Pharmacological treatment of T2DM

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Outline

- Classification of diabetes mellitus
- Pathophysiology and natural history of T2DM
- Lifestyle modification in T2DM
- Pharmacotherapy of T2DM
- Surgery in the T2DM patient

- Type 1 diabetes
  - Autoimmune β-cell destruction
- Type 2 diabetes
  - Insulin resistance followed by progressive insulin secretory defect
- Other specific types of diabetes
  - Genetic defects in β-cell function, insulin action
  - Diseases of the exocrine pancreas
  - Drug- or chemical-induced
- Gestational diabetes mellitus (GDM)

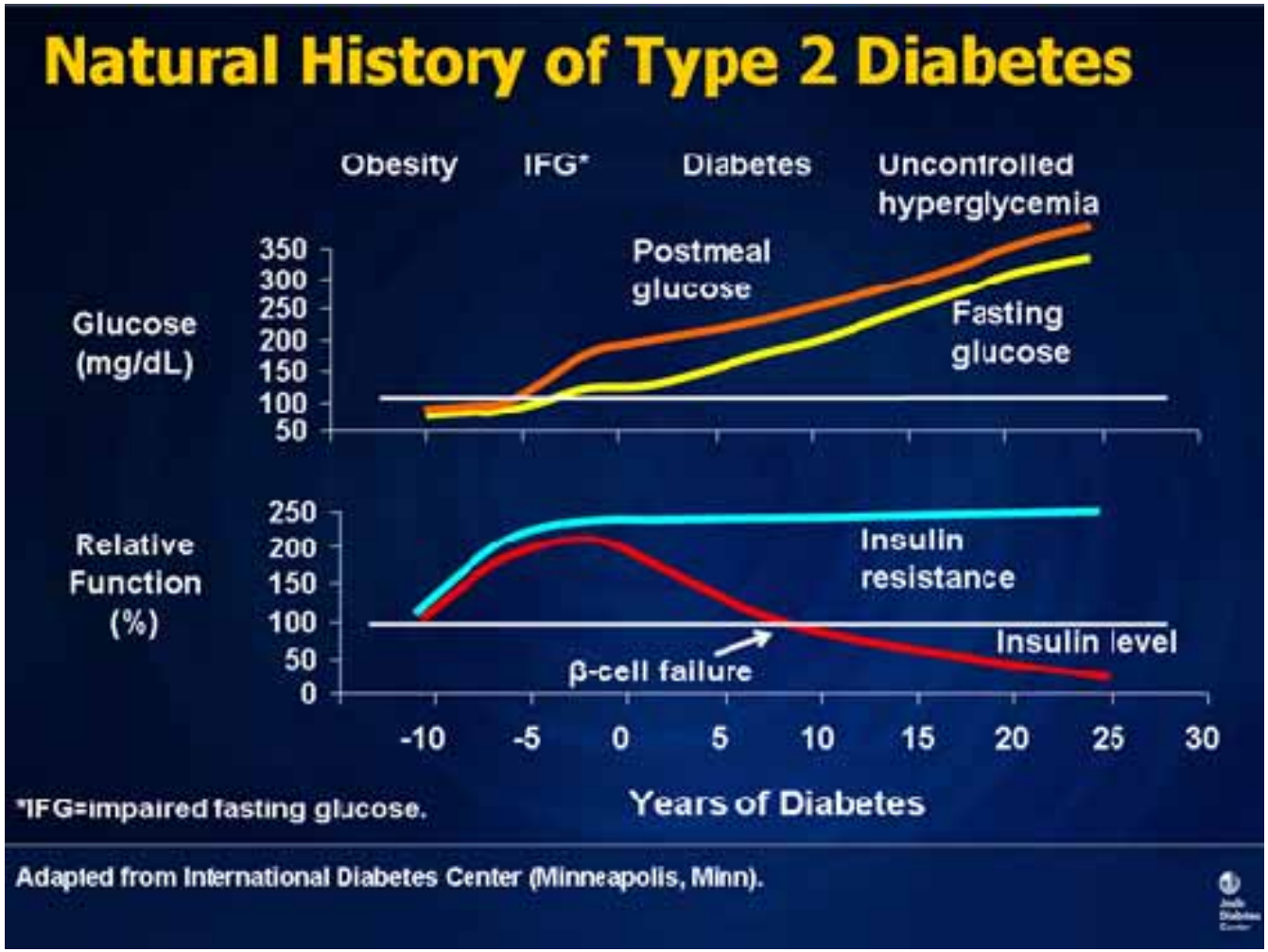
Pathophysiology of T2DM

- Genetic or acquired lesion(s) conferring insensitivity to the effects of circulating insulin
- Defect in glucagon secretion – levels inappropriate for degree of hyperglycaemia
- Gradual failure of insulin secretion in response to hyperglycaaemia resulting from gluco- and lipo-toxicity and amyloid deposition in islet cells
- May present with ketosis, and ketoacidosis (DKA)

Insulin resistance

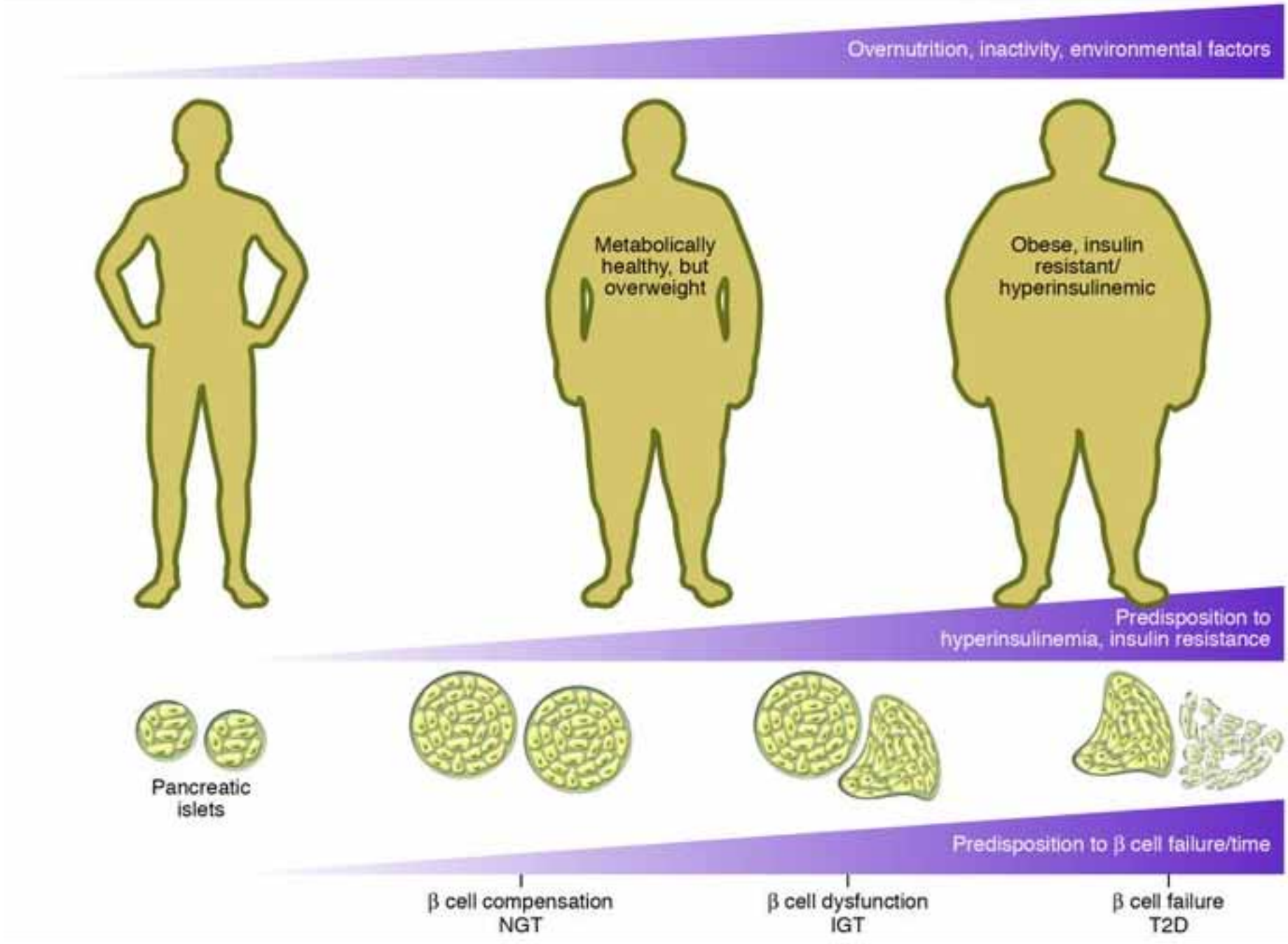
- May occur at the level of the insulin receptor (genetic lesion, or acquired: eg obesity, glucocorticoids, thyroxine , growth hormone excess)
- May be post-receptor
- Increased pro-insulin, insulin and C-peptide concentrations
- Beta-cell hyperplasia

Natural History of Type 2 Diabetes

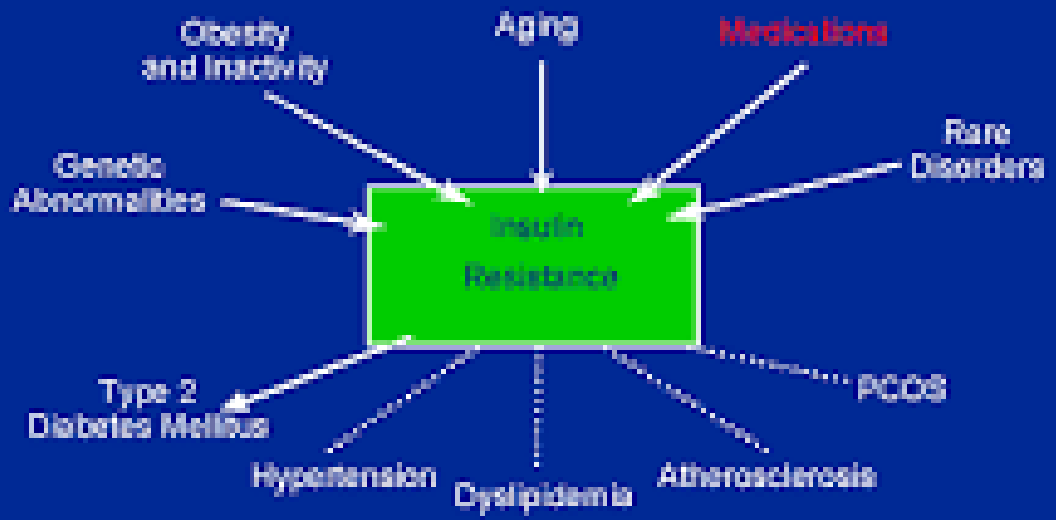


*IFG=impaired fasting glucose.

Adapted from International Diabetes Center (Minneapolis, Minn).

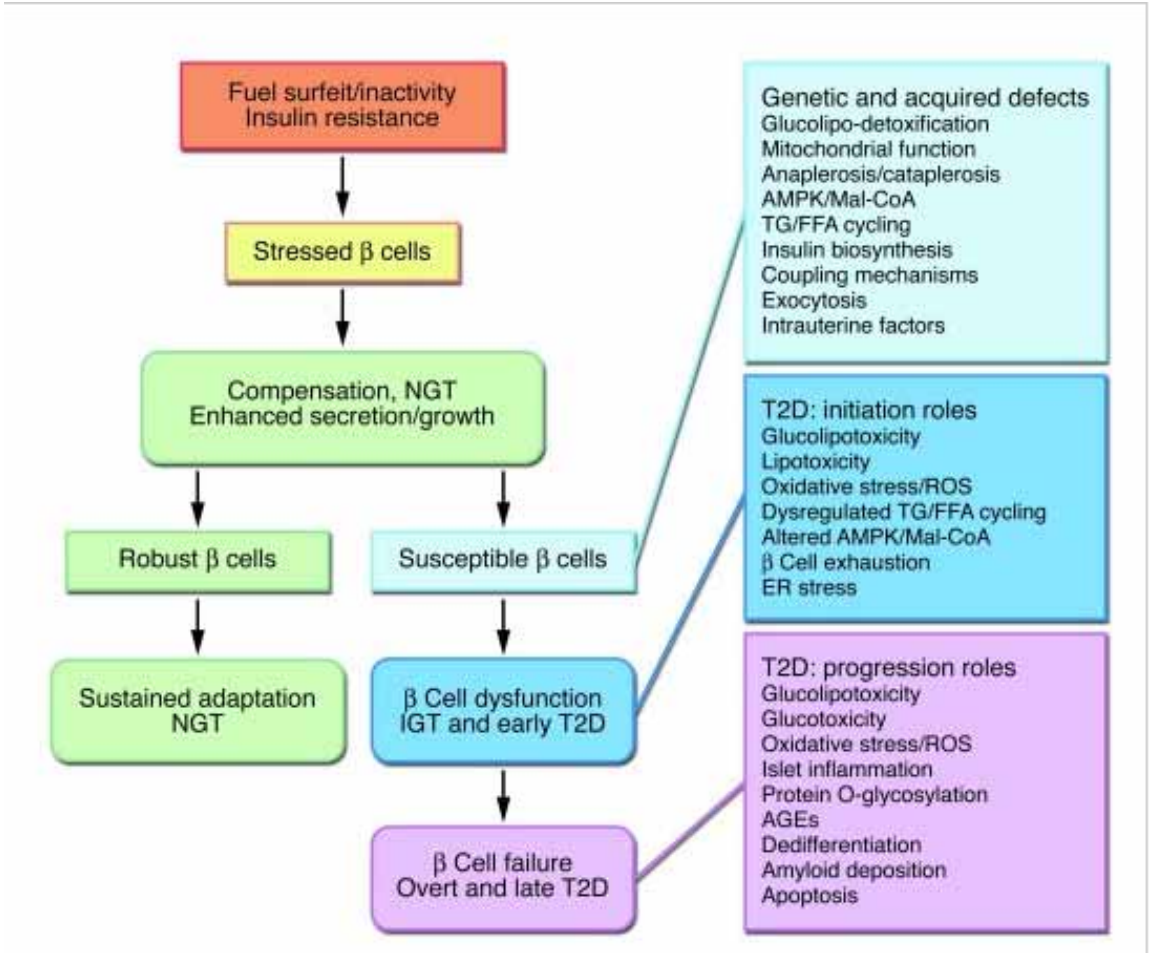

Overnutrition, inactivity, environmental factors
Metabolically healthy, but overweight
Obese, insulin resistant/ hyperinsulinemic
Predisposition to hyperinsulinemia, insulin resistance
Pancreatic islets
Predisposition to β cell failure/time
β cell compensation NGT
β cell dysfunction IGT
β cell failure T2D

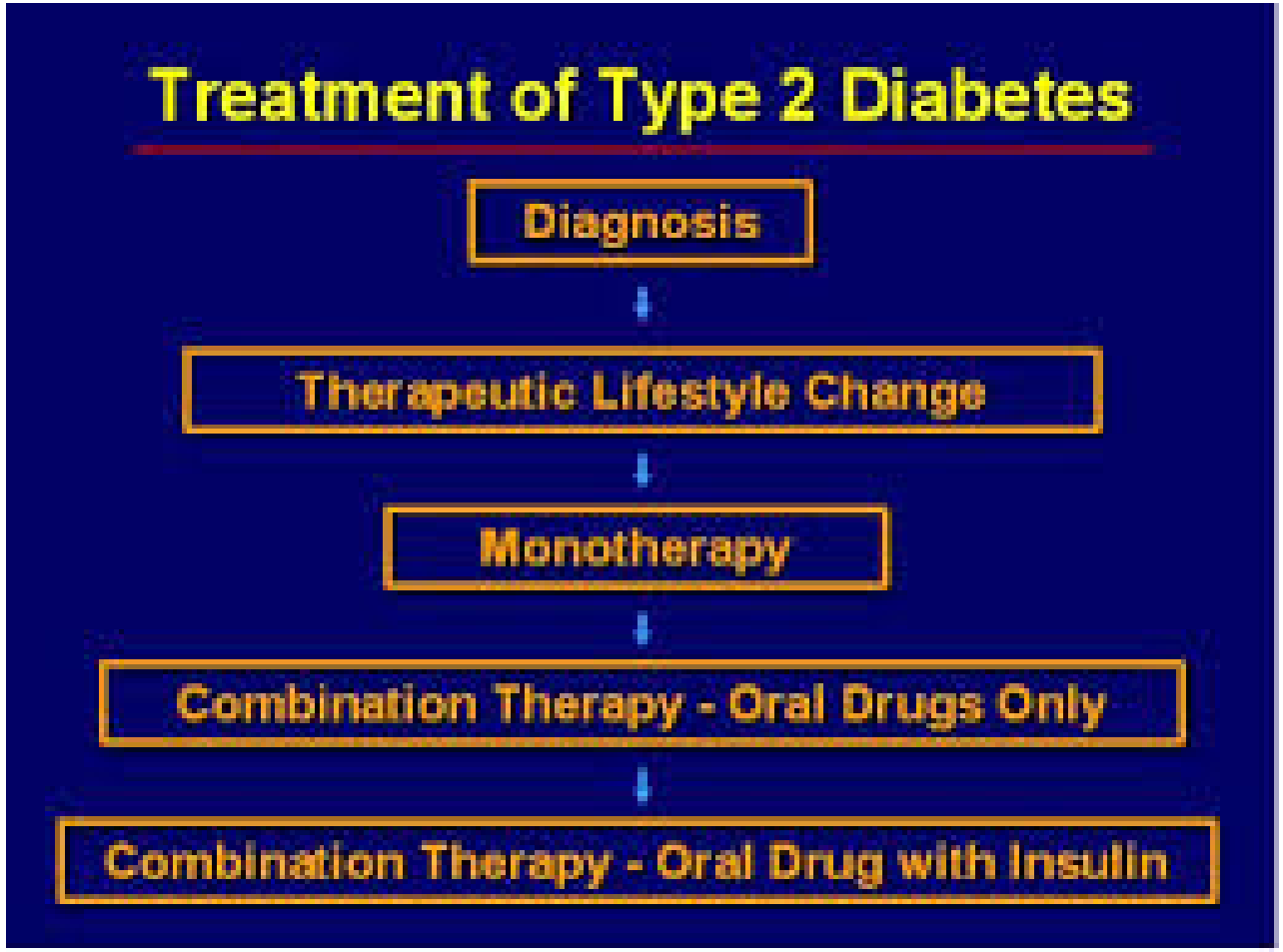
Insulin Resistance: *An Underlying Cause of Type 2 Diabetes Mellitus*



PCOS = polycystic ovary syndrome.

Reaven GM. *Physiol Rev.* 1995;73:473–486.
Clauser E et al. *Horm Res.* 1992;38:5–12.


Fuel surfeit/inactivity
Insulin resistance
Stressed β cells
Compensation, NGT
Enhanced secretion/growth
Robust β cells
Susceptible β cells
Sustained adaptation
NGT
β Cell dysfunction
IGT and early T2D
β Cell failure
Overt and late T2D
Genetic and acquired defects
Glucolipo-detoxification
Mitochondrial function
Anaplerosis/cataplerosis
AMPK/Mal-CoA
TG/FFA cycling
Insulin biosynthesis
Coupling mechanisms
Exocytosis
Intrauterine factors
T2D: initiation roles
Glucolipotoxicity
Lipotoxicity
Oxidative stress/ROS
Dysregulated TG/FFA cycling
Altered AMPK/Mal-CoA
β Cell exhaustion
ER stress
T2D: progression roles
Glucolipotoxicity
Glucotoxicity
Oxidative stress/ROS
Islet inflammation
Protein O-glycosylation
AGEs
Dedifferentiation
Amyloid deposition
Apoptosis


Treatment of Type 2 Diabetes
Diagnosis
Therapeutic Lifestyle Change
Monotherapy
Combination Therapy - Oral Drugs Only
Combination Therapy - Oral Drug with Insulin

Lifestyle intervention

- Physical activity (30 min daily vigorous activity)
- Weight reduction (low CHO intake, concentrating on low glycaemic index foods)
- In DPP, more effective than the usual first line treatments in preventing onset

Principles of T2DM management

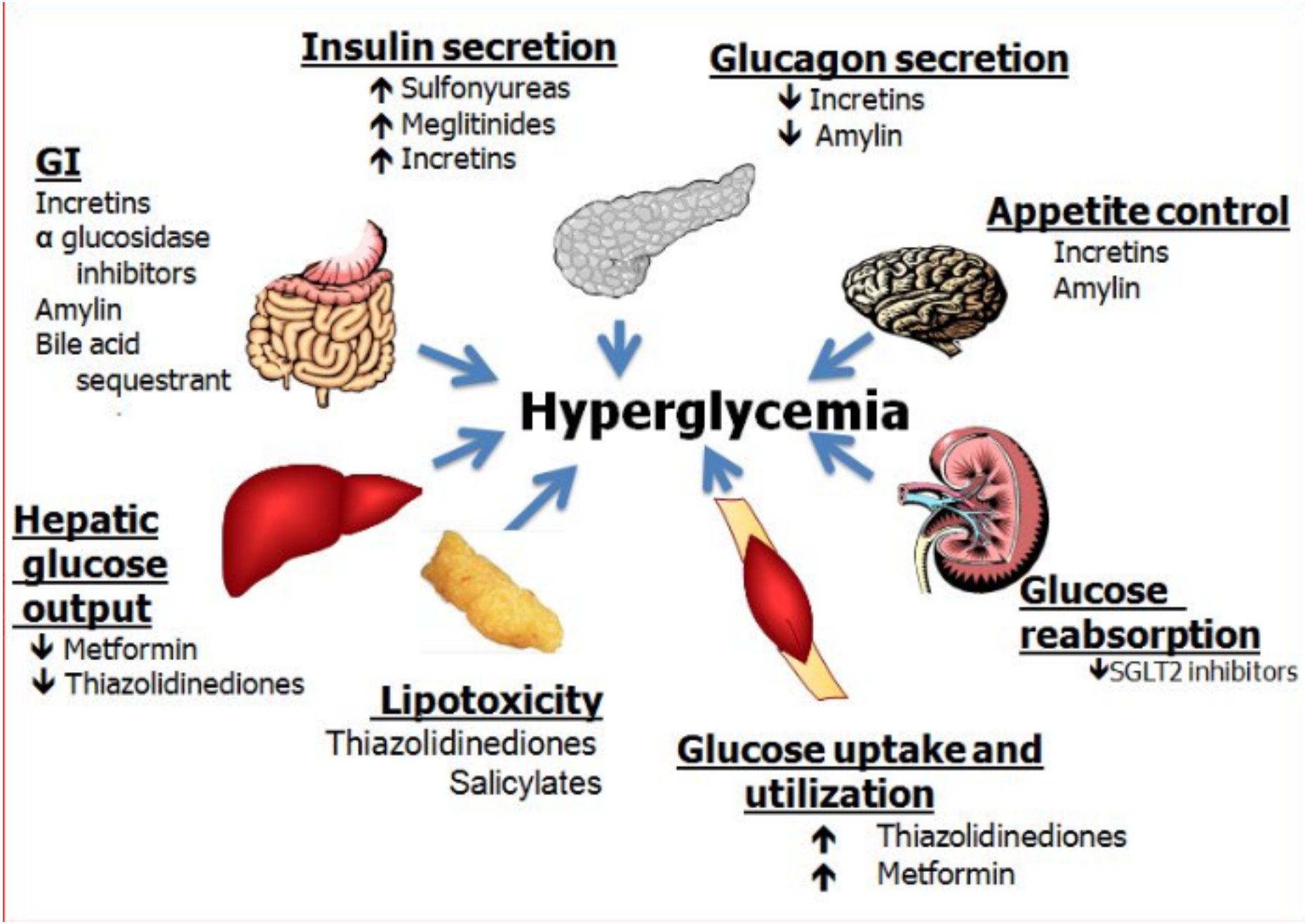
- Monitoring of glucose, (HbA1c) lipid and blood pressure levels
- Diabetes education programmes and dietary /exercise advice
- Pharmacotherapy:
- - control blood glucose
- - prevent vascular (blood vessel) disease
- - reduce blood pressure
- - improve lipid levels
- The detection and ongoing management (with referral to a specialist if necessary) of complications:
- - Eye disease (retinopathy screening and treatment)
- - Kidney disease (screening for urinary microalbumin/GFR)
- - Nerve damage (somatic and autonomic) and nerve pain
- - Macrovascular disease (CAD, PVD)
- - Depression.

Orally active agents in T2DM

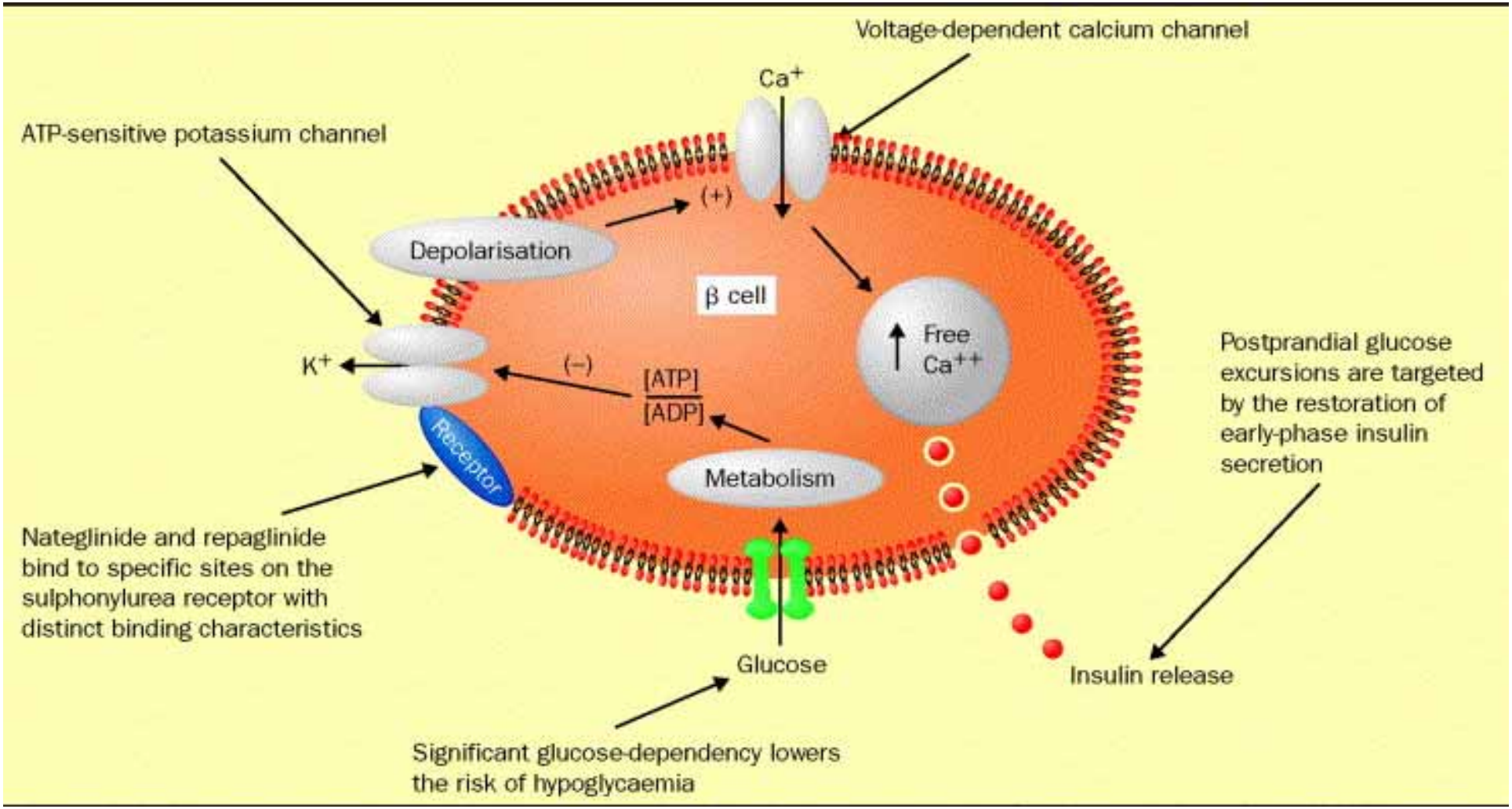
- **Metformin**
- Sulphonylureas and meglinitides
- Thiazolidinediones
- Acarbose (alpha glucosidase inhibition)
- Bromocriptine
- Bile acid sequestrants (eg colesevelam: FXR/TGR5 actions, stimulation of incretins)
- SGLT1 inhibitors (dapagliflozin)
- Gliptins (DPP 4 inhibitors)
- GLP-1 agonists

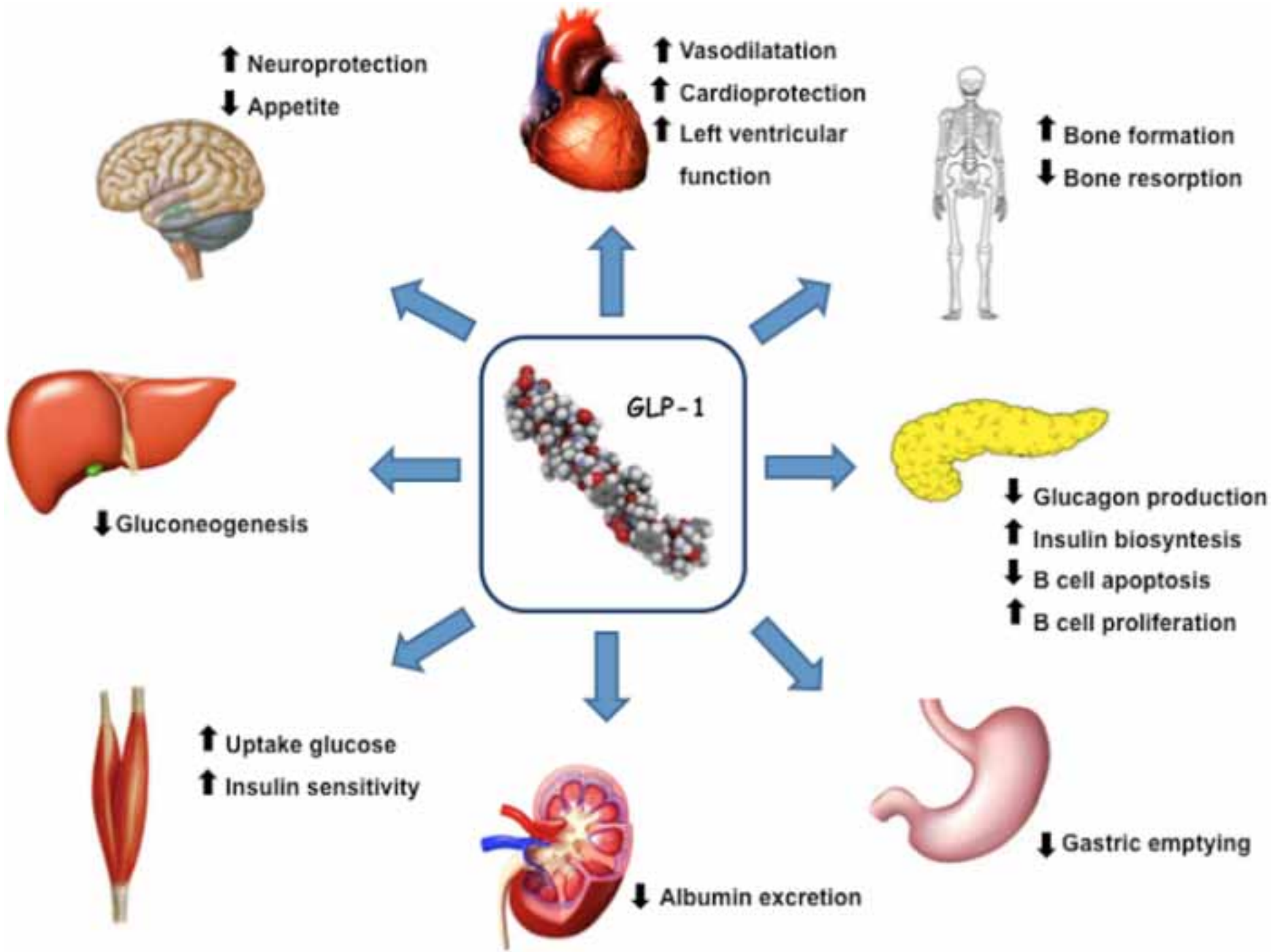
Pharmacotherapy

- Metformin
- Sulphonylureas
- Acarbose
- Gliptins
- GLP1 agonists
- Dopamine agonists
- SGPT inhibitors (eg dapagliflozin)
- Amylin
- Resins (Coleveratam)
- Testosterone
- Insulin (long acting)

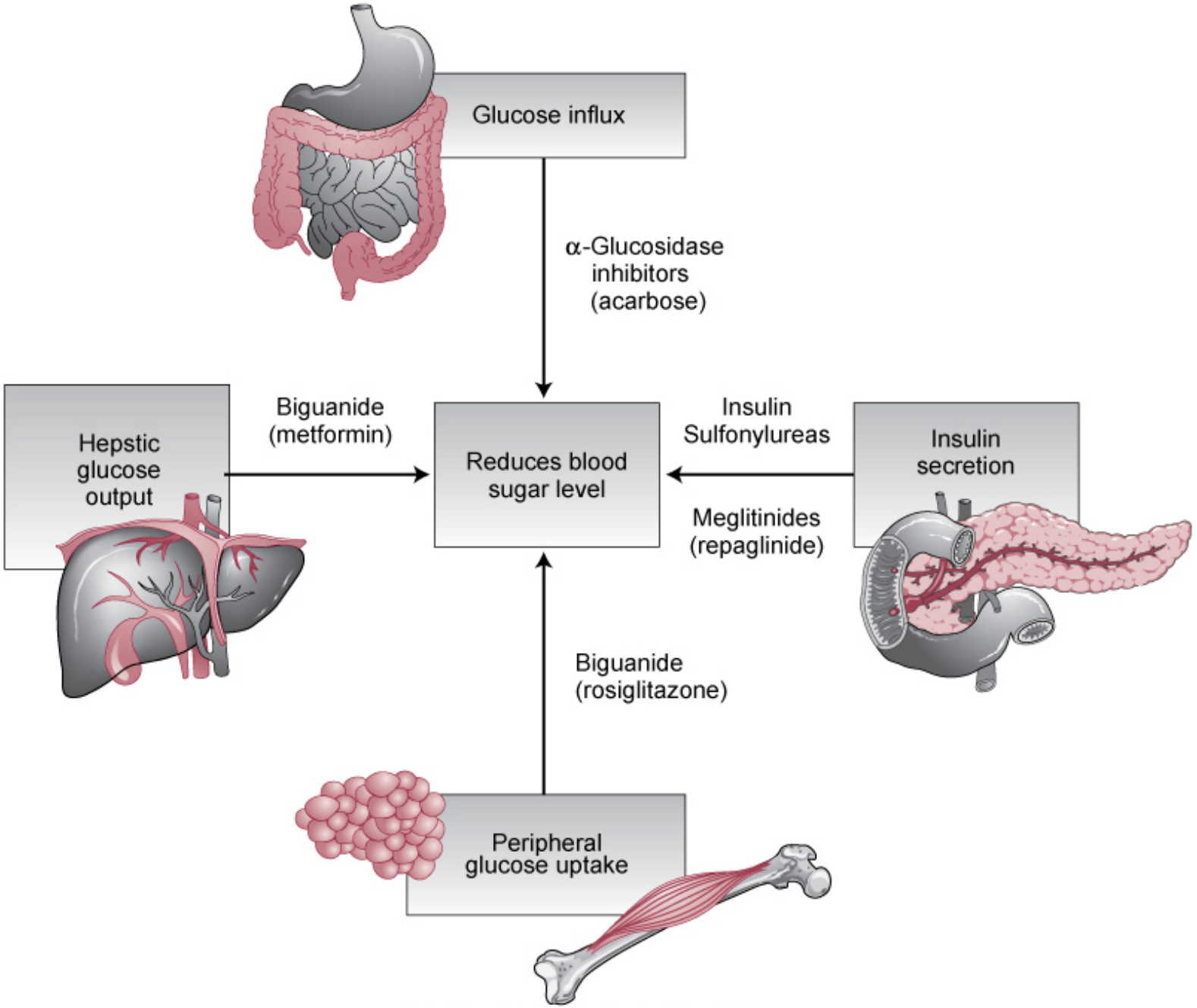

Insulin secretion
↑ Sulfonyureas
↑ Meglitinides
↑ Incretins
Glucagon secretion
↓ Incretins
↓ Amylin
GI
Incretins
α glucosidase inhibitors
Amylin
Bile acid sequestrant
Appetite control
Incretins
Amylin
Hyperglycemia
Hepatic glucose output
↓ Metformin
↓ Thiazolidinediones
Glucose reabsorption
↓SGLT2 inhibitors
Lipotoxicity
Thiazolidinediones
Salicylates
Glucose uptake and utilization
↑ Thiazolidinediones
↑ Metformin

Mode of action of sulphonylureas/meglinitides




⬆ Neuroprotection
⬇ Appetite
⬆ Vasodilatation
⬆ Cardioprotection
⬆ Left ventricular function
⬆ Bone formation
⬇ Bone resorption
GLP-1
⬇ Gluconeogenesis
⬇ Glucagon production
⬆ Insulin biosynthesis
⬇ B cell apoptosis
⬆ B cell proliferation
⬆ Uptake glucose
⬆ Insulin sensitivity
⬇ Albumin excretion
⬇ Gastric emptying

Current Therapies for Diabetes Do Not Address All Deranged Pathways



Set A1C Target for the Newly Diagnosed Type 2 Diabetic Patient

Life style intervention +/- metformin

Stage 1

A1c ≥7.5%: Consider combination therapy

A1c ≥ 9: consider insulin

HbA1c not at target (3-6 months): Add

BMI<30	35>BMI>30	BMI>35
DPP-4 inhibitor (Consider GLP-1)	GLP-1 DPP-4 inhibitors	GLP-1 Consider bariatric surgery in non-responders

Stage 2

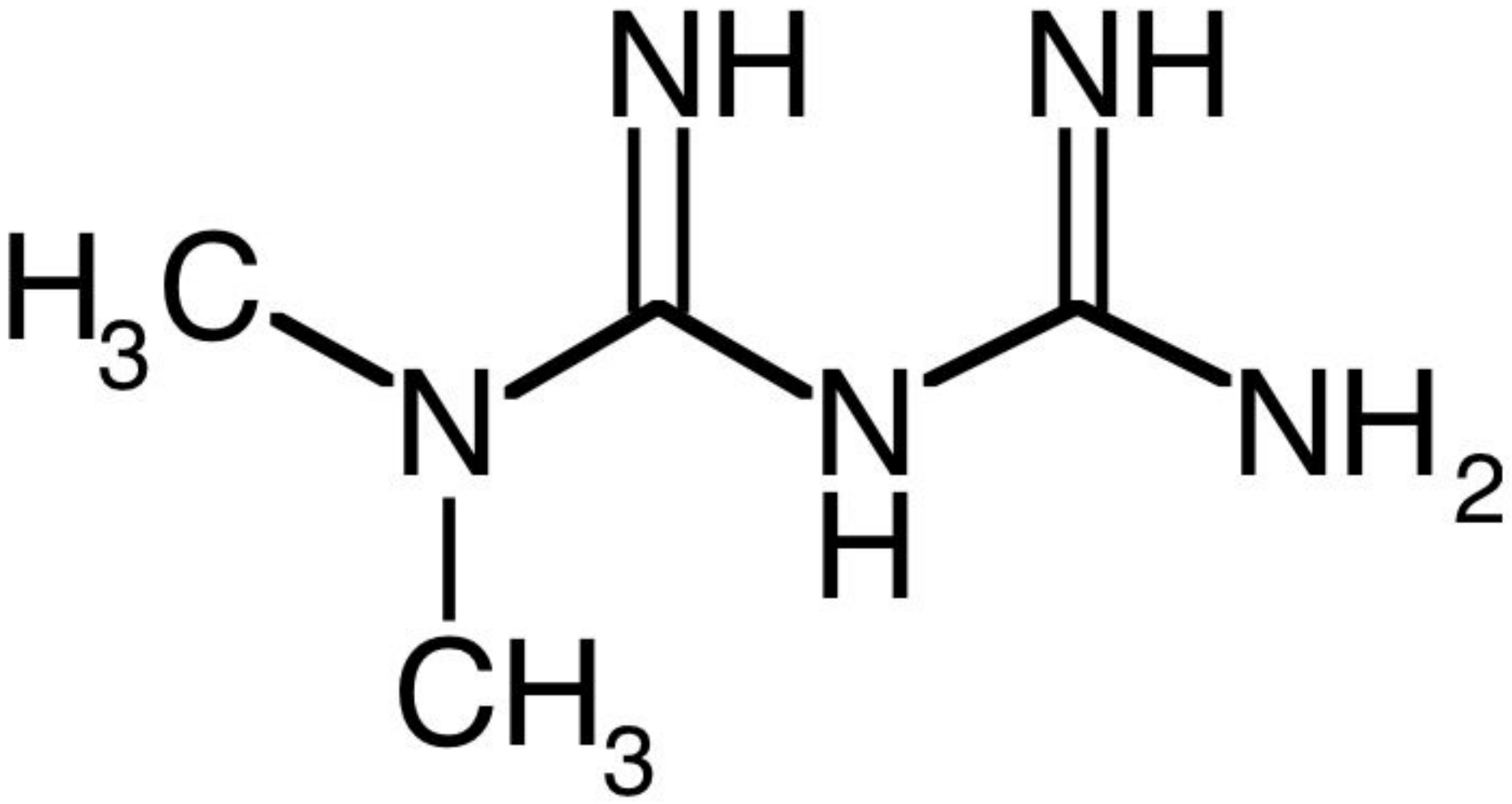
HbA1c not at target (3-6 months):

High post prandial	High fasting glucose
SU/Glinides – pioglitazone - rapid/mix insulin	Basal insulin (consider pioglitazone)

Stage 3

	Mean plasma glucose	
A1C (%)	mg/dL	mmol/L
6	126	7.0
7	154	8.6
8	183	10.2
9	212	11.8
10	240	13.4
11	269	14.9
12	298	16.5

A1C	7.0%*
Preprandial capillary plasma glucose	3.9–7.2 mmol
Peak postprandial capillary plasma glucose†	<10.0 mmol


NH
NH
H3C
N
N
NH2
H
CH3

The biguanides

- **Phenformin** and **buformin** found to be more potent than metformin
- The greater risk of lactic acidosis led to their discontinuation in the 1970s.
- Growing awareness that metformin offered a unique range of effects that countered insulin resistance- substantiated by the **United Kingdom Prospective Diabetes Study (UKPDS) :** Early use of metformin reduced CV mortality and increased survival in overweight and obese type 2 diabetic patients **beyond that expected for the prevailing level of glycaemic control**

Metformin Reduces Cardiovascular Risk in Type 2 Diabetes

Intensive glucose control policy in overweight type 2 diabetes patients using metformin as primary therapy in the UKPDS

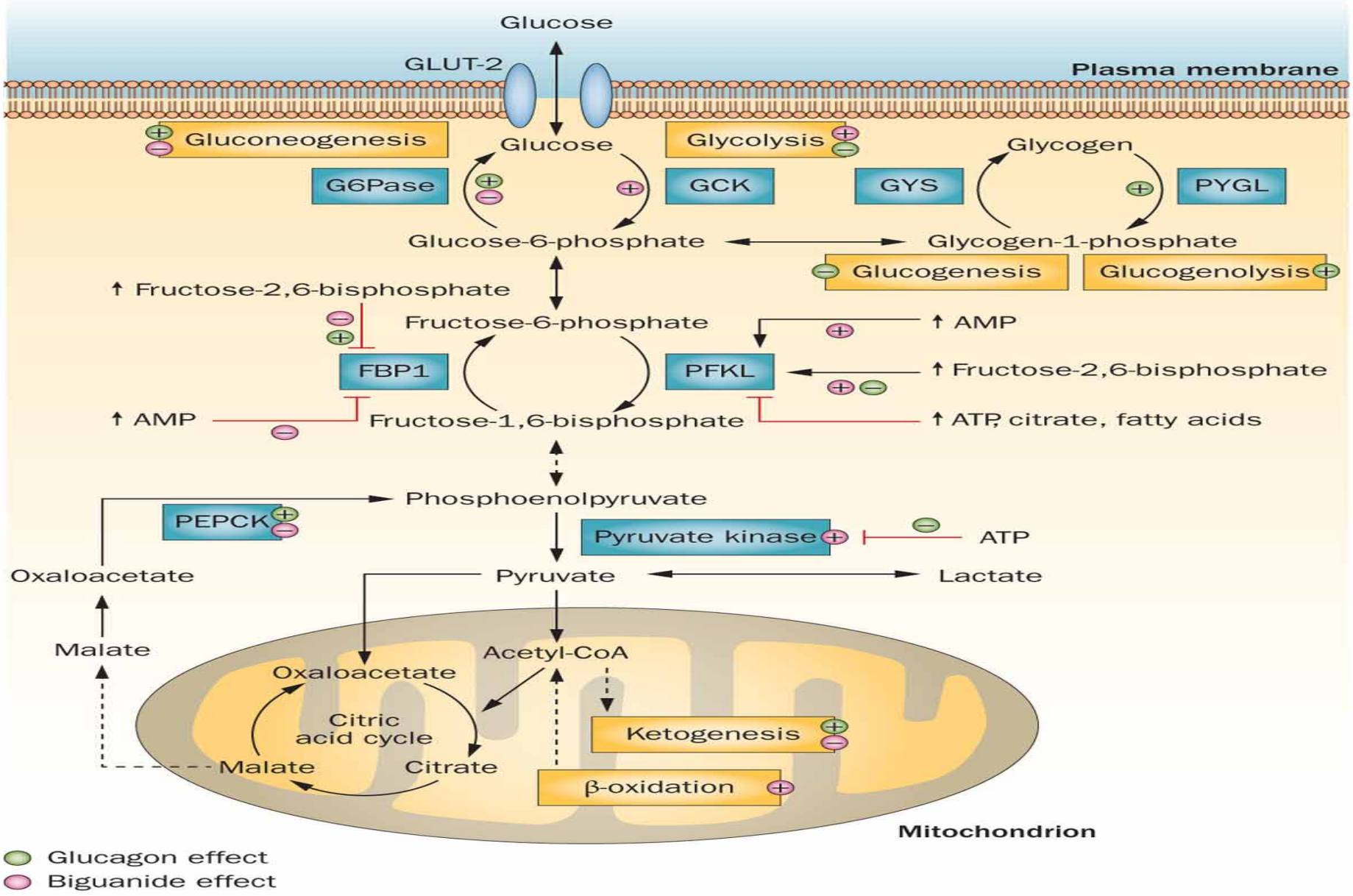
- Reduced A1C by 0.6% over 10 years
- Reduced the risk of diabetic complications

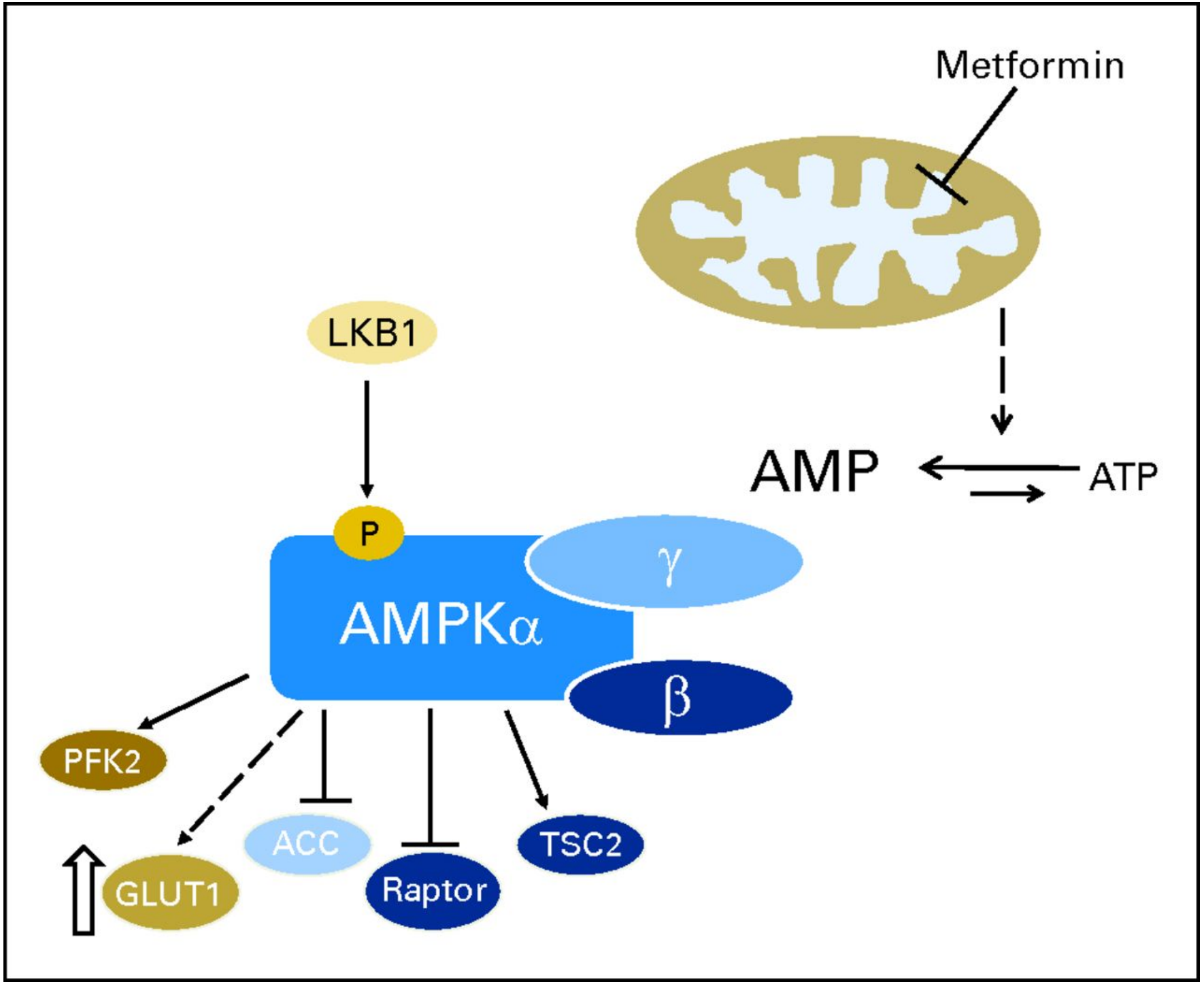
	Change in risk *	P value
Any diabetes-related endpoint	↓ 32%	0.0023
Diabetes-related deaths	↓ 42%	0.017
All-cause mortality	↓ 36%	0.011
Myocardial infarction	↓ 39%	0.01

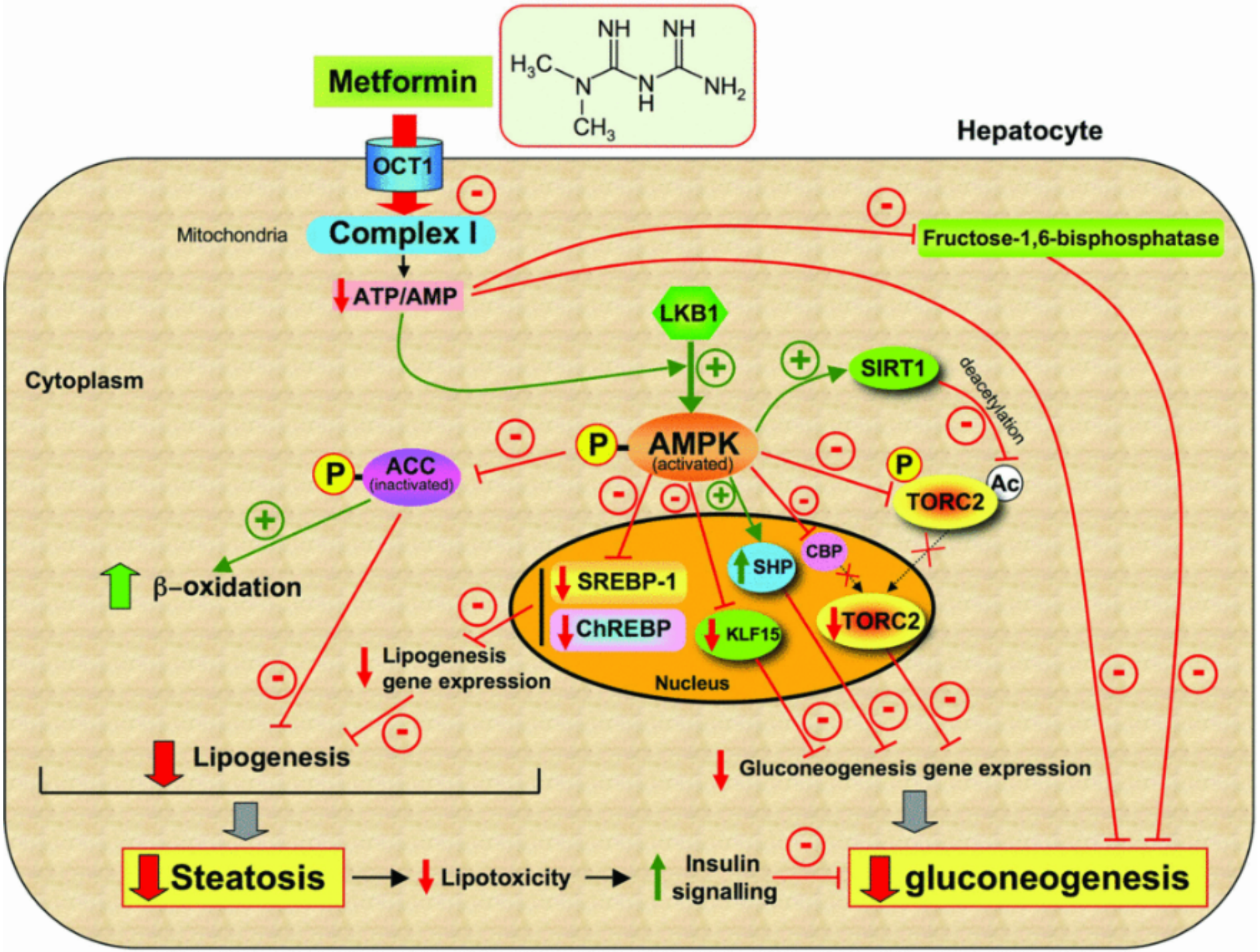
* Versus conventional policy

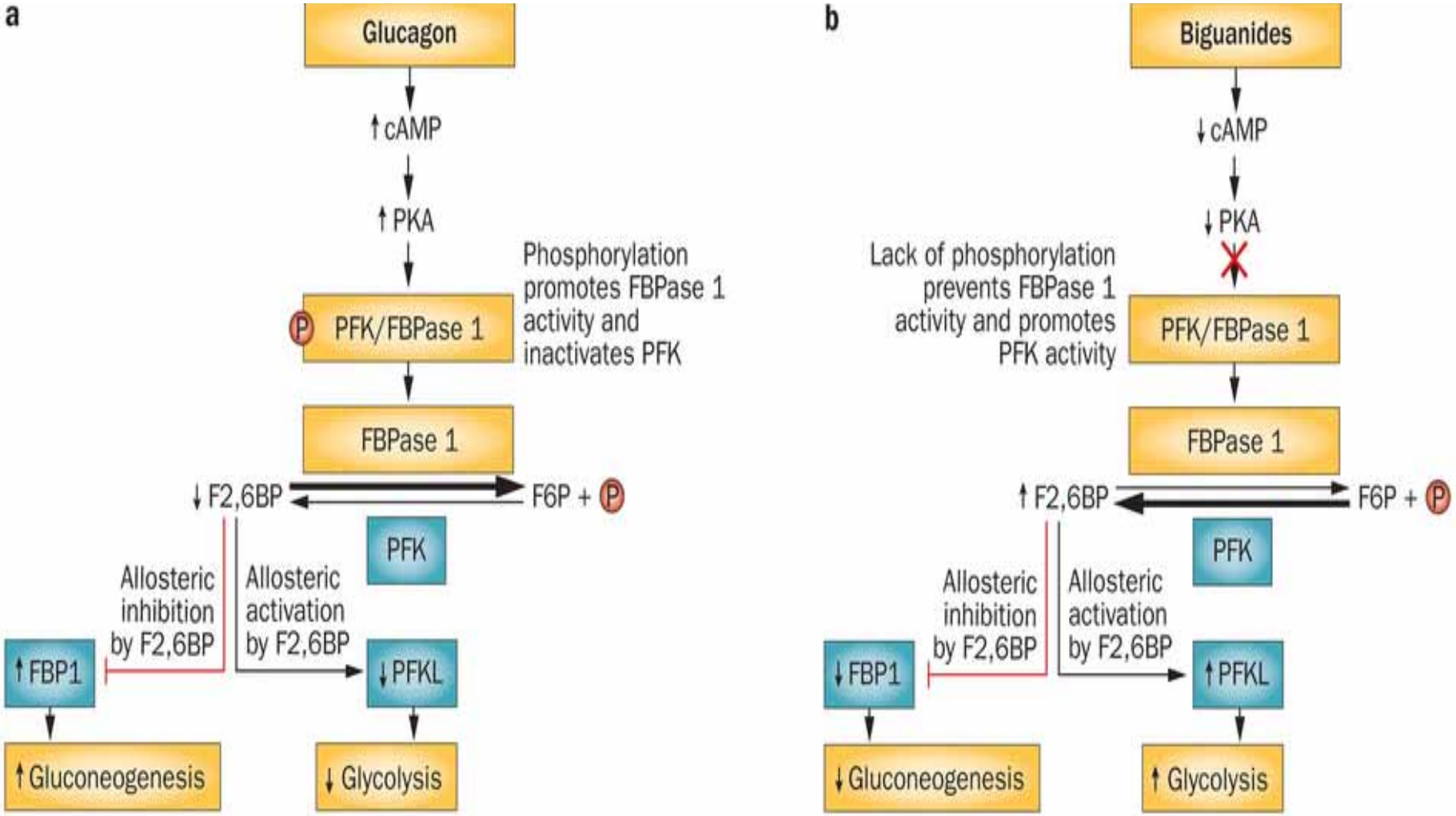
UKPDS Group. Lancet. 1998;352:854-65.

The effects of glucagon and biguanides on gluconeogenic and glycolytic fluxes




Metformin
LKB1
AMP
ATP
P
γ
AMPKα
β
PFK2
ACC
TSC2
GLUT1
Raptor


Metformin
OCT1
Mitochondria
Complex I
ATP/AMP
Hepatocyte
Fructose-1,6-bisphosphatase
LKB1
Cytoplasm
SIRT1
deacetylation
AMPK
(activated)
P
ACC
(inactivated)
TORC2
Ac
β–oxidation
SREBP-1
ChREBP
SHP
CBP
KLF15
TORC2
Nucleus
Lipogenesis
gene expression
Lipogenesis
Gluconeogenesis gene expression
Steatosis
Lipotoxicity
Insulin
signalling
gluconeogenesis



nature REVIEWS ENDOCRINOLOGY

HbA1C ≥6.5%

OR

Fasting plasma glucose (FPG)
≥126 mg/dL (7.0 mmol/L)

OR

2-h plasma glucose ≥200 mg/dL
(11.1 mmol/L) during an OGTT

OR

A random plasma glucose ≥200 mg/dL
(11.1 mmol/L)

Categories of increased risk for diabetes (prediabetes)*

FPG 100–125 mg/dL (5.6–6.9 mmol/L): IFG

OR

2-h plasma glucose in the 75-g OGTT 140–199 mg/dL (7.8–11.0 mmol/L): IGT

OR

A1C 5.7–6.4%

Ketosis prone T2DM (Winter 1987)

•β-cell function apparently preserved within 1–2 weeks of the index DKA and improves further when measured after 6–12 months.

•Several observational and prospective studies suggest that ~70% of such patients achieve near-normoglycemia remission within 10 weeks of follow-up

•40% of patients remained free of insulin injections 10 years after their first presentation .

Ketosis prone T2DM

- β-cell response to non-glucose secretagogues (e.g., glucagon, arginine, and β-adrenergic agonists) often preserved in presence of hyperglycemia .
- **Glucagon stimulation test**: C-peptide levels measured before and within 10 min after iv glucagon (1 mg) .
- Fasting C-peptide levels >1.0 ng/dl (0.33 nmol/l) and stimulated C-peptide levels >1.5 ng/dl (0.5 nmol/l) shortly after presentation predictive of long-term remission .
- **Fasting C-peptide >1.0 ng/dl (0.33 nmol/l)** within 2 weeks of presentation correlates well with the glucagon-stimulated C-peptide response in predicting long-term normoglycemic remission in subjects with a history of DKA . Mr MR C peptide **0.87nmol/l** fasting, and **2.3** after glucagon

In those without risk factors, begin testing at age 45 years (B)

Criteria for Testing for Diabetes in Asymptomatic Adult Individuals (1)

1. Testing should be considered in all adults who are overweight (BMI ≥25 kg/m^2*) and have additional risk factors:

-
-
-
- African
-
-
-
-
-
-

Refer patients with IGT (A), IFG (E), or A1C 5.7–6.4% (E) to ongoing support program

- Targeting weight loss of 7% of body weight
- At least 150 min/week moderate physical activity

Follow-up counseling important for success (B)

Based on cost-effectiveness of diabetes prevention, third-party payers should cover such programs (E)

Patients on multiple-dose insulin (MDI) or insulin pump therapy should do SMBG (B)

- At least prior to meals and snacks
- Occasionally postprandially
- At bedtime
- Prior to exercise
- When they suspect low blood glucose
- After treating low blood glucose until they are normoglycemic
- Prior to critical tasks such as driving

Lowering A1C to below or around 7% has been shown to reduce microvascular complications and, if implemented soon after the diagnosis of diabetes, is associated with long-term reduction in macrovascular disease (B)

Therefore, a reasonable A1C goal for many nonpregnant adults is <7% (B)

Case vignette 1

MR, 33 year old Kuwaiti man, referred by KHO for management of diabetes.

February 2014: weakness, ‘collapse at work’, admitted to hospital. Glucose 520mg/dl. Ketones +++ pH 7.32 Bicarbonate 18.

Put on insulin for a short time, discharged on metformin 850mg bid, but stopped the drug 4 months ago. Acanthosis on neck.

October 2014: Glucose 5.2 and HbA1c 5.1%. No treatment. Patient clinically well

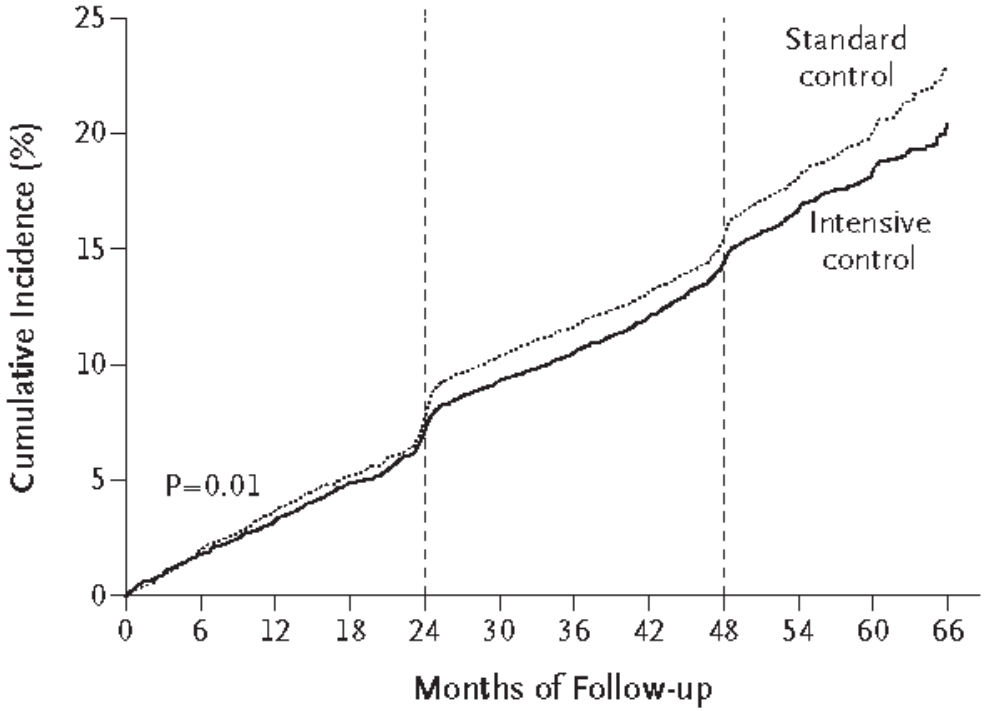
How can I prevent a recurrence of my diabetes?

What is his diagnosis?

What is the defect in his glucose homeostasis?

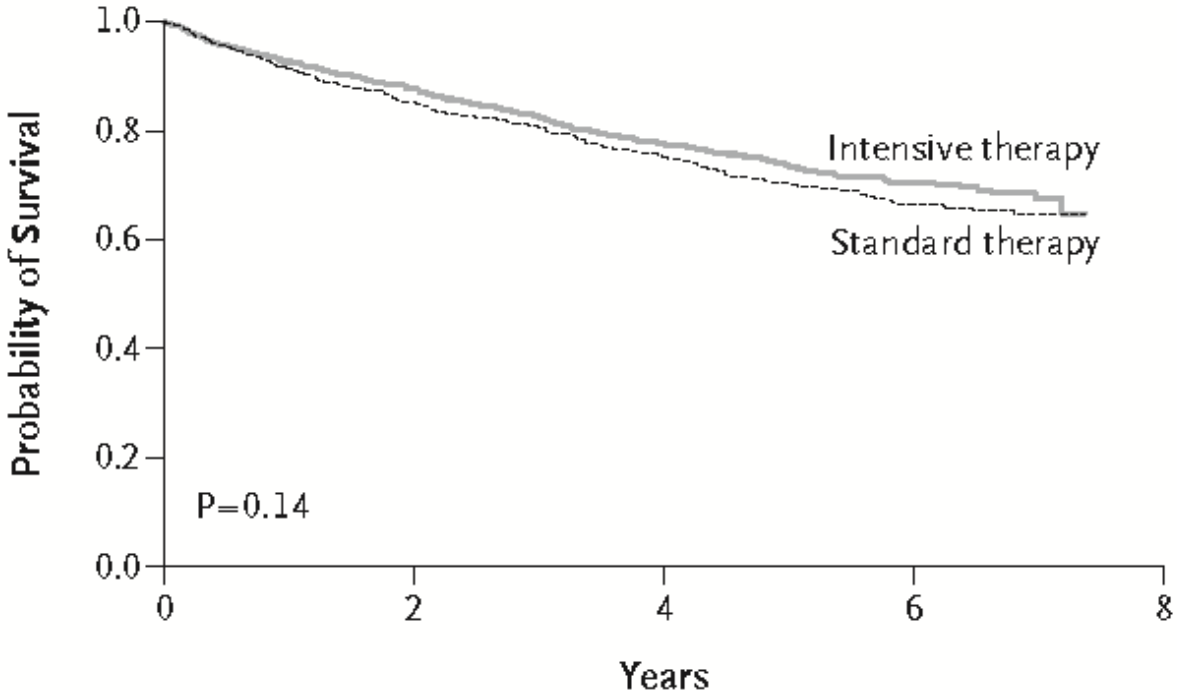
Ketosis prone diabetes mellitus

- Negative GAD 65 Ab, IA-2
- Normal TFT, ferritin
- Father and mother T2DM
- June 2013. Weight 124kg. Diet and health club
- December 2013 Weight 96kg
- December to February 2014: carbohydrate binge +++.' Insatiable urge to feast on CHO'
- February 2014. DM with ketoacidosis
- October 2014. Weight 89kg. Stable with lifestyle modification alone

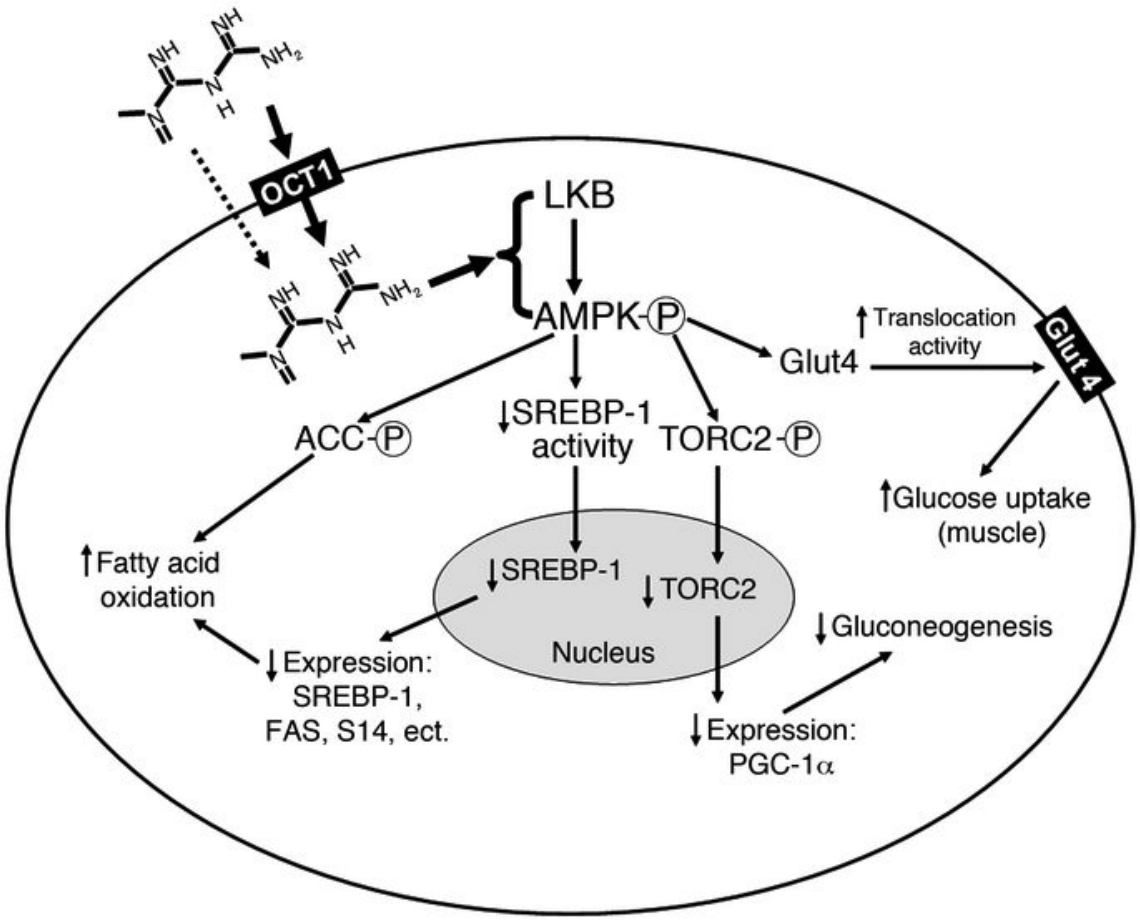


No. at Risk

Intensive	5570	5457	5369	5256	5100	4957	4867	4756	4599	4044	1883	447
Standard	5569	5448	5342	5240	5065	4903	4808	4703	4545	3992	1921	470



No. at Risk									
Standard therapy	899	770	693	637	570	471	240	55	0
Intensive therapy	892	774	707	639	582	510	252	62	0


OCT1
LKB
AMPK-Ⓟ
Glut4
↑Translocation activity
Glut 4
ACC-Ⓟ
↓SREBP-1 activity
TORC2-Ⓟ
↑Glucose uptake (muscle)
↑Fatty acid oxidation
↓SREBP-1
↓TORC2
Nucleus
↓Gluconeogenesis
↓Expression: SREBP-1, FAS, S14, ect.
↓Expression: PGC-1α

One third of T2DM patients do not respond to metformin.

WHY?

Metformin, if not contraindicated and if tolerated, is the preferred initial pharmacological agent for type 2 diabetes (A)

In newly diagnosed type 2 diabetic patients with markedly symptomatic and/or elevated blood glucose levels or A1C, consider insulin therapy, with or without additional agents, from the outset (E)

Advise people with diabetes to perform at least 150 min/week of moderate-intensity aerobic physical activity (50–70% of maximum heart rate), spread over at least 3 days per week with no more than
2 consecutive days without exercise (A)

In absence of contraindications, adults with type 2 diabetes should be encouraged to perform resistance training at least twice per week (A)

Consider bariatric surgery for adults with BMI ≥35 kg/m^2 and type 2 diabetes (B)

After surgery, life-long lifestyle support and medical monitoring is necessary (B)

Insufficient evidence to recommend surgery in patients with BMI <35 kg/m^2 outside of a research protocol (E)

Well-designed, randomized controlled trials comparing optimal medical/lifestyle therapy needed to determine long-term benefits, cost-effectiveness, risks (E)

- Provide influenza vaccine annually to all diabetic patients ≥6 months of age (C)
- Administer pneumococcal polysaccharide vaccine to all diabetic patients ≥2 years ©
- One-time revaccination recommended for those >64 years previously immunized at <65 years if administered >5 years ago
- Other indications for repeat vaccination: nephrotic syndrome, chronic renal disease, immunocompromised states

- CVD is the major cause of morbidity, mortality for those with diabetes
- Common conditions coexisting with type 2 diabetes (e.g., hypertension, dyslipidemia) are clear risk factors for CVD
- Diabetes itself confers independent risk
- Benefits observed when individual cardiovascular risk factors are controlled to prevent/slow CVD in people with diabetes

- People with diabetes and hypertension should be treated to a systolic blood pressure goal of <140 mmHg (B)

- Lower systolic targets, such as <130 mmHg, may be appropriate for certain individuals, such as younger patients, if it can be achieved without undue treatment burden (C)

- Patients with diabetes should be treated to a diastolic blood pressure <80 mmHg (B)

- Patients with a blood pressure (BP) >120/80 mmHg should be advised on lifestyle changes to reduce BP (B)

- Patients with confirmed BP ≥140/80 mmHg should, in addition to lifestyle therapy, have prompt initiation and timely subsequent titration of pharmacological therapy to achieve BP goals (B)

Metformin and its place in the pharmacological management of T2DM

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Disclosure

MERCK SERONO are sponsoring my travel arrangements, accommodation and are giving me an honorarium for lecturing in Kuwait. They have had no input into the educational content of my lecture, nor opinions I am expressing.

Content of lecture

- Case vignette
- Pathogenesis of T2DM
- Insulin resistance and beta cell failure
- Management of T2DM / NICE guidelines
- Modes of action of drugs used in pharmacotherapy
- Metformin and its mode of action
- Metformin vs lifestyle intervention
- Metformin non- responders
- Metformin and cancer

Galega officinalis

- *G. officinalis* used in folklore medicine to treat symptoms now ascribed to type 2 diabetes ; versions of Culpeper's herbal suggest it had anti-diabetic properties.
- Studies in the late 1800s indicated that *G. officinalis* was rich in **guanidine** , and in 1918 guanidine shown to possess **hypoglycaemic activity in animals**
- Detailed accounts of extracts of *G. officinalis* used to treat diabetes in France up to the 1930s

Historical perspective

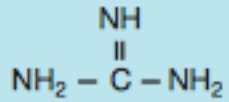
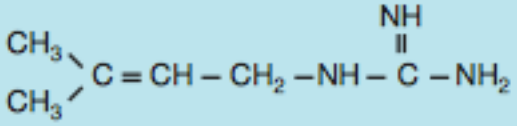
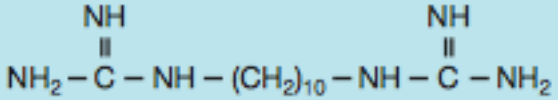
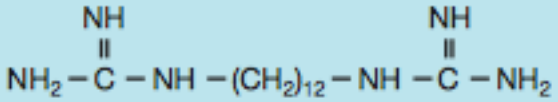
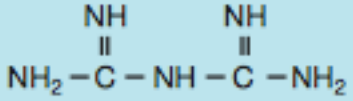
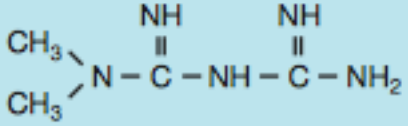
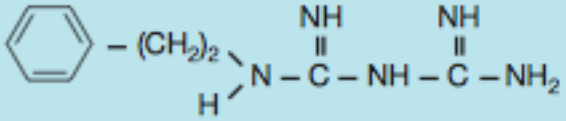
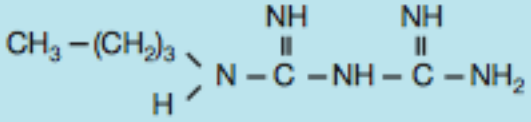
- Guanidine too toxic for clinical use; **galegine** (isoamylene guanidine), a less toxic extract of *G. officinalis* used briefly as an antidiabetic agent in the 1920s
- Two synthetic diguanides, namely decamethylene diguanide (Synthalin A) and dodecamethylene diguanide (Synthalin B), better tolerated and more effective, and used clinically in the 1920s.
- 1940s the antimalarial **chloroguanidine hydrochloride** was found to have a weak glucose-lowering effect
- 1949 dimethylbiguanide (known then as flumamine) was used against influenza in the Philippines. The latter prompted **Jean Sterne** to investigate the glucose-lowering activity of dimethylbiguanide.

Historical perspective

- Collaboration with Denise Duval and others, Sterne explored the anti-diabetic properties of several biguanides, unaware of the German studies in 1929. Sterne selected **dimethylbiguanide (metformin)** for clinical development and proposed the name **'Glucophage' (glucose eater)**. His results were published in 1957.
- In 1957, Ungar also published trials with **phenformin**

1995

Gerry Daniel brings metformin to the USA, where it enjoys blockbuster status under franchise to Bristol Myers Squibb

Guanidine	
Galegine	
Synthelin A	
Synthelin B	
Biguanide	
Metformin	
Phenformin	
Buformin	

What is the mode(s) of action of metformin?

Metformin transporter	Encoded by	Function
SLC22A1 (also known as OCT1)	*SLC22A1*	Main transporter accountable for metformin uptake[18] Expressed in liver and kidney Some SNPs shown to associate with reduced metformin uptake, increased metformin elimination as a result of reduced renal tubular reabsorption and lower therapeutic response owing to diminished action of metformin in the liver[144] Wide disparity in frequency distribution of SNPs among ethnic groups[18]
SLC22A2 (also known as OCT2)	*SLC22A2*	Mediates metformin secretion (kidney) Accountable for 80% of the total metformin clearance[85]
SLC22A3 (also known as OCT3)	*SLC22A3*	Expressed in multiple tissues (including liver, kidney, heart, skeletal muscle, brain, placenta) May be important in the uptake of metformin in muscle[145]
SLC22A4 (also known as OCTN1)	*SLC22A4*	Involved in the gastrointestinal absorption of metformin[146] Role in the mitochondrial uptake of phenformin[17]
MATE1	*SLC47A1*	Mediates metformin secretion (kidney; liver–excretion into bile) Rs2289669 polymorphism was associated with an amplified glucose-lowering effect of metformin in diabetic patients[147]
MATE2	*SLC47A2*	Mediates metformin secretion (kidney)
hENT4 (also known as PMAT)	*SLC29A4*	Mediates renal and intestinal metformin uptake[148]

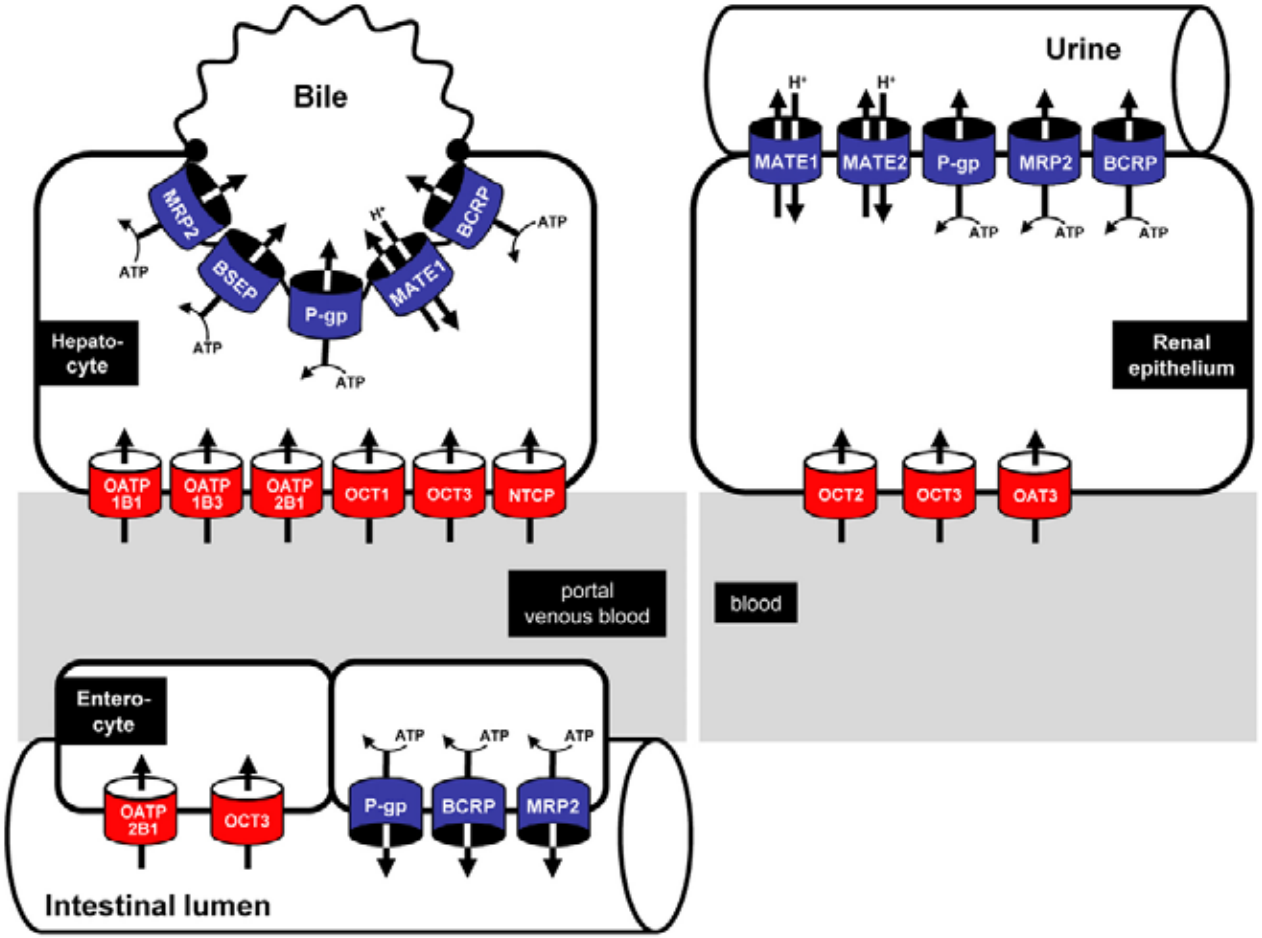
Determinants of response to metformin

- SNPs of SP1 (regulates OCT expression)
- SNPs of OCT1, OCT3, MATE (blocked by pyrimethamine)
- SNPS of ATM gene
- SNPs of LKB1 gene
- Genetic variants in other transcription factors, peroxisome proliferator–activated receptor-α and hepatocyte nuclear factor 4-α, significantly associated with HbA1c change to metformin

OCT= organic cation transporter

MATE= multidrug and toxin extrusion transporter

Metformin, the OCTs/MATEs



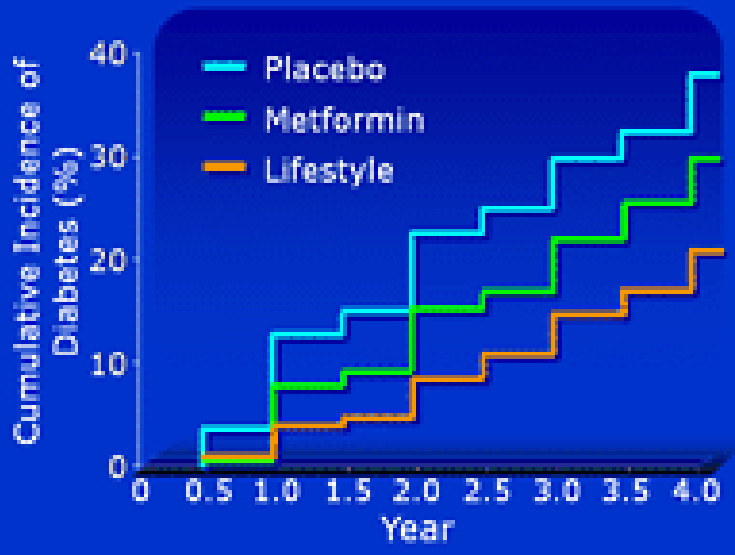
Diabetes Prevention Program (DPP) Study Population

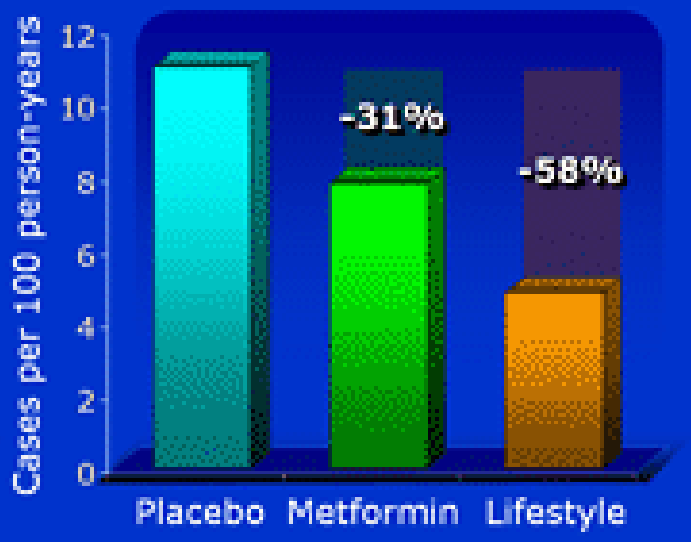
- 3,234 subjects with impaired glucose tolerance (IGT)
  - Fasting plasma glucose: 95-125 mg/dl
  - 2 hour plasma glucose: 140-199 mg/dl
- Age $\geq$ 25 years (mean 51 years)
- BMI $\geq$ 24 kg/m^2 (mean 34 kg/m^2)
- 68% women
- 45% minorities

Diabetes Prevention Program Research Group. *N Engl J Med* 2002;346:393-403.

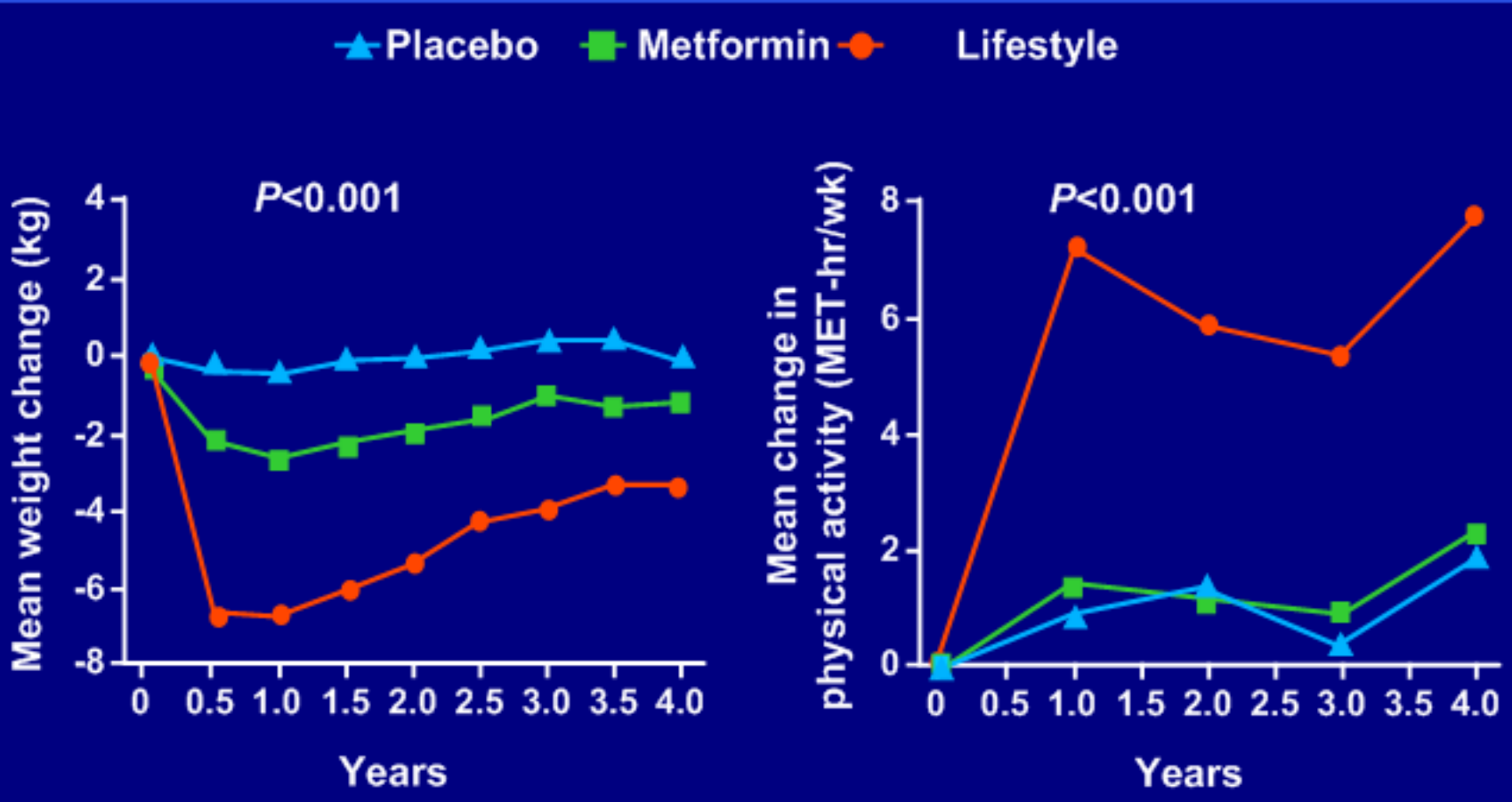
Diabetes Prevention Program (DPP)

- 3,234 individuals at risk for diabetes
- Randomized to placebo, metformin or lifestyle modification
- Mean follow-up 2.8 years





DPP: Weight Loss and Activity



Diabetes Prevention Program Research Group.
N Engl J Med. 2002;346:393-403.

Lifestyle Interventions Summary

- Lifestyle intervention continues to have an effect; most drugs do not

Lifestyle

Study		N	Intervention	Treatment	Risk Reduction
Da Qing	IGT	577	Lifestyle	6 years 20 years	34% - 69%
Finnish DPS	IGT	523	Lifestyle	3+ years 7 years	58%
DPP	IGT	3324	Lifestyle	3 years	58%

Pharmacologic

Study		N	Intervention	Treatment	Risk Reduction
DPP	IGT	3324	Metformin	3 years	31%
DREAM	IGT	5269	Rosiglitazone	3 years	60%
STOP-NIDDM	IGT	1429	Acarbose	3 years	21%
ACT NOW	IFG	~600	Pioglitazone	3 years	81%

American Diabetes Association.

Diabetes Care. 1997;20:537-544; *N Engl J Med*. 2002;344:1343-1350; *N Engl J Med. 2002*;346;393-403; *Diabetes Care*. 2011;34:1265-1269; *Lancet*. 2002;359(9323): 2072-2077 *N Engl J Med*. 2011;364:1104-1115.

Cost-Effectiveness of Lifestyle Modification or Metformin: DPP

- Active interventions (vs placebo) would:

	Intensive Lifestyle	Metformin
Delay onset of type 2 diabetes by	11.1 years	3.4 years
Reduce incidence of type 2 diabetes by	20%	8%
Increase life expectancy by	0.5 years	0.2 years
Cost per QALY	$1,124	$31,286

QALY = Quality Adjusted Life Years

American Diabetes Association.

Herman WH, et al for the Diabetes Prevention Program Research Group. *Ann Intern Med*. 2005:142:323-332.

Drug interactions between drugs used in T2DM

- Demonstration *in vitro* analyzing OCT1- and OCT2-mediated metformin uptake and uptake inhibition by the DPP-4 inhibitor sitagliptin. The study showed that sitagliptin inhibited OCT1- and OCT2-mediated metformin uptake with IC50 values of 34.9 μM and 40.8 μM, respectively.

ADA Guidelines: Recommendations for Prevention/Delay of Type 2 Diabetes

- Refer patients with IGT, IFG, or A1C 5.7%–6.4% to ongoing support program targeting
  - weight loss: 7% of body weight
  - increased physical activity: 150 min/week moderate activity
- Consider metformin therapy for diabetes prevention among those with IGT, IFG, or A1C 5.7%–6.4%
  - give particular consideration to those with BMI >35 kg/m^2, aged <60 years, and women with prior GDM
- Annually monitor those with prediabetes for diabetes development

BMI=body mass index.
GDM=gestational diabetes mellitus.
IFG=impaired fasting glucose.
IGT=impaired glucose tolerance.

ADA. *Diabetes Care*. 2012;35(suppl 1):S11-S63.

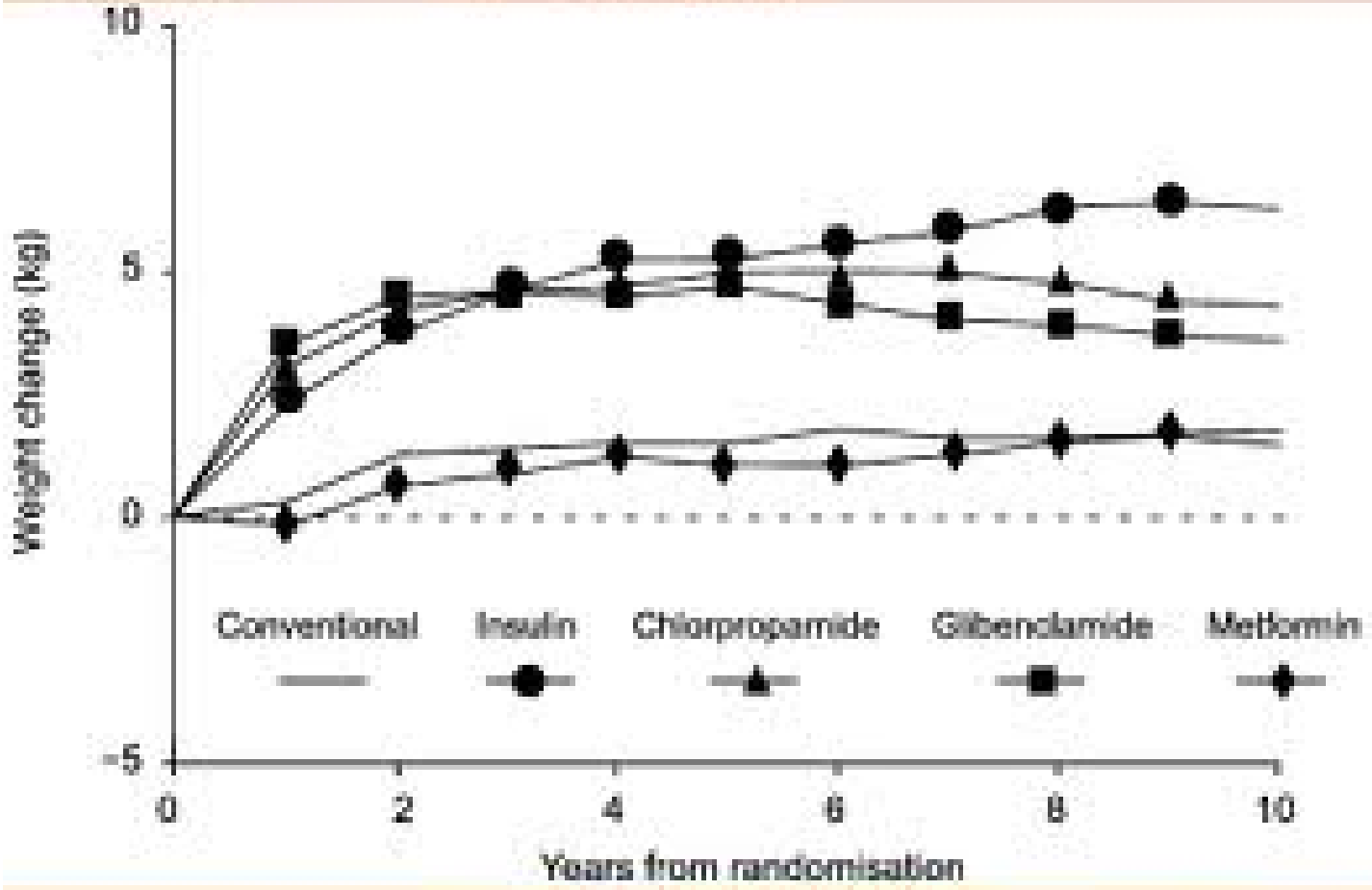
Membrane Biology:

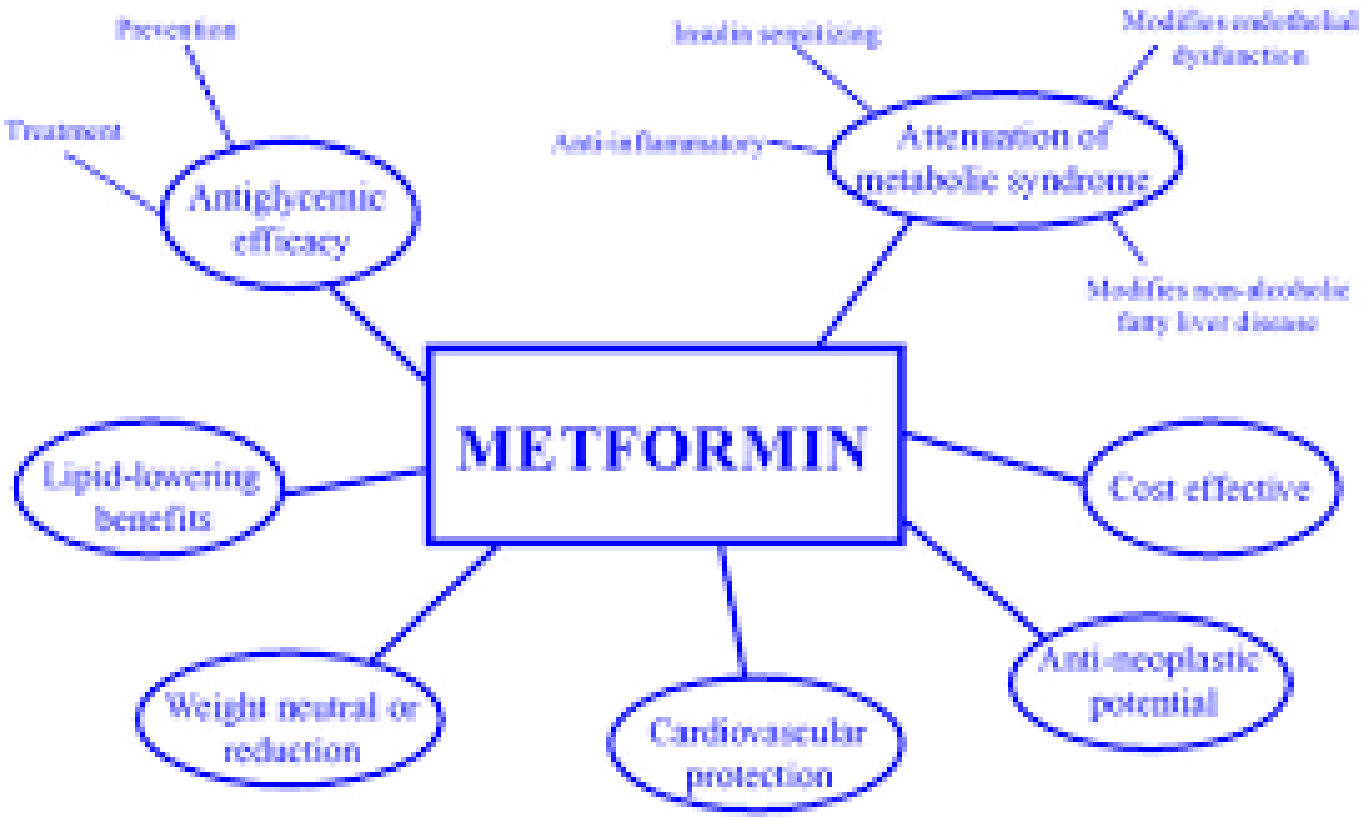
Taste of a Pill: ORGANIC CATION TRANSPORTER-3 (OCT3) MEDIATES METFORMIN ACCUMULATION AND SECRETION IN SALIVARY GLANDS

Nora Lee, Haichuan Duan, Mary F. Hebert, C.
Jason Liang, Kenneth M. Rice and Joanne Wang

J. Biol. Chem. 2014, 289:27055-27064.

How does metformin compare to lifestyle intervention?




METFORMIN
Antiglycemic efficacy
Prevention
Treatment
Attenuation of metabolic syndrome
Insulin sensitizing
Anti-inflammatory
Modifies endothelial dysfunction
Modifies non-alcoholic fatty liver disease
Lipid-lowering benefits
Weight neutral or reduction
Cardiovascular protection
Cost effective
Anti-neoplastic potential

Metformin

Start metformin treatment in a person who is overweight or obese (tailoring the assessment of body-weight-associated risk according to ethnic group and whose blood glucose is inadequately controlled by lifestyle interventions (nutrition and exercise) alone.

Consider metformin as an option for first-line glucose-lowering therapy for a person who is not overweight.

Metformin

Continue with metformin if blood glucose control remains or becomes inadequate and another oral glucose-lowering medication (usually a sulfonylurea) is added.

Step up metformin therapy gradually over weeks to minimise risk of gastro-intestinal (GI) side effects. Consider a trial of extended-absorption metformin tablets where GI tolerability prevents continuation of metformin therapy.

Metformin

Review the dose of metformin if the serum creatinine exceeds **130 micromol/litre** or the estimated glomerular filtration rate (eGFR) is below 45 ml/minute/1.73-m^2.

Stop the metformin if the serum creatinine exceeds 150 micromol/litre or the eGFR is below 30 ml/minute/1.73-m2.

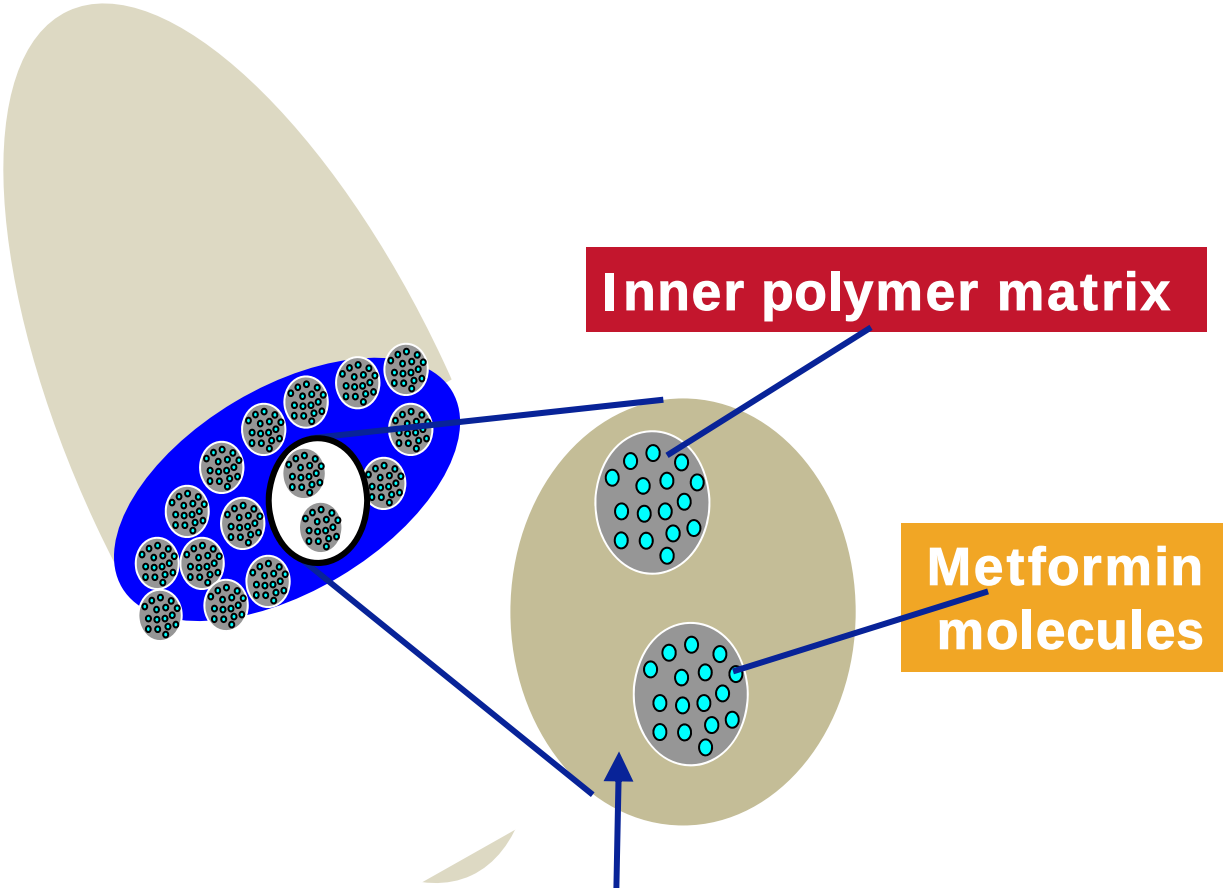
Prescribe metformin **with caution** for those at risk of a sudden deterioration in kidney function and those at risk of eGFR falling below 45 ml/minute/1.73-m^2.

Metformin

The benefits of metformin therapy should be discussed with a person with mild to moderate liver dysfunction or cardiac impairment so that:

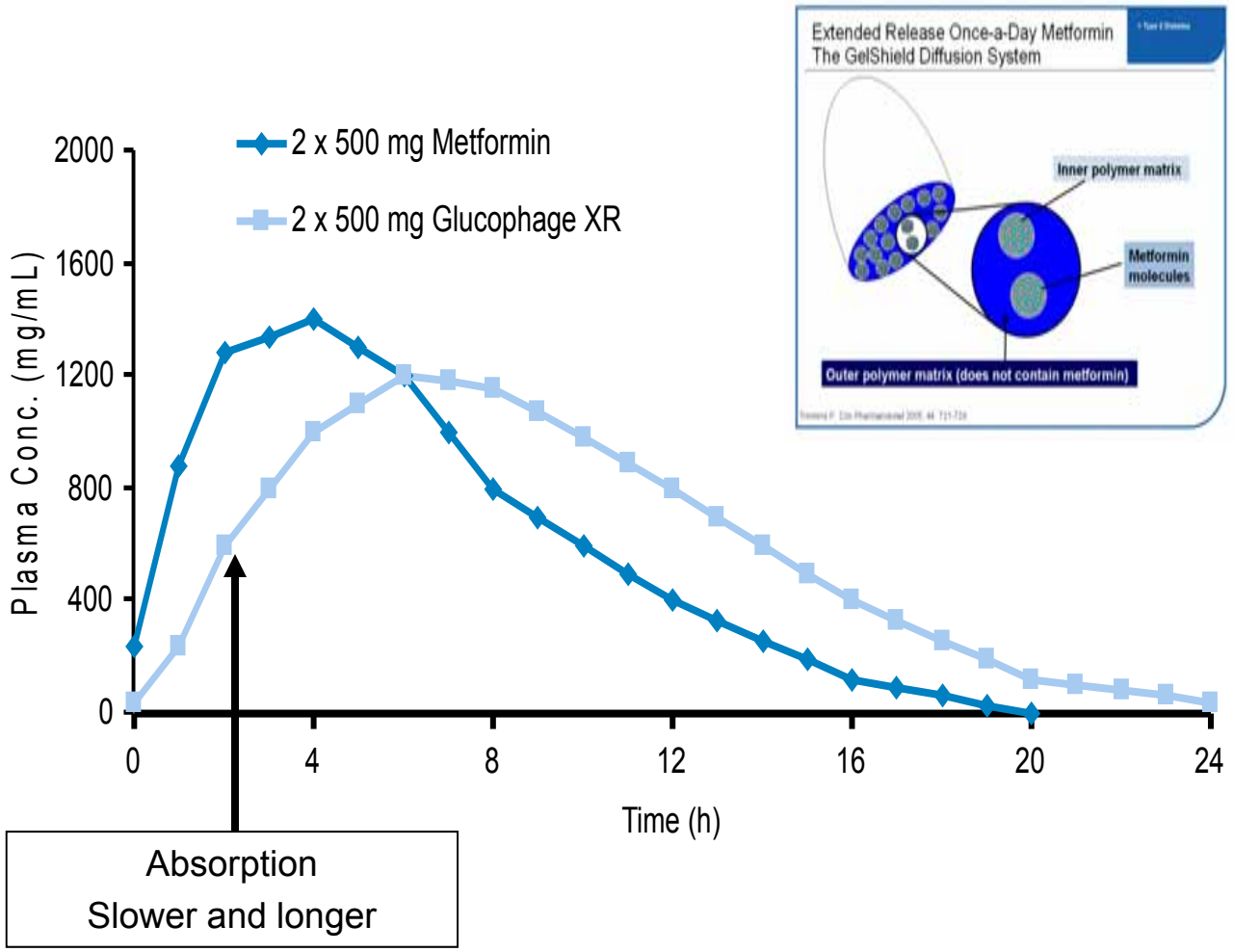
- due consideration can be given to the cardiovascular-protective effects of the drug
- an informed decision can be made on whether to continue or stop the metformin.

Extended Release Once-a-Day Metformin
The GelShield Diffusion System



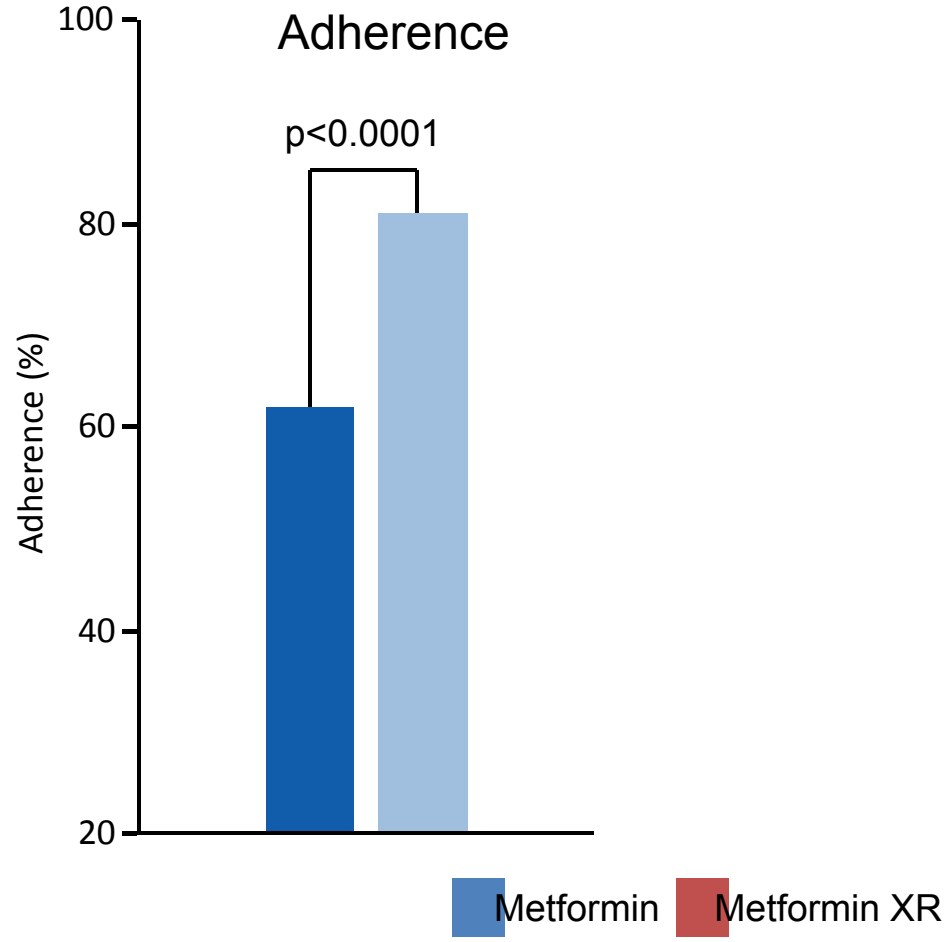
Timmins P. Clin Pharmacokinet 2005; 44: 721-729

Sustained Metformin Release from the Metformin® XR Tablet



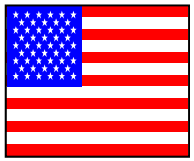
Timmins P. *Clin Pharmacokinet* 2005; 44:721–729

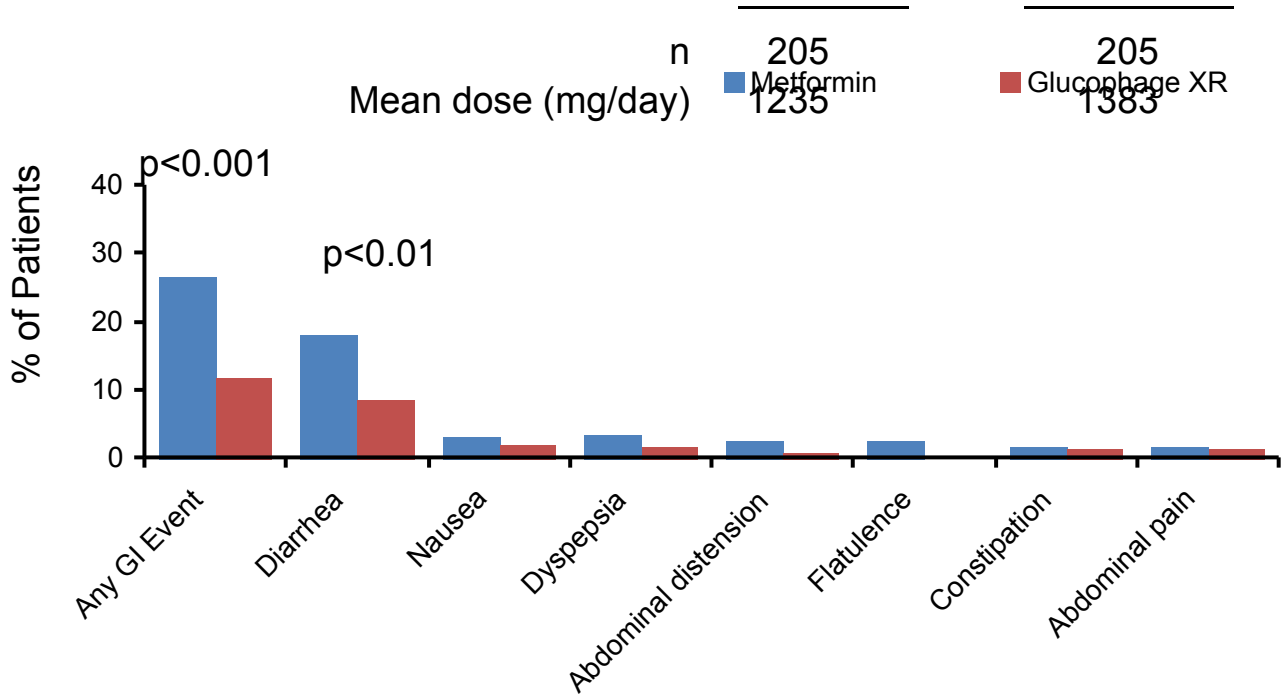
Switchover to Metformin XR Improves Adherence in Routine General Practice



Donnelly LA. *Diabetes,Obesity and Metabolism* 2009;11:338–342

Patients Switched from Standard Metformin to Metfromin® XR

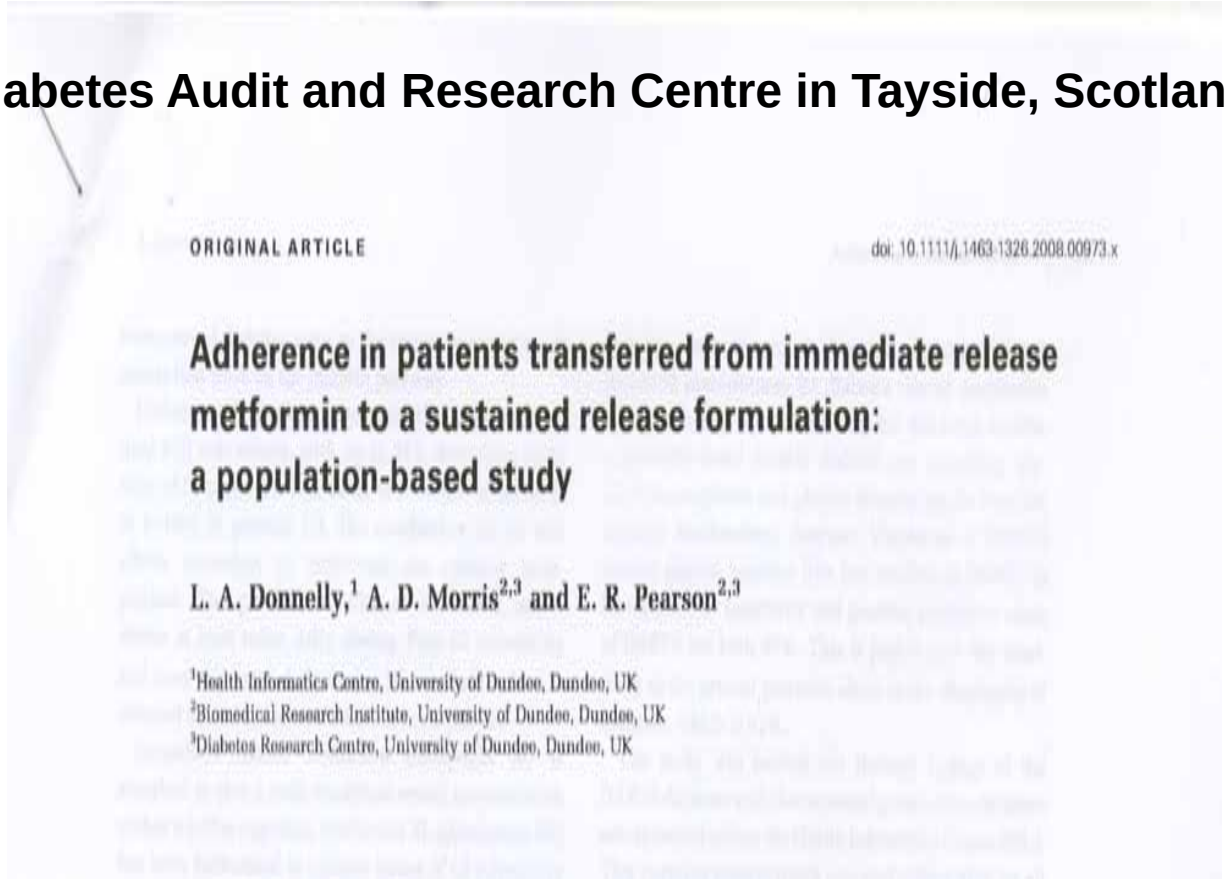




Blonde. *Curr Med Res Opin* 2004; 20:565–72

Metformin® XR and Improved Adherence

Diabetes Audit and Research Centre in Tayside, Scotland



ORIGINAL ARTICLE

doi: 10.1111/j.1463-1326.2008.00973.x

Adherence in patients transferred from immediate release metformin to a sustained release formulation: a population-based study

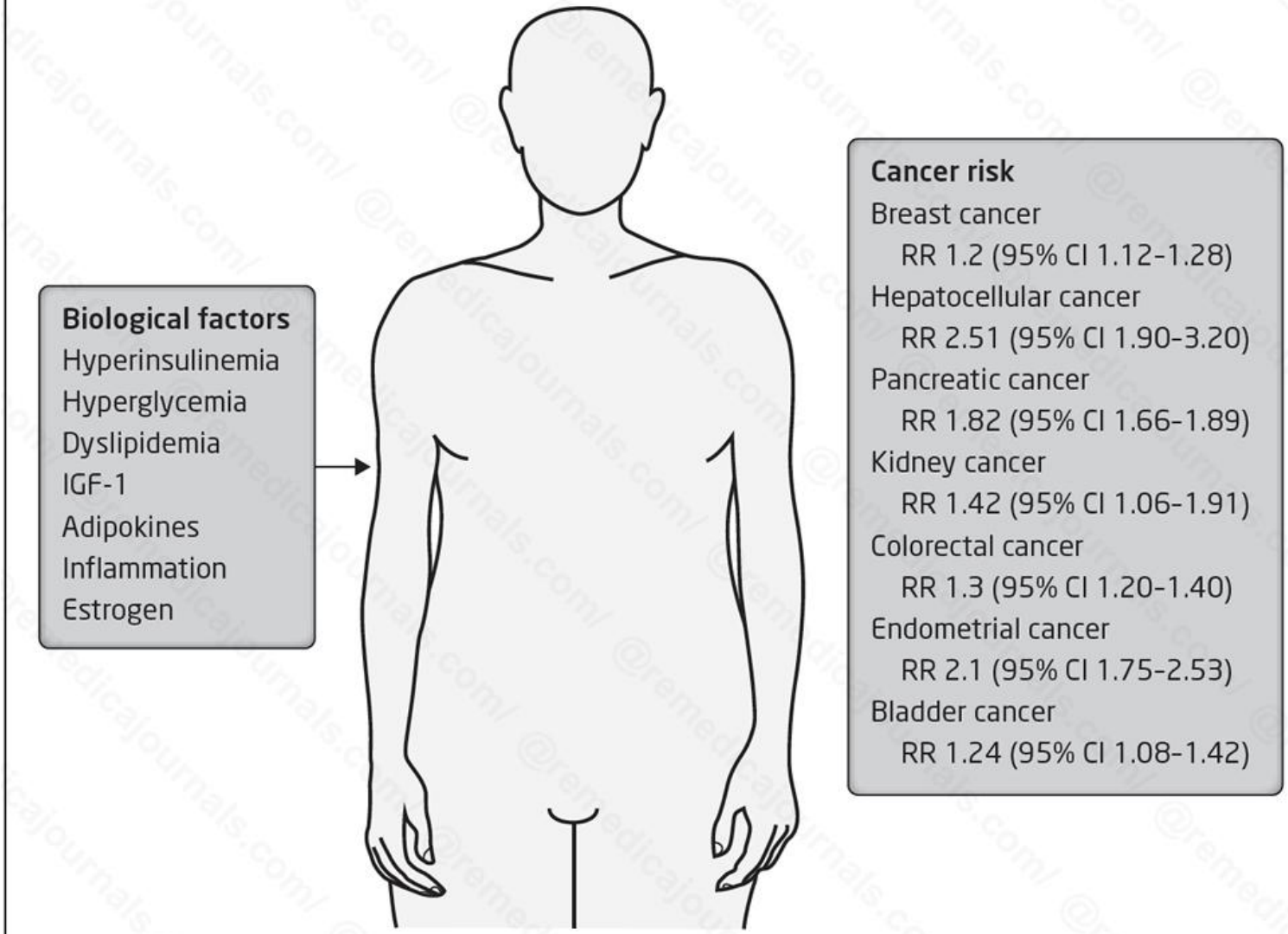
L. A. Donnelly,[1] A. D. Morris[2,3] and E. R. Pearson[2,3]

[1]Health Informatics Centre, University of Dundee, Dundee, UK
[2]Biomedical Research Institute, University of Dundee, Dundee, UK
[3]Diabetes Research Centre, University of Dundee, Dundee, UK

Donnelly LA. *Diabetes,Obesity and Metabolism* 2009;11:338–342

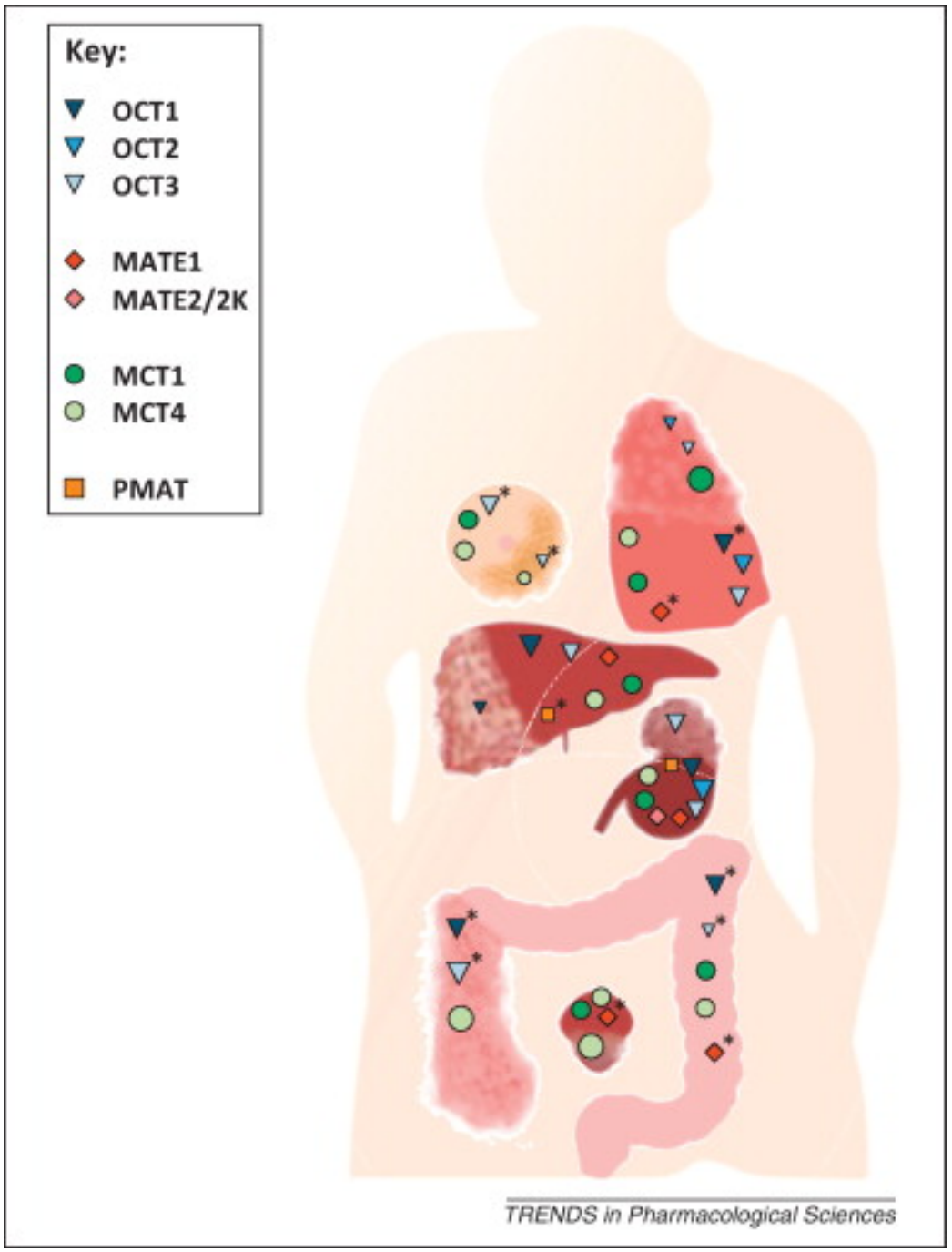
Metformin and cancer

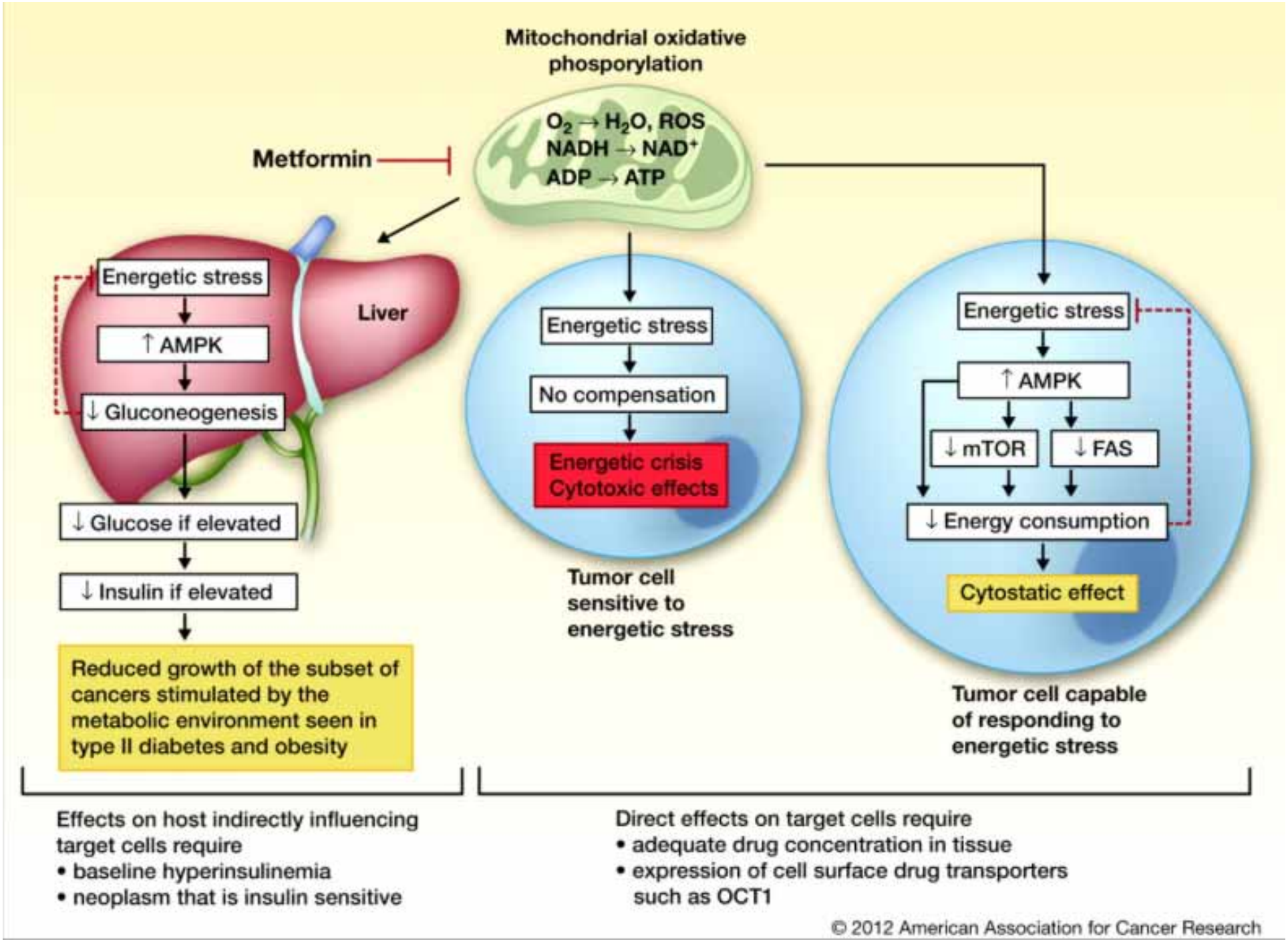
Figure 1. Type 2 diabetes and cancer risk. The figure lists the biological factors that contribute to the increased risk of cancer and the cancers that occur at an increased incidence in patients with type 2 diabetes. The relative risks are based on the results of meta-analyses [8-15].

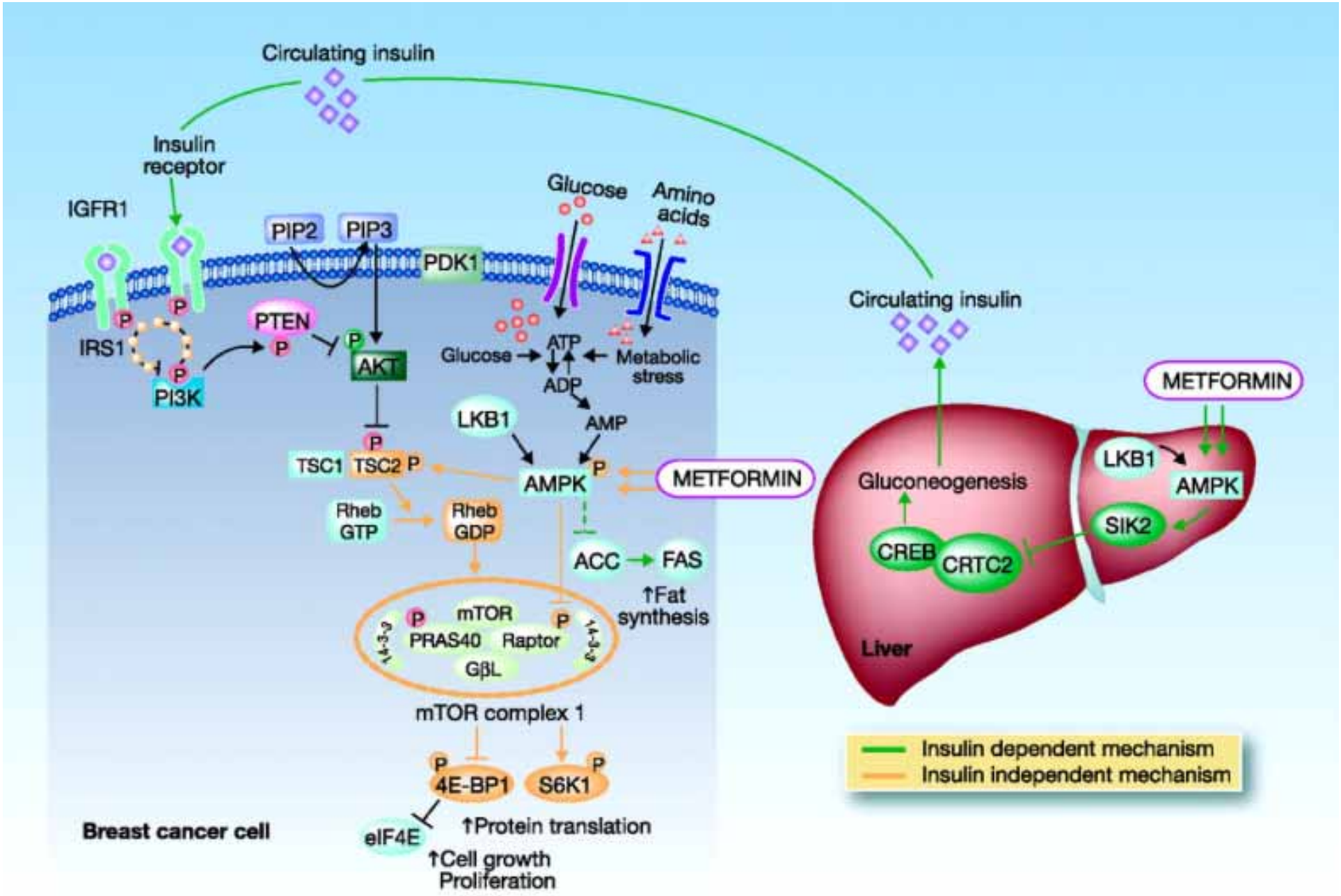


CI: confidence interval; IGF-1: insulin-like growth factor-1; RR: relative risk.

Relative risk of cancers in diabetes patients


Key:
OCT1
OCT2
OCT3
MATE1
MATE2/2K
MCT1
MCT4
PMAT
TRENDS in Pharmacological Sciences




Circulating insulin
Insulin receptor
IGFR1
IRS1
PI3K
PIP2
PIP3
PDK1
PTEN
AKT
Glucose
Amino acids
ATP
ADP
AMP
Metabolic stress
LKB1
AMPK
TSC1
TSC2
Rheb GTP
Rheb GDP
METFORMIN
ACC
FAS
↑Fat synthesis
mTOR
PRAS40
Raptor
GβL
14-3-3
mTOR complex 1
4E-BP1
S6K1
eIF4E
↑Protein translation
↑Cell growth
Proliferation
Breast cancer cell
Circulating insulin
METFORMIN
Gluconeogenesis
CREB
CRTC2
LKB1
AMPK
SIK2
Liver
Insulin dependent mechanism
Insulin independent mechanism

Conclusions

- T2DM is a complex metabolic disorder, with significant genetic component
- Optimal management achieved with education, lifestyle modification and pharmacotherapy
- ‘Treatment to target’ has certain limitations
- Understanding the mode of action of biguanide has broadened our understanding of the link between nutrition, cellular energetics and cancer