

Farmacoterapia no DM tipo 2



1921



Frederick Banting e Charles Best extraem insulina do pâncreas de cães, injetam em animais pancreatetectomizados e provam o conceito. James Collip purifica o extrato para uso em humanos. Primeira injustiça na história da diabetologia.

1936 a 1950



Hans Christian Hägedorn desenvolve a insulina NPH (“Neutral Protamine Hägedorn”). Eli Lilly nos EUA e Nordisk, na Dinamarca, iniciam produção.

1947-1949

A detailed medical form titled "BRIEF CARDIOVASCULAR EXAMINATION FOR SUBJECT SCREENING". The form is divided into several sections, including "GENERAL", "HEART", "LUNGS", "BLOOD PRESSURE", "ECG", "X-RAY", "LABORATORY", and "REMARKS". It contains various fields for recording patient information, examination findings, and test results. A circled number "1" is visible in the "ECG" section.

Primeiros estudos longitudinais epidemiológicos avaliando fatores de risco (Framingham, Twin Cities). Academia pede estudos de intervenção. Inicia a era do ECR.

1936 a 1950



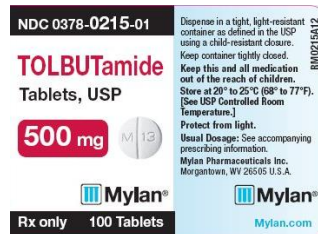
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1955



Tolbutamida é comercializada pela primeira vez

1957

CLINICAL EXPERIENCE WITH
THE PHENFORMIN IN THE
MANAGEMENT OF DIABETES*

J. A. WATSON, M.D., M.B., F.R.C.P. (C),
F.R.S. (Edin.), F.R.C.P. (Lond.), and
W. J. HALL, M.D., F.R.C.P. (C)

The search for more effective substitutes for insulin has been greatly accelerated by the advent of the synthetic compounds of which phenformin (Ariston, Myristin) is the best known example. However, review of this field must be based on the studies which have assessed the safety and efficacy of the synthetic compounds of which phenformin is the best known example. In this review, the authors have considered the safety and efficacy of phenformin in the management of diabetes mellitus. The authors have also considered the safety and efficacy of phenformin in the management of diabetes mellitus in the presence of other complications of diabetes mellitus.

Received for publication Oct. 15, 1956.

*From the Department of Medicine, University of Toronto, Ontario, Canada.

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Fenformina nos EUA Metformina na França

1958



Clorpropamida

Perguntas se acumulavam. Controle da glicose? Como? Complicações do DM?



1959-1970: University Group Diabetes Program (UGDP)





ADA 1970:

Insulina não confere benefício adicional à dieta.

Por consequência, não há razão para crer que drogas que estimulam insulina (por exemplo, tolbutamida, clorpropamida) sejam úteis.

Fenformina retirada do mercado americano em 1978.

Metformina termina discriminada nas Américas, também.

Em 1975, ingleses começam o UKPDS, para responder adequadamente às perguntas deixadas abertas pelo UGDP.

1983



Segunda geração de sulfonilureias chega ao mercado. Meia vida mais curta, menor potência, menos hipoglicemia. ECR escassos. Alguns estudos com gliclazida.

1993:

DCCT responde a questão do controle:

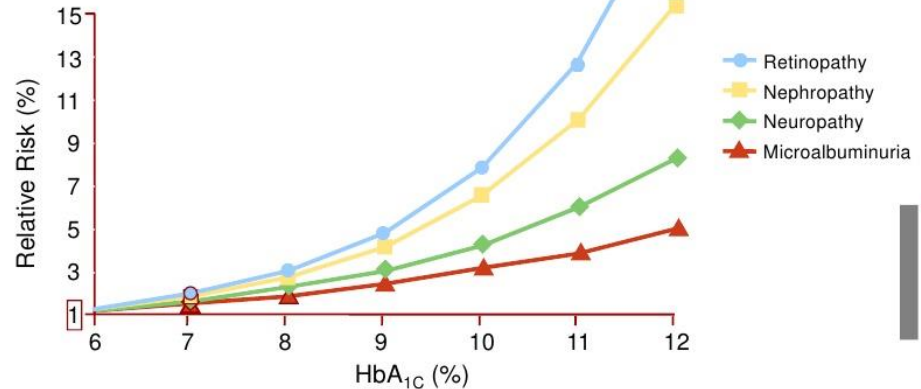
Melhor controle glicêmico reduz incidência de complicações microvasculares no DM tipo 1.

Meta de HbA1c 7,0 %.

DCCT e EDIC sugerem que bom controle possa impactar DCV

Relationship of HbA_{1c} to Risk of Microvascular Complications

Diabetes Control and Complications Trial (DCCT)



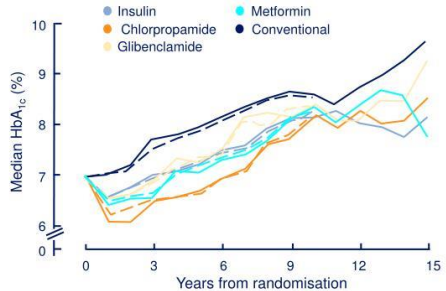
Skyler JS. Endocrinol Metab Clin North Am. 1996;25:243-254.



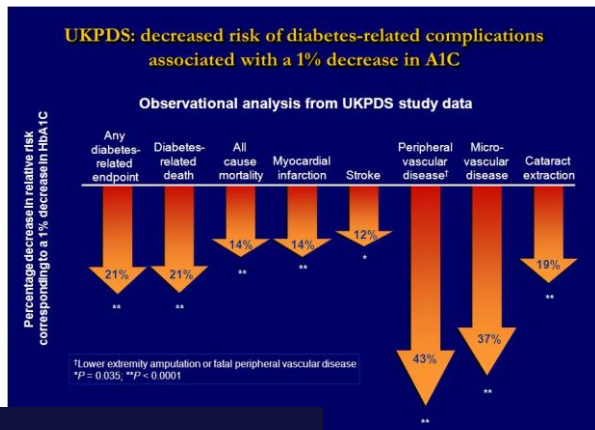
A group of men in cowboy attire, including dark jackets with yellow accents, light blue trousers, and black hats, are riding horses through a wooded area. They are holding rifles and pistols, suggesting a hunt or a military-style ride. The scene is captured in a cinematic style with a slightly desaturated color palette. The text 'UKPDS 1997' is overlaid in the center in a bold, blue, sans-serif font.

**UKPDS
1997**

UKPDS 34: intensive therapy reduced HbA_{1c}



Adapted from: *Lancet* 1998;352:854-65
Dashed lines indicate patients followed for 10 years
Solid lines indicate all patients assigned to regimen



3500 pacientes

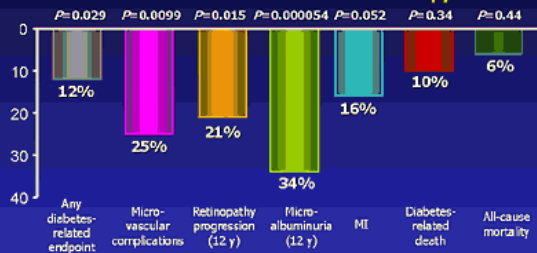
Mais de 10 anos de acompanhamento

Distingue obesos de não obesos

Primeiro ECR examinando modificação de fatores de risco e morbi-mortalidade em DM2.

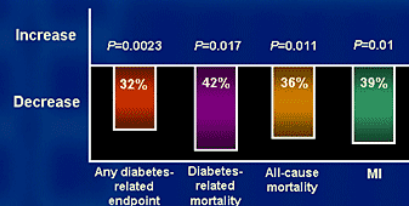
UKPDS Results of Intensive Therapy: Sulfonylurea/Insulin

Risk Reduction vs Conventional Therapy



UKPDS Group. *Lancet*. 1998;352:837-853.

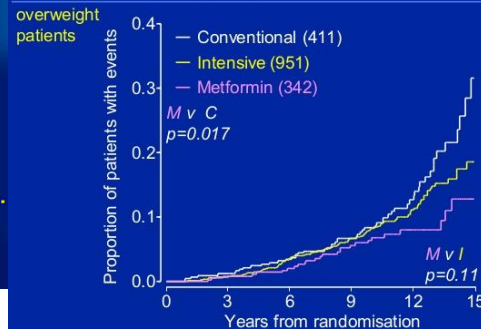
UKPDS Results of Intensive Therapy: Risk Decrease* - Diet + Metformin



*Risk reduction compared with conventional therapy.

American Diabetes Association. *Diabetes Care*. 1999;22(suppl 1):S27-S31.
UKPDS Group. *Lancet*. 1998;352:854-866.

Diabetes related deaths

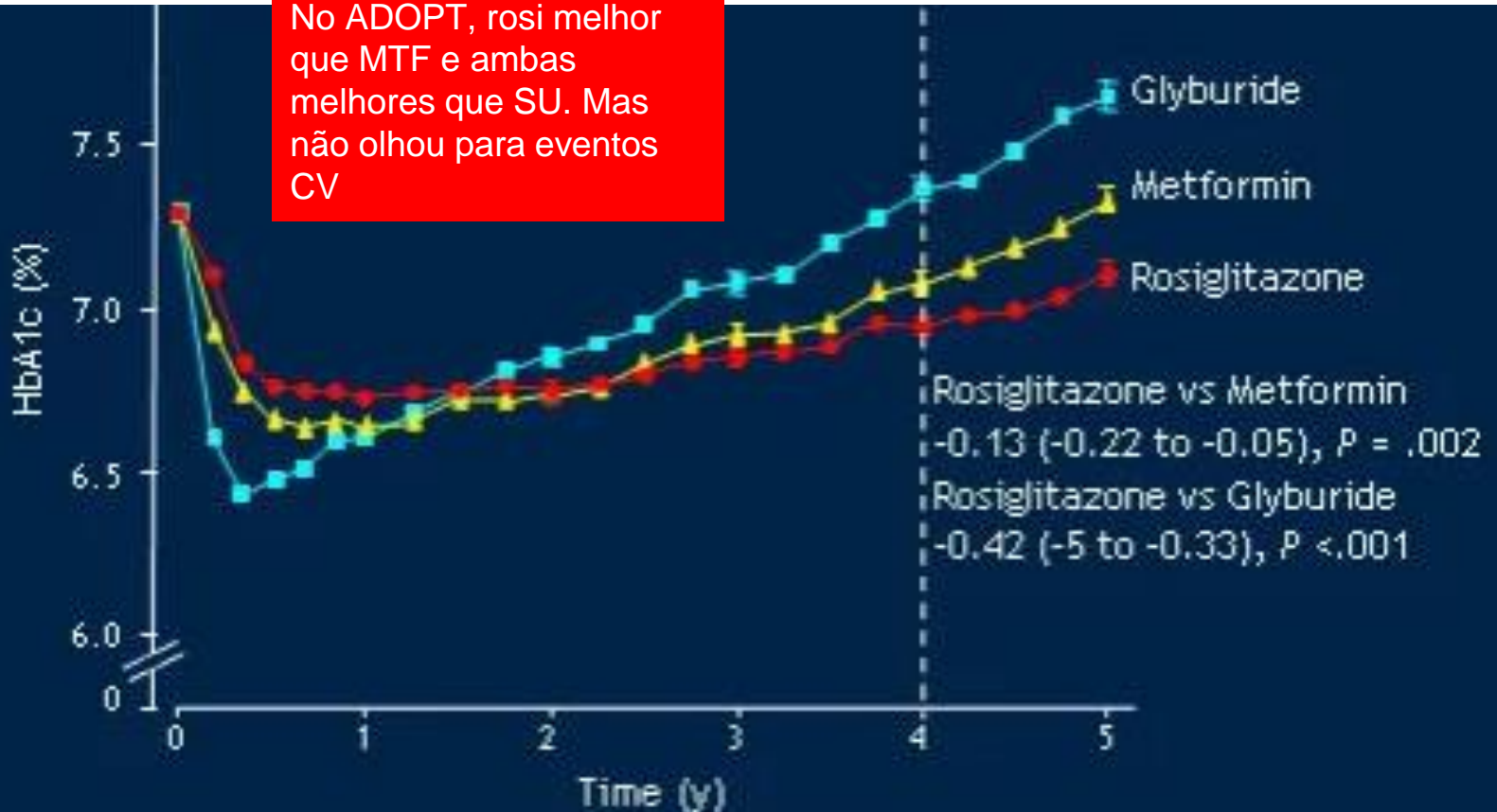


ukpds

- 1990 Primeira glitazona (tiazolidinediona): troglitazona. Atua em PPAR-gama. Reduz insulinemia, reduz resistência insulínica. Ganho de peso. Em pós-marketing: mortes por hepatotoxicidade. Retirada em 1997.
- 1996 Inibidores da alfa-glucosidase: acarbose. Redução de eventos CV em pre-diabetes
- 1996 Meglitinidas. Ação mais rápida e breve que SUs. Menor incidência de hipoglicemias (?). Menor ganho de peso (?)
- 1999 Rosiglitazona. Sem hepatotoxicidade. Edema. Ganho de peso.

2002 ADOPT

No ADOPT, rosi melhor que MTF e ambas melhores que SU. Mas não olhou para eventos CV



2007 – metanálise Nissen no NEJM. Maior mortalidade CV com rosiglitazona?

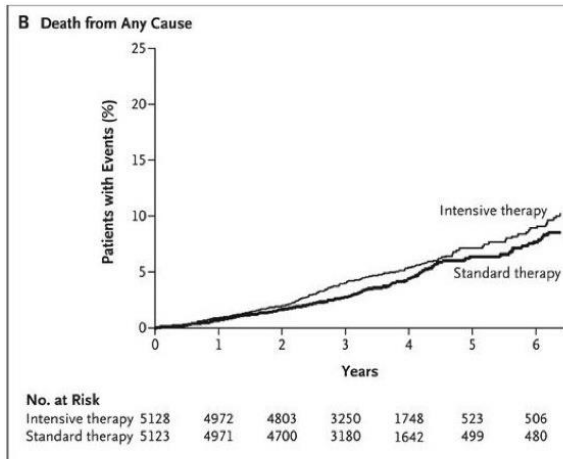


Estima-se que o custo de desenvolvimento foi superior a US\$ 2 bi

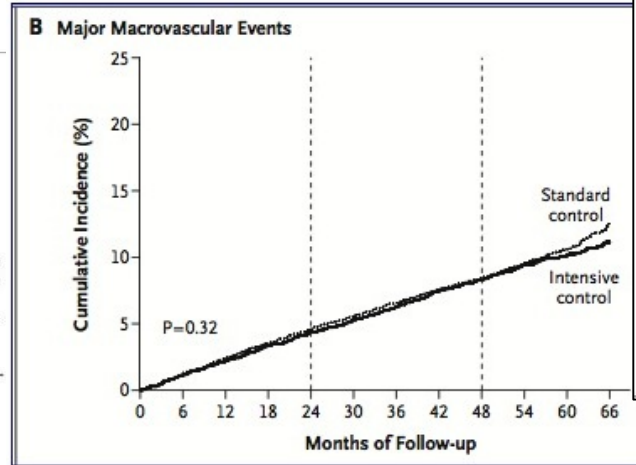
O “market share” da GSK caiu 40% em 2007, após publicação no NEJM

FDA e EMEA passam a exigir ECRs de segurança cardiovascular para submissões de novos agentes anti-hiperglicemiantes.

2008 - ano de grandes ECRs em DM2

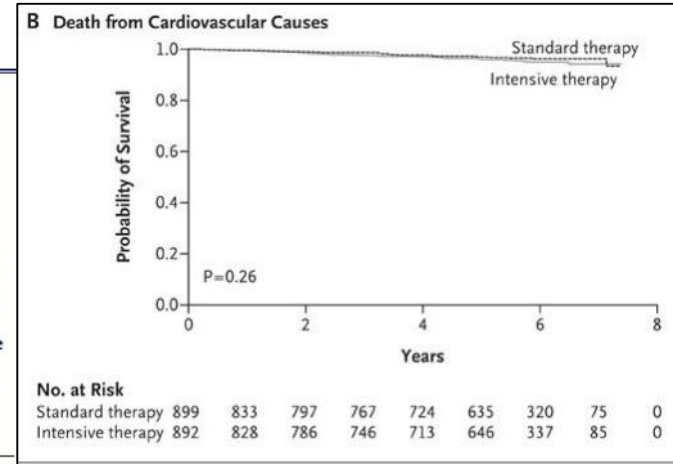


ACCORD N Engl J Med 2008;358:2545-59.



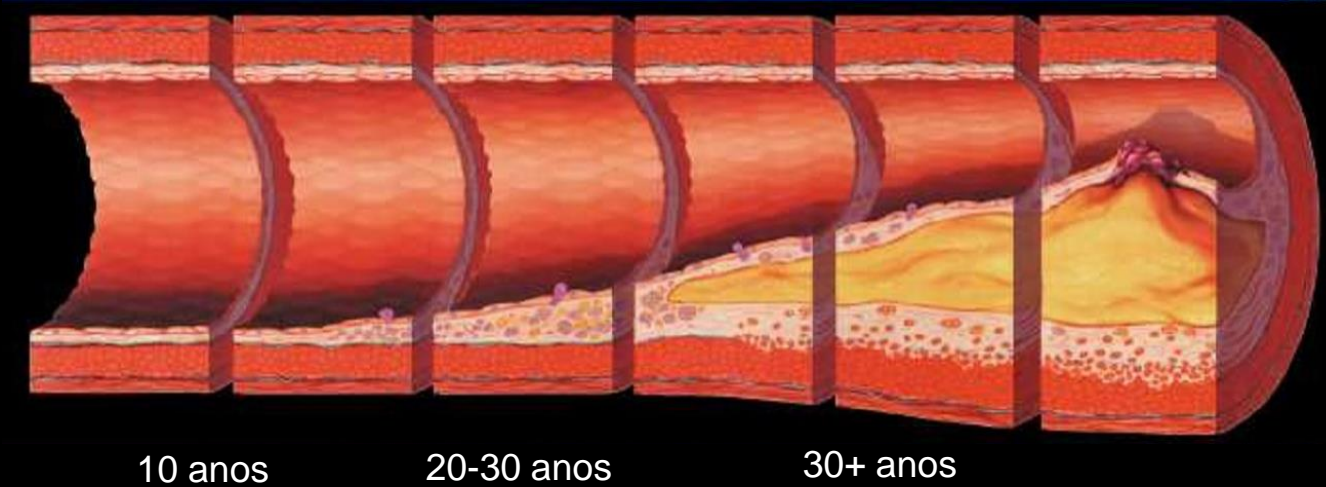
N Engl J Med 2008;358:2560-72.

ADVANCE



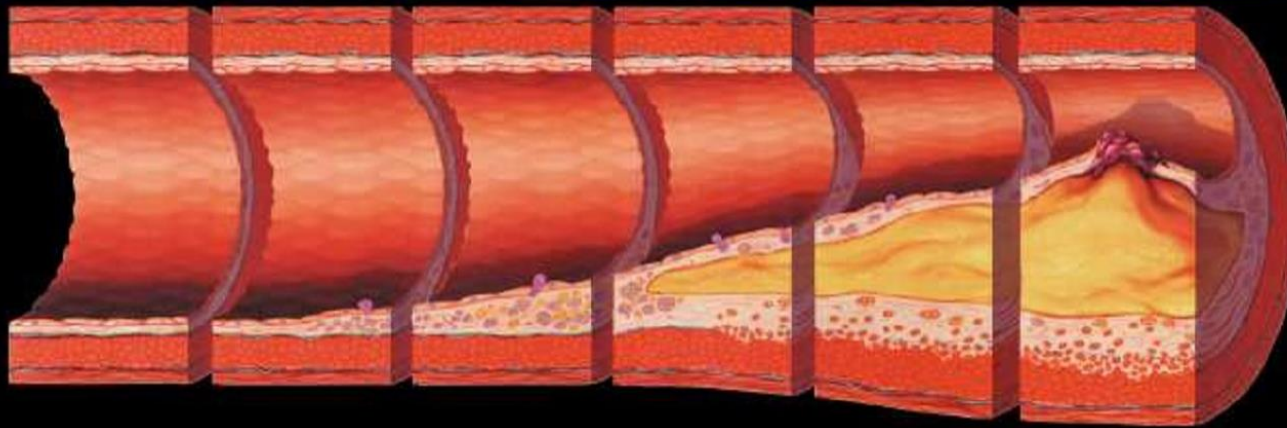
VADT

O controle intenso do DM2 não parece aumentar mortalidade cardiovascular, mas também não a reduz. Questões levantadas: hipoglicemia, janela de oportunidade (intensificar nos primeiros 5-10 anos), uso de glitazona nos ensaios, manejo de outros fatores.



Janela de oportunidade para controle da glicemia

Possibilidade de dano por hipoglicemia. Risco de eventos aumenta progressivamente.



10 anos

20-30 anos

30+ anos

HAS, lipídios, inflamação, disfunção endotelial, massa corporal, hiperinsulinemia

Células
esponjosas

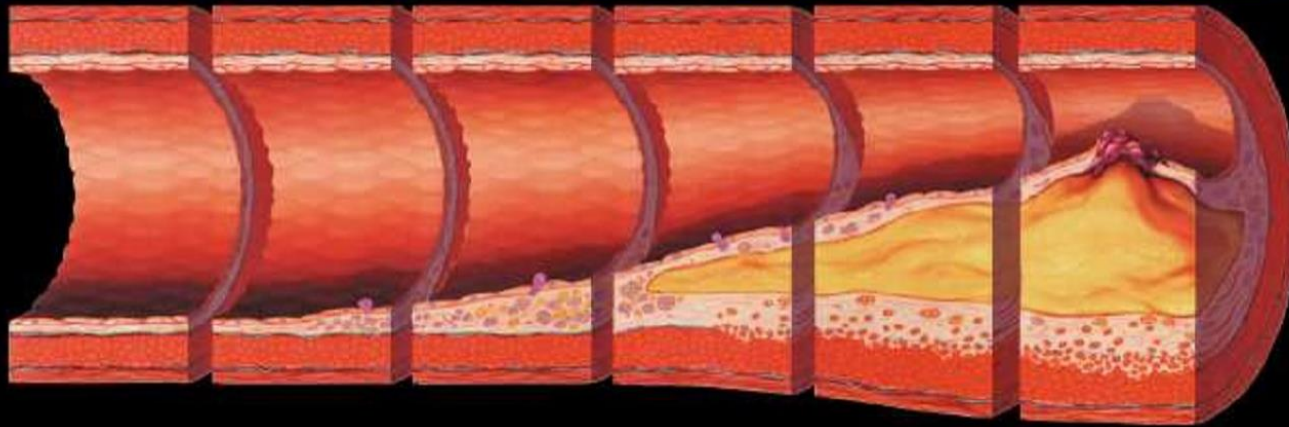
Estria
gordurosa

Lesão
intermediária

Ateroma

Placa
fibrosa

Lesão
complicada
(ruptura)



10 anos

20-30 anos

30+ anos

Drogas
específicas

~~HAS~~, ~~lipídios~~, inflamação, disfunção endotelial, massa corporal, hiperinsulinemia

Células
esponjosas

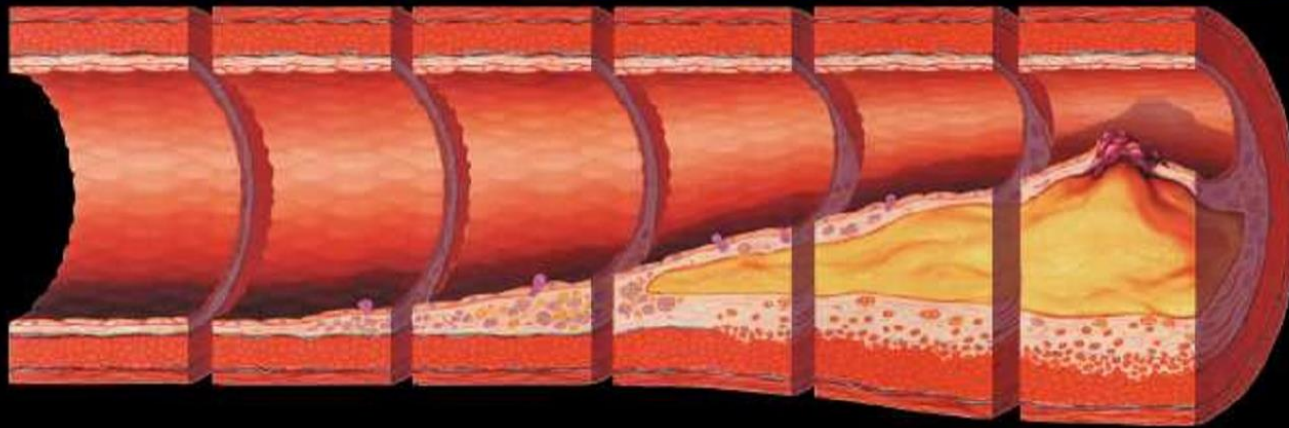
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?

?

HAS, lipídios, **inflamação**, **disfunção endotelial**, **massa corporal**, **hiperinsulinemia**

Células
esponjosas

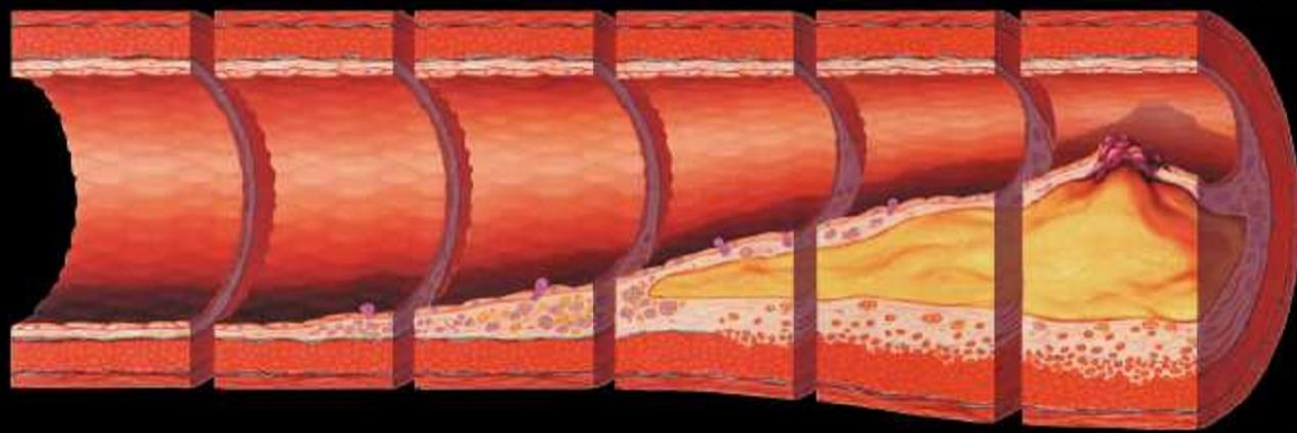
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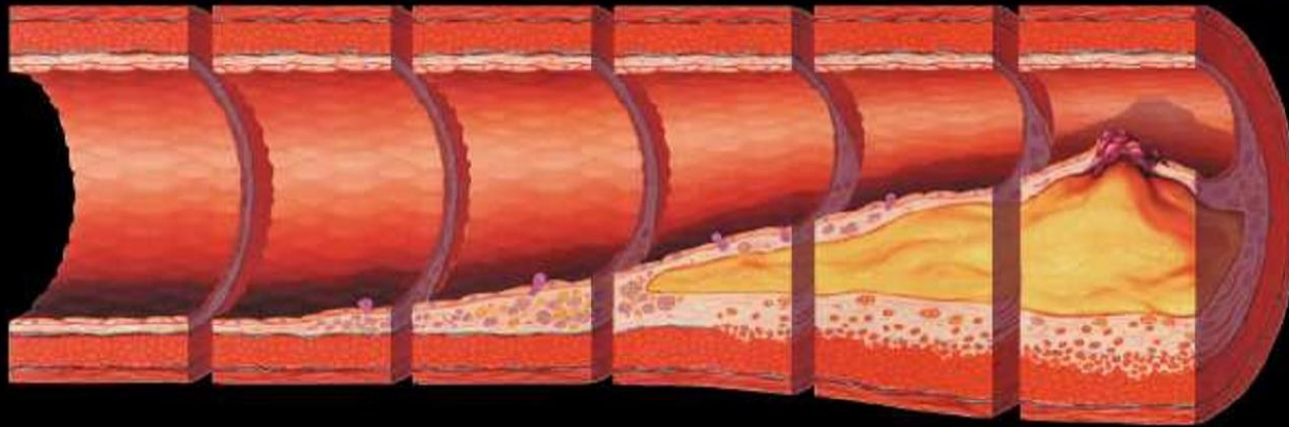
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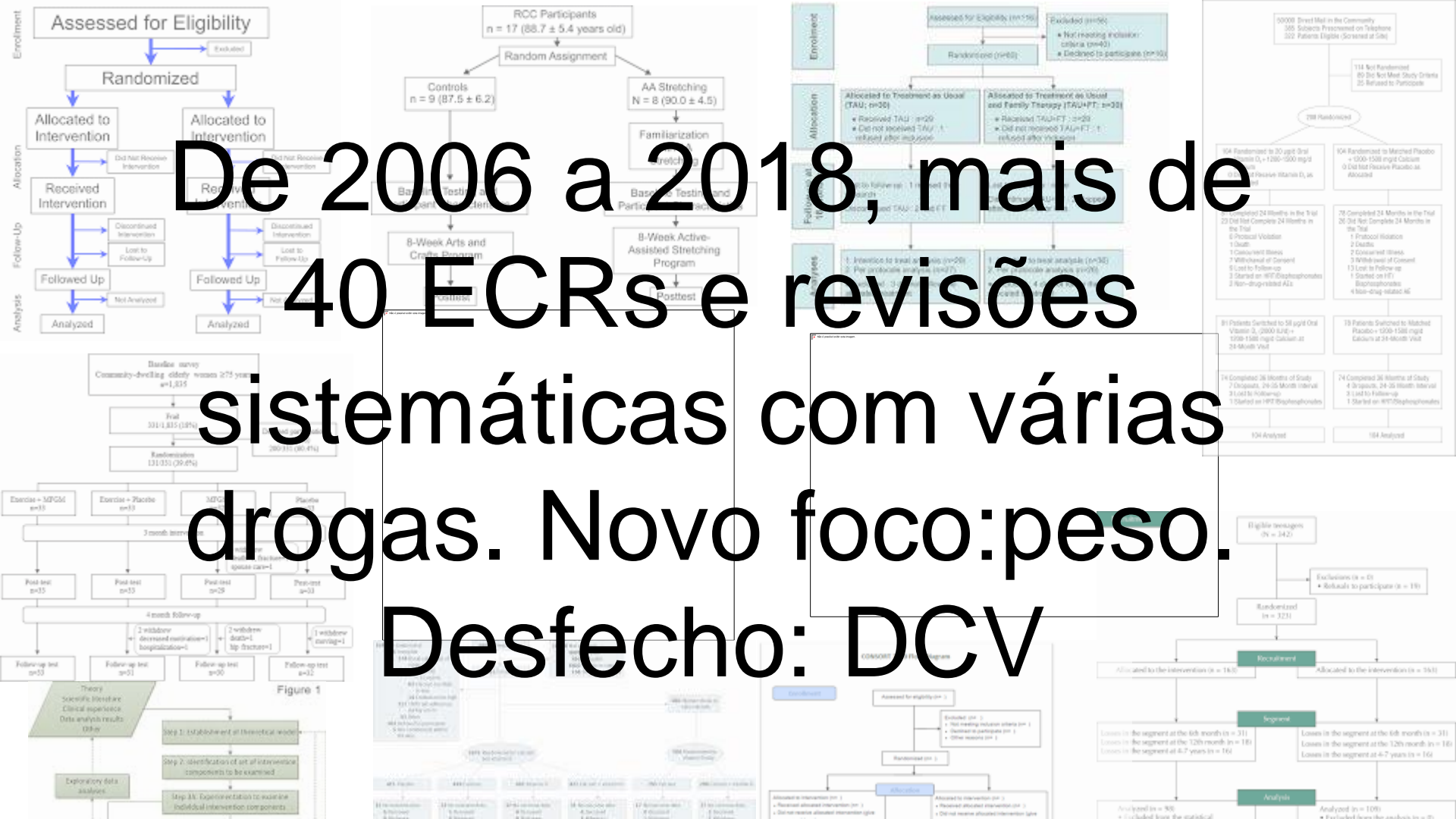


10 anos

20-30 anos

30+ anos

De 2006 a 2018, mais de 40 ECRs e revisões sistemáticas com várias drogas. Novo foco: peso. Desfecho: DCV



2006: era dos incretinomiméticos

Análogos do GLP1:

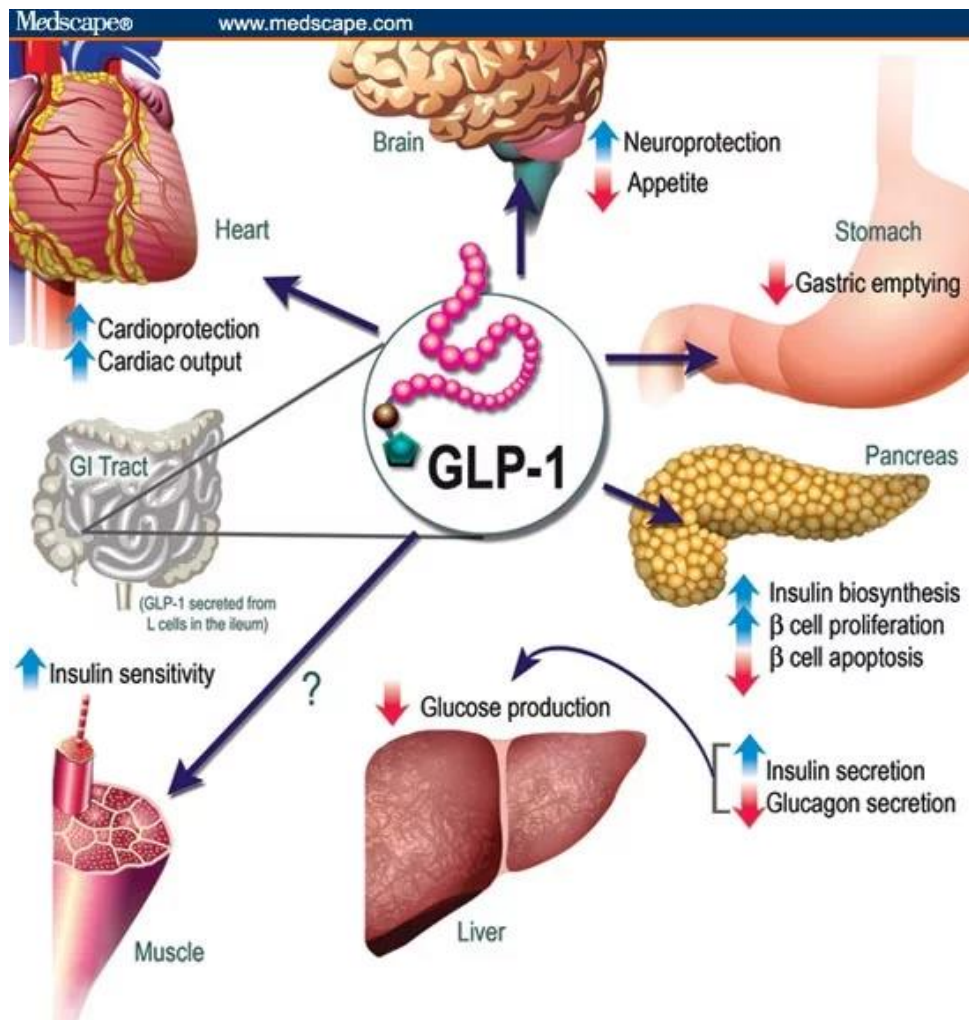
Exenatida
Liraglutida
Dulaglutida
Lixisenatida
Semaglutida

Maior potência.
Induzem perda de peso.

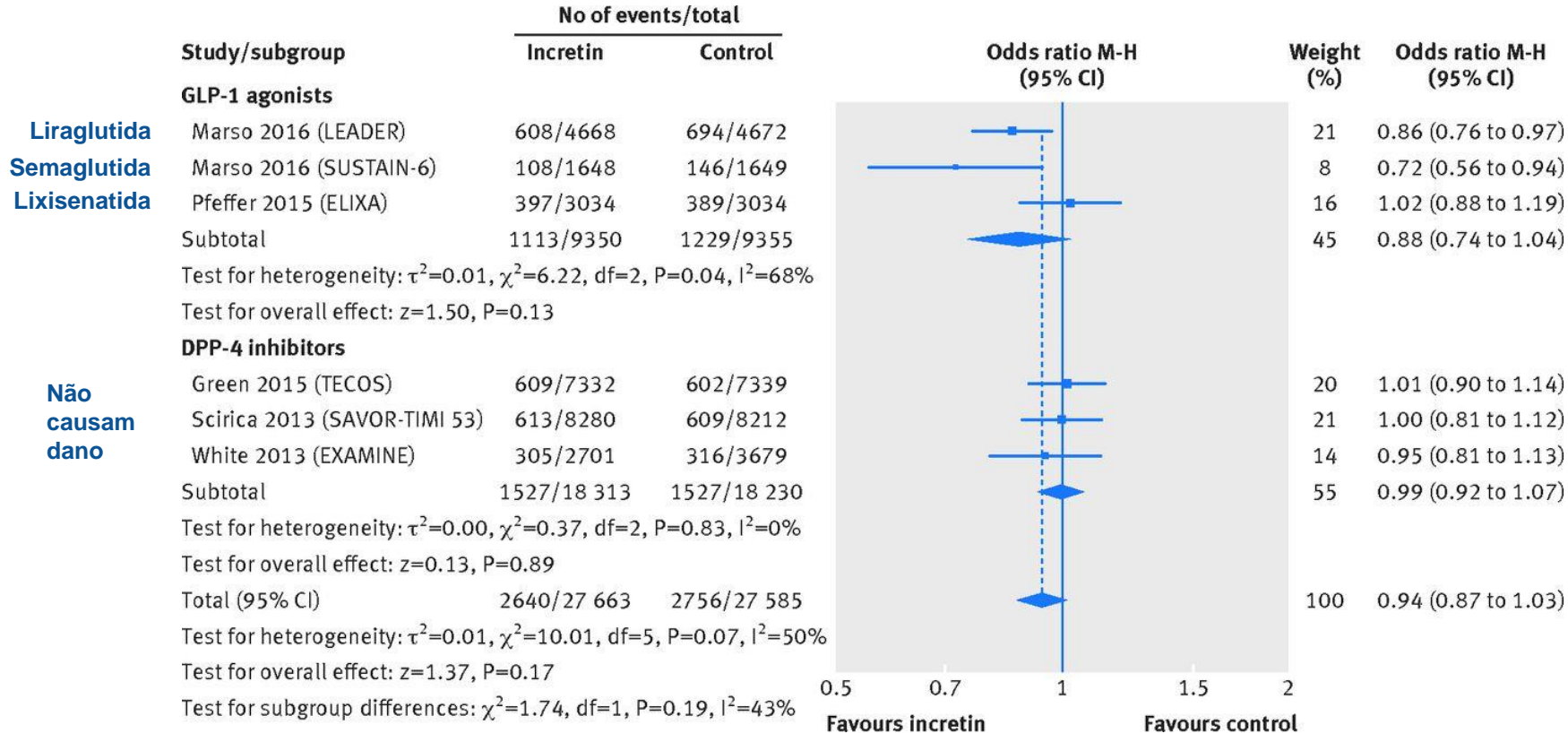
Bloqueadores da DPP4 (aumentam vida plasmática do GLP1 nativo):

Sitagliptina
Vildagliptina
Saxagliptina
Linagliptina

Menor potência.
Não induzem ganho de peso.



Incretinomiméticos não aumentam mortalidade CV. Lira e Sema podem ser protetoras.



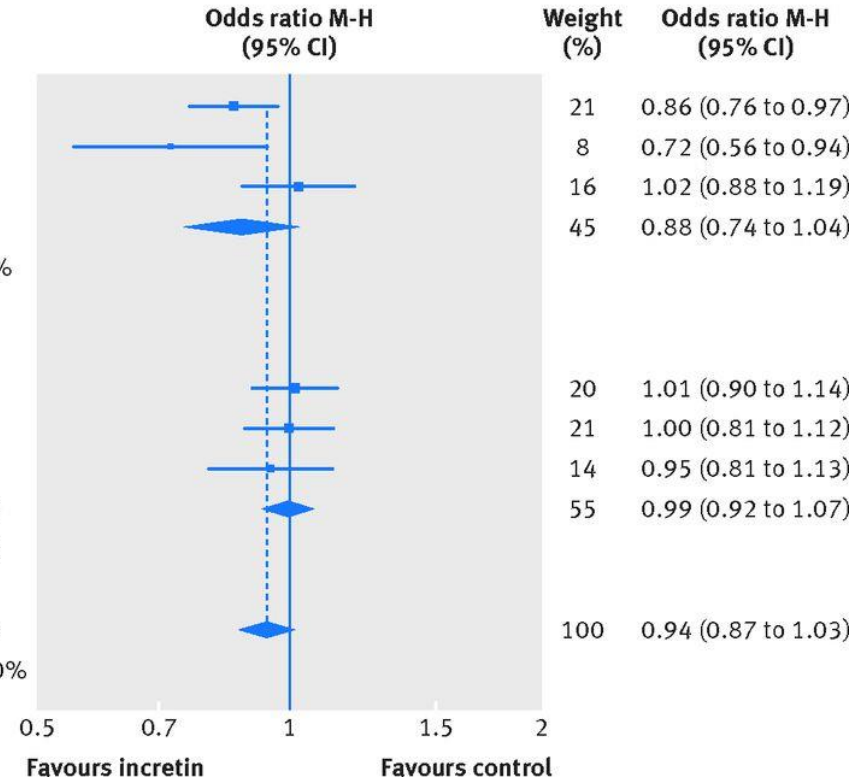
Incretinomiméticos não aumentam mortalidade CV. Lira e Sema podem ser protetoras.

Liraglutida
Semaglutida



Peso?
Inflamação
Pressão?
Função VE?

Study/subgroup	No of events/total	
	Incretin	Control
GLP-1 agonists		
Marso 2016 (LEADER)	608/4668	694/4672
Marso 2016 (SUSTAIN-6)	108/1648	146/1649
Pfeffer 2015 (ELIXA)	397/3034	389/3034
Subtotal	1113/9350	1229/9355
Test for heterogeneity: $\tau^2=0.01$, $\chi^2=6.22$, $df=2$, $P=0.04$, $I^2=68\%$		
Test for overall effect: $z=1.50$, $P=0.13$		
DPP-4 inhibitors		
Green 2015 (TECOS)	609/7332	602/7339
Scirica 2013 (SAVOR-TIMI 53)	613/8280	609/8212
White 2013 (EXAMINE)	305/2701	316/3679
Subtotal	1527/18 313	1527/18 230
Test for heterogeneity: $\tau^2=0.00$, $\chi^2=0.37$, $df=2$, $P=0.83$, $I^2=0\%$		
Test for overall effect: $z=0.13$, $P=0.89$		
Total (95% CI)	2640/27 663	2756/27 585
Test for heterogeneity: $\tau^2=0.01$, $\chi^2=10.01$, $df=5$, $P=0.07$, $I^2=50\%$		
Test for overall effect: $z=1.37$, $P=0.17$		
Test for subgroup differences: $\chi^2=1.74$, $df=1$, $P=0.19$, $I^2=43\%$		



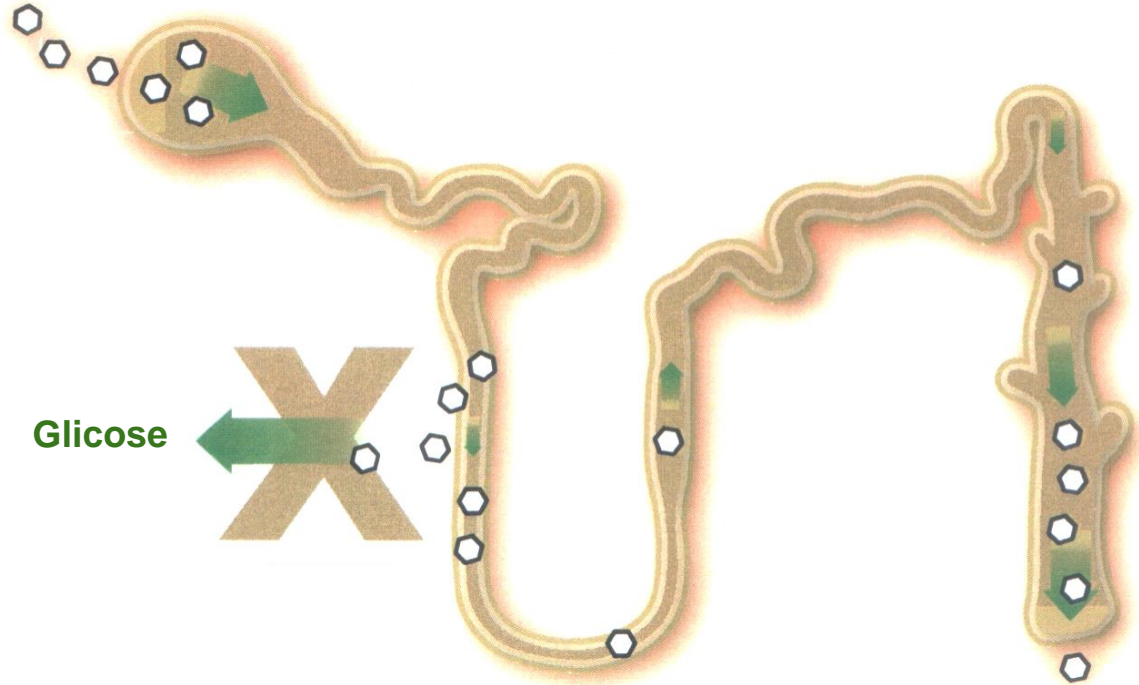
2009-2010

Inibidores do SGLT-2

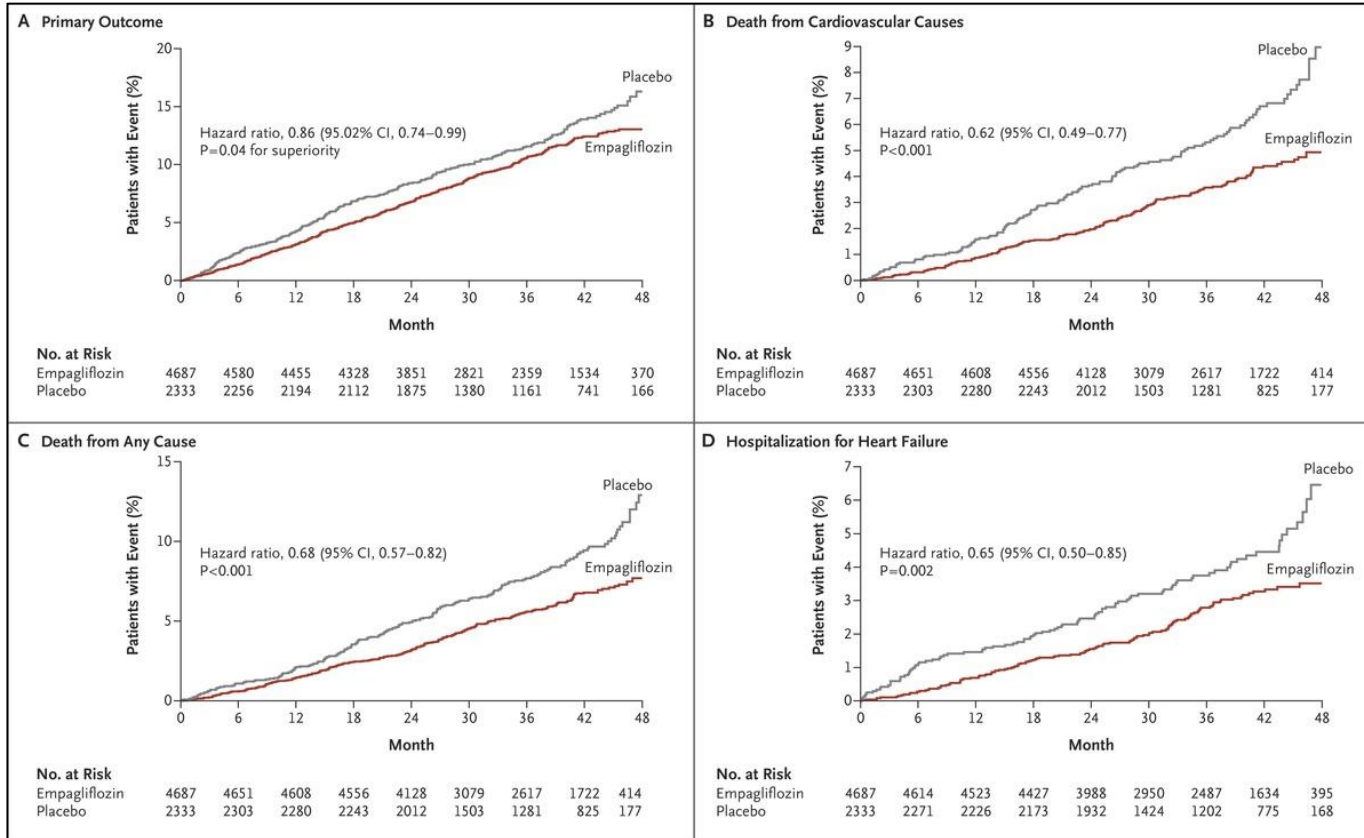
Conceito: indução de glicosúria por inibição da reabsorção tubular de glicose.

Efeito esperado: redução da glicemia.

Efeito inesperado: modesta redução de peso.



2015: Empaglifozina reduz incidência de eventos cardiovasculares maiores, morte por qualquer causa e hospitalização por ICC em comparação a placebo (EMPA-REG)



A era das especulações:

Efeito não pode ser pelo controle glicêmico (tempo, momento).

Pacientes de muito alto risco (DM2 e DCV prévia)

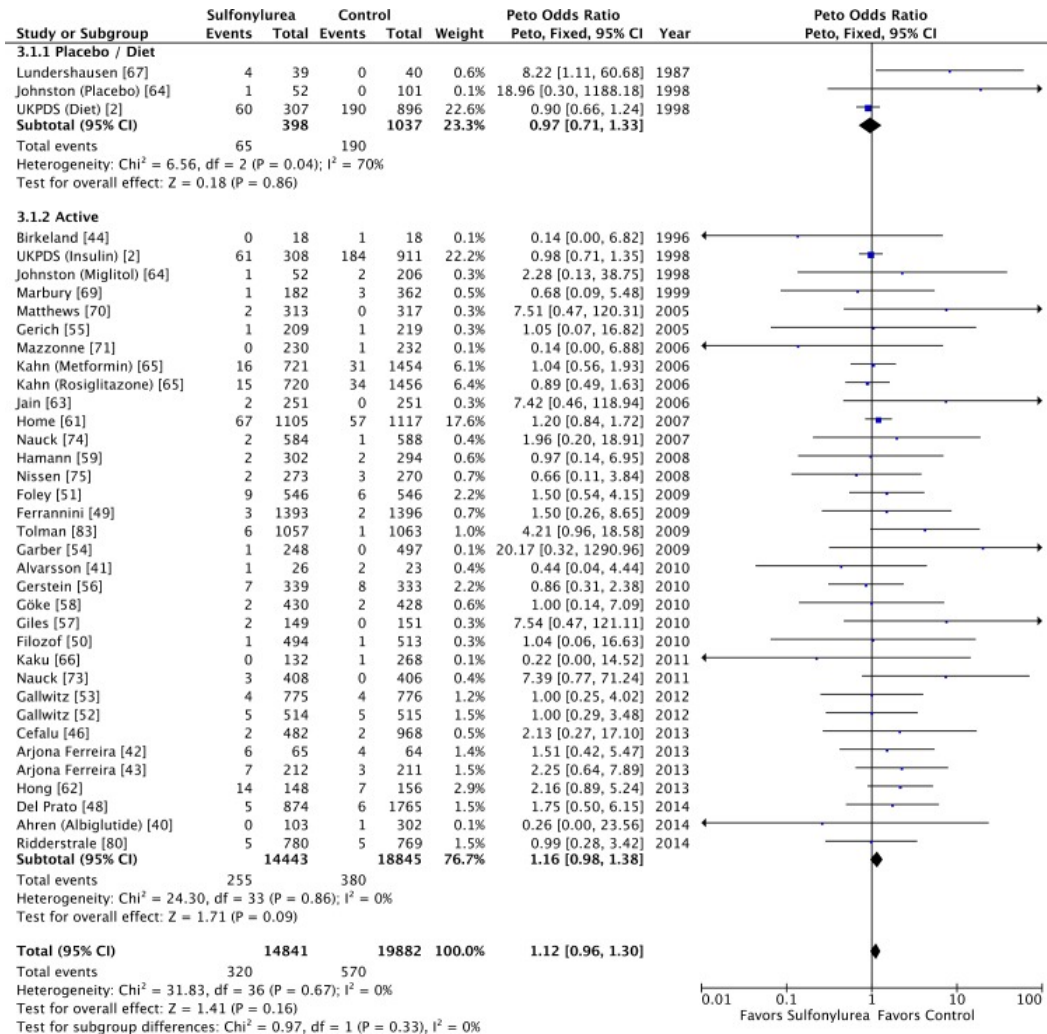
Peso?

Pressão arterial?

Risco de cetoacidose.

Rados et al, HCPA 2016:

Sulfonilureias NÃO aumentam mortalidade geral ou cardiovascular em pacientes com DM2.





NDC 0378-0215-01

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Tablets, USP

500 mg

Mylan
Rx only 100 Tablets

Dispense in a light, light-resistant container as defined in the USP using a child-resistant closure.
Keep container tightly closed.
Keep this and all medication out of the reach of children.
Store in U.S. USP Temperature.
Protect from Heat.
Keep Dry.
Protect from Light.
Mylan Pharmaceuticals
Mylan Philadelphia, PA



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