Metformina : uma senhora moderna

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Serviço de Endocrinologia e Metabologia do
Hospital de Clínicas da Universidade Federal do Paraná

SEMPR

Declaração de potencial conflito de interesse

De acordo com a Norma 1595/2000 do CFM

Integrante do Board da BMS, Novo Nordisk, Sanofi
Palestrante patrocinada pelos laboratórios Eli Lilly, Sanofi, MSD, Novo Nordisk
Pesquisador Clínico: Abbott, Astra Zeneca, Boehringer Ingelheim, Eli Lilly, Novo Nordisk, Sanofi, Takeda
Patrocínio para participações em eventos médicos científicos: Boehringer Ingelheim, Eli Lilly, MSD, Novo Nordisk, Sanofi

Apesar de haver pelo menos 10 classes de fármacos disponíveis para o tratamento da DM2, a metformina continua a ser a farmacoterapia de primeira linha mais amplamente utilizada

Goats Rue

Species Name: Galega officinalis Papilionaceae.

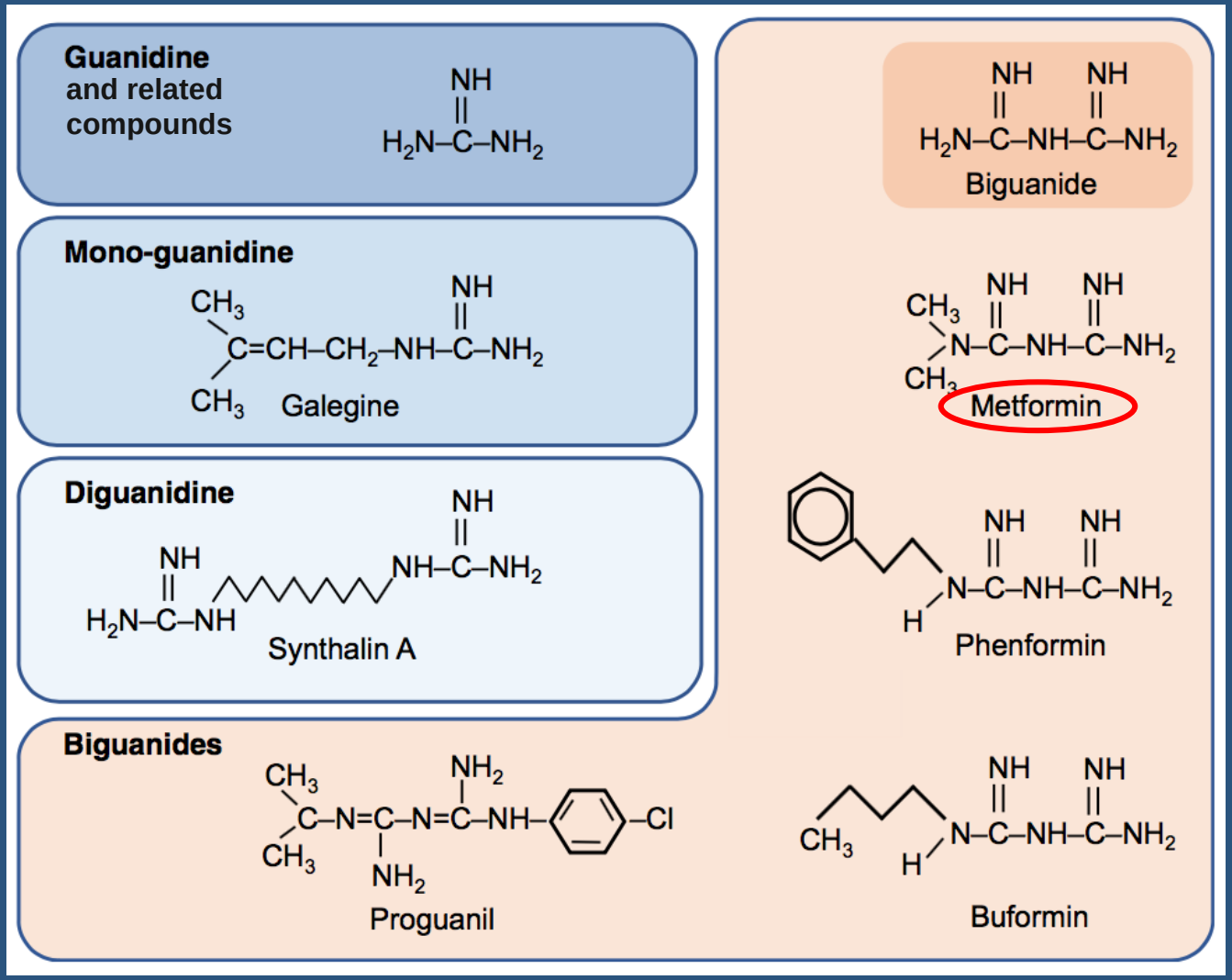
Also known as: American Garden Rue, Catgut, Devil's Shoestring, Rabbit-pea, Horey turkey peas, Virginia Pea, Virginia Tephrosia.

Benefits of Goats Rue:

This herb is used to reduce blood sugar and is helpful in managing diabetes.

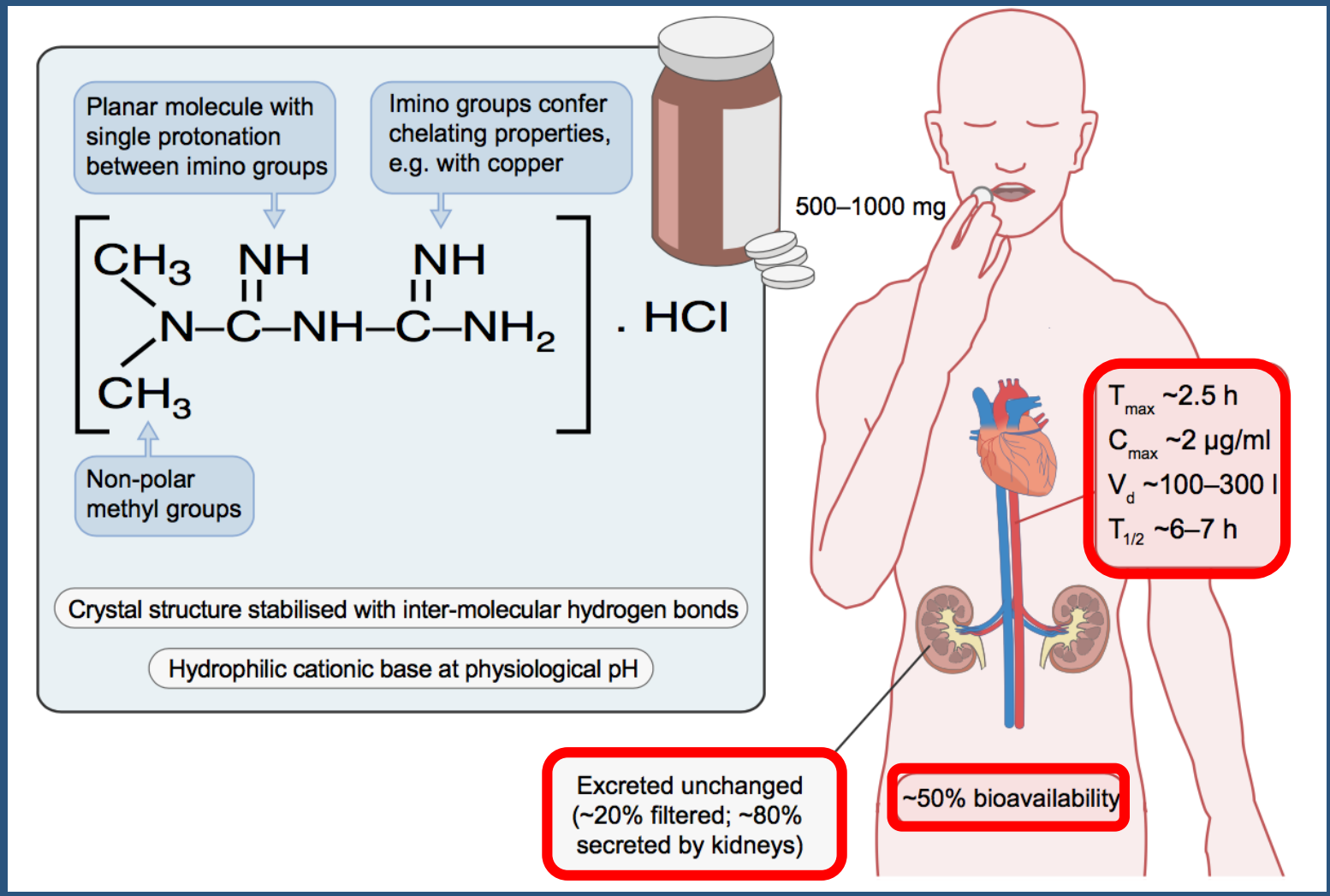
Because of this blood sugar effect, it can be helpful in reducing the threat of diabetes related complications.

Estrutura e Farmacocinética da Metformino



Bailey, CJ Diabetologia (2017) 60:1566–1576

Estrutura e Farmacocinética da Metformino



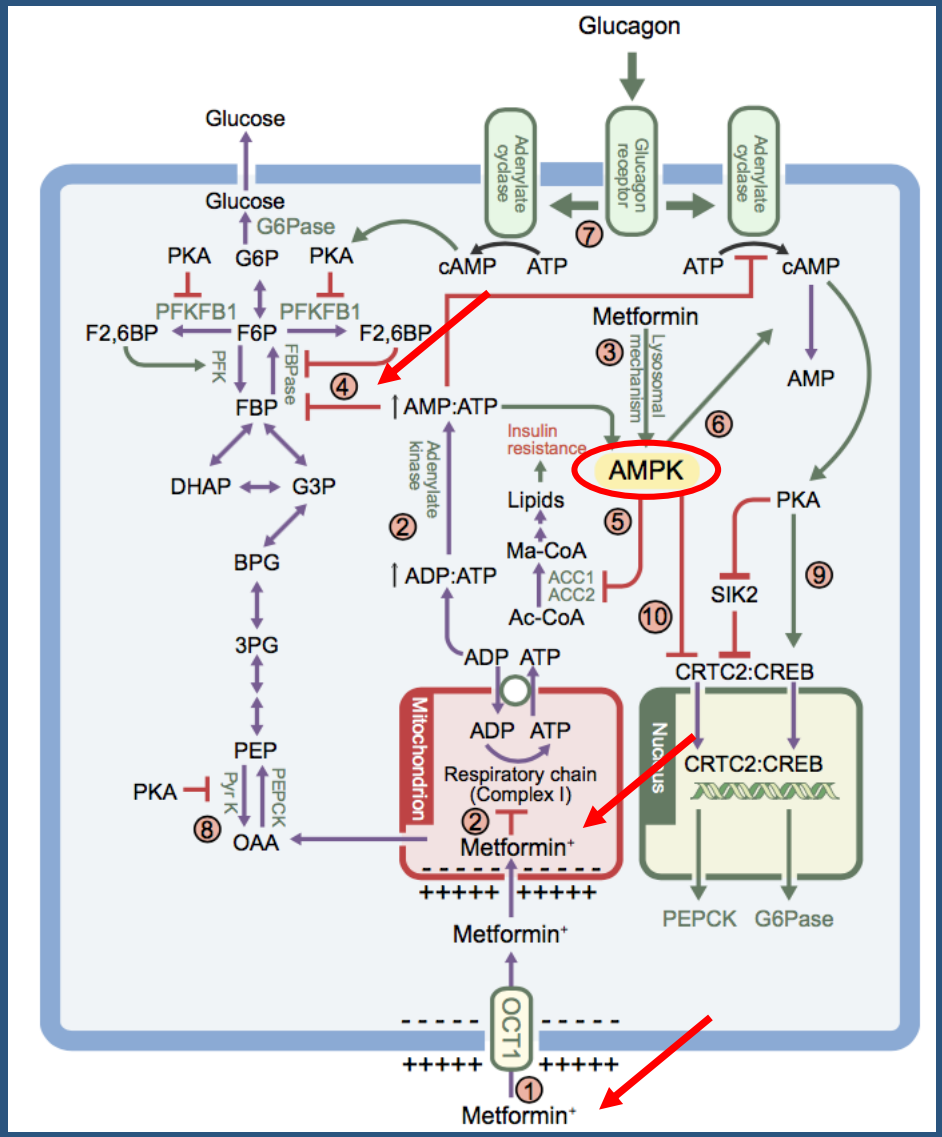
Bailey, CJ Diabetologia (2017) 60:1566–1576

O mecanismo de ação da metformina

3. O aumento na taxa AMP: ATP também resulta na inibição aguda da gliconeogênese

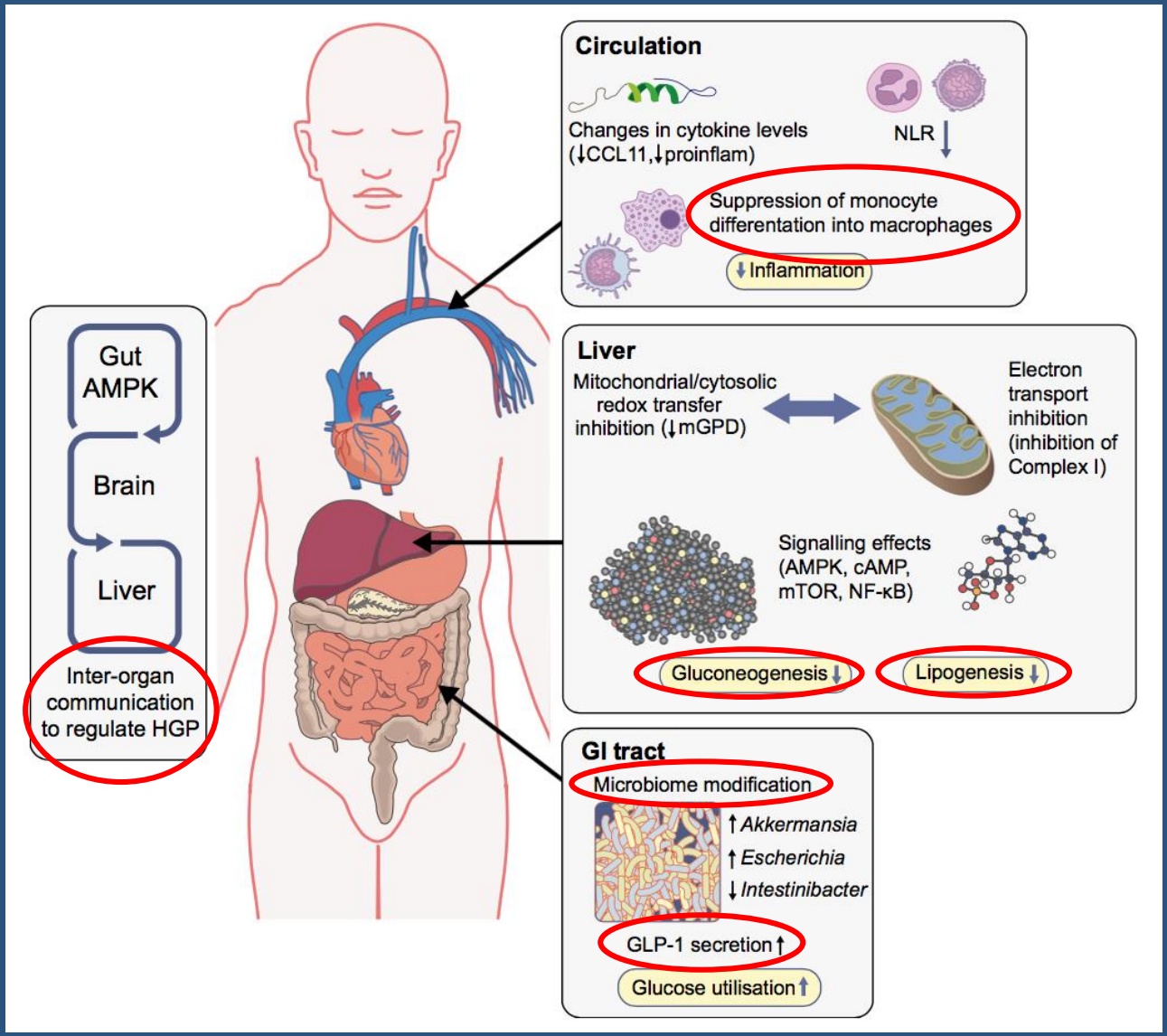
2. Inibição do Complexo I, evitando a produção mitocondrial de ATP e ↑taxas citoplasmáticas de ADP: ATP e AMP: ATP, o que leva à ativação da AMPK

1. Captação catalisada pelo transportador de cátions orgânicos-1 (OCT1)



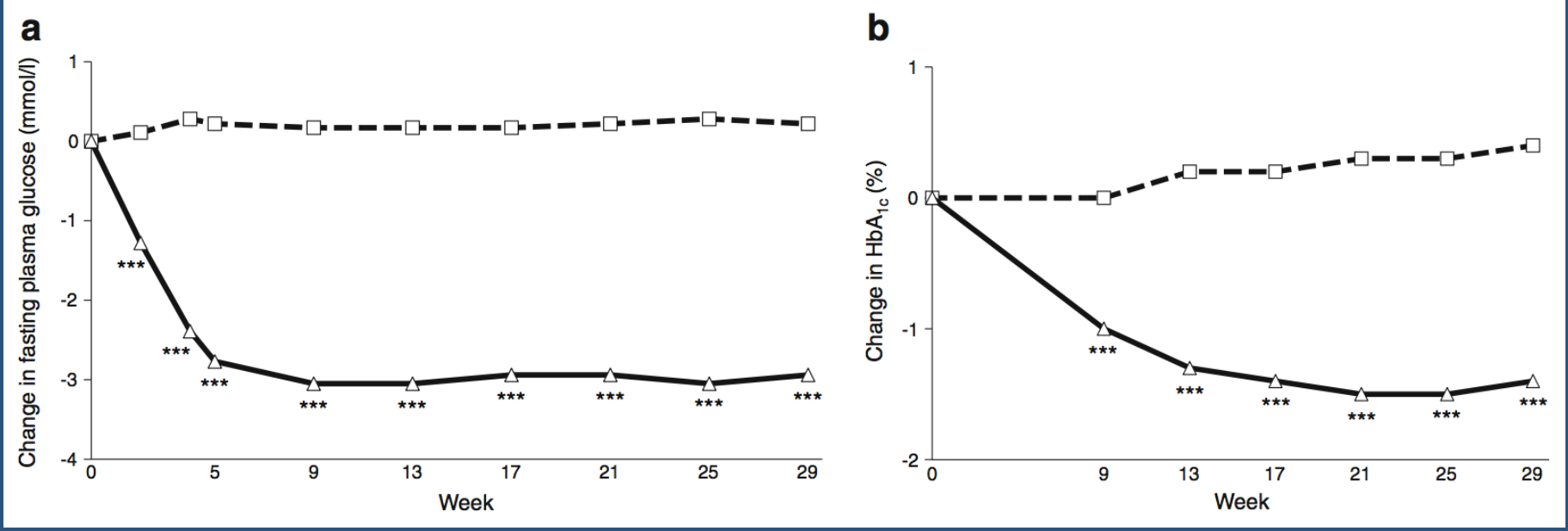
Rena G, Hardie DG, Pearson ER. Diabetologia (2017) 60:1577–1585

Ações da metformina no metabolismo e inflamação



Rena G,. Hardie DG, Pearson ER. Diabetologia (2017) 60:1577–1585

Uso clínico no DM2
Multicenter Metformin Study



Participantes (n = 143) com DM2 descontrolados randomizados para metformina (triângulos com linha contínua) vs participantes (n = 146) randomizado para placebo (quadrados com linha tracejada) *** p <0,001 vs placebo.

DeFronzo et al. NEJM (1995) 333:541-549.

Cardiovascular and metabolic effects of metformin in patients with type 1 diabetes (REMOVAL): a double-blind, randomised, placebo-controlled trial

*John R Petrie, Nishi Chaturvedi, Ian Ford, Martijn C G J Brouwers, Nicola Greenlaw, Therese Tillin, Irene Hramiak, Alun D Hughes, Alicia J Jenkins, Barbara E K Klein, Ronald Klein, Teik C Ooi, Peter Rossing, Coen D A Stehouwer, Naveed Sattar, Helen M Colhoun, for the REMOVAL Study Group**

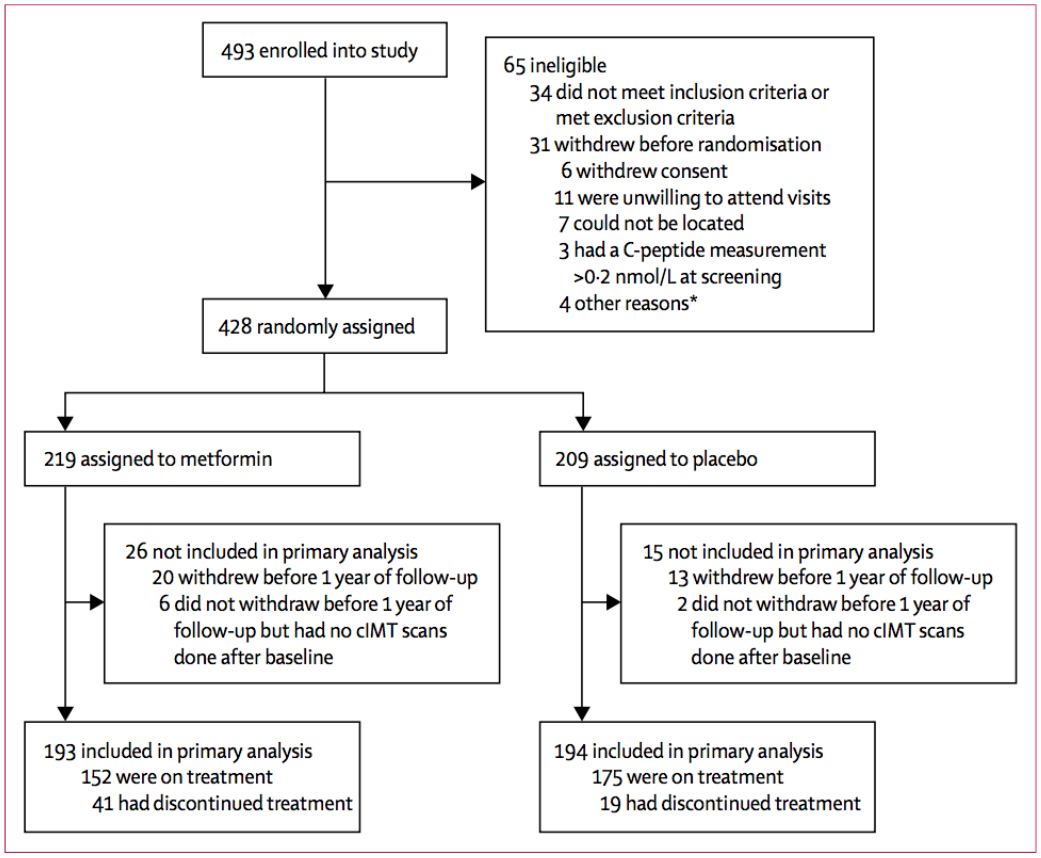


Figure 1: **Trial profile**
cIMT=common carotid artery intima-media thickness. *One patient did not wish to proceed following a serious adverse event, one had a flare-up of irritable bowel syndrome, one withdrew because her husband became unwell, and one had a dislike of taking study medication.

A1c

Dose de insulina

LDL

Peso

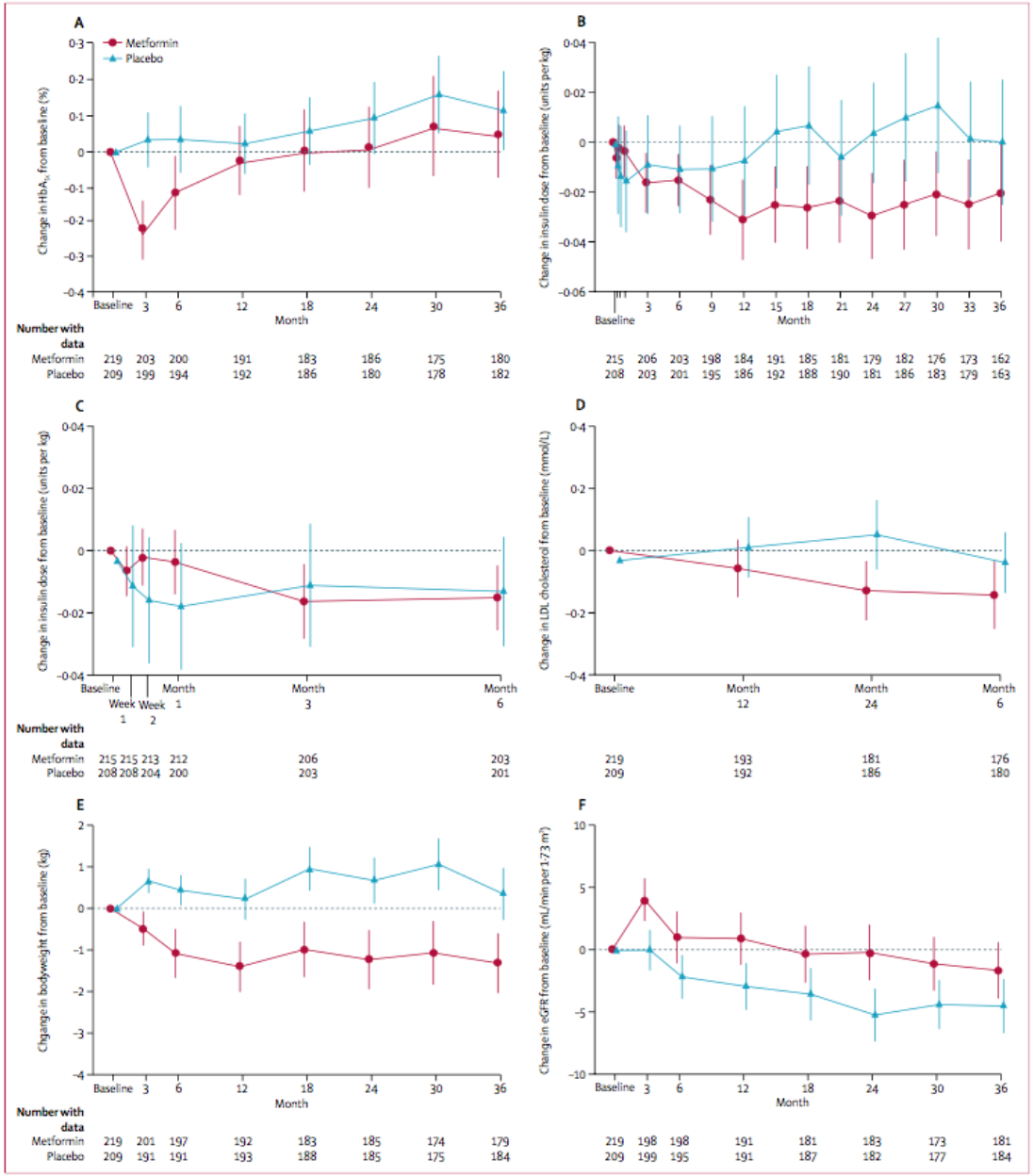


Figure 3: **Changes from baseline in secondary outcomes**
Mean change from baseline for up to 3 years is shown for (A) HbA_{1c}, (B) insulin dose requirement, (C) insulin dose requirement during first 6 months only, (D) LDL cholesterol, (E) bodyweight, and (F) estimated glomerular filtration rate (eGFR). Error bars show 95% CIs.

Cardiovascular and metabolic effects of metformin in patients with type 1 diabetes (REMOVAL): a double-blind, randomised, placebo-controlled trial

*John R Petrie, Nishi Chaturvedi, Ian Ford, Martijn C G J Brouwers, Nicola Greenlaw, Therese Tillin, Irene Hramiak, Alun D Hughes, Alicia J Jenkins, Barbara E K Klein, Ronald Klein, Teik C Ooi, Peter Rossing, Coen D A Stehouwer, Naveed Sattar, Helen M Colhoun, for the REMOVAL Study Group**

IMT

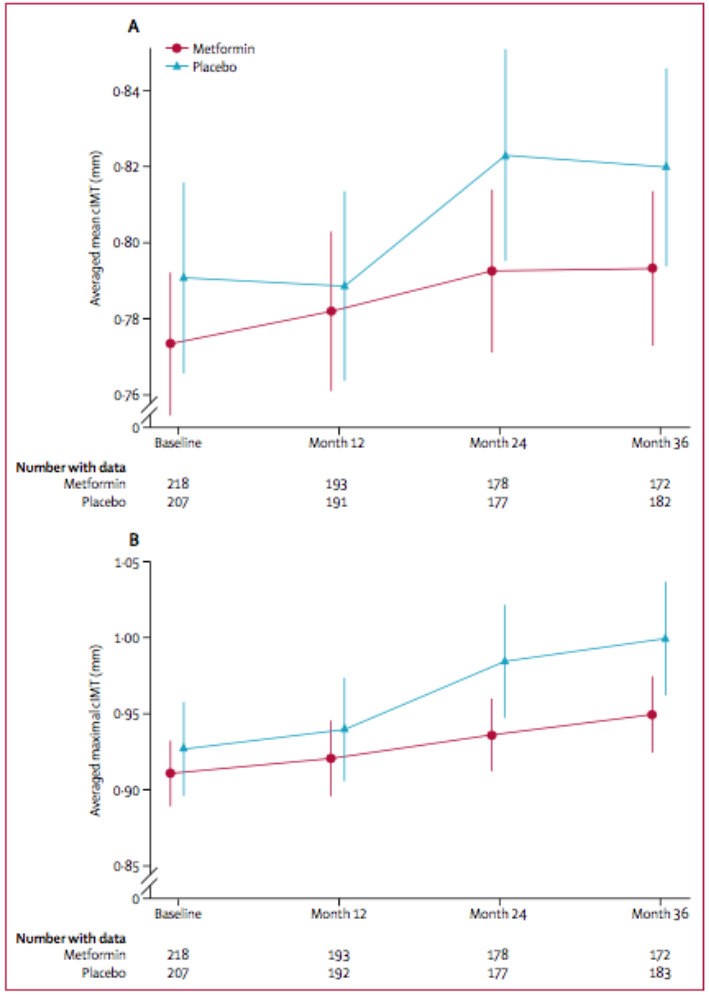


Figure 2: **Progression in (A) mean cIMT (primary outcome) and (B) maximal cIMT (tertiary outcome)**
Error bars show 95% CIs. cIMT=common carotid artery intima-media thickness (far wall).

Uma nova perspectiva na terapia do DM1 com metformina

Summary of outcomes of metformin use in type 1 diabetes

Guidelines for use Guidelines recommend metformin for overweight individuals with type 1 diabetes who wish to improve their glucose control and reduce their insulin dose but these recommendations are based on only a few small studies

Glycaemic control In the recent T1D Exchange and REMOVAL trials, reduction in HbA_{1c} with metformin in type 1 diabetes was not sustained after 3 months

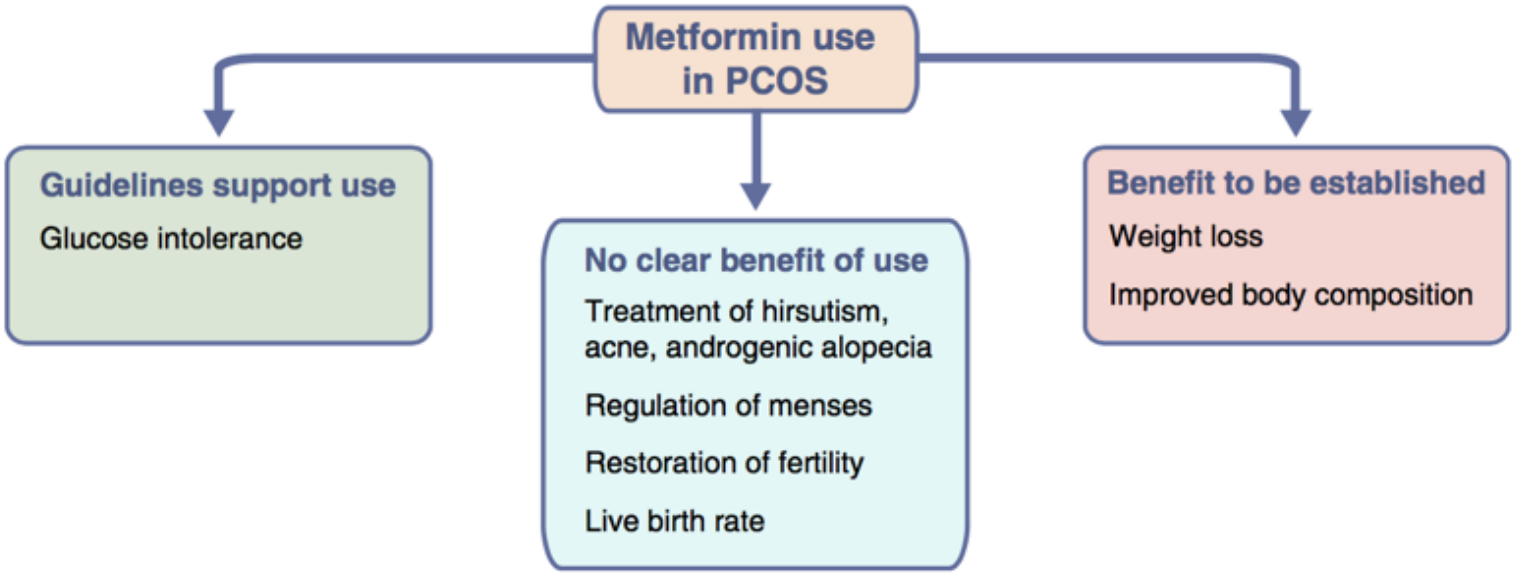
LDL-cholesterol and weight In REMOVAL, the largest and longest trial of metformin therapy in type 1 diabetes to date, small but sustained reductions in LDL-cholesterol and weight were observed over 3 years in middle-aged adults

cIMT These changes observed in REMOVAL were accompanied by a reduction in progression of maximal cIMT (one of two pre-specified carotid outcomes), despite treatment of cholesterol to target with statins

Cardiovascular risk REMOVAL suggests that metformin has a profile associated with cardiovascular risk reduction rather than sustained glucose-lowering in type 1 diabetes

Livingstone R, Boyle JG & Petrie JR on behalf of The REMOVAL Study Team
Diabetologia (2017) 60:1586–1593

Para a reprodução e consequências metabólicas da SOPs



Sam S, Ehrmann DA
Diabetologia (2017) 60:1656–1661

Uso da Metformina na gestação: promessas e incertezas

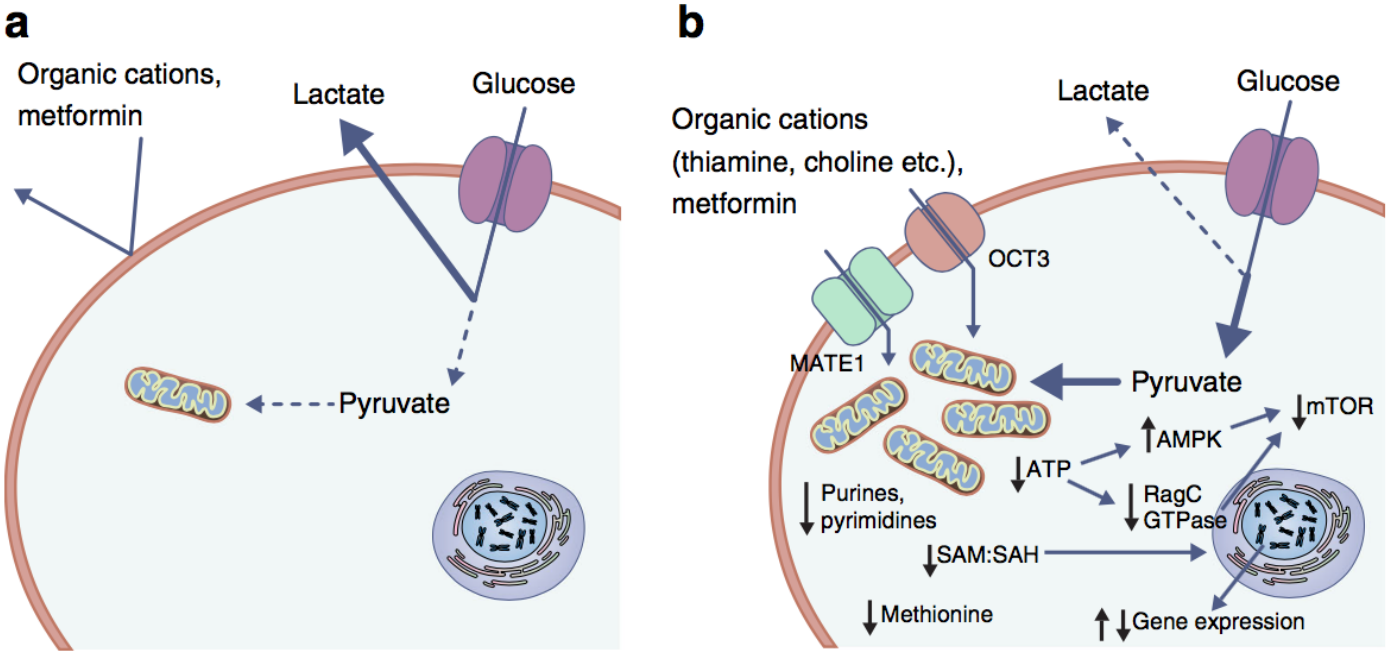


Fig. 1 Model showing that susceptibility to metformin depends on the presence of metformin transporters and maturity of mitochondrial function. (**a**) Early post-implantation embryo cells (and, possibly, fetal progenitor cells) are metformin-resistant because of negligible transporter expression. Metabolism is predominantly glycolytic and mitochondrial content is low. (**b**) Differentiated placental ESC (conditioned for high glucose culture). *Caenorhabditis elegans* cells (and, potentially, fetal cells) express higher levels of metformin transporters and are metformin-responsive through effects on mitochondria and gene expression. Metabolism is predominantly oxidative and mitochondrial content is high. RagC, Ras-related GTP-binging protein C; SAH, S-adenosylhomocysteine; SAM, S-adenosylmethionine

Lindsay, RS, Loeken MR
Diabetologia (2017) 60:1612–1619

Uso da Metformina na gestação: promessas e incertezas

Metformin use in pregnancy: summary of evidence

The evidence outlined below is majorly based on small sample sizes and non-randomised trial data and must, therefore, be interpreted with caution.

GDM Good safety profile in mothers; reduced rates of severe hypoglycaemia (< 1.6 mmol/l) vs other agents; reduced pregnancy weight gain vs insulin; superior to glibenclamide for glucose control; more likely to fail in women with higher baseline glucose or presenting with diabetes earlier in pregnancy. Similar effects on newborn health vs insulin.

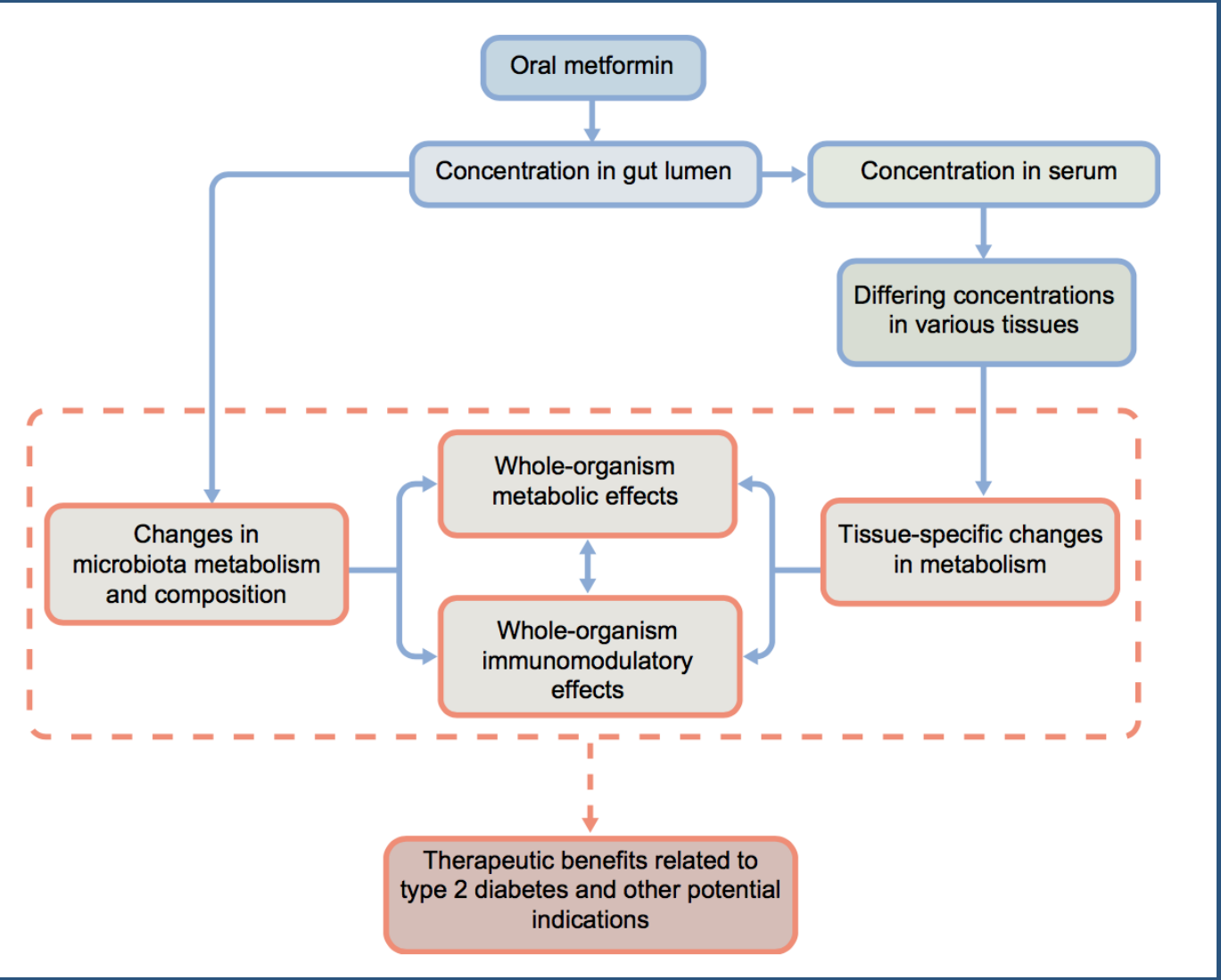
Type 2 diabetes Only observational evidence.

Long-term effects in offspring Equivocal evidence for changes in body composition; no differences in BP; no differences in motor, social and linguistic development at 18 months.

Fetal effects No convincing evidence for increase in congenital malformations or miscarriage; long-term effects on health or metabolism during adulthood not known.

Lindsay, RS, Loeken MR
Diabetologia (2017) 60:1612–1619

Efeitos na microbiota intestinal e no sistema imunológico



Pollack M.
Diabetologia (2017) 60:1662–1667

Para prevenção e recorrência de câncer

- **Dados sobre os mecanismos potenciais da ação da metformina** para prevenção e tratamento do câncer, bem como dados epidemiológicos longitudinais adicionais de coortes novas e previamente examinadas, **continuam a se acumular**

- **Existe uma plausibilidade biológica** para um efeito preventivo do câncer da metformina, **dadas as múltiplas maneiras pelas quais podem interferir nas vias sinalizadoras promotoras do câncer**

- No entanto, tanto **estudos** animais como epidemiológicos **mostraram efeitos um tanto variados**

Heckman-Stoddard BM, DeCensi A, Sahasrabuddhe VV, Ford LG
Diabetologia (2017) 60:1639–1647

Meta-análise de estudos randomizados entre pessoas com DM2

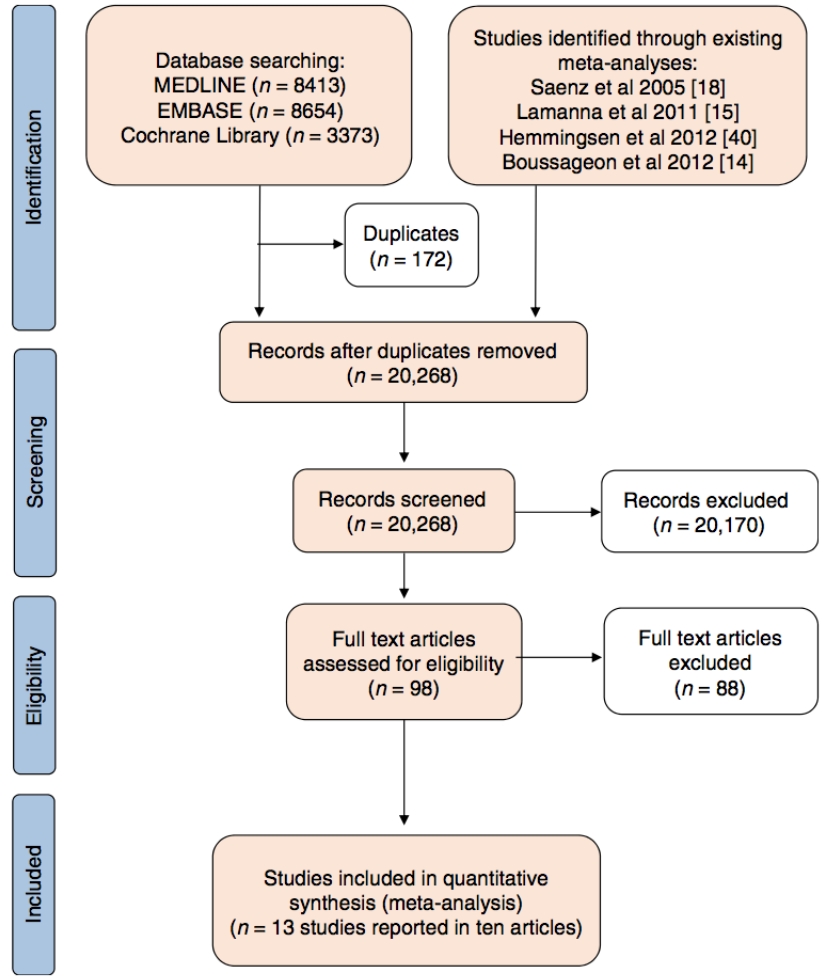


Fig. 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram [40]

Griffin SJ, Leaver JK, Irving GJ
Diabetologia (2017) 60:1620–1629

Meta-análise de estudos randomizados entre pessoas com DM2

Study or subgroup	Metformin Events	Metformin Total	Control Events	Control Total	Weight	RR M–H, fixed (95% CI)
Chiasson et al (2001a) [24]	0	83	0	83		Not estimable
Chiasson et al (2001b) [24]	0	76	0	82		Not estimable
DeFronzo et al (1995a) [25]	0	143	0	146		Not estimable
DeFronzo et al (1995b) [25]	0	213	0	209		Not estimable
Hermann et al (2001) [20]	0	16	0	15		Not estimable
Holman et al (2008) [21]	81	342	120	411	62.3 %	0.81 (0.64, 1.03)
Horton et al (2000a) [26]	1	178	0	172	0.3 %	2.90 (0.12, 70.69)
Horton et al (2000b) [26]	0	135	0	134		Not estimable
Hällsten et al (2002) [19]	0	13	0	14		Not estimable
Kooy et al (2009) [22]	4	196	1	194	0.6 %	3.96 (0.45, 35.10)
Rachmani et al (2002) [27]	50	195	52	198	29.5 %	0.98 (0.70, 1.36)
UKPDS (1998) [12]	25	268	13	269	7.4 %	1.93 (1.01, 3.69)
Total (95% CI)		**1858**		**1927**	**100.0 %**	**0.97 (0.80, 1.16)**
Total events	161		186			

Heterogeneity: $\chi^2 = 8.44$, $df = 4$ ($p = 0.08$); $I^2 = 53\%$

Test for overall effect: $Z = 0.36$ ($p = 0.72$)

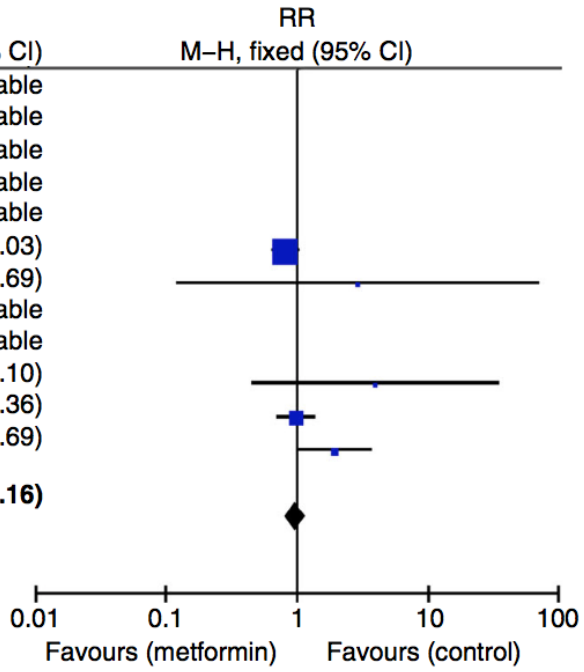


Fig. 4 Forest plot showing the effect of metformin on risk of cardiovascular death

Griffin SJ, Leaver JK, Irving GJ
Diabetologia (2017) 60:1620–1629

Meta-análise de estudos randomizados entre pessoas com DM2

Study or subgroup	Metformin Events	Metformin Total	Control Events	Control Total	Weight	RR M–H, fixed (95% CI)
Gram et al (2011) [23]	15	184	16	187	7.3 %	0.95 (0.49, 1.87)
Hermann et al (2001) [20]	1	16	0	15	0.2 %	2.82 (0.12, 64.39)
Holman et al (2008) [21]	81	342	126	411	52.3 %	0.77 (0.61, 0.98)
Hällsten et al (2002) [19]	1	13	0	14	0.2 %	3.21 (0.14, 72.55)
Kooy et al (2009) [22]	4	196	4	194	1.8 %	0.99 (0.25, 3.90)
Rachmani et al (2002) [27]	51	195	53	198	24.0 %	0.98 (0.70, 1.36)
UKPDS (1998) [12]	33	268	31	269	14.1 %	1.07 (0.67, 1.69)
Total (95% CI)		**1214**		**1288**	**100.0%**	**0.89 (0.75, 1.06)**
Total events	186		230			

Heterogeneity: $\chi^2 = 3.50$, $df = 6$ ($p = 0.74$); $I^2 = 0\%$

Test for overall effect: $Z = 1.33$ ($p = 0.18$)

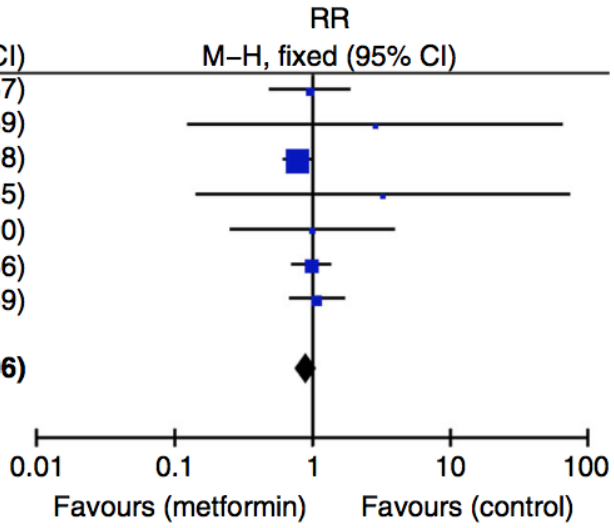


Fig. 5 Forest plot showing the effect of metformin on risk of myocardial infarction

Griffin SJ, Leaver JK, Irving GJ
Diabetologia (2017) 60:1620–1629

Meta-análise de estudos randomizados entre pessoas com DM2

Study or subgroup	Metformin Events	Metformin Total	Control Events	Control Total	Weight	RR M–H, fixed (95% CI)
Gram et al (2011) [23]	3	184	2	187	3.7 %	1.52 (0.26, 9.02)
Holman et al (2008) [21]	34	342	42	411	70.5 %	0.97 (0.63, 1.49)
Kooy et al (2009) [22]	1	196	1	194	1.9 %	0.99 (0.06, 15.71)
UKPDS (1998) [12]	15	268	13	269	24.0 %	1.16 (0.56, 2.39)
Total (95% CI)		**990**		**1061**	**100.0 %**	**1.04 (0.73, 1.48)**
Total events	53		58			

Heterogeneity: $\chi^2 = 0.36$, $df = 3$ ($p = 0.95$); $I^2 = 0\%$

Test for overall effect: $Z = 0.20$ ($p = 0.84$)

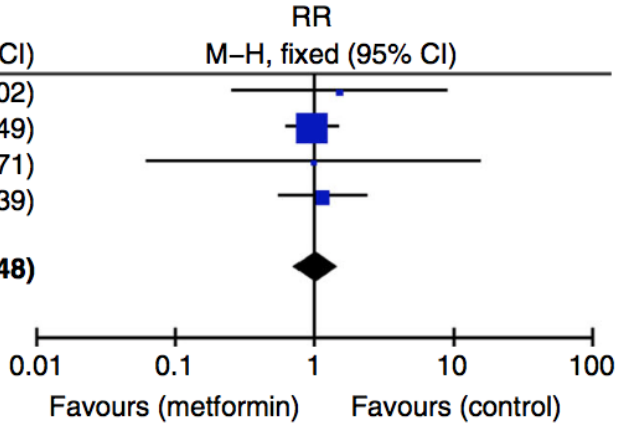


Fig. 6 Forest plot showing the effect of metformin on risk of stroke

Griffin SJ, Leaver JK, Irving GJ
Diabetologia (2017) 60:1620–1629

Meta-análise de estudos randomizados entre pessoas com DM2

Study or subgroup	Metformin Events	Metformin Total	Control Events	Control Total	Weight	RR M–H, fixed (95% CI)
Gram et al (2011) [23]	6	184	8	187	22.0 %	0.76 (0.27, 2.15)
Holman et al (2008) [21]	13	342	21	411	52.9 %	0.74 (0.38, 1.46)
Kooy et al (2009) [22]	7	196	8	194	22.3 %	0.87 (0.32, 2.34)
UKPDS (1998) [12]	2	268	1	269	2.8 %	2.01 (0.18, 22.01)
Total (95% CI)		**990**		**1061**	**100.0 %**	**0.81 (0.50, 1.31)**
Total events	28		38			

Heterogeneity: $\chi^2 = 0.64$, $df = 3$ ($p = 0.89$); $I^2 = 0\%$

Test for overall effect: $Z = 0.86$ ($p = 0.39$)

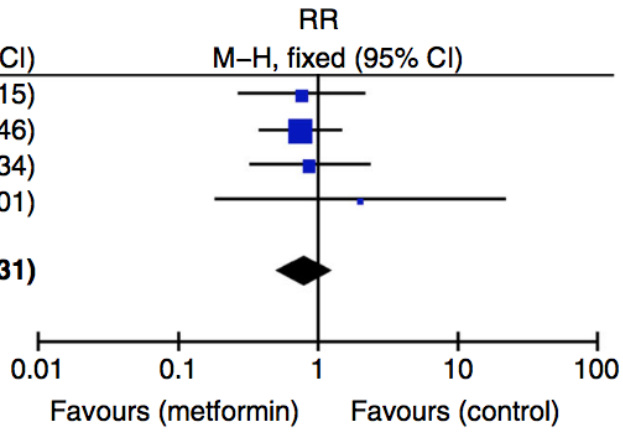


Fig. 7 Forest plot showing the effect of metformin on risk of peripheral vascular disease

Griffin SJ, Leaver JK, Irving GJ
Diabetologia (2017) 60:1620–1629

Meta-análise de estudos randomizados entre pessoas com DM2

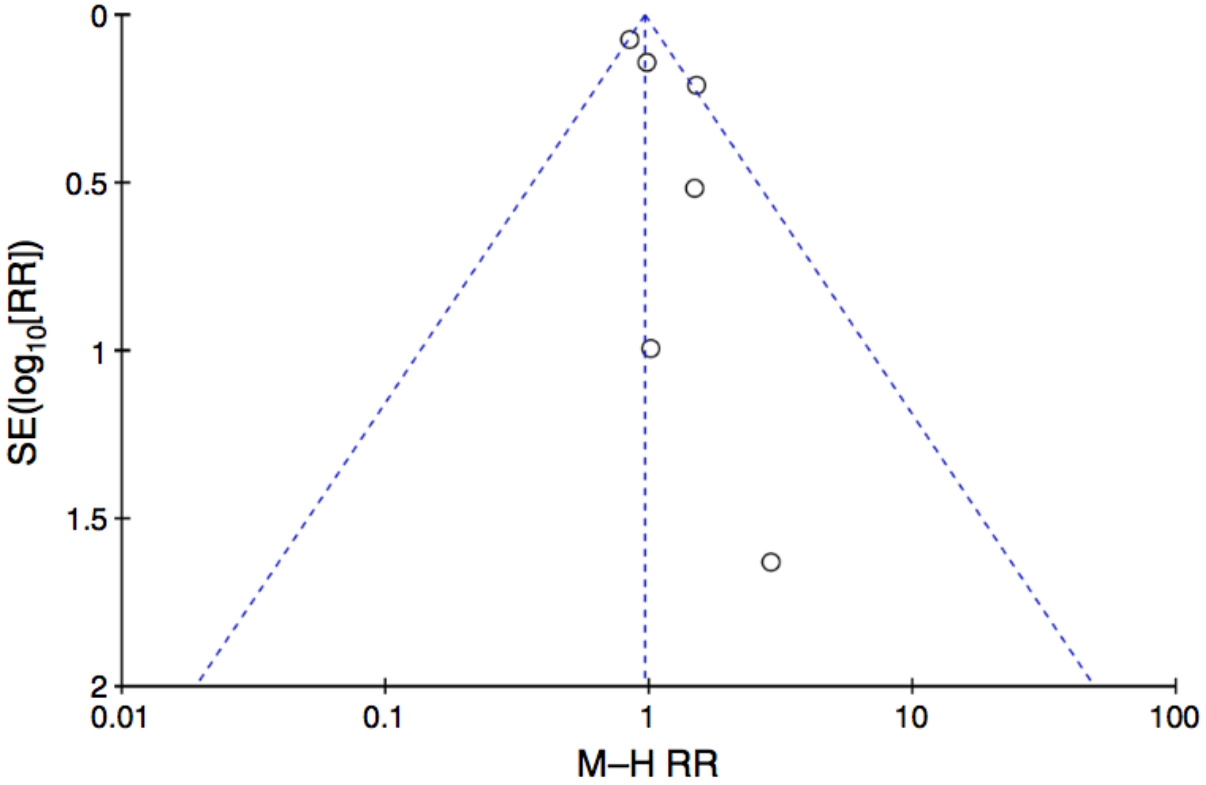


Fig. 8 Funnel plot of effect size estimates for all-cause mortality to assess risk of publication bias. Circles represent M–H RR estimates for all-cause mortality comparing metformin vs control groups

Griffin SJ, Leaver JK, Irving GJ
Diabetologia (2017) 60:1620–1629

Meta-análise de estudos randomizados entre pessoas com DM2

- A metformina é barata, amplamente disponível, segura, respaldada por evidências fármaco-epidemiológicas e anedóticas derivadas de 60 anos de uso regular na prática, **e parece ser mais provável que reduza o risco de doença cardiovascular do que aumente**

- No entanto , **a última afirmação baseia-se em alguns pequenos estudos, com limitações notáveis**, em um subconjunto não representativo de pacientes

- **Agentes mais recentes** que poderiam potencialmente ser usados no início da doença estão agora disponíveis e são **apoiados por dados de estudos de desfechos cardiovasculares rigorosos**. No entanto, eles **permanecem muito caros e carecem de dados sobre o uso a longo prazo**

Talvez, apesar de, e não por causa das evidências, a metformina provavelmente continue a ser o tratamento de primeira linha para a hiperglicemia associada ao diabetes tipo 2 em um futuro previsível

Griffin SJ, Leaver JK, Irving GJ
Diabetologia (2017) 60:1620–1629

Deficiência de Vit B12

- Malabsorção convicentemente demonstrada em múltiplos estudos

- Em um ensaio clínico randomizado, 256 participantes e 52 meses
  19 indivíduos **(9,9%)** com metformina desenvolveram def. de B12
  5 **(2,7%)** no grupo placebo

- NO DPPOS (Diabetes Prevention Program Outcomes Study)
  risco aumentado de níveis baixos de B12 levels
  > prevalência de neuropatia periférica naqueles com baixa B12,
  porém com n = 13

Entretanto, com base nas alterações bioquímicas e dadas as potenciais sequelas neurológicas irreversíveis da deficiência de B12 não reconhecida é sugerido:
dosagens periódicos de B12, pp se anemia ou neuropatia periférica
ou suplementos profiláticos

Sanchez-Rangel E, Inzucchi SE. Diabetologia (2017) 60:1586–1593

Insuficiência Renal

- De acordo com as novas diretrizes do FDA, o uso de metformina é agora permitido quando a TFGe cai abaixo de 60 ml/min/1,73 m^2
- Abaixo de 45 ml/min/1,73 m^2, uma análise cuidadosa do risco/ benefício deve ser conduzida para cada paciente, mas a medicação pode ser cautelosamente continuada (aconselhada uma dose reduzida nesta conjuntura)
- A metformina permanece contraindicada quando a TFGe cai abaixo de 30 ml/min/1,73 m^2

Em indivíduos com doença renal lábil, especialmente se ocorrerem frequentes deteriorações na função renal, essa droga é uma má escolha.

- O uso deve ser interrompido antes dos procedimentos com contraste iodados se a TFGe for de 30 a 60 ml/min/ 1,73 m^2, se doença hepática, alcoolismo ou insuficiência cardíaca, ou contraste intra-arterial. A TFGe deve ser verificada 48 hs após e o medicamento reiniciado se a função renal permanecer estável

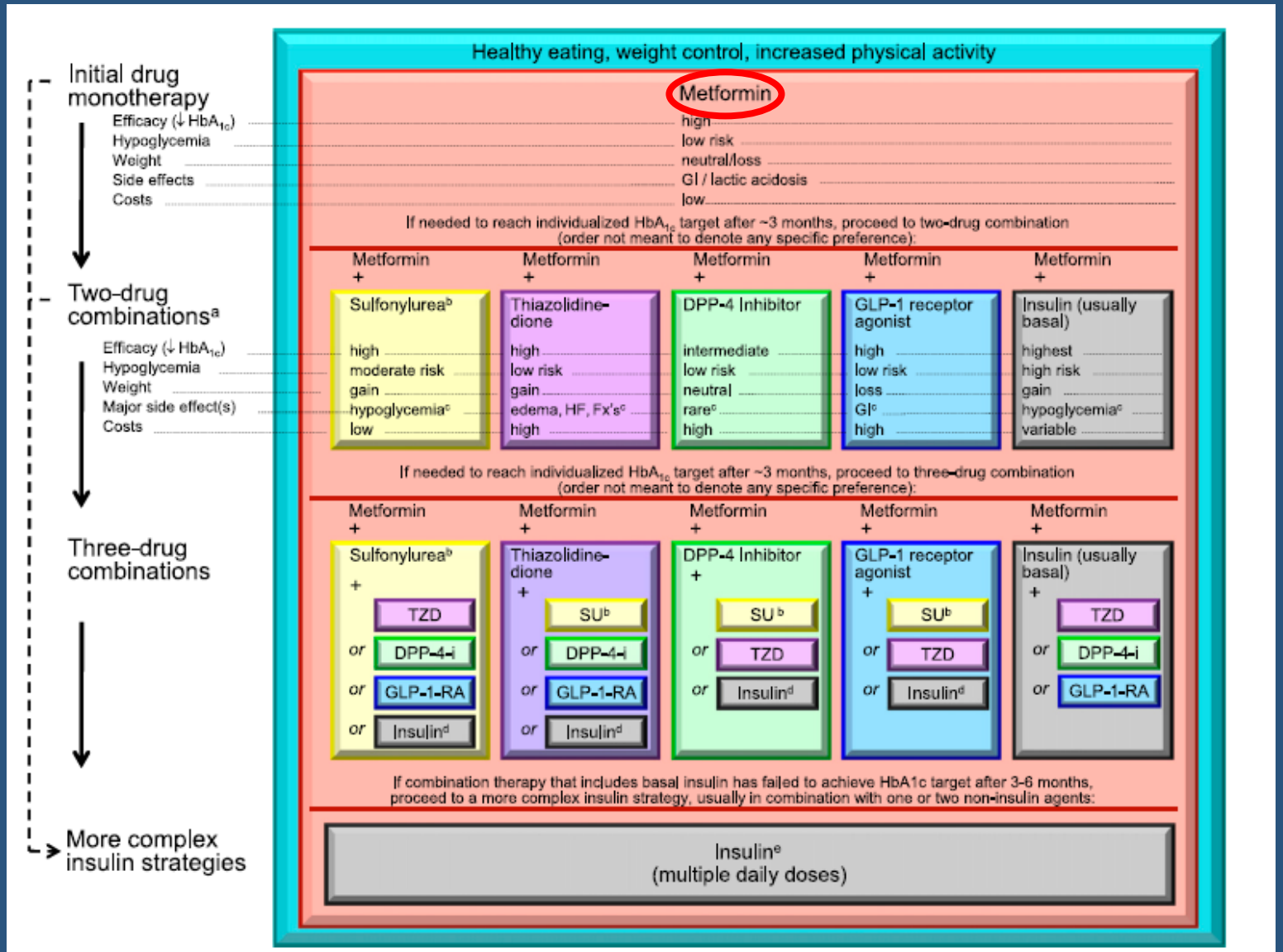
Sanchez-Rangel E, Inzucchi SE. Diabetologia (2017) 60:1586–1593

Resumo do Uso Clínico no DM2

Summary of metformin use in type 2 diabetes

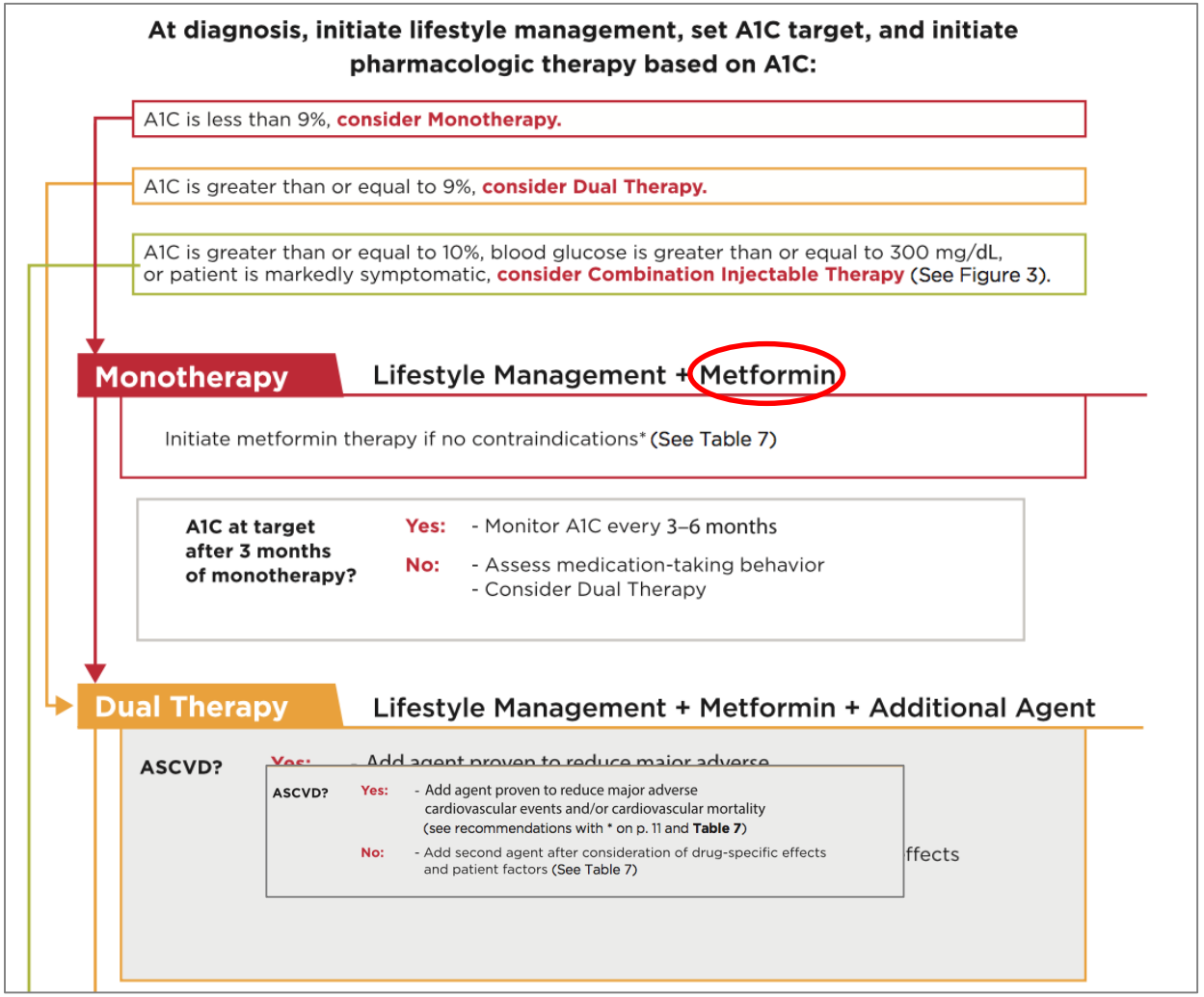
1. Effective glucose lowering as monotherapy and in combination with other agents, including insulin
2. Does not increase hypoglycaemia risk and is weight-neutral
3. Possible cardiovascular benefits
4. Maximally effective dose is usually 2000 mg daily
5. Major side effect is GI disturbance
6. Lactic acidosis risk is low; occurs mainly in those with advanced chronic kidney disease

Sanchez-Rangel E, Inzucchi SE. Diabetologia (2017) 60:1586–1593



Diabetes Care Publish Ahead of Print, April 19, 2012

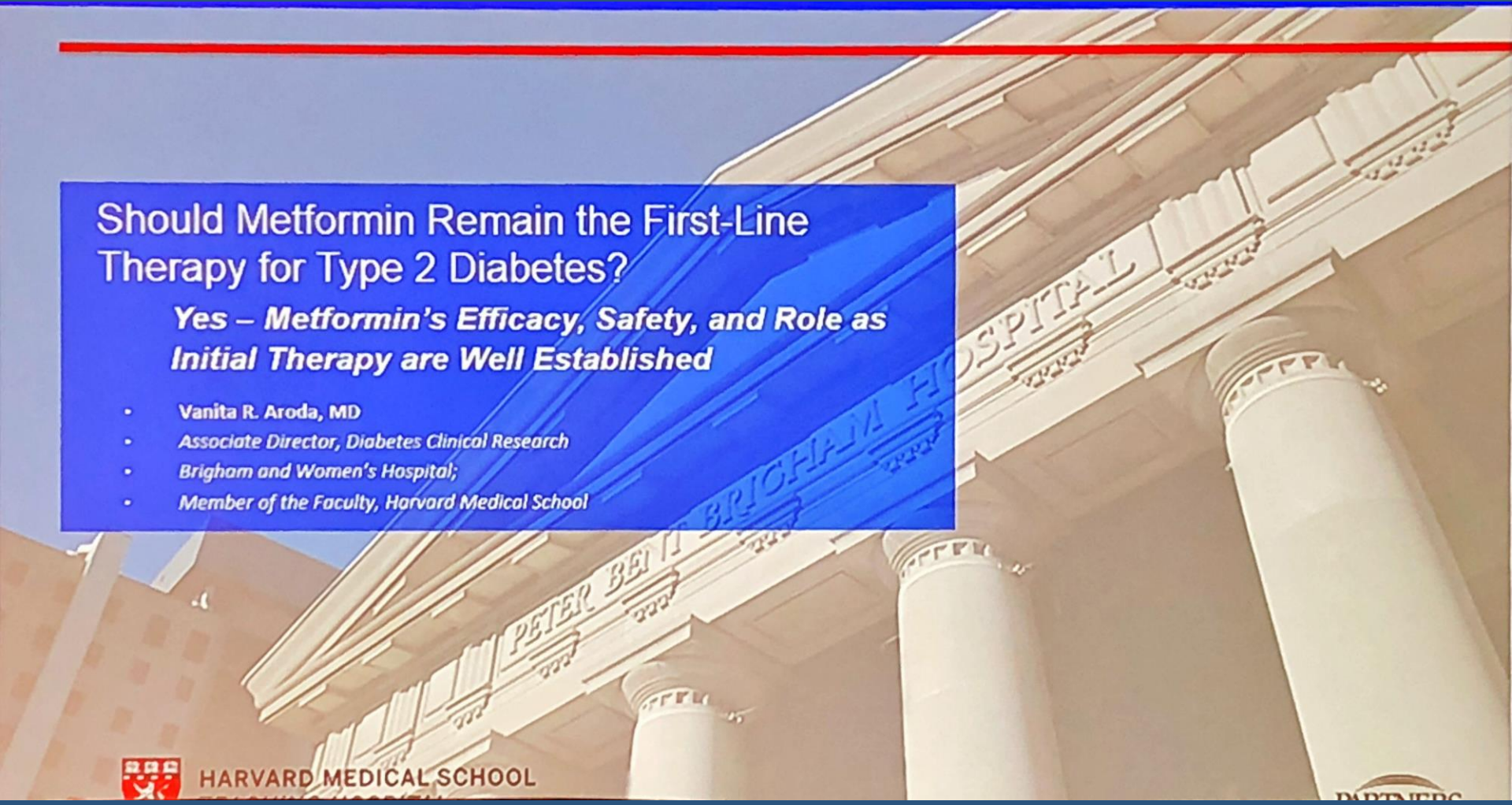
Terapia redutora da glicemia em adultos com DM2



ASCVD, atherosclerotic cardiovascular disease

Diabetes Association's Standards of Medical Care in Diabetes—2018. *Diabetes Care* 2018;41(Suppl. 1):S1–S159

American Diabetes Association®
78TH SCIENTIFIC SESSIONS
ORLANDO, FL • JUNE 22 – 26, 2018



Should Metformin Remain the First-Line Therapy for Type 2 Diabetes?

Yes – Metformin's Efficacy, Safety, and Role as Initial Therapy are Well Established

- **Vanita R. Aroda, MD**
- *Associate Director, Diabetes Clinical Research*
- *Brigham and Women's Hospital;*
- *Member of the Faculty, Harvard Medical School*

HARVARD MEDICAL SCHOOL

Trial	% Participants with Metformin as Glucose-Lowering Therapy at Baseline
EMPA-REG OUTCOME Trial (empagliflozin)	74%
LEADER (liraglutide)	76%
SUSTAIN-6 (semaglutide)	73%
CANVAS (canagliflozin)	77%
CVD-REAL (SGLT2i vs other glucose-lowering drugs)	80%

REVIEW

Annals of Internal Medicine

Diabetes Medications as Monotherapy or Metformin-Based Combination Therapy for Type 2 Diabetes

A Systematic Review and Meta-analysis

MET vs TZDs (n=23 studies): no between-group differences in HbA1c; weight difference favors MET (-2.6 kg)

MET vs Sulfonylureas (n=17 studies): no differences in A1c; weight difference favors MET (-2.7 kg); risk of hypoglycemia favors MET; CV mortality favors MET

MET vs DPP-4 inhibitors (n=6 studies): greater reductions in A1c with metformin (pooled between-group difference A1c -0.4%, 95% CI -0.5% to -0.3%); weight difference favors MET

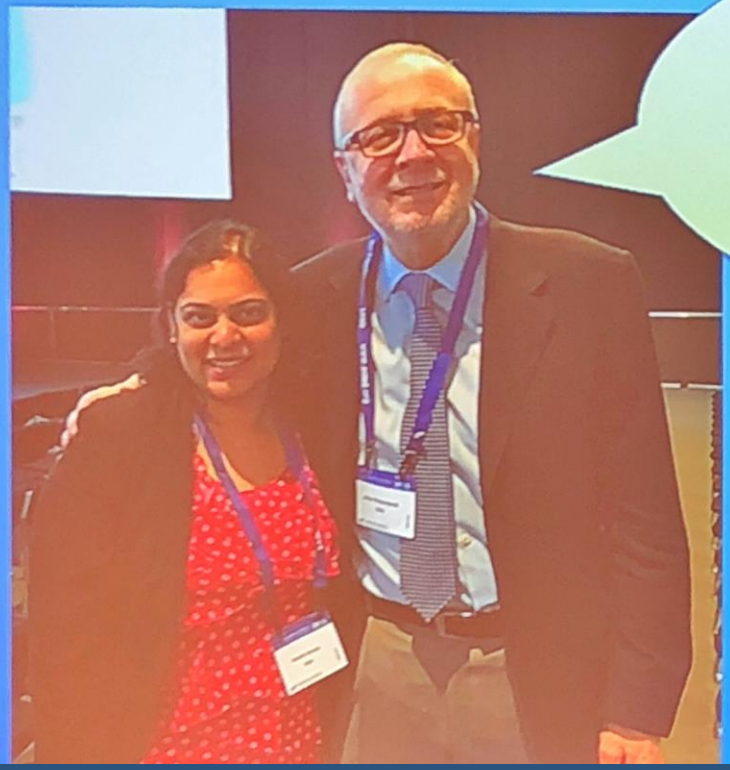
MET vs SGLT-2 inhibitors (n=4 studies): no consistent between-group differences in A1c (not combined for meta-analysis)

"In summary, …
metformin as the recommended first-line agent to treat adults with type 2 diabetes, given its beneficial effects on hemoglobin A1c, weight, and cardiovascular mortality (versus sulfonylureas) and relative safety profile.

All of the medications have specific side effects, and the newer medications are not necessarily safer than the older medications."

Maruthur N et al; *Ann Int Med;* 164:740-751, 2016
Bennett WL et al; *Ann Int Med* ; 154:602-613, 2011

Just a word on cost...



"Vanita, no amount of data is ever going to replace a $4 a month medication, ***especially*** metformin!"

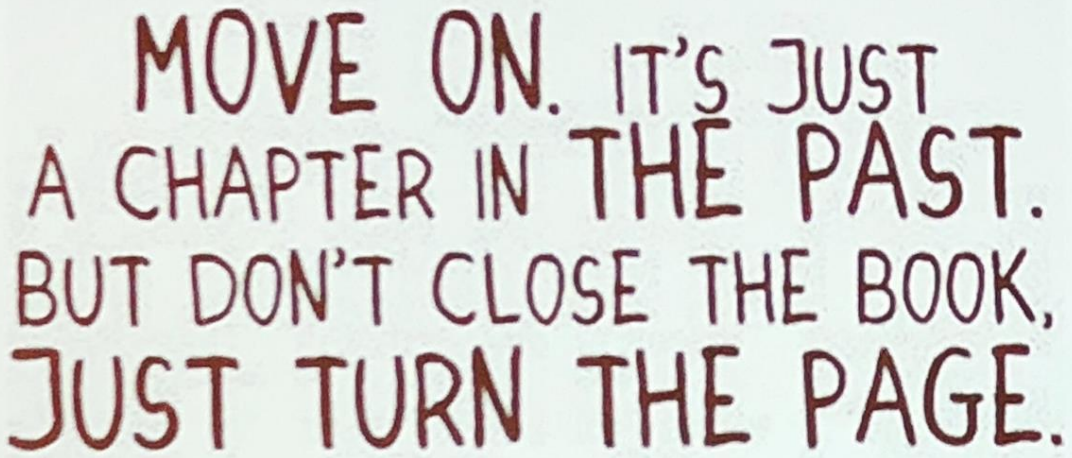
"And that too when the data doesn't directly translate to 87% of our population"

American Diabetes Association Standards of Care, 2018

5 Reasons to Break Up with Metformin

1. Core needs
2. Metabolic parameters
3. Microvascular benefits
4. Macrovascular benefits
5. Mortality

We can still be friends ☺



You are already playing the field!

FDC	Available doses (mg)
Metformin + TZDs	
+ Pioglitazone	500/15; 850/15
+ Pioglitazone (with Met XR)	1000/15; 1000/30
Metformin + DPP-4is	
+ Vildagliptin	850/50; 1000/50
+ Sitagliptin	850/50; 1000/50
+ Sitagliptin (with Met XR)	500/50; 1000/50; 1000/100
+ Saxagliptin	850/2.5; 1000/2.5
+ Linagliptin	850/2.5; 1000/2.5
+ Alogliptin	850/12.5; 1000/12.5
Metformin + SGLT2is	
+ Dapagliflozin	500/5; 1000/5; 500/10; 1000/10; 850/5
+ Canagliflozin	500/50; 500/150; 850/50; 850/150;1000/50; 1000/150
+ Empagliflozin	500/5; 1000/5; 500/12.5; 1000/12.5

FDC	Available doses (mg)
Metformin + meglitinides	
+ Repaglinide	500/1; 500/2
Metformin + sulfonylureas	
+ Glyburide	250/1.25; 500/2.5; 500/5
Other FDCs	
Pioglitazone + Glimepiride	30/2; 30/4; 45/4
Pioglitazone + Alogliptin	15/12.5; 15/25; 30/12.5; 45/12.5; 30/25; 45/25
Glimepiride + Rosiglitazone	1/4; 2/4; 4/4; 2/8; 4/8
Linagliptin + Empagliflozin	5/10; 5/25

Obrigada!