CENTRO HOSPITALAR
VILA NOVA DE GAIA|ESPINHO

Risco CV no doente com DM2

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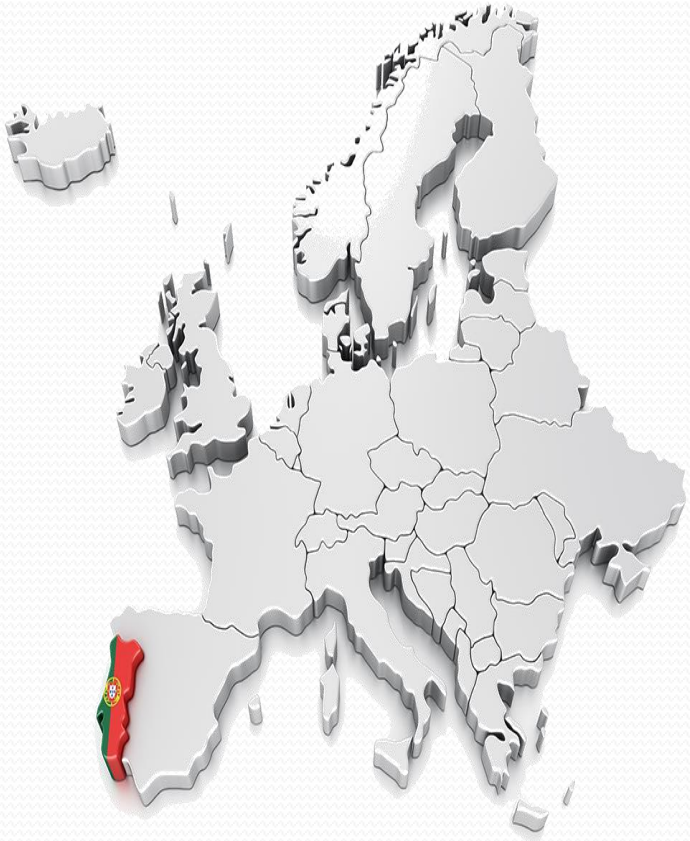
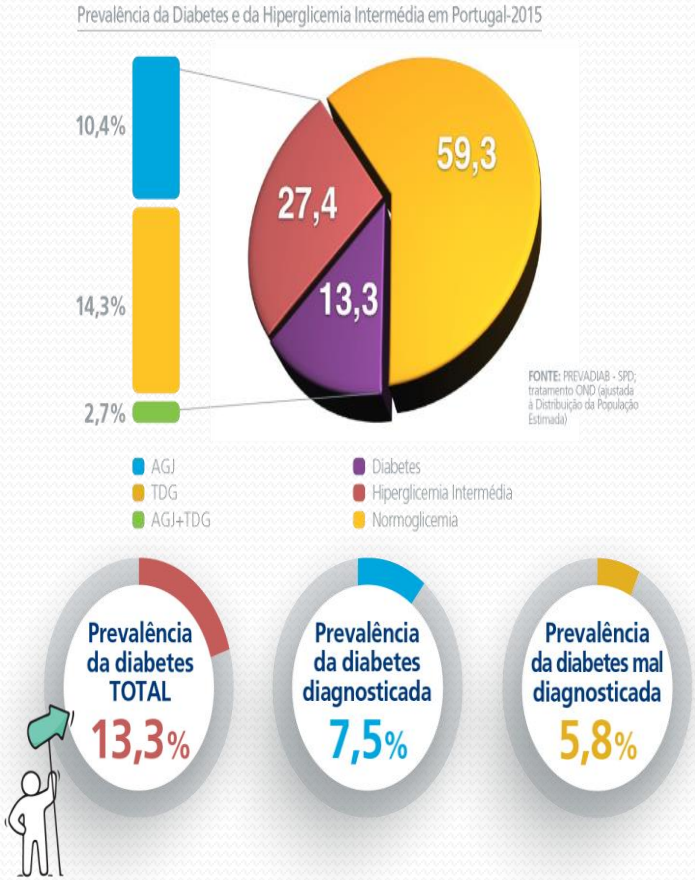
Diabetes em Portugal

Prevalência total muito elevada e a aumentar todos os anos





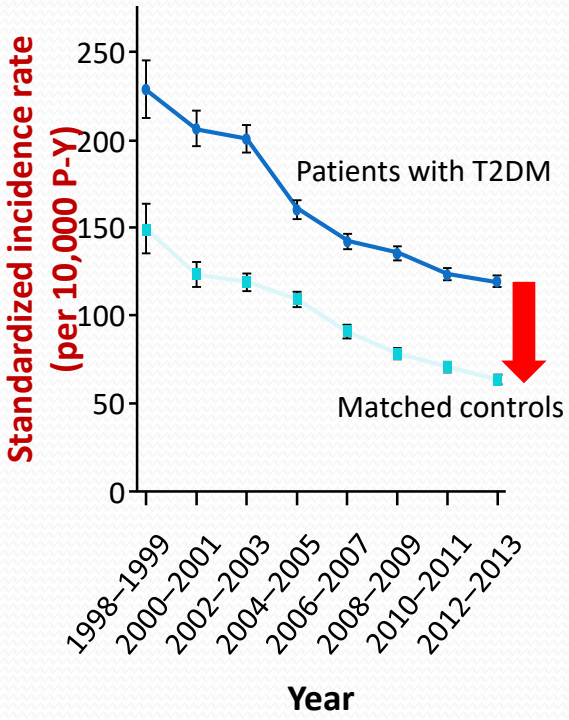
PREVADIAB - SPD; tratamento OND (ajustada à Distribuição da População Estimada)

NOTA: Por prevalência ajustada entende-se a aplicação das taxas de prevalência por escalão etário e por sexo à distribuição da população no ano em análise.de 2015.

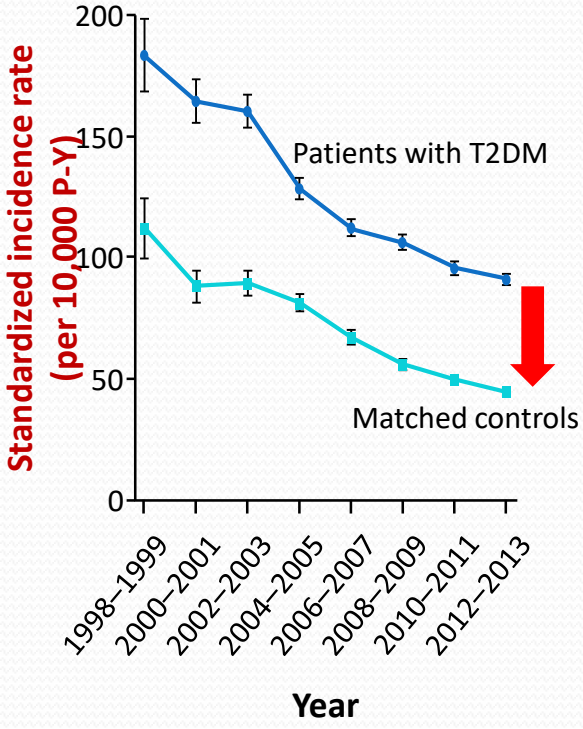
Remaining burden of CVD in the T2DM population

Using records from the Swedish National Diabetes register, data were examined from 457,473 patients with T2DM and matched controls (mean follow-up: 6.5 years)

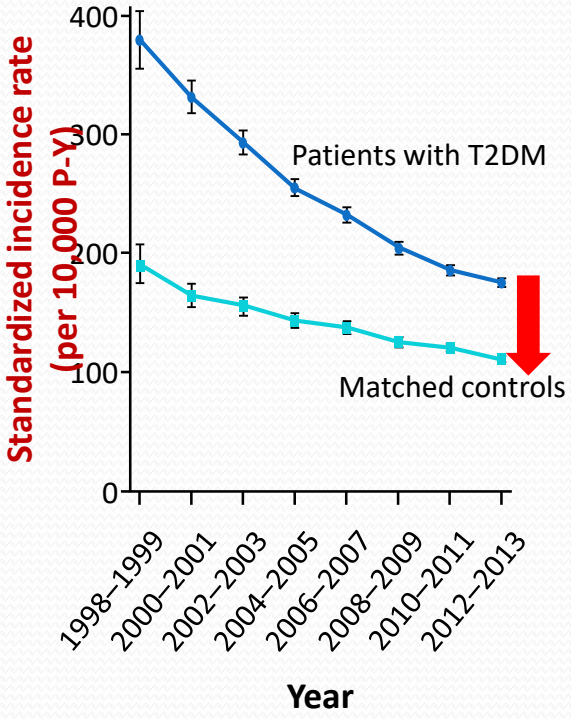
Death from CVD



Death from coronary heart disease



Hospitalization for CVD



CVD, cardiovascular disease; P-Y, patient-years; T2DM, Type 2 diabetes mellitus

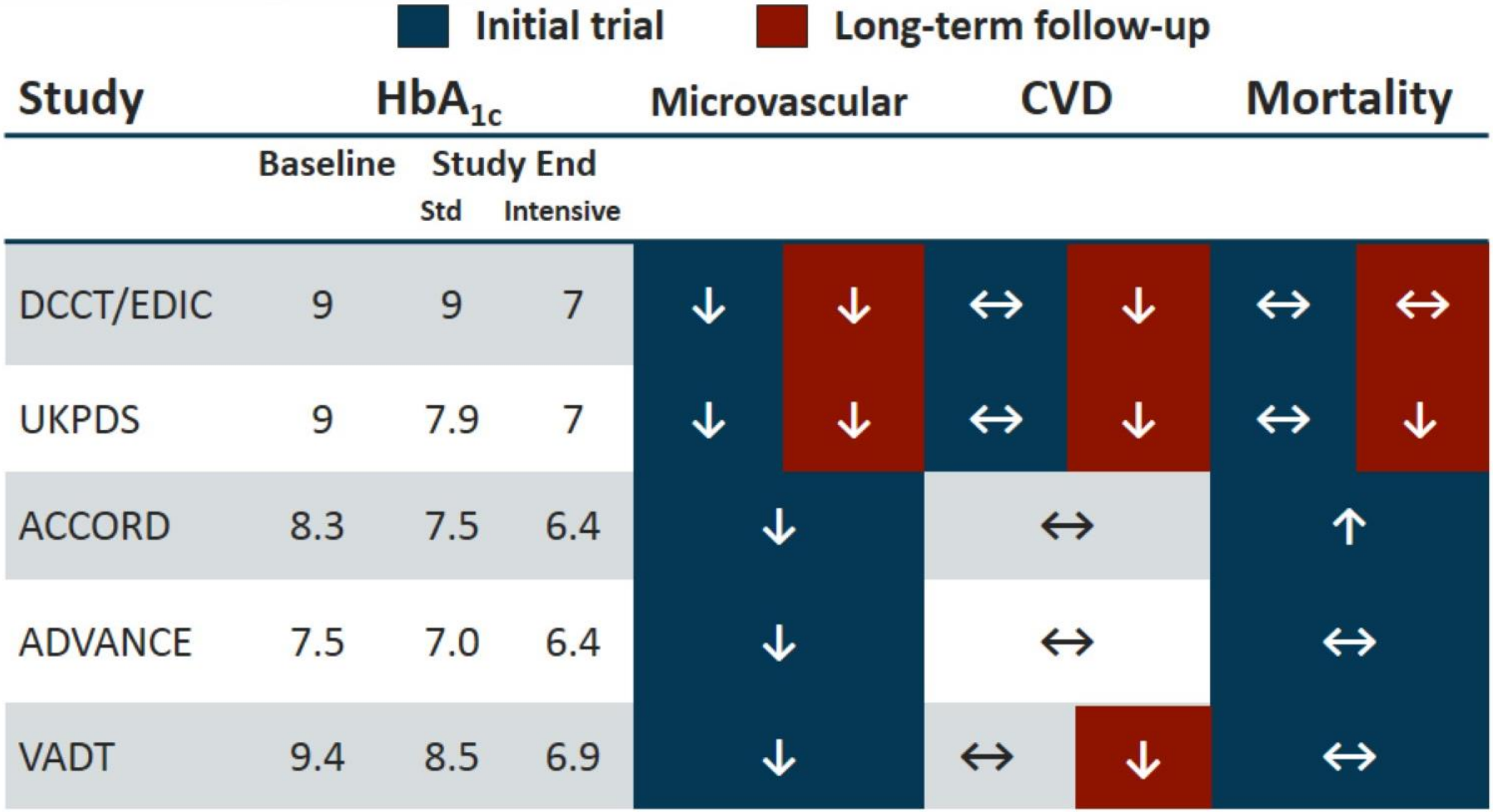
Rawshani A, et al. *N Engl J Med* 2017;376:1407–1418

O controle intensivo das glicemias permite uma redução significativa das complicações macrovasculares?

a) Sim

b) Não.

Tempo e memória na DM 2

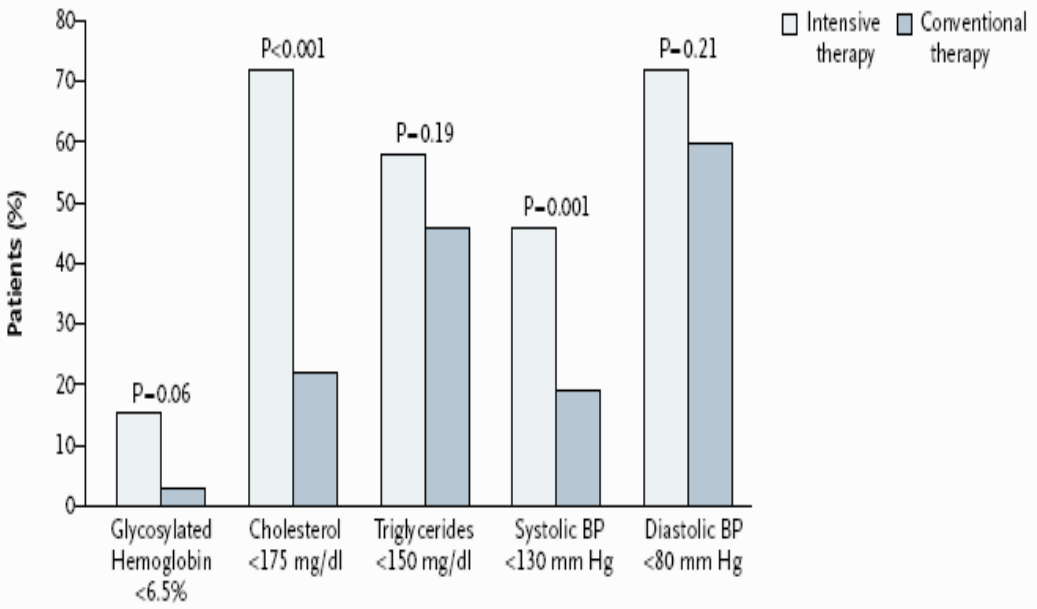


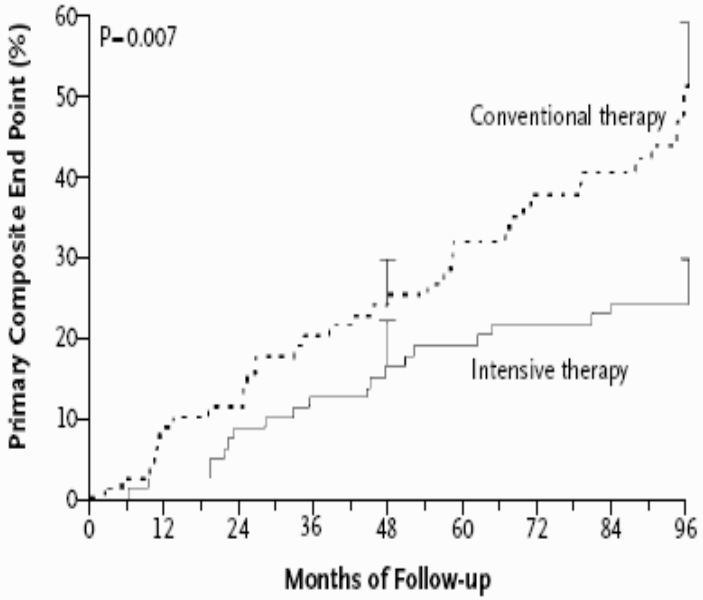
10 Bergenstal RM, et al. *Am J Med.* 2010;123:374e9-e18.

Medscape EDUCATION

Steno 2 – controle multifactorial

180 DM tipo 2 microalbuminúria; 7,8 anos; intervenção multifactorial/convencional;
End-point primário = doença cardio e cerebrovascular e amputação.





"…A target-driven, long-term, intensified intervention aimed at multiple risk factors in patients with type 2 diabetes and microalbuminuria reduces the risk of cardiovascular and microvascular events by about 50 percent…"

Peter Gæde, M.D, et al. NEJM. 348;5. january 30, 2003

Identificação

Homem, 61 anos, fotografo

Antecedentes Pessoais e Familiares Relevantes

DM tipo 2 - 8 anos de duração

HTA

Dislipidemia

Obesidade visceral.

Terapêutica farmacológica atual

- Bisoprolol 2,5 mg id
- Sinvastatina 20 mg id
- Metformina 1.000 mg + Vildagliptina 50 mg bid
- Olmesartan 20mg id
- AAS 100 mg id.

Perfil do doente

TA: 150/89 mmHg, FC: 72 bpm

Peso: 88 kg; Alt.: 166 cm – IMC 31

PA: 98 cm.

EAD:

Microalb/creat ocasional 42,8 mg/g

Colesterol total 174 mg/dL

Triglicerídeos 228 mg/dL

HDL - Colesterol 34 mg/dL

LDL - Colesterol Calculado 116 mg/dL

Hemoglobina A1c (DCCT/NGSP) 7,9%.

O que fazer?

GOALS FOR GLYCEMIC CONTROL

INDIVIDUALIZE GOALS

A1C ≤ 6.5%

For patients without concurrent serious illness and at low hypoglycemic risk

A1C > 6.5%

For patients with concurrent serious illness and at risk for hypoglycemia

Table 6.2—Summary of glycemic recommendations for many nonpregnant adults with diabetes

A1C	<7.0% (53 mmol/mol)*
Preprandial capillary plasma glucose	80–130 mg/dL* (4.4–7.2 mmol/L)
Peak postprandial capillary plasma glucose†	<180 mg/dL* (10.0 mmol/L)

Effects of Aspirin for Primary Prevention in Persons with Diabetes Mellitus

Type of Event	Aspirin (N=7740)	Placebo (N=7740)	Rate Ratio (95% CI)	P Value
	no. of participants with event (%)			
Vascular Outcomes				
Nonfatal myocardial infarction	191 (2.5)	195 (2.5)	0.98 (0.80–1.19)	
Nonfatal presumed ischemic stroke	202 (2.6)	229 (3.0)	0.88 (0.73–1.06)	
Vascular death excluding intracranial hemorrhage	197 (2.5)	217 (2.8)	0.91 (0.75–1.10)	
Any serious vascular event excluding TIA	**542 (7.0)**	**587 (7.6)**	**0.92 (0.82–1.03)**	
TIA	168 (2.2)	197 (2.5)	0.85 (0.69–1.04)	
Any serious vascular event including TIA	**658 (8.5)**	**743 (9.6)**	**0.88 (0.79–0.97)**	**0.01**
Any arterial revascularization	340 (4.4)	384 (5.0)	0.88 (0.76–1.02)	
Any serious vascular event or revascularization	**833 (10.8)**	**936 (12.1)**	**0.88 (0.80–0.97)**	
Major Bleeding				
Intracranial hemorrhage	55 (0.7)	45 (0.6)	1.22 (0.82–1.81)	
Sight-threatening bleeding in eye	57 (0.7)	64 (0.8)	0.89 (0.62–1.27)	
Serious gastrointestinal bleeding	137 (1.8)	101 (1.3)	1.36 (1.05–1.75)	
Other major bleeding	74 (1.0)	43 (0.6)	1.70 (1.18–2.44)	
Any major bleeding	**314 (4.1)**	**245 (3.2)**	**1.29 (1.09–1.52)**	**0.003**

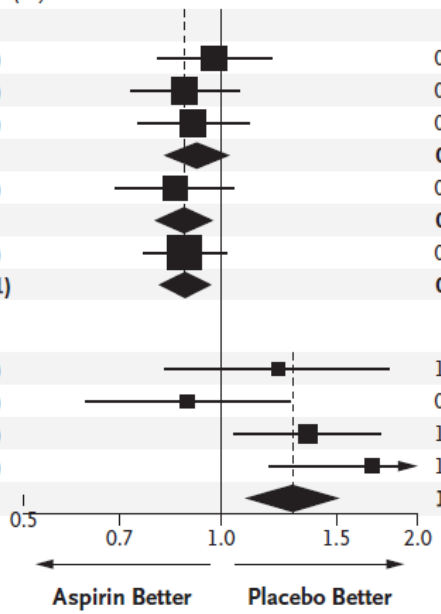
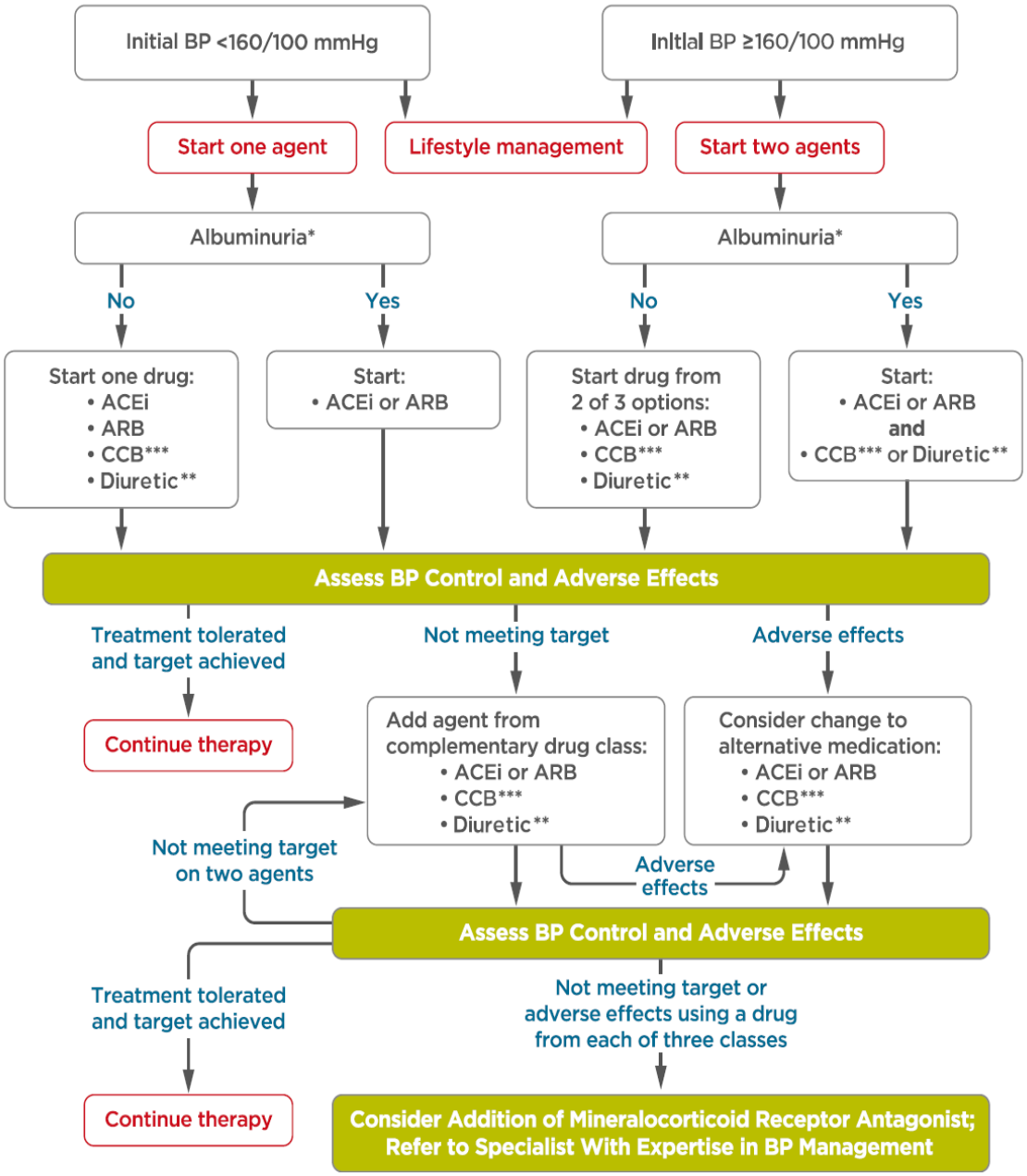


Figure 2. Effect of Assignment to Aspirin Group on Components of Serious Vascular Events, the Combined Outcome of Serious Vascular Event or Revascularization, and Major Bleeding and Its Components.

"The use of low-dose aspirin led to a lower risk of serious vascular events than placebo among persons with DM who did not have evident CVD…However, the absolute lower rates of serious vascular events were of similar magnitude to the absolute higher rates of major bleeding, even among participants who had a high vascular risk".

The ASCEND Study Collaborative Group. NEJM. 2018

Recommendations for the Treatment of Confirmed Hypertension in People With Diabetes



DM2 at higher cardiovascular risk CV disease BP target < 130/80 mmHg

DM2 at lower risk CV disease BP target <140/90 mmHg.

ACE inhibitor or angiotensin receptor blocker, is the recommended first-line treatment for hypertension in patients with DM and albuminuria

EVOLUÇÃO CLÍNICA

Avaliação a 6 meses

Optimização do estilo de vida

Evolução da HbA_{1c} ao longo do tempo:

8,1% → 8,0%

6 meses

Dor torácica com a marcha; AngioTAC coronária – score cálcio elevado

Cateterismo:

Tronco comum, longo, com estenose distal excêntrica de 30%.

Descendente anterior com irregularidades, estenose de 50% no 1/3 proximal envolvendo a primeira diagonal e a primeira septal e estenose de 80% no 1/3 distal.

Primeira diagonal, bifurcada, com estenose de 60-70% no início.

Angioplastia da descendente anterior proximal...sem lesão residual.

Neutral effects of DPP-4 inhibitors on the risk of MACE

	DPP-4 inhibitors		
Trial →	SAVOR HR, 95% CI	EXAMINE HR, 95% CI	TECOS HR, 95% CI
	Saxagliptin	Alogliptin	Sitagliptin
3pt MACE	1.0 0.89, 1.08	0.96 Upper ≤1.16	0.98[b] 0.89, 1.08
CV death	1.03 0.87, 1.22	0.79 0.60, 1.04	1.03 0.89, 1.19
Non-fatal MI	0.95 0.80, 1.12	1.08 0.88, 1.33	0.95[c] 0.81, 1.11
Non-fatal stroke	1.11 0.88, 1.39	0.91 0.55, 1.50	0.97[c] 0.89, 1.08
Hospital HF	1.27[a] 1.07, 1.51	1.07 0.78, 1.15	1.00 0.83, 1.20
All cause death	1.11 0.96, 1.27	0.88 0.71, 1.09	1.01 0.90, 1.14

Diabetes Obes Metab. 2019;21:3–14.

Comparative characteristics of GLP-1 RA CVOTs

	LEADER	SUSTAIN-6	EXSCEL	HARMONY
Drug	Liraglutide	Semaglutide	Exenatide MR	Albiglutide
Population (n)	9340	3297	14752	9463
Follow-up (years)	3.8	2.1	3.2	1.6
Known atherosclerotic CVD	81	71	73	100
Renal Impairment [a]	23	24	22	23
Insulin baseline	45	58	14	59
HbA1c (%)	8.7 ± 1.5	8.7 ± 1.5	8.0	8.7 ± 1.5
Failed to finish on medication	NG	20	44	26
Placebo event rate (%/year)	3.9	4.2	4.0	5.9

Addapted from Home P. Diabetologia 2019. https://doi.org/10.1007/s00125-018-4801 (ahead of print)

Data are % unless otherwise stated
Some variables have been calculated by the author of this review and may be inaccurate to one significant figure
a Excluding ELIXA, which was conducted in individuals with prior ACS
b Defined as <60 ml min−1 [1.73 m]−2 MR, modified release (long-acting); NG, not given

Comparative characteristics of GLP-1 RA CVOTs

Variable	3-MACE[a]	CV death	All death	HHF
LEADER	**0.87** (0.78, 0.97)	**0.78** (0.66, 0.93)	**0.85** (0.74, 0.97)	**0.87** (0.73, 1.05)
SUSTAIN-6	**0.74** (0.58, 0.95)	**0.98** (0.65, 1.48)	**1.05** (0.74, 1.50)	**1.11** (0.77, 1.61)
EXSCEL	**0.91** (0.83, 1.00)	**0.88** (0.76, 1.02)	**0.86** (0.77, 0.97)	**0.94** (0.78, 1.13)
HARMONY	**0.78** (0.68, 0.90	**0.93** (0.73, 1.19)	**0.95** (0.79, 1.16)	NG

Addapted from Home P. Diabetologia 2019. https://doi.org/10.1007/s00125-018-4801 (ahead of print)

HR findings are derived from intention-to-treat analyses
a MACE: CV death, MI, stroke
bComposite of variables, not including albuminuria
cComposed of two studies
MR, modified release (long-acting); NG, not given

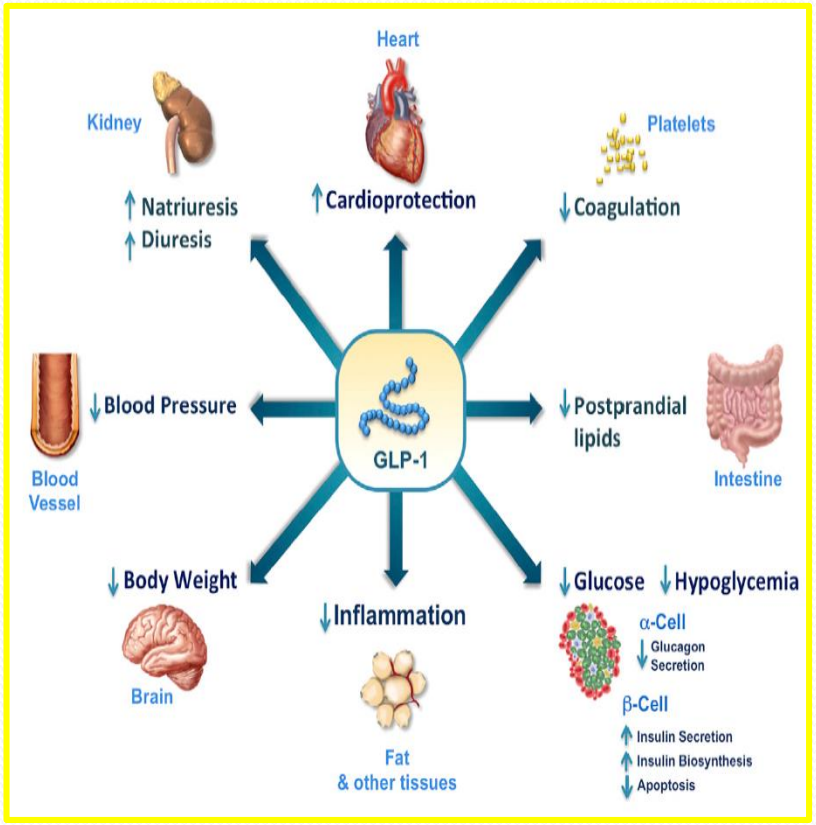
Comparative characteristics of GLP-1 RA CVOTs

Trial →	LEADER HR, 95% CI	SUSTAIN HR, 95% CI	EXSCEL HR, 95% CI
	Liraglutide	Semaglutide	Exenatide
3pt MACE	0.87[a] 0.78, 0.97	0.74[a] 0.58, 0.95	0.91 0.83, 1.00
CV death	0.78[a] 0.66, 0.93	0.98 0.65, 1.48	0.88 0.76, 1.02
Non-fatal MI	0.88 0.75, 1.03	0.74 0.51, 1.08	0.97[c] 0.85, 1.10
Non-fatal stroke	0.89 0.72, 1.11	0.61[a] 0.38, 0.99	0.85[c] 0.70, 1.03
Hospital HF	0.87 0.73, 1.05	1.11 0.77, 1.61	0.94 0.78, 1.13
All cause death	0.85[a] 0.74, 0.97	1.05 0.74, 1.50	0.86 0.77, 0.97

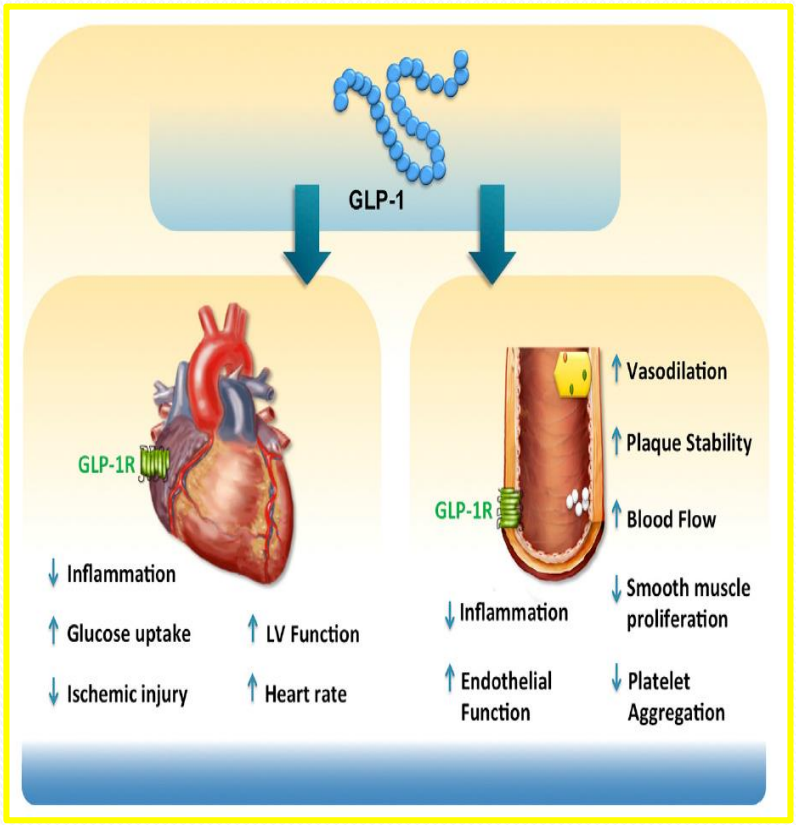
Diabetes Obes Metab. 2019;21:3–14.

What are the mechanisms of GLP-1 receptor agonist on CV protection?

Indirect systemic?



Direct cardiovascular effects?



CV, cardiovascular; GLP-1, glucagon-like peptide-1; LV, left ventricular

Drucker DJ. *Cell Metab* 2016;24:15–30

Comparative characteristics of SGLT2 inhibitor CVOTs

Variable	EMPA-REG OUTCOME	CANVAS Program	DECLARE
Drug	Empagliflozin	Canagliflozin	Dapagiflozin
Population (n)	7020	10142	17160
Follow-up (years)	3.1	3.6	4.2
Known atherosclerotic CVD	99	66	41
Renal Impairment[a]	26	20	7
Hx heart failure	10	14	10
Insulin baseline	48	50	41
HbA1c (%)	8.1 ± 0.8	8.7 ± 1.5	8.7 ± 1.5
Failed to finish on medication	25	30	23
Placebo event rate (%/year)	4.4	3.2	2.4

Addapted from Home P. Diabetologia 2019. https://doi.org/10.1007/s00125-018-4801 (ahead of print)

Data are % unless otherwise stated
Some variables have been calculated by the author of this review and may be inaccurate to one significant figure
a Composite median of two studies combined; individual study follow-up, 5.7 and 2.1 years
Defined as <60 ml min [1.73 m] NG, not given

SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes

Major adverse cardiovascular events (MACE)

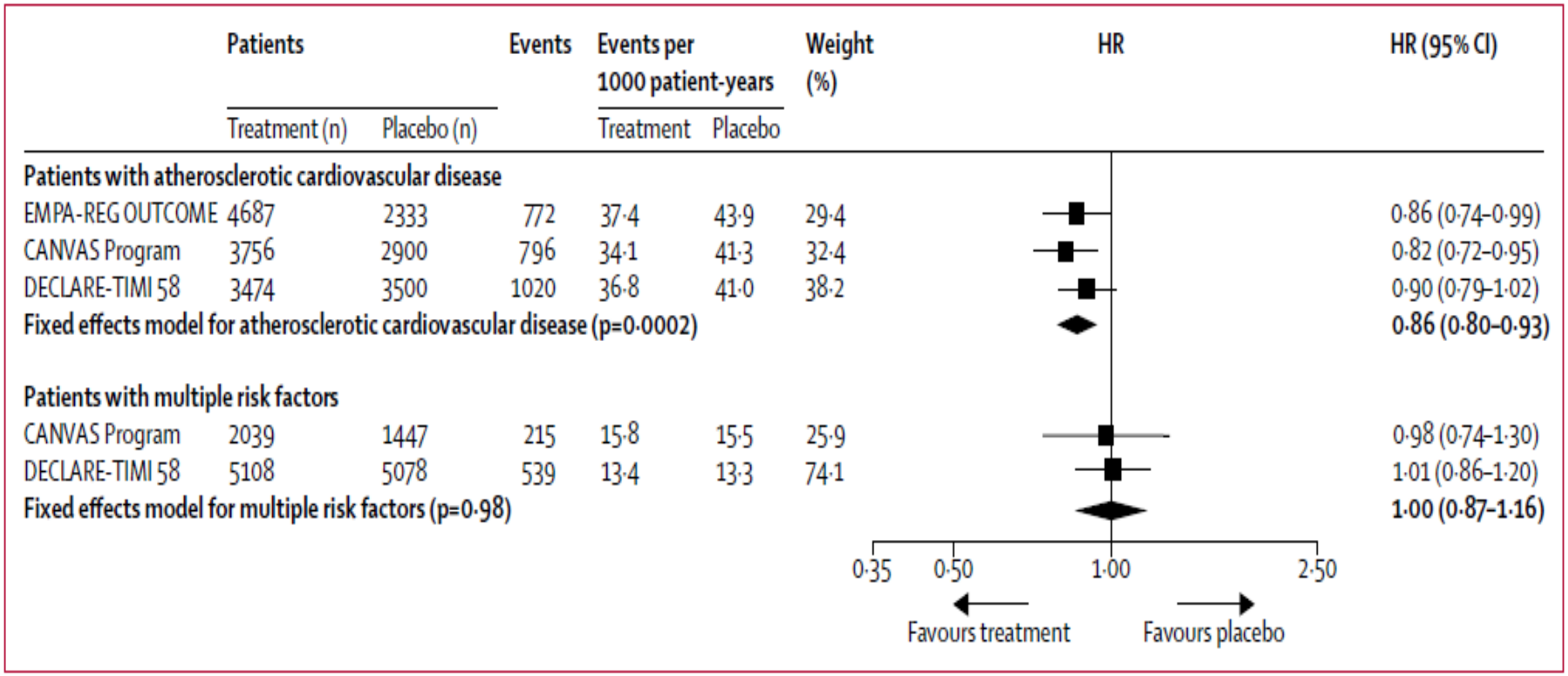


Figure 1: Meta-analysis of SGLT2i trials on the composite of myocardial infarction, stroke, and cardiovascular death (major adverse cardiovascular events) stratified by the presence of established atherosclerotic cardiovascular disease

Lancet 2019; 393: 31–39

SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes

Hospitalisation for HF and CVdeath

	Patients		Events	Events per 1000 patient-years		Weight (%)	HR	HR (95% CI)
	Treatment (n)	Placebo (n)		Treatment	Placebo			
Patients with atherosclerotic cardiovascular disease								
EMPA-REG OUTCOME	4687	2333	463	19·7	30·1	30·9		0·66 (0·55–0·79)
CANVAS Program	3756	2900	524	21·0	27·4	32·8		0·77 (0·65–0·92)
DECLARE-TIMI 58	3474	3500	597	19·9	23·9	36·4		0·83 (0·71–0·98
Fixed effects model for atherosclerotic cardiovascular disease (p<0·0001)								**0·76 (0·69–0·84)**
Patients with multiple risk factors								
CANVAS Program	2039	1447	128	8·9	9·8	30·2		0·83 (0·58–1·19)
DECLARE-TIMI 58	5108	5078	316	7·0	8·4	69·8		0·84 (0·67–1·04)
Fixed effects model for multiple risk factors (p=0·0634)								**0·84 (0·69–1·01)**

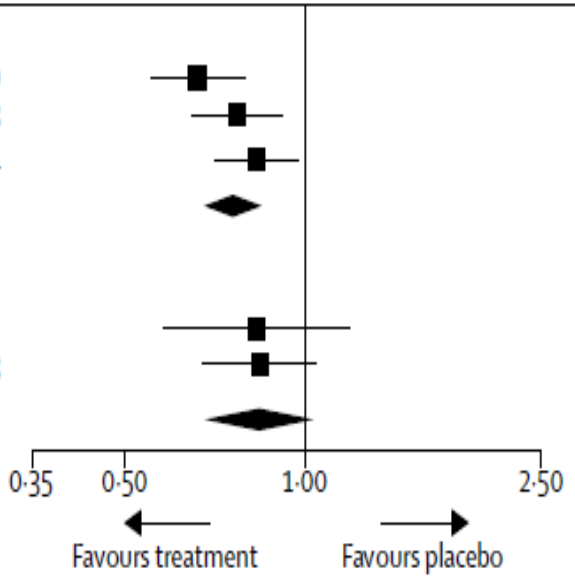
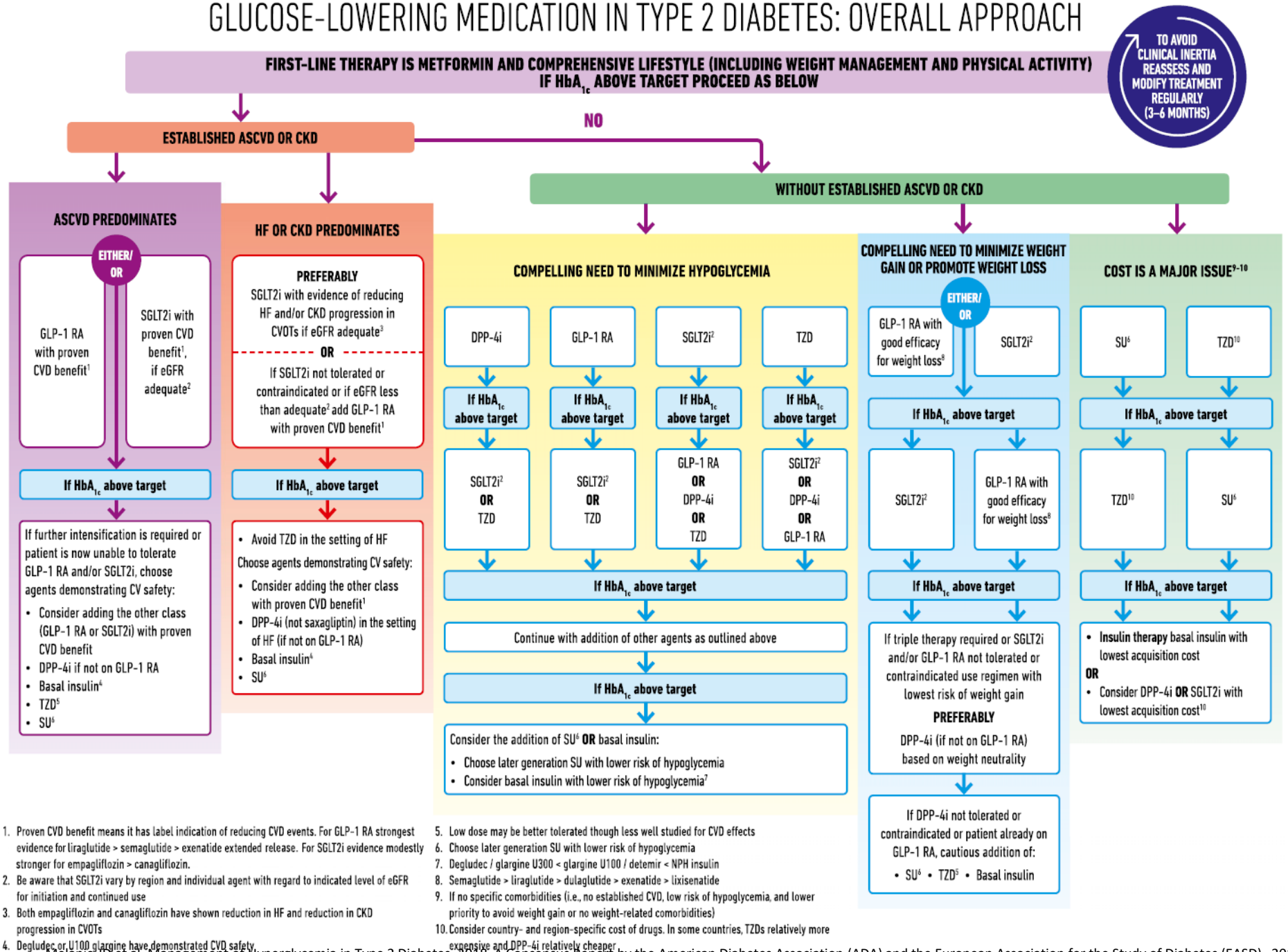


Figure 2: Meta-analysis of SGLT2i trials on hospitalisation for heart failure and cardiovascular death stratified by the presence of established atherosclerotic cardiovascular disease

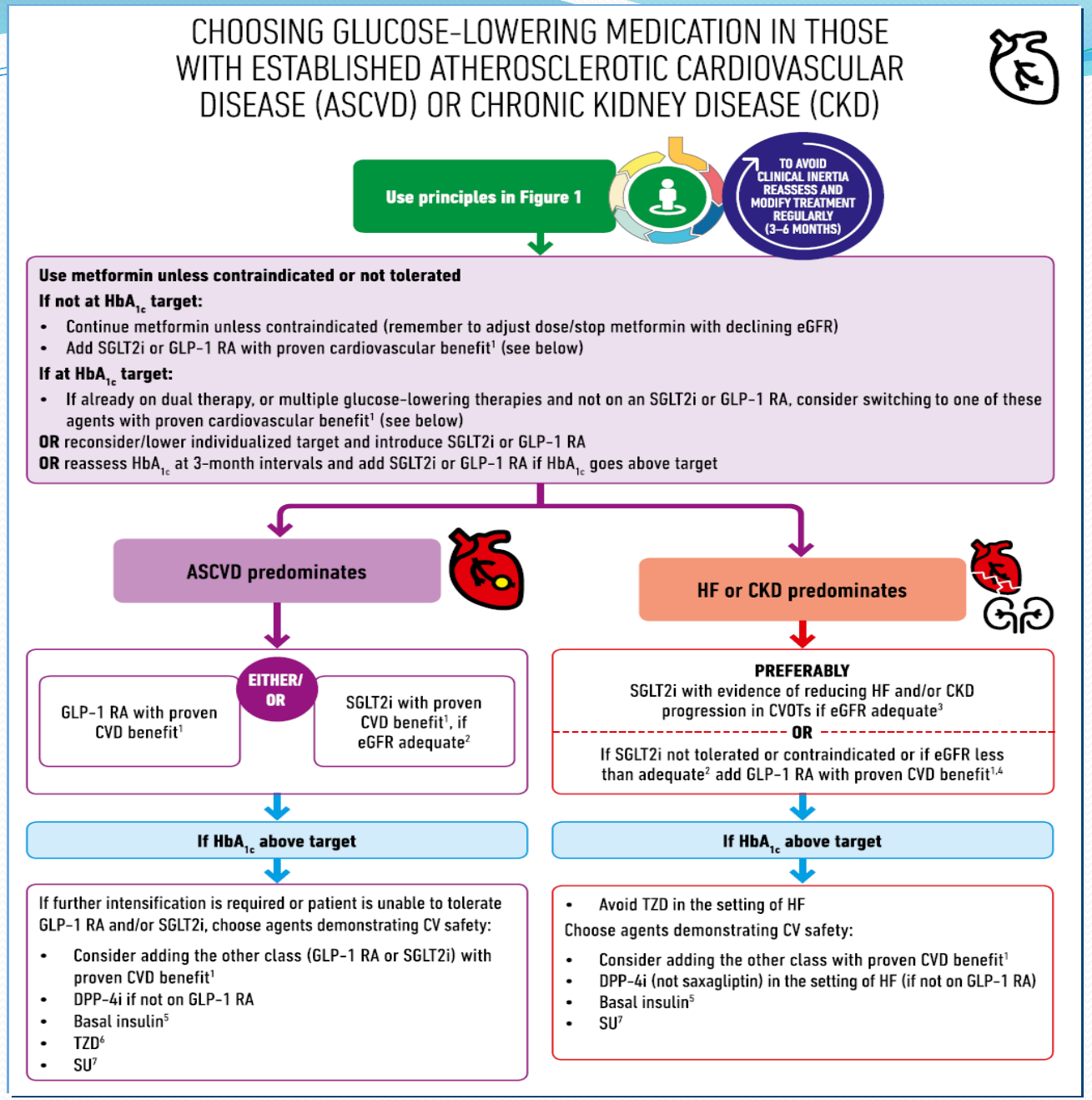
Lancet 2019; 393: 31–39

GLUCOSE-LOWERING MEDICATION IN TYPE 2 DIABETES: OVERALL APPROACH



1. Proven CVD benefit means it has label indication of reducing CVD events. For GLP-1 RA strongest evidence for liraglutide > semaglutide > exenatide extended release. For SGLT2i evidence modestly stronger for empagliflozin > canagliflozin.
2. Be aware that SGLT2i 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 and reduction in CKD progression in CVOTs
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 hypoglycemia
7. Degludec / glargine U300 < glargine U100 / detemir < NPH insulin
8. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
9. If no specific comorbidities (i.e., no established CVD, low risk of hypoglycemia, and lower priority to avoid weight gain or no weight-related comorbidities)
10. Consider country- and region-specific cost of drugs. In some countries, TZDs relatively more expensive and DPP-4i relatively cheaper

Melanie JD et al. Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) , 2018



Melanie JD et al. Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) , 2018

Avaliação do risco cardiovascular

SCORE system estimates the 10 year risk of a first fatal atherosclerotic event

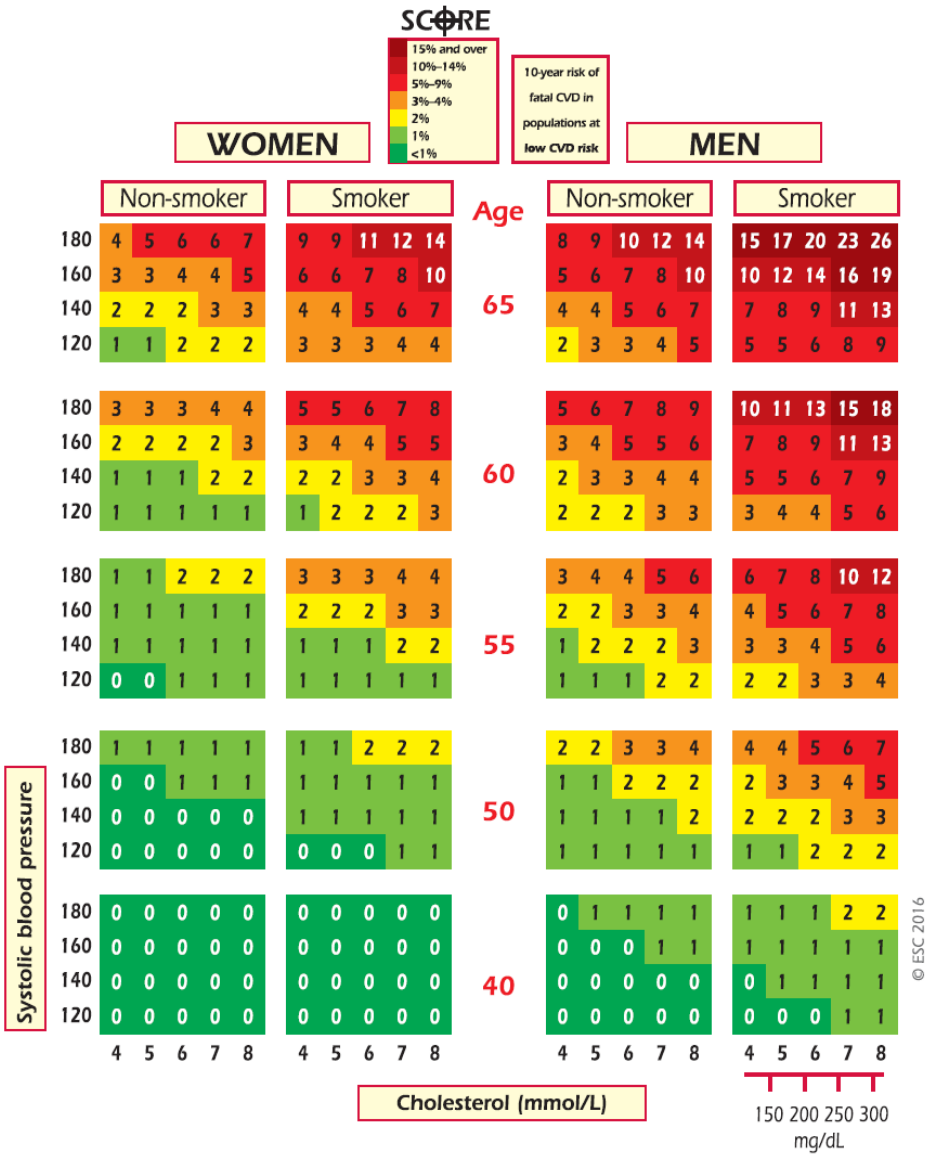
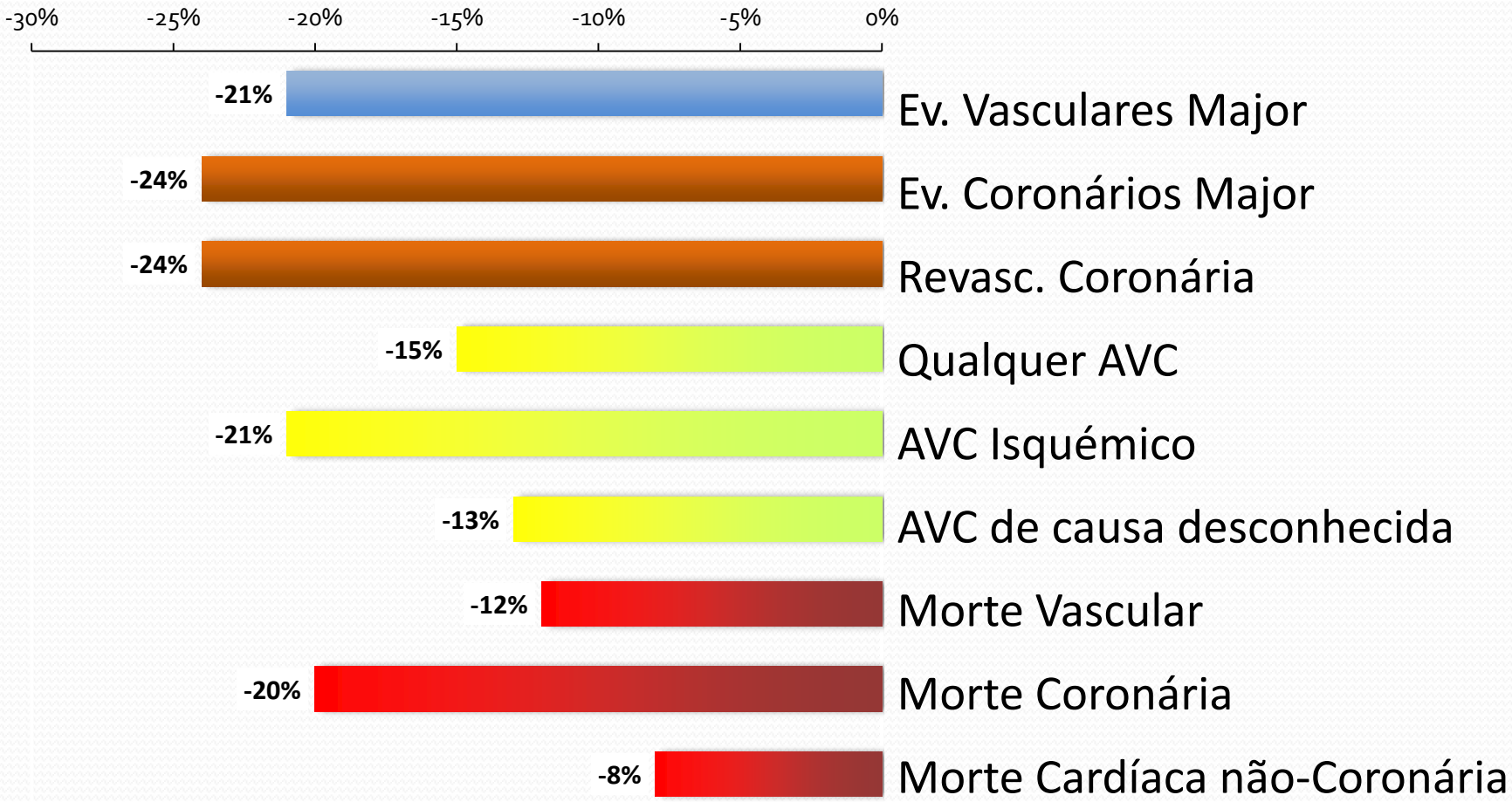


Table 5 Risk categories

Very high-risk	Subjects with any of the following: • Documented CVD, clinical or unequivocal on imaging. Documented clinical CVD includes previous AMI, ACS, coronary revascularization and other arterial revascularization procedures, stroke and TIA, aortic aneurysm and PAD. Unequivocally documented CVD on imaging includes significant plaque on coronary angiography or carotid ultrasound. It does NOT include some increase in continuous imaging parameters such as intima–media thickness of the carotid artery. • DM with target organ damage such as proteinuria or with a major risk factor such as smoking or marked hypercholesterolaemia or marked hypertension. • Severe CKD (GFR <30 mL/min/1.73 m2). • A calculated SCORE ≥10%.
High-risk	Subjects with: • Markedly elevated single risk factors, in particular cholesterol >8 mmol/L (>310 mg/dL) (e.g. in familial hypercholesterolaemia) or BP ≥180/110 mmHg. • Most other people with DM (with the exception of young people with type 1 DM and without major risk factors that may be at low or moderate risk). • Moderate CKD (GFR 30–59 mL/min/1.73 m²). • A calculated SCORE ≥5% and <10%.
Moderate-risk	SCORE is ≥1% and <5% at 10 years. Many middle-aged subjects belong to this category.
Low-risk	SCORE <1%.

Tratar o risco

Efeito da redução de 1 mmol/L no nível de LDL



Metanálise de 174.149 doentes incluídos em 27 ensaios clínicos de estatinas

CTT Collaborators. Lancet **2012**;380:581

Abordagem da dislipidemia pelas *Guidelines* da ESH/EAS

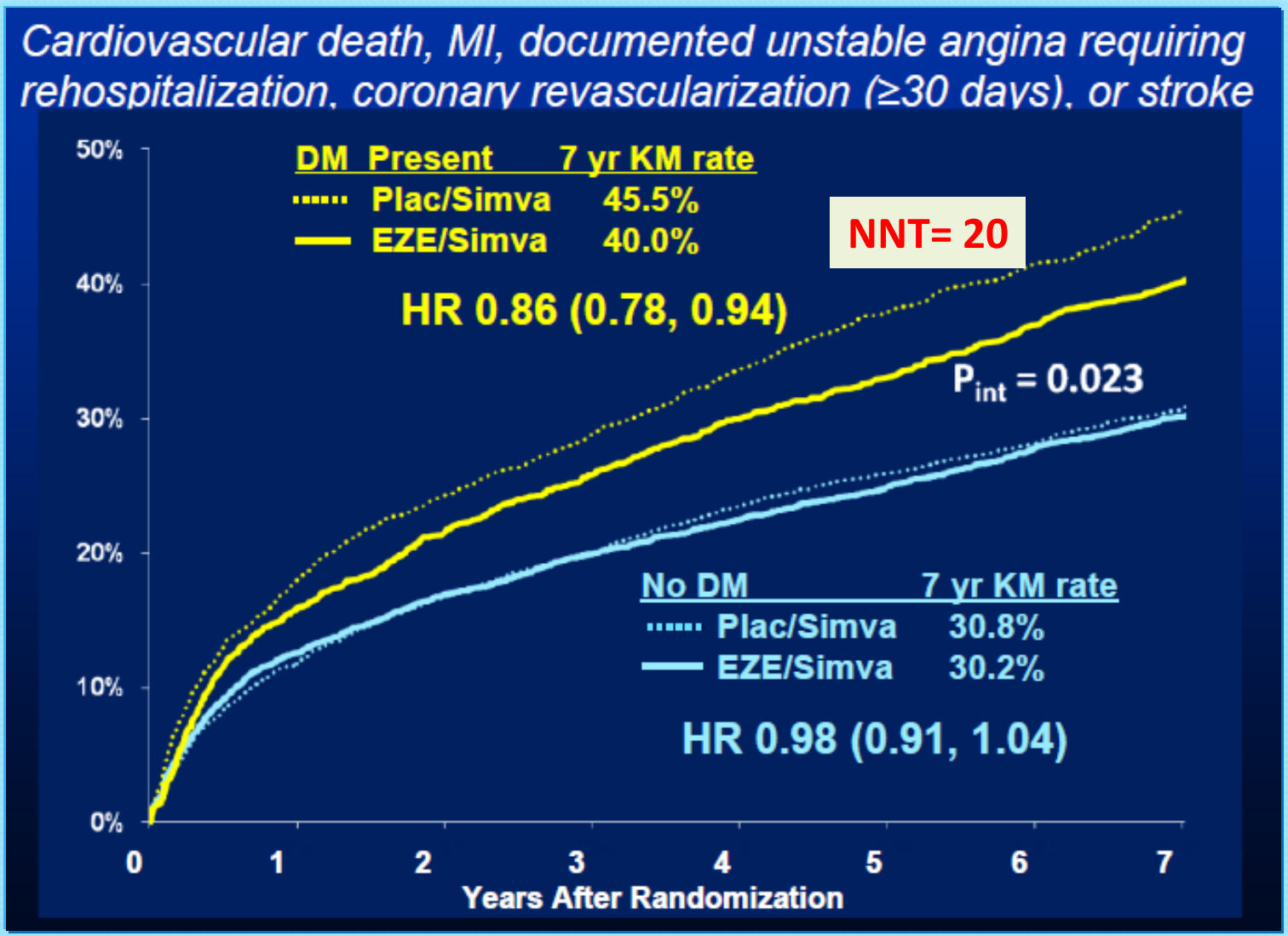
C-LDL É O OBJECTIVO TERAPÊUTICO PRINCIPAL

Recommendations	Class [a]	Level [b]	Ref [c]
LDL-C is recommended as the primary target for treatment.	I	A	64, 68
TC should be considered as a treatment target if other analyses are not available.	IIa	A	64, 123
Non-HDL-C should be considered as a secondary treatment target.	IIa	B	103
ApoB should be considered as a secondary treatment target, when available.	IIa	B	103, 124
HDL-C is not recommended as a target for treatment.	III	A	92, 93
The ratios apoB/apoAI and non-HDL-C/HDL-C are not recommended as targets for treatment.	III	B	103

RISCO CARDIOVASCULAR	OBJETIVO TERAPÊUTICO
Risco CV Muito Alto	**C-LDL inferior a 70 mg/dl** Se não for possível atingir o valor alvo é desejável atingir uma redução igual ou superior a 50% do C-LDL
Risco CV Alto	**C-LDL inferior a 100 mg/d** Se não for possível atingir o valor alvo de é desejável atingir uma redução igual ou superior a 50% do C-LDL
Risco CV Baixo a Moderado	**C-LDL inferior a 115 mg/d**

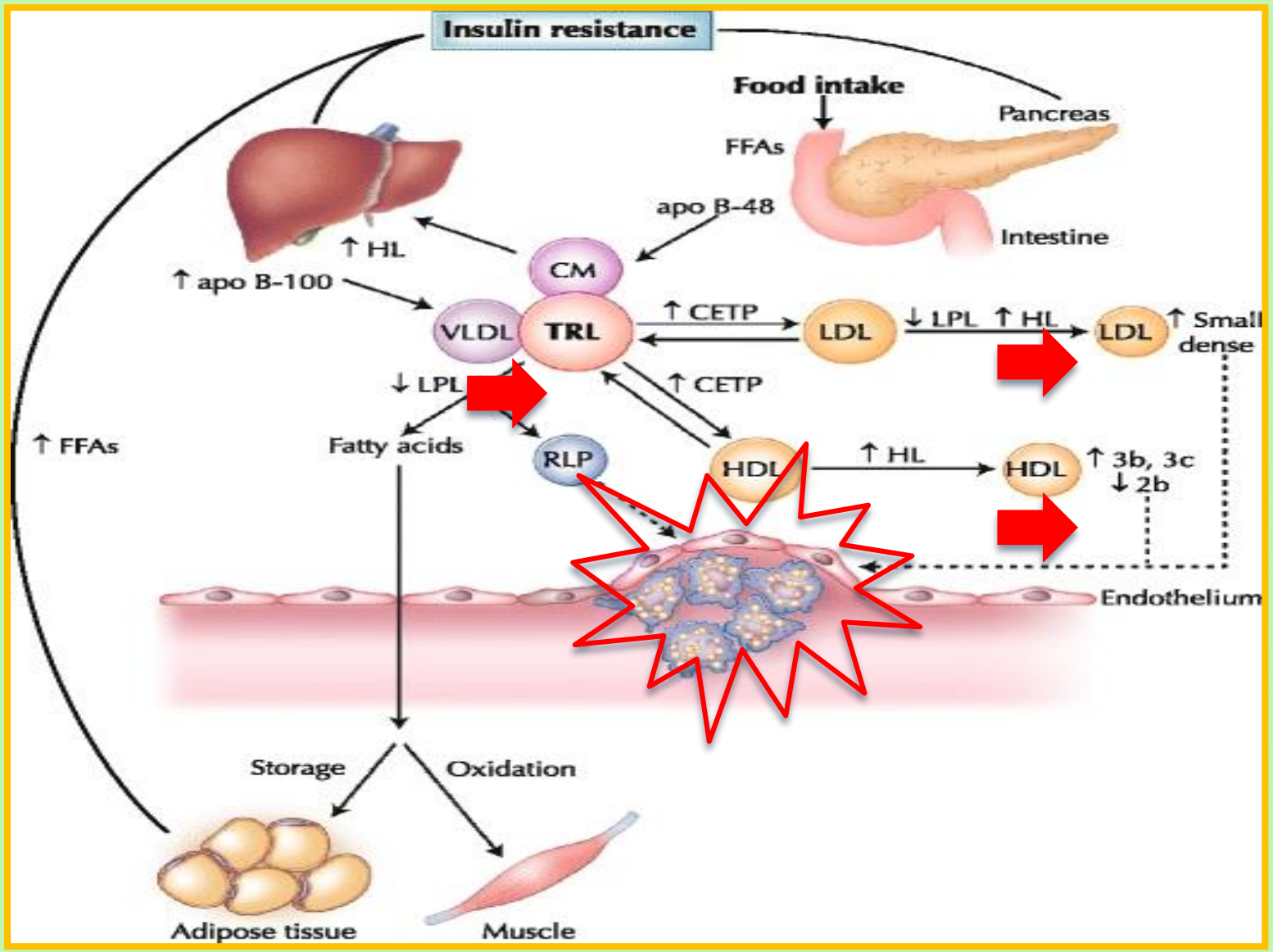
Adaptado de:
Catapano, A.L., et al., 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias. European Heart Journal, 2016. 37(39): p. 2999-3058.
Norma 019/2011: Abordagem Terapêutica das Dislipidemias no Adulto. 2017, Direção-Geral da Saúde.

Endpoint primário — ITT



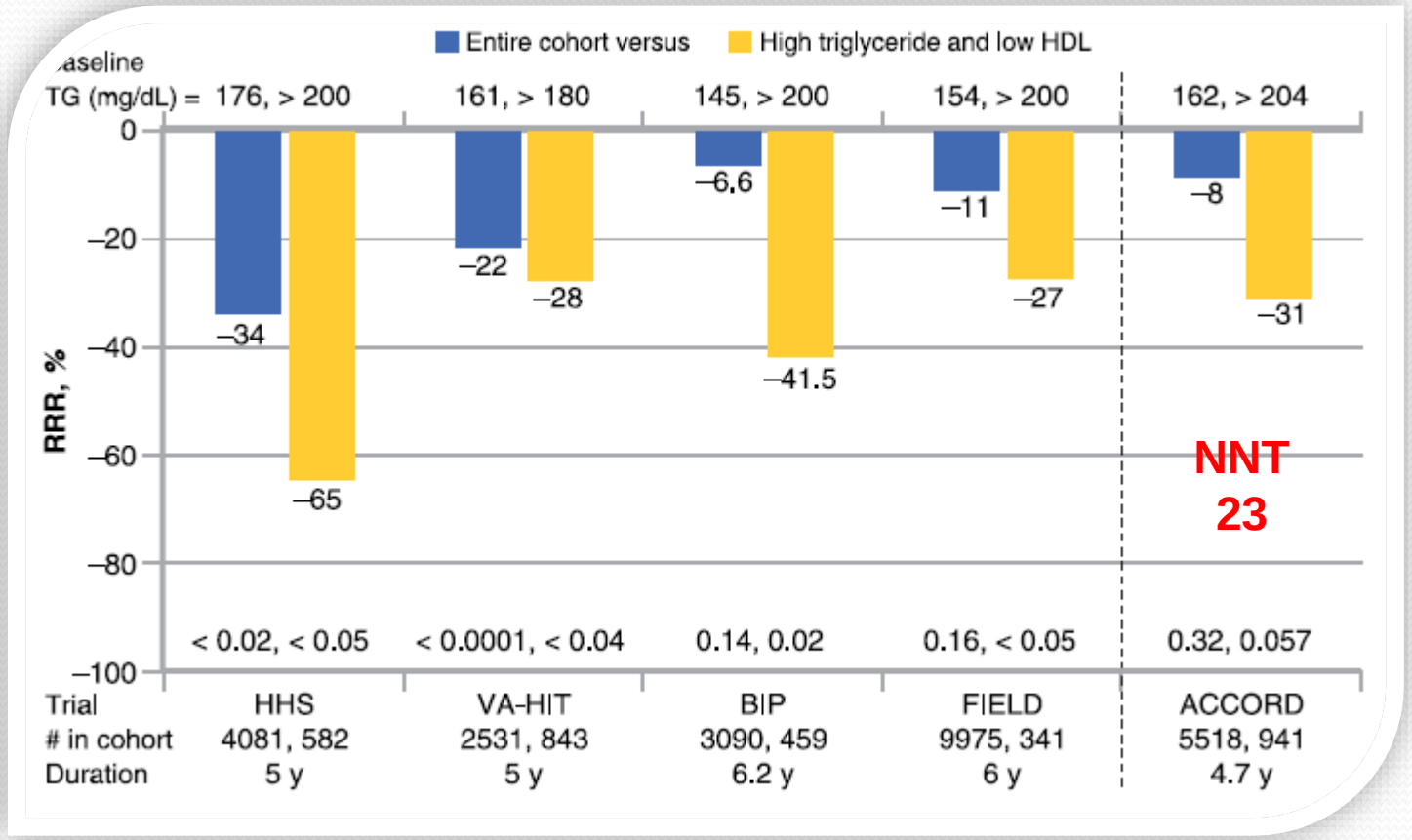
Insulinoresistênica e dislipidemia aterogénica

Redução do risco vascular persistente "não residual"



Aterosclerose

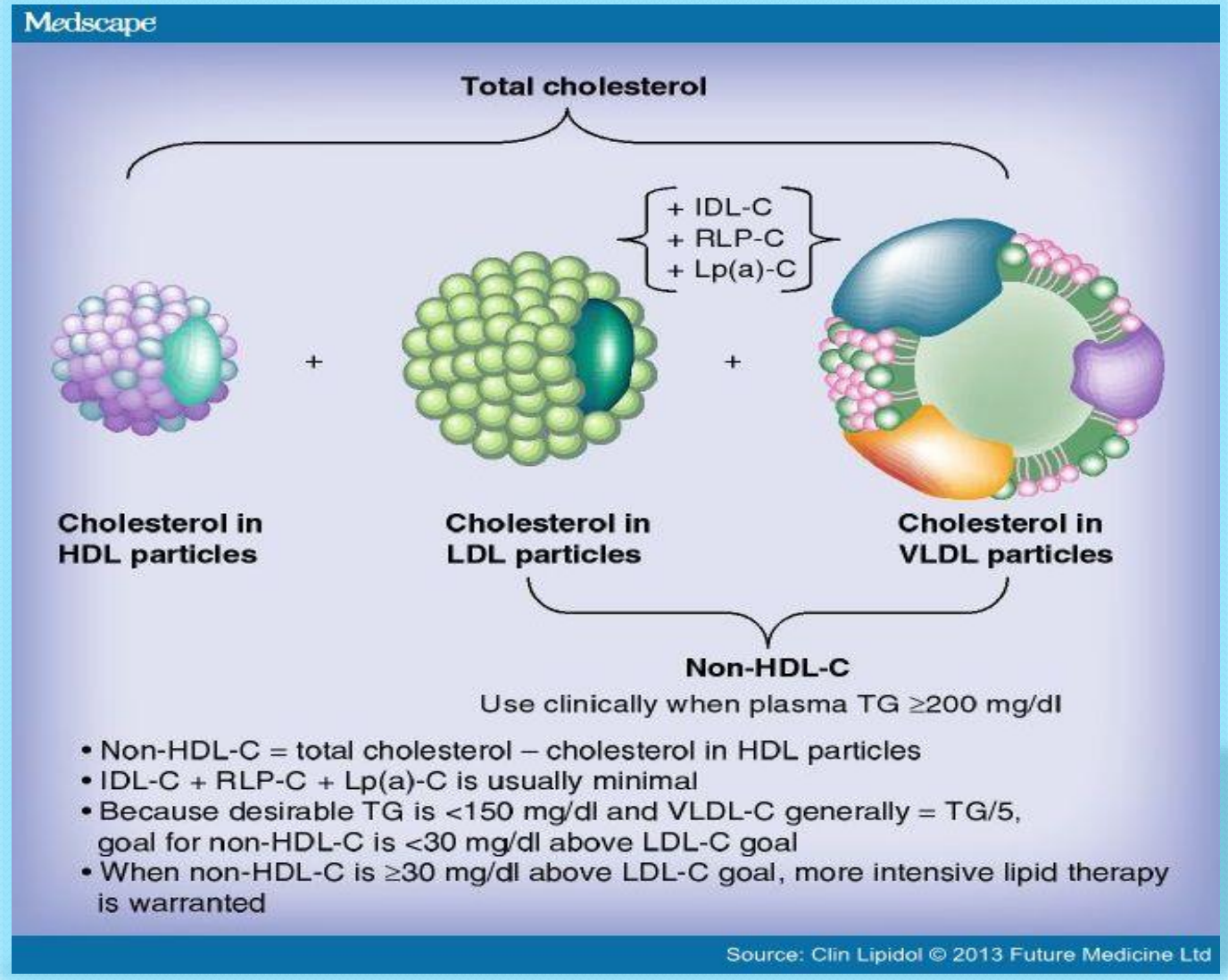
Dislipidemia aterogénica



ACCORD—Action to Control Cardiovascular Risk in Diabetes; BIP—Bezafibrate Infarction Prevention; FIELD—Fenofibrate Intervention and Event Lowering in Diabetes; HDL—high-density lipoprotein; HHH—Helsinki Heart Study; RRR—relative risk reduction; TG—triglycerides; VA-HIT—Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial.

2016 ESC/EAS Guidelines Management of Dyslipidaemias

C-não HDL



2016 ESC/EAS Guidelines Management of Dyslipidaemias
C-não HDL

Table 7 Recommendations for lipid analyses in cardiovascular disease risk estimation

Recommendations	Class [a]	Level [b]
TC is to be used for the estimation of total CV risk by means of the SCORE system.	I	C
LDL-C is recommended to be used as the primary lipid analysis for screening, risk estimation, diagnosis and management. HDL-C is a strong independent risk factor and is recommended to be used in the HeartScore algorithm.	I	C
TG adds information on risk and is indicated for risk estimation.	I	C
Non-HDL-C is a strong independent risk factor and should be considered as a risk marker, especially in subjects with high TG.	I	C

Table 9 Recommendations for lipid analyses as treatment targets in the prevention of cardiovascular disease

Recommendations	Class [a]	Level [b]	Ref [c]
LDL-C is recommended as the primary target for treatment.	I	A	64, 68
TC should be considered as a treatment target if other analyses are not available.	IIa	A	64, 123
Non-HDL-C should be considered as a secondary treatment target.	IIa	B	103
ApoB should be considered as a secondary treatment target, when available.	IIa	B	103, 124
HDL-C is not recommended as a target for treatment.	III	A	92, 93
The ratios apoB/apoA1 and non-HDL-C/HDL-C are not recommended as targets for treatment.	III	B	103

Medicação proposta

Bisoprolol 2,5 mg id

Olmesartan 20mg + Amlodipina 5 mg id

AAS 100 mg id

Clopidogrel 75 mg id

Metformina/iDPP4 bid

iSGLT2 id

Pantoprazol 20 mg id

Estatina/Ezetimiba 20 mg + 10 mg id.

EVOLUÇÃO CLÍNICA

Avaliação a 24 meses

Albumina/Creatinina (urina) 40,65 mg/g

Colesterol total 110 mg/dL

Triglicerídeos 168 mg/dL

HDL - Colesterol 43 mg/dL

LDL - Colesterol Calculado 52 mg/dL

Evolução da HbA_{1c} ao longo do tempo:

Pontos a reter

- O doente com preDM/DM2 possui muito-muito elevado risco cardiovascular
- Dislipidemia no doente com alterações glicémicas caracteriza-se por elevação dos triglicerideos (e seus remanescentes), diminuição do C-HDL e partículas de C-LDLpd
- Necessidade de alcançar valor alvo de C-LDL para o calculo de risco CV
- A ⇩ TG (nomeadamente das partículas remanescentes) possibilita a diminuição dos eventos CV em doentes diabéticos tipo 2 de elevado risco CV
- O C-não HDL é um marcador de risco CV e alvo terapêutico em doentes com elevado risco CV e elevação dos TG (> 200 mg/dl).