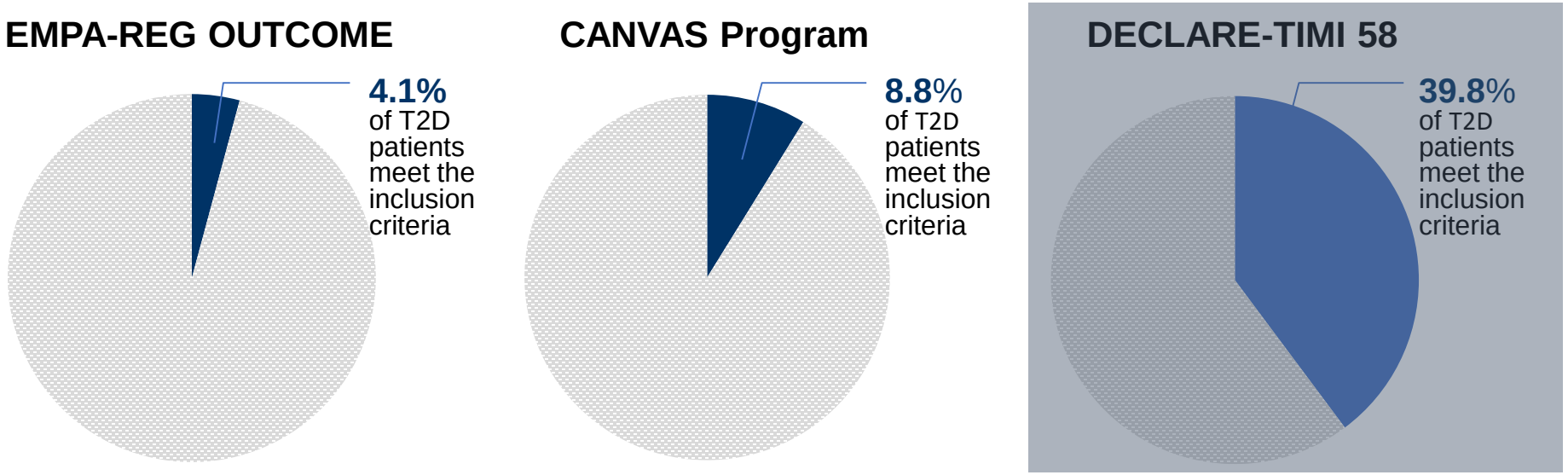
8th CHALLENGES in CARDIOLOGY

	EMPA-REG[1]	(CANVAS+CANVAS-R)[2]	LEADER[3]*
n	7020	10,143	9340
Interventions	EMPA/PBO (1:1:1) (10 mg, 25 mg, PBO)	CANA/PBO (1:1:1) (100mg, 300mg, PBO)	LIRA/PBO (1:1) (1,2-1,8 mg, PBO)
Key inclusion criteria	• HbA_{1c} ≥7% and ≤10% • eGFR >30 mL/min • Age ≥18 years • Secondary prevention (99%) ◦ Previous CV event	• HbA_{1c} ≥7% and ≤10.5% • eGFR >30 ml/min • Primary prevention: ~35% ◦ ≥2 CV risk factors • Secondary prevention: ~65% ◦ Established vascular complications	• T2DM uncontrolled • Primary prevention (~20%) ◦ Age ≥60 + 1 or more risk factor • Secondary prevention (-80%) ◦ Established vascular complications
Primary endpoint	MACE (CV death, non-fatal MI, non-fatal stroke)	Pooled MACE (CV death, non-fatal MI, non-fatal stroke) from CANVAS & CANVAS-R	MACE (CV death, non-fatal MI, non-fatal ischemic stroke)

1. Zinman B et al. N Engl J Med 2015;373:2117–2128; 2. https://clinicaltrials.gov/ct2/show/NCT01032629; 3 Marso SP, et al. N Engl J Med 2016;375:311-22

Generalizability of the eligibility criteria for CVOTs in diabetes

8th CHALLENGES in CARDIOLOGY



The generalizability of the eligibility criteria of the 3 SGLT2 inhibitor CVOTs was assessed in the 2009−2010 and 2011−2012 NHANES databases

CV, cardiovascular; CVOT, cardiovascular outcome trial; NHANES, National Health and Nutrition Examination Survey; SGLT2, sodium-glucose co-transporter 2; T2D, type 2 diabetes.
Wittbrodt ET et al. *Am J Manag Care*. 2018;24:S138-S145.
O Estudo DECLARE-TIMI 58 está a decorrer: https://clinicaltrials.gov/ct2/show/NCT01730534

Antihyperglycemic Therapy in Adults with Type 2 Diabetes

8th CHALLENGES in CARDIOLOGY

Monotherapy — Lifestyle Management + Metformin

Initiate metformin therapy if no contraindications* (See Table 8.1)

A1C at target after 3 months of monotherapy?

Yes: - Monitor A1C every 3–6 months

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

Dual Therapy — Lifestyle Management + Metformin + Additional Agent

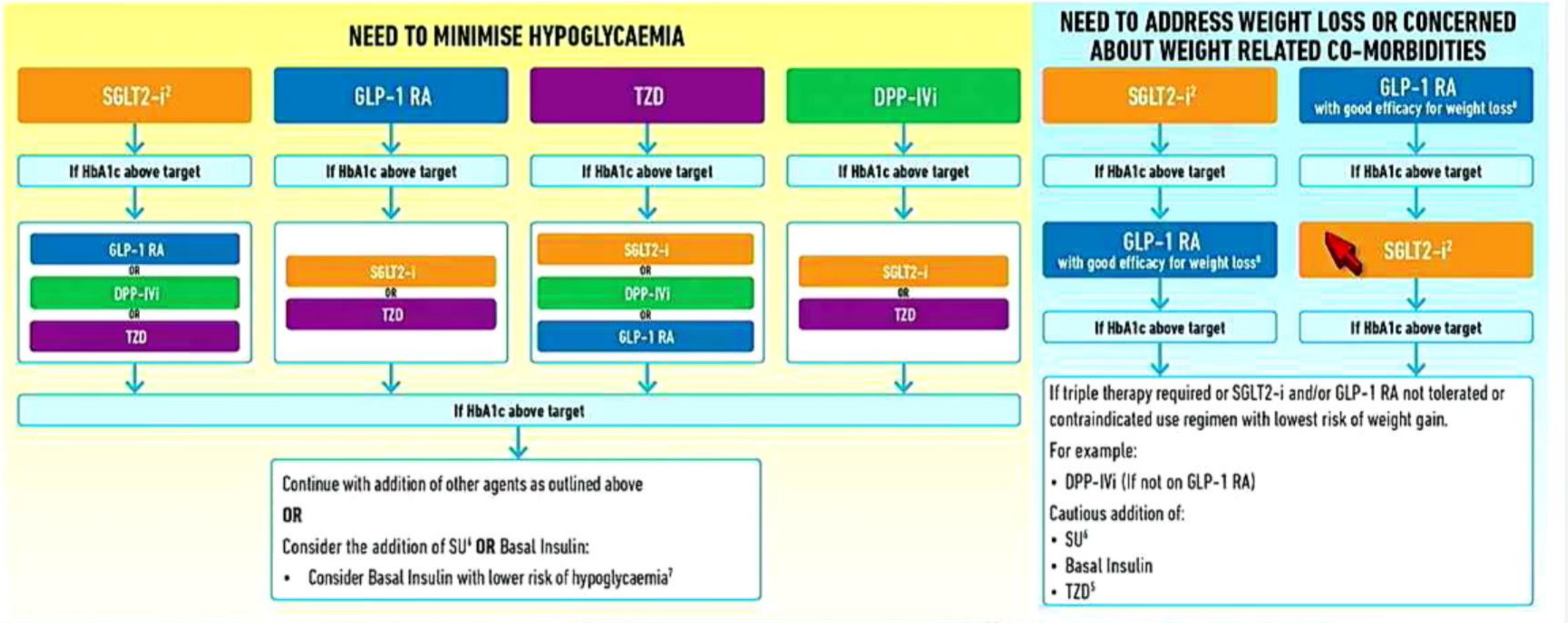
ASCVD?

Yes: - Add agent proven to reduce major adverse cardiovascular events and/or cardiovascular mortality (see recommendations with * on p. S75 and **Table 8.1**)

No: - Add second agent after consideration of drug-specific effects and patient factors (See Table 8.1)

Diabetes Care 2018;41(Suppl. 1):S73–S85

ANTIHYPERGLYCEMIC MEDICATION IN TYPE 2 DIABETES: OVERALL APPROACH



1. SGLT2-i = Empagliflozin preferred, GLP1-RA = Liraglutide preferred. Proven CVD benefit means it has label indication of reducing CVD events please see Section X to see hierarchy of evidence for CVD benefits for agents within the GLP-1 RA and SGLT2-i class
2. Be aware that SGLT2-i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use
3. Both Empagliflozin and Canagliflozin have shown reduction in HF in CVOT trials
4. Degludec or U100 Glargine have demonstrated CVD safety
5. Low dose may be better tolerated though less well studied for CVD effects
6. Choose later generation SU with lower risk of risk of hypoglycaemia
7. Degludec / Glargine U300 < Glagine U100 / Detemir < NPH insulin
8. GLP-1 RA with best efficacy for weight loss Semaglutide > Liraglutide > Dulaglutide > Exenatide > Lixisenatide
9. If no specific co-morbidities (i.e. established CVD), low risk of hypoglycaemia and lower priority to avoid weight gain or no weight related co-morbidities: using the algorithm to minimize medication costs
10. Consider country and region specific cost of drugs. In some countries TZD relatively more expensive and DPP-IVi relatively cheaper

Proposed revised version of ADA/EASD Consensus for the treatment of hyperglycemia (under discussion)

Elderly patients: pitfalls in the treatment of hyperglycemia

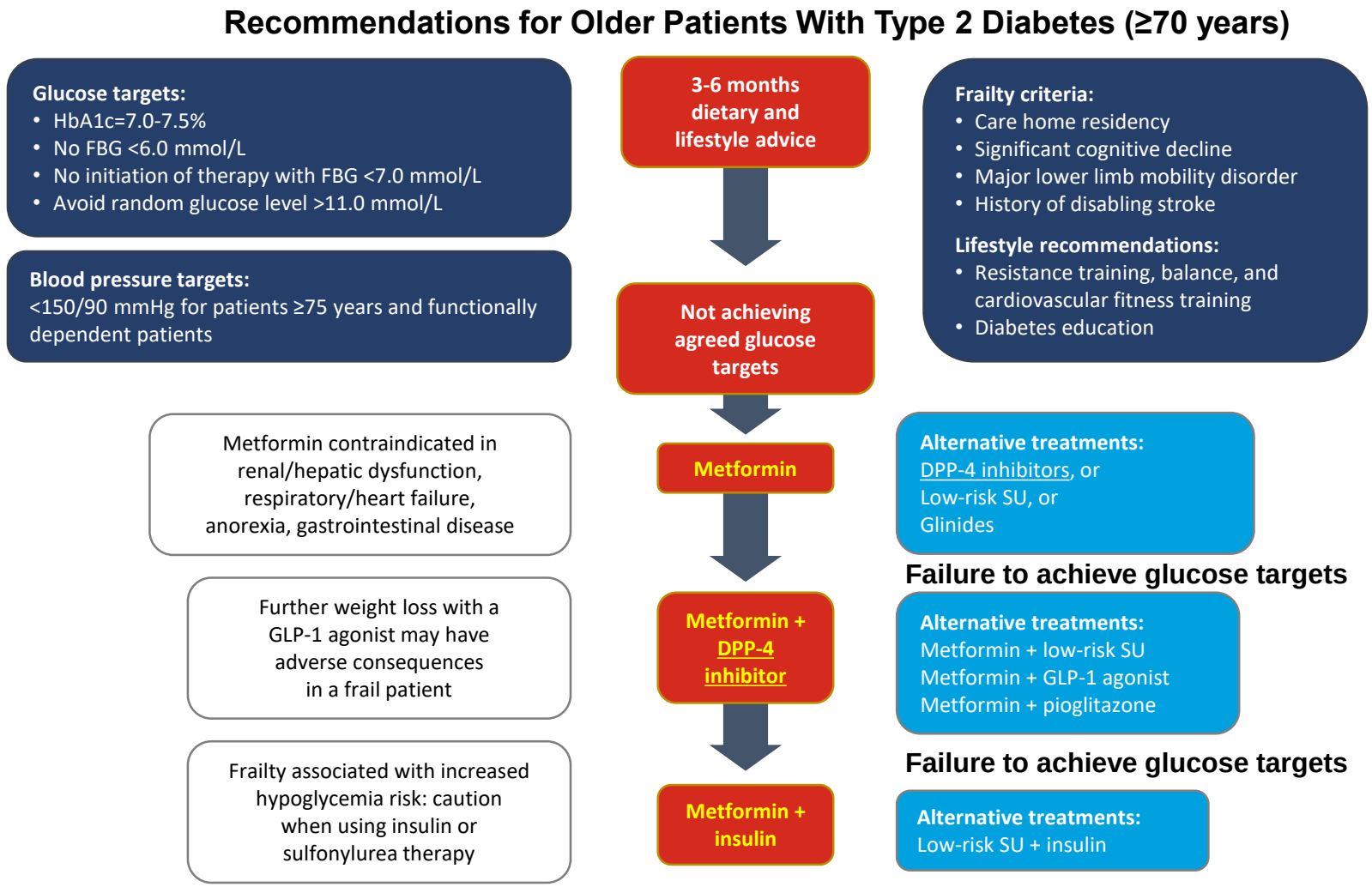
8th CHALLENGES in CARDIOLOGY

Problem	Drug class
Hypoglycemia risk	SU, insulin
Gradual decline of GFR	SU, metformin, iSGLT2*
Frailty	GLP-1R agonists, iSGLT2
Therapeutic education with devices/ Caregivers support	GLP-1R agonists, insulin

* Loss of efficacy with reduction of GFR. Higher number of side effects related to volume deplection.

Therapeutic Algorithm: IAGG/European Diabetes Working Party for Older People[1,2]

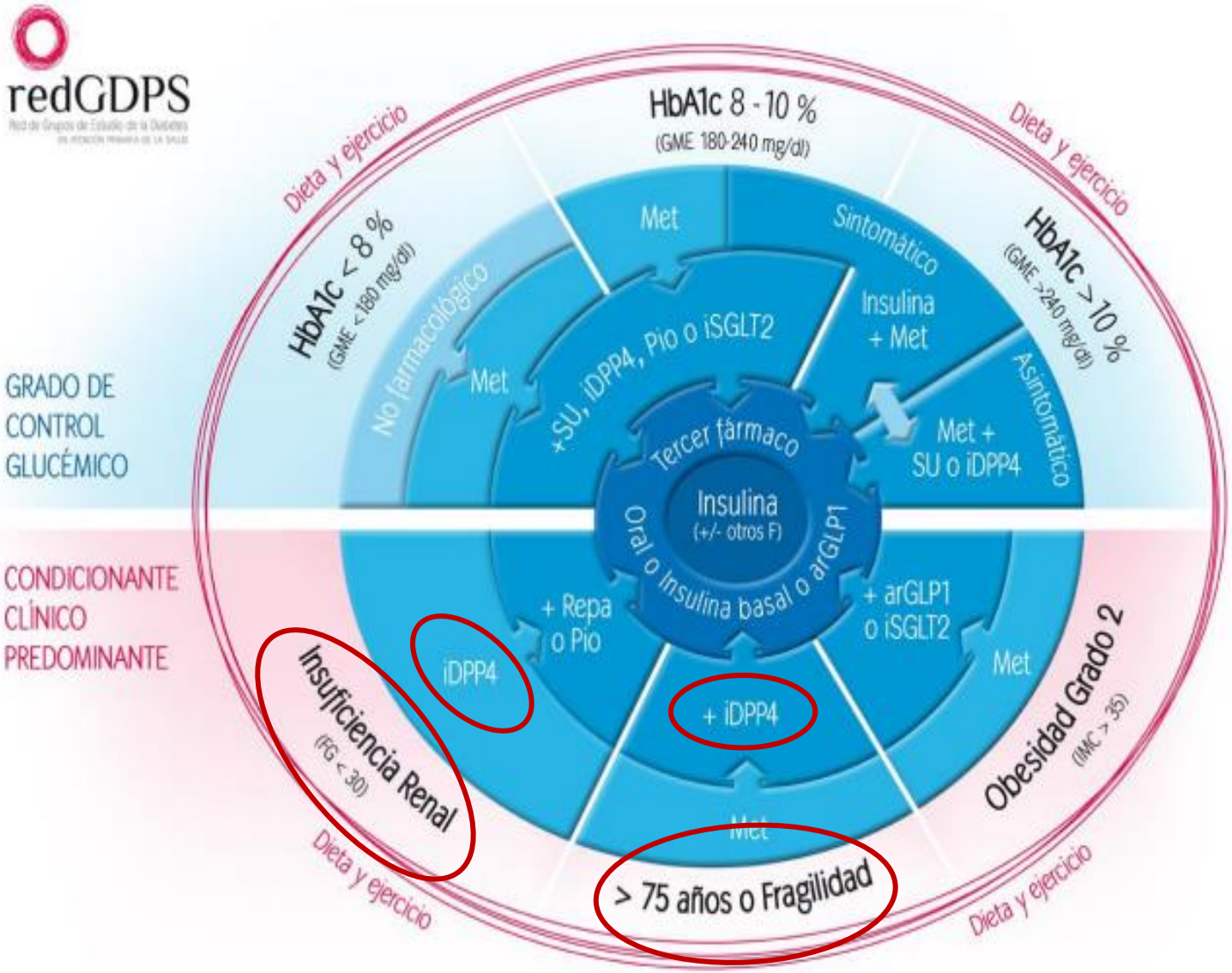
8th CHALLENGES in CARDIOLOGY



1. Sinclair AJ et al. *Diabetes Metab* 2011;37(Suppl 3):S27-38
2. Sinclair A et al. *J Am Med Dir Assoc* 2012;13:497-502

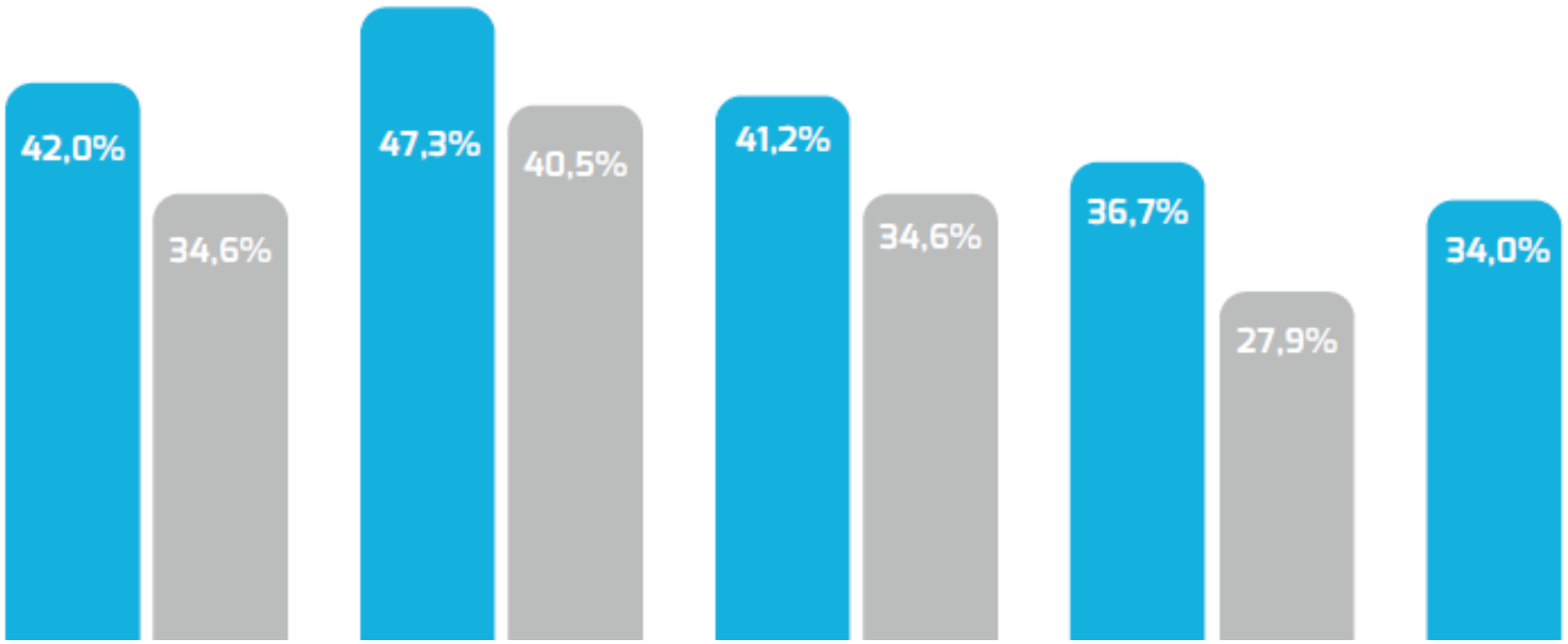
Spanish Primary Care Network redGDPS

8th CHALLENGES in CARDIOLOGY



redGDPS2017

Compliance and persistence in the treatment of diabetes



Farr AM, et al. Adv Ther. 2014 Dec;31(12): 1287-305 21.
Buysman EK, et al. Adv Ther (2015) 32:341–355

Conclusions

8th CHALLENGES in CARDIOLOGY

- Gliptins are a cornerstone in the oral treatment of hyperglycemia, allowing improved control with low risk of hypoglycemia and weight neutrality.
- Gliptins have excellent tolerability and rare side effects.
  - May be used through the whole spectrum of diabetes history:
    - Elderly
    - Chronic kidney Disease
  - Higher compliance when compared to other options.
- Gliptins were the first class to prove cardiovascular safety in dedicated CVOTs.