La metformina ancora come primo farmaco?

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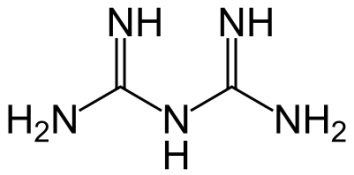
Il sottoscritto Prof. Francesco Dotta dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

- **Bristol Myers & Squibb**
- **Eli Lilly**
- **GlaxoSmithKline**
- **Johnson & Johnson**
- **Merck Sharp & Dohme**
- **Novo Nordisk**

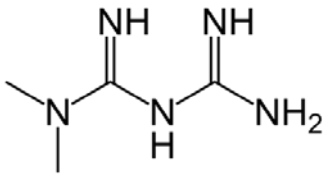
Metformin (N, N-dimethylbiguanide)

Metformin belongs to the biguanide class of antidiabetic drugs (containing two linked guanidine rings).

Biguanide



Metformin



- Originally derived from galegine (isoamylene guanidine), a guanidine derivative found in the **herb *Galega Officinalis*.**

- Metformin has been used in Europe for treatment of hyperglycemia since 1957 and in the USA since FDA approval in 1994.

The exact molecular mechanisms of its therapeutic action remain obscure.

Pharmacokinetics of Metformin

- ✓ After a single oral dose, metformin is rapidly distributed to many tissues following partial absorbition by the small intestine.
- ✓ The peak plasma concentration occurs in 3 hr with a mean plasma half-life of about 20 hr.
- ✓ Biodistribution studies in mice using ^{14}C-labeled metformin showed accumulation mainly in the gastrointestinal tract, kidney and liver.
- ✓ The clearance of metformin is dependent on renal elimination, as metformin does not undergo relevant biotransformation in the liver or biliary excretion.

Cellular Uptake of Metformin

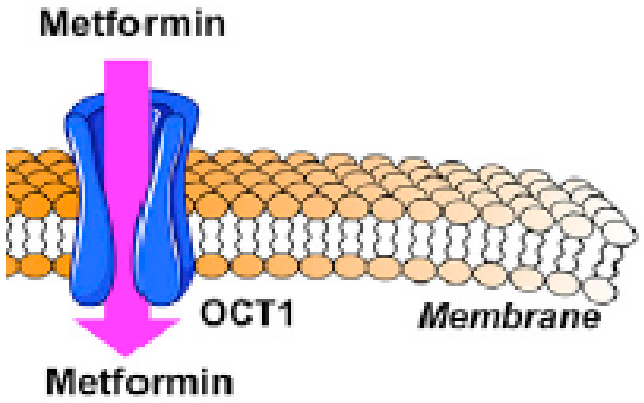
Metformin is an unusually hydrophilic drug that mostly exists in a positively charged protonated form under physiological conditions.

- **These physicochemical properties make rapid and passive diffusion through cell membranes unlikely. Indeed, transport of metformin involves an active uptake process via solute carrier organic transporters (OCTs).**

- **Intestinal absorbition**: **PMAT** (plasma membrane monoamine transporter) localized on the luminal side of enterocytes and **OCT1** expressed on the basolateral membrane.

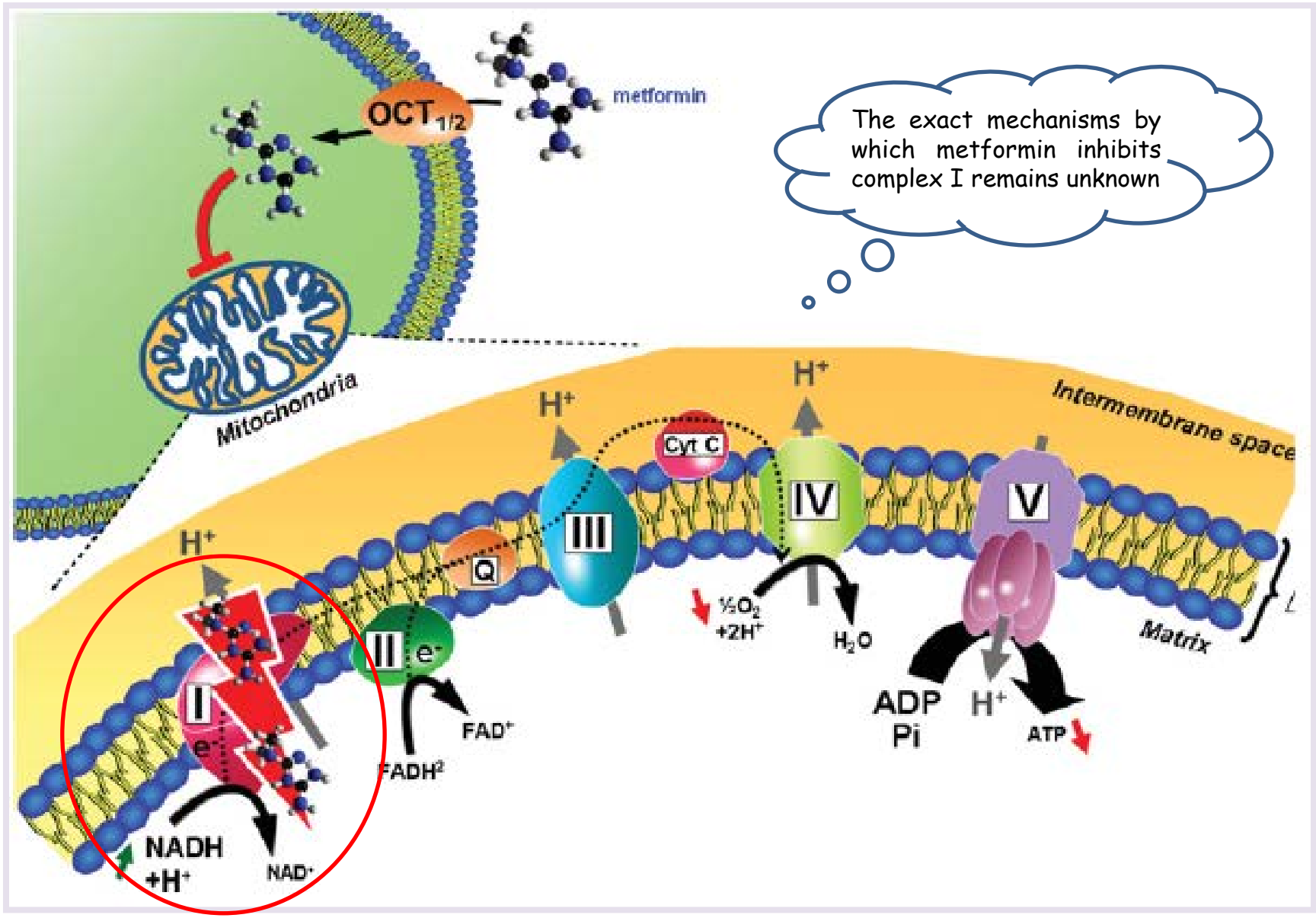
- **Hepatic uptake**: **OCT1** expressed on the basolateral membrane of hepatocytes (and possibly **OCT3**).

- **Kidney uptake**: **OCT2** expressed on the basolateral membrane of renal epithelial cells.

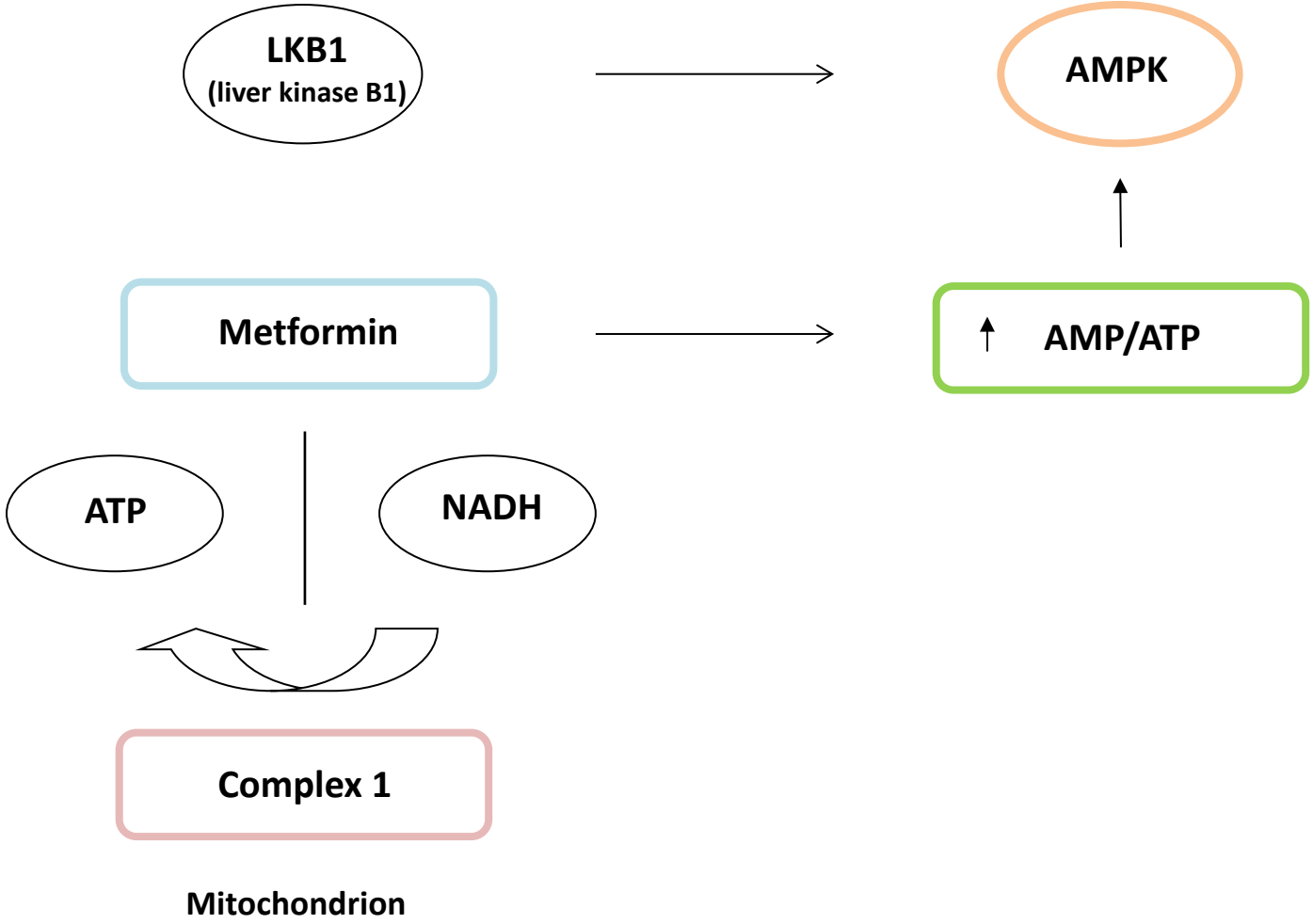


Mechanism of Metformin Action

The mitochondrial respiratory chain complex I is the primary target of metformin.



Metformin inhibits mitochondrial complex I and increases the AMP/ATP ratio, which leads to the activation of the AMP- activated energy-sensing kinase (**AMPK**), a critical energy sensor of cellular energy homeostasis.

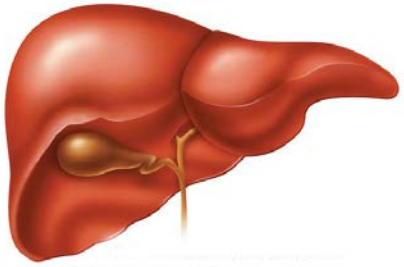


Metformin and treatment of type 2 diabetes

- Metformin exerts its glucose-lowering effect primarily by **decreasing hepatic glucose production** through **suppression of gluconeogenesis** and, to a lesser extent, by reducing intestinal glucose absorption and possibly improving glucose uptake and utilization by peripheral tissues, such as skeletal muscle and adipose tissue.

- Additionally, metformin may also improve glucose homeostasis by interacting with the incretin axis through the action of glucagon-like peptide 1 (GLP-1).

Metformina: effetti sul fegato



2001: *activated serine/threonine kinase 11-5'AMP-activated kinase signaling pathway, which decreases gluconeogenesis (Zhou GC, JCI 2001)*

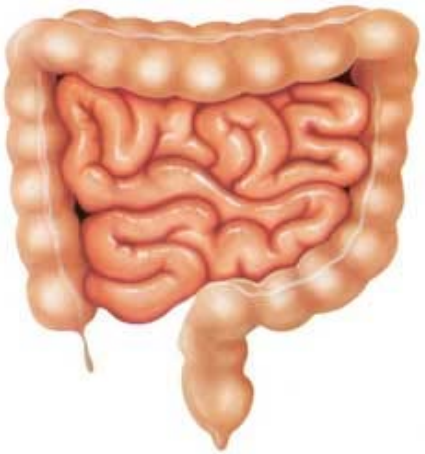
2010: *decreases gluconeogenesis, independent of the AMPK pathway, by inhibiting mitochondrial electron transport complex I in knockout mice cells deficient in AMPK (Foretz M, JCI 2010)*

2013: *increased cellular AMP inhibits adenylyl cyclase and glucagon induced gluconeogenesis (Miller RA, Nature 2013)*

2014: *decreases selenoprotein P, a hepatokine that causes insulin resistance by activating AMPK (Takayam H, J Biol Chem 2014)*

2014: *inhibits mitochondrial glycerol phosphate dehydrogenase and conversion of lactate and glycerol to glucose (Madiraju AK, Nature 2014)*

Metformina: effetti sull'intestino

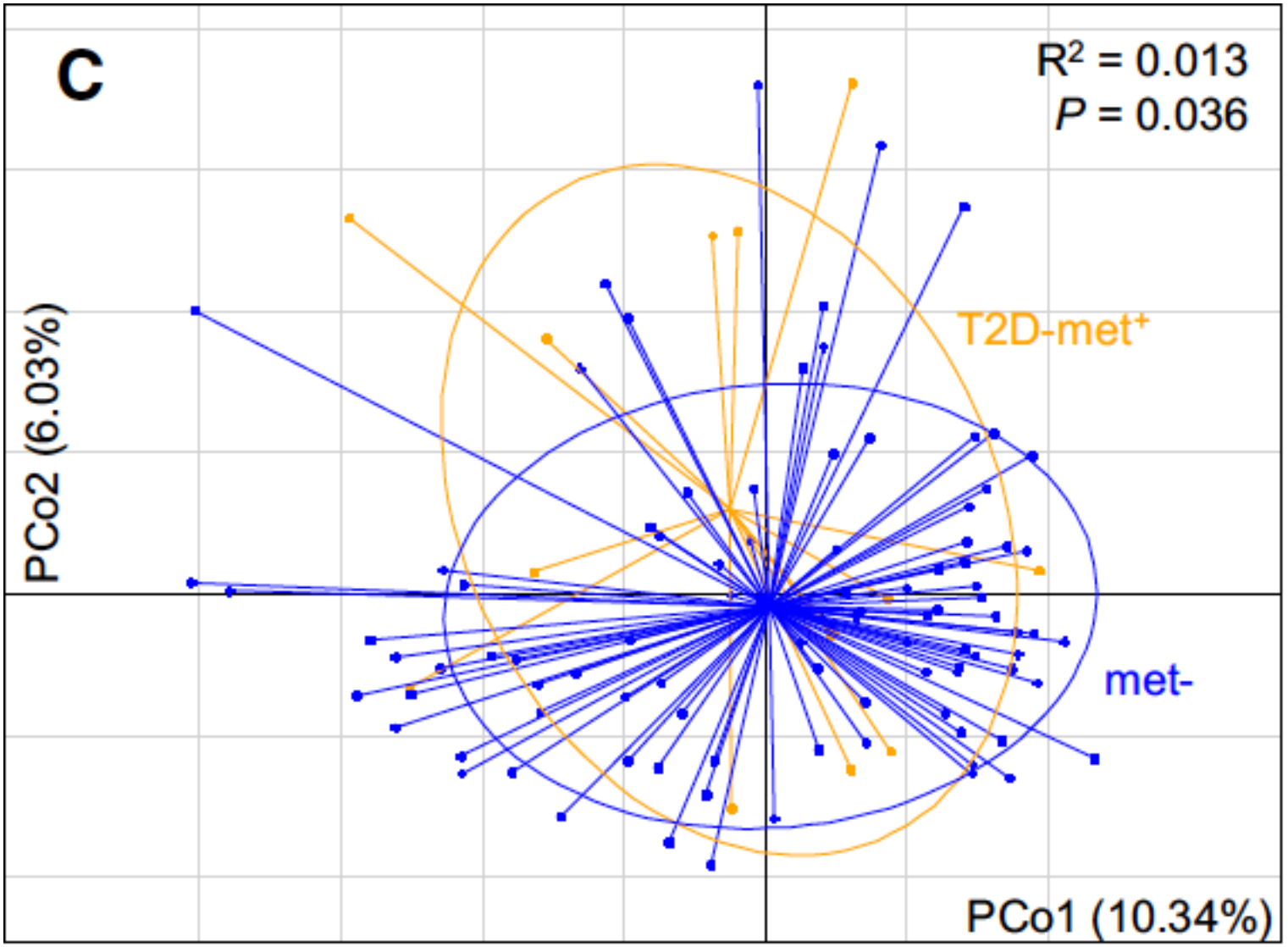


2004: *increases plasma GLP-1 (Mannucci E, DNM 2004)*

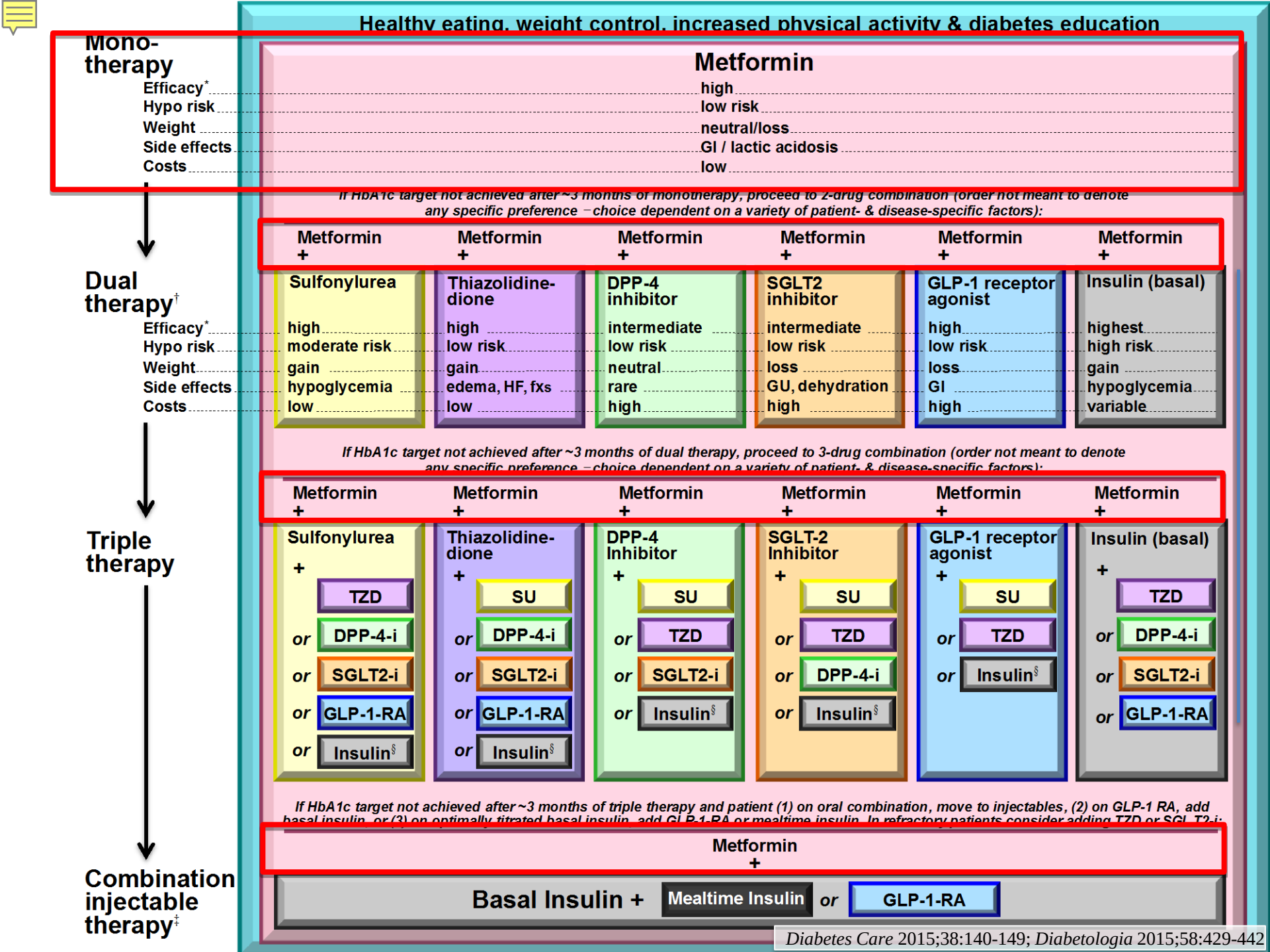
2015: *activates duodenal AMP kinase and decreases glucose production (Duca FA, Nat Med 2015)*

2016: *metformin DR acts mainly in ileum and stimulates L-cells to increase plasma GLP-1 which, in turn, decreases hepatic gluconeogenesis (Buse J, Diabetes Care 2016)*

Metformina: effetti sul microbiota intestinale



de la Cuesta-Zuluaga J, Diabetes Care, published online November 14, 2016

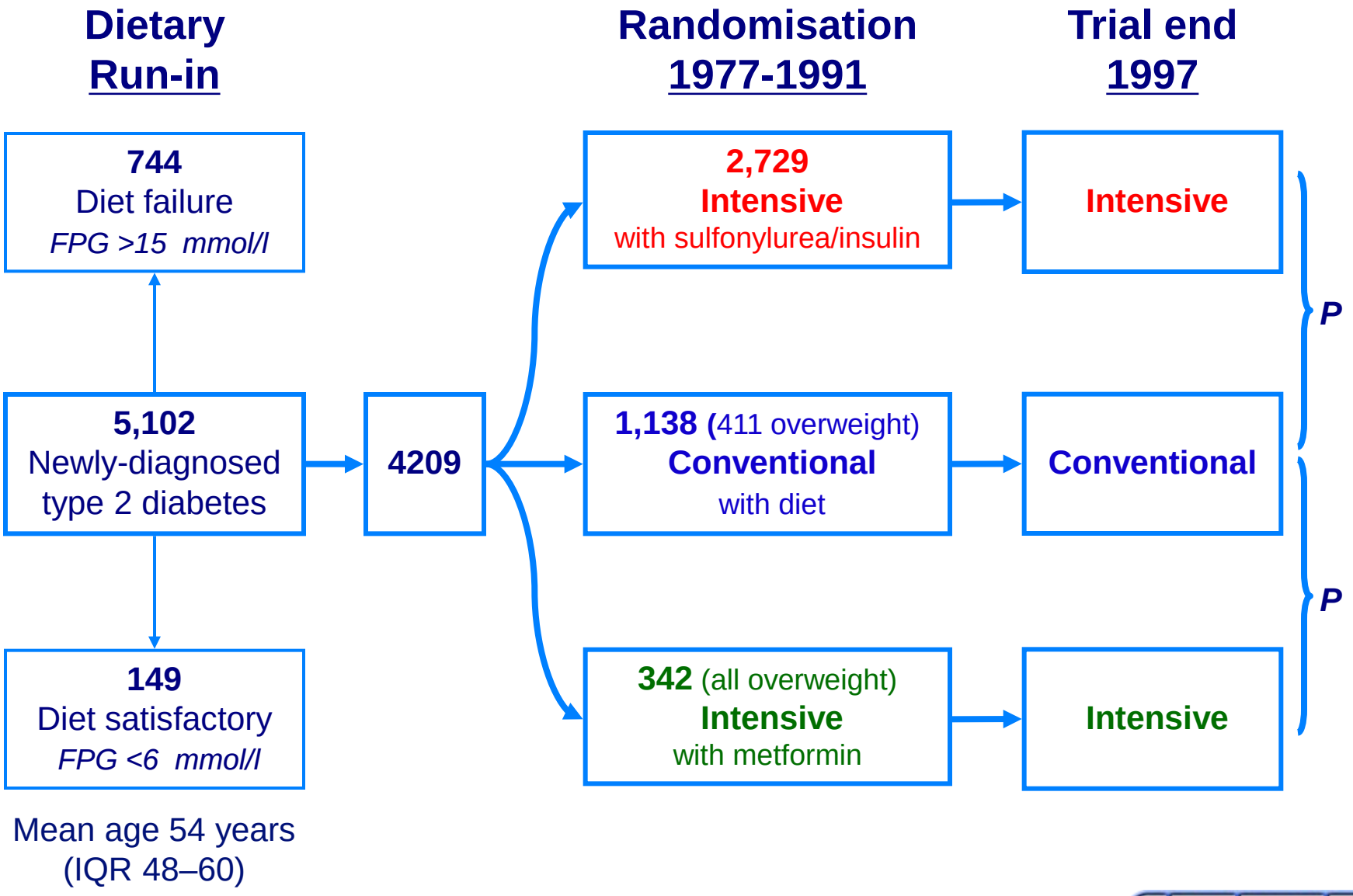


Diabetes Care 2015;38:140-149; *Diabetologia* 2015;58:429-442

UK Prospective Diabetes Study

Does metformin in overweight diabetic patients have any advantages or disadvantages?

Glucose Interventional Trial



UKPDS 80. N Eng J Med 2008; ***359****:*

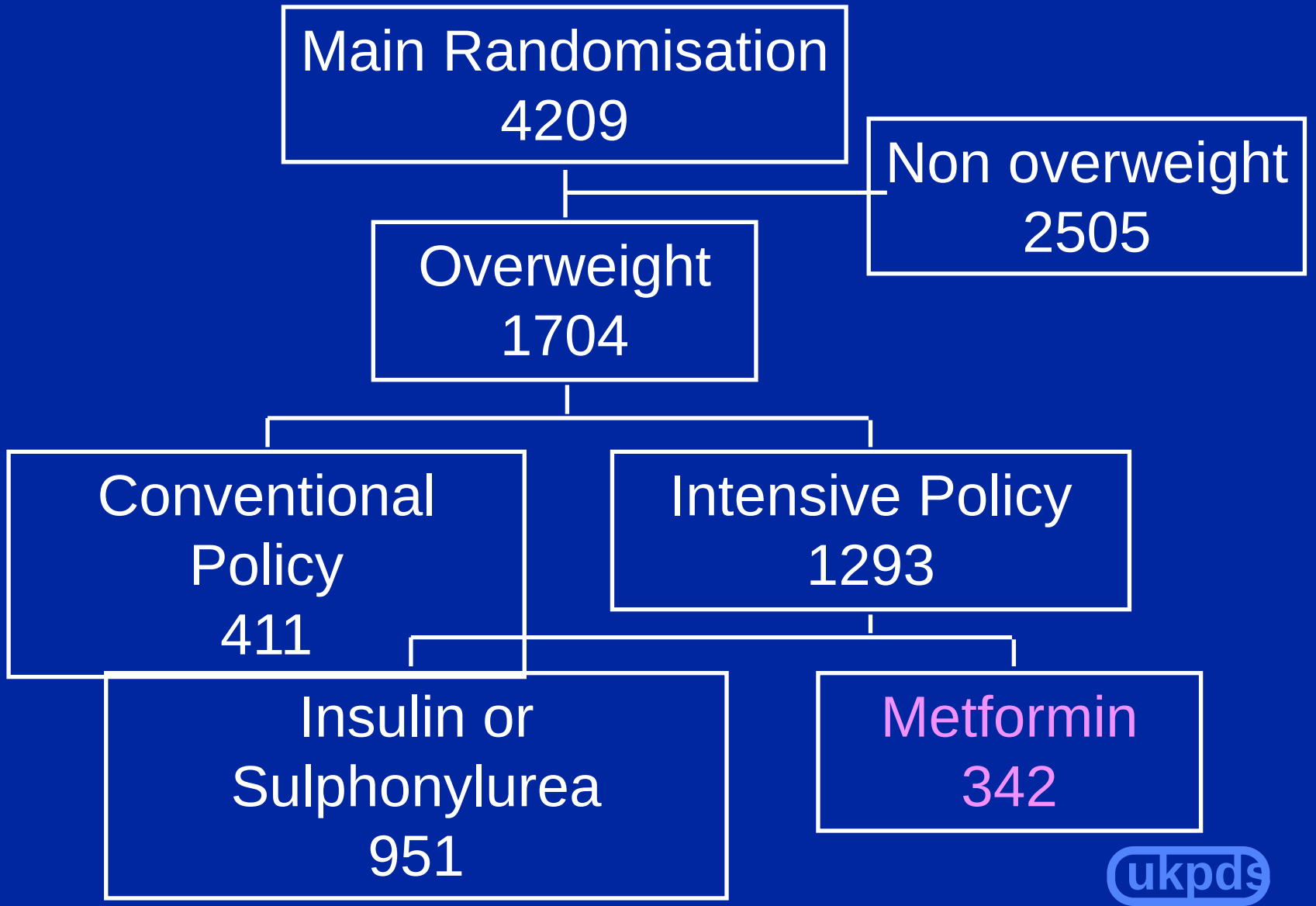
ukpds~ptm

Introduction

- the UKPDS has shown that an intensive glucose control policy using sulphonylurea or insulin therapy is effective in reducing the risk of complications in both overweight and normal weight patients
- overweight (>120% Ideal Body Weight) UKPDS patients could be randomised to an intensive glucose control policy with metformin instead of diet, sulphonylurea or insulin

ukpds

Randomisation



Patient Characteristics

overweight patients > 120% ideal body weight
after three months' diet therapy

age	*mean*	53 years
gender	male / female	46% / 54%
ethnic groups	Caucasian	86%
	Asian	6%
	Afro-caribbean	8%
Body Mass Index	*mean*	31 kg/m^2
fasting plasma glucose	*median*	8.1 mmol/L
HbA_{1c}	*mean*	7.2 %

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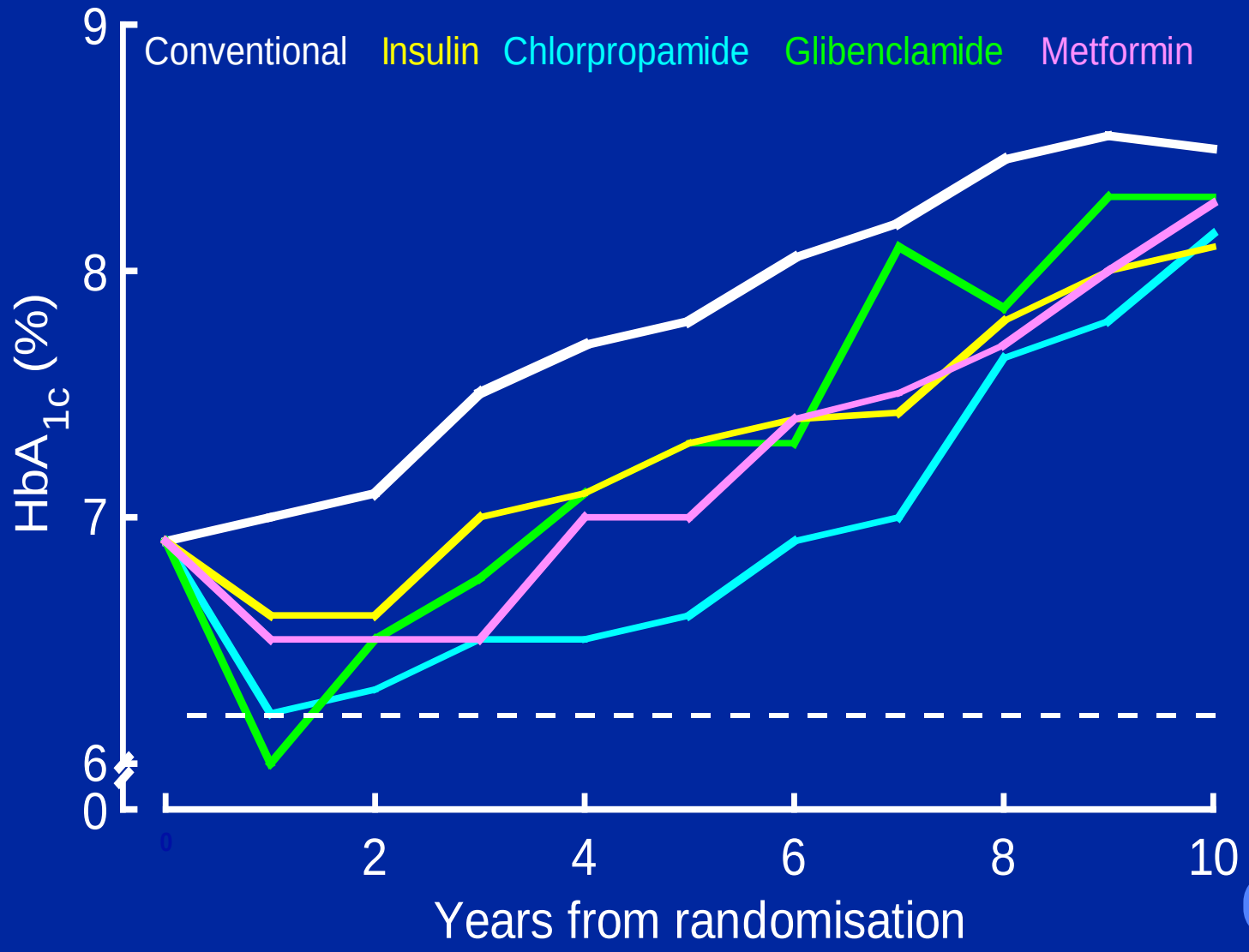
HbA_{1c}

overweight patients

cohort, median values



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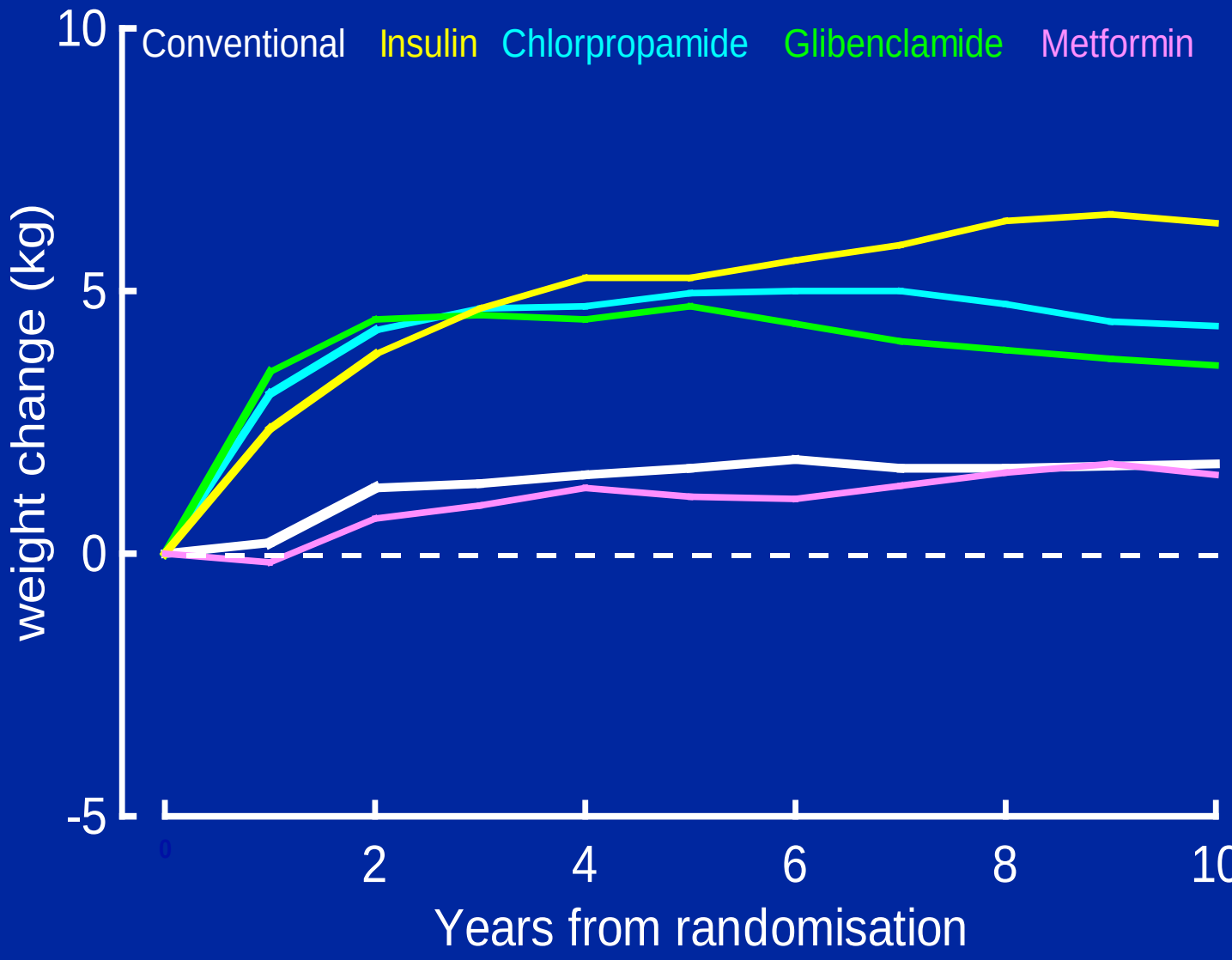
Change in Weight

overweight patients

cohort, mean values



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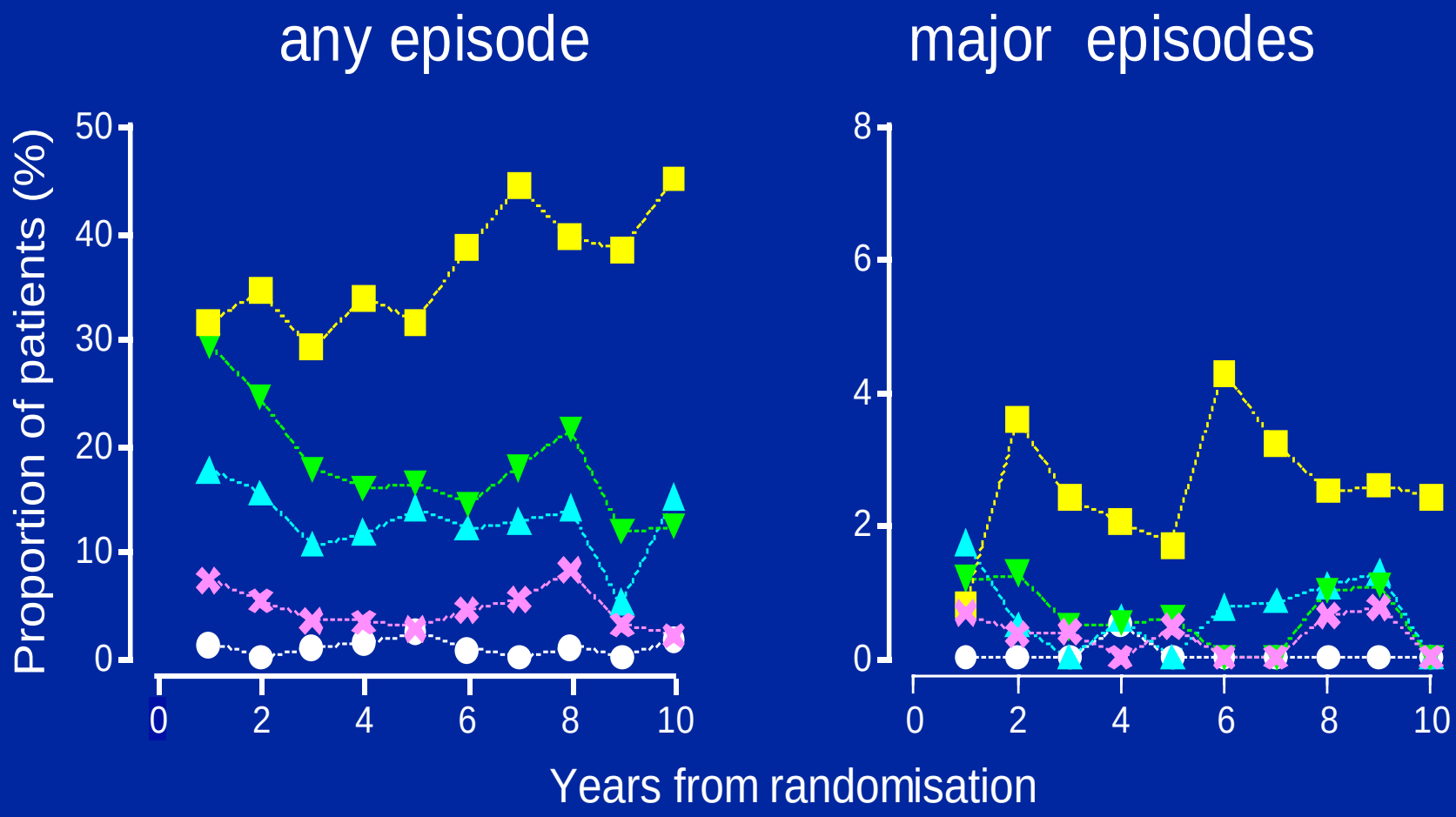
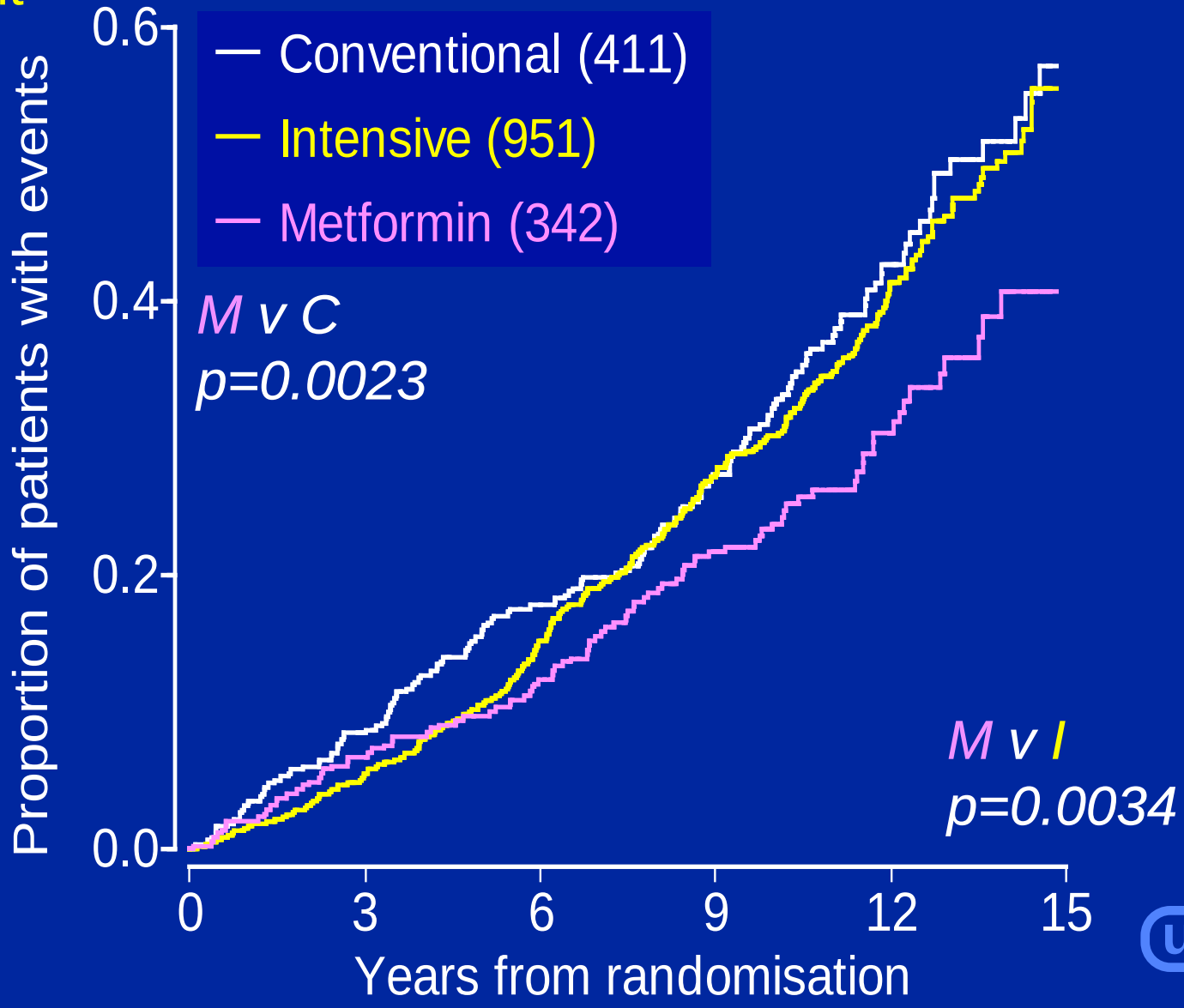
Hypoglycaemic episodes per annum

overweight patients Actual Therapy analysis



Any diabetes related endpoint

overweight patients



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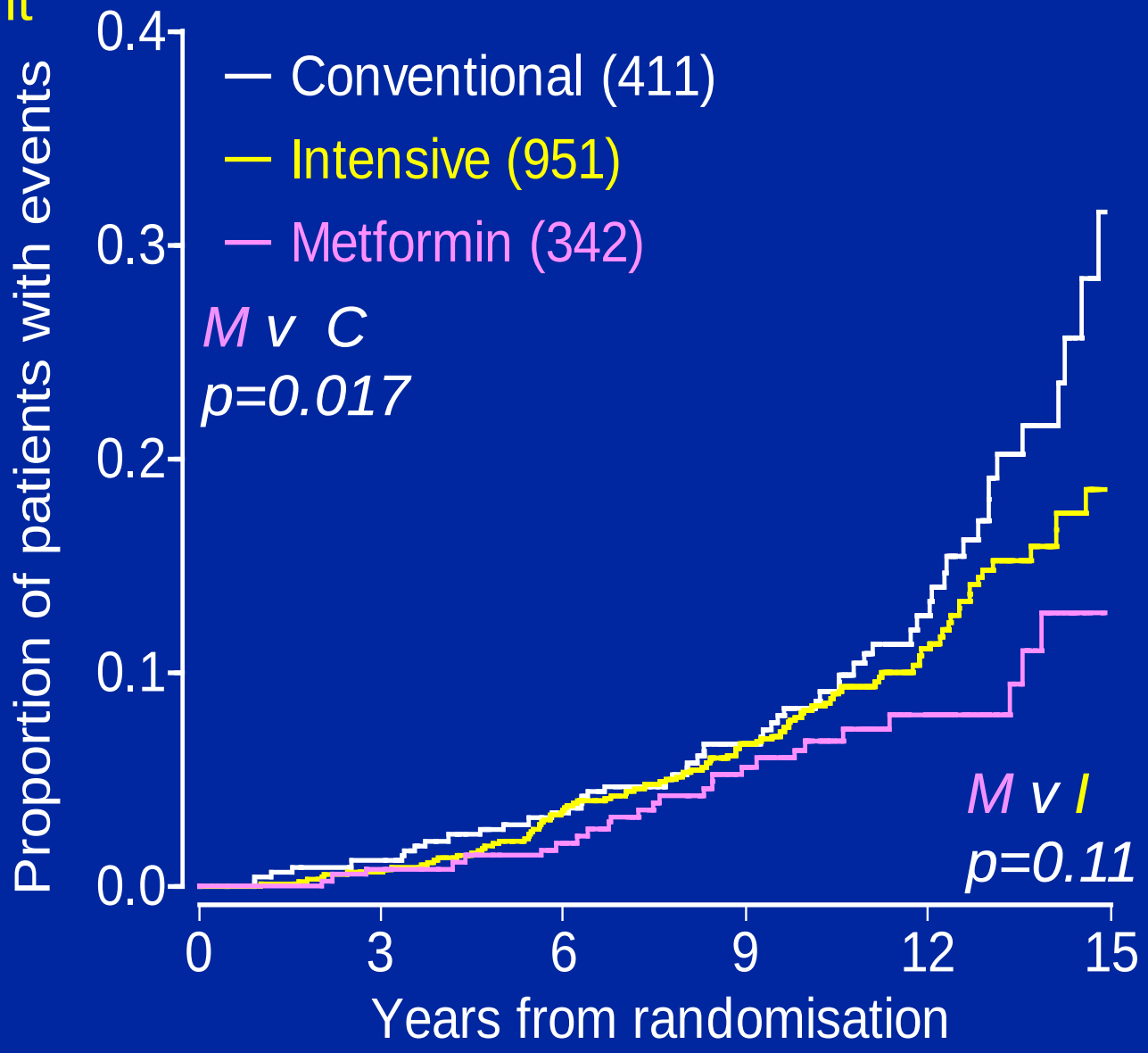
Diabetes related deaths

overweight patients



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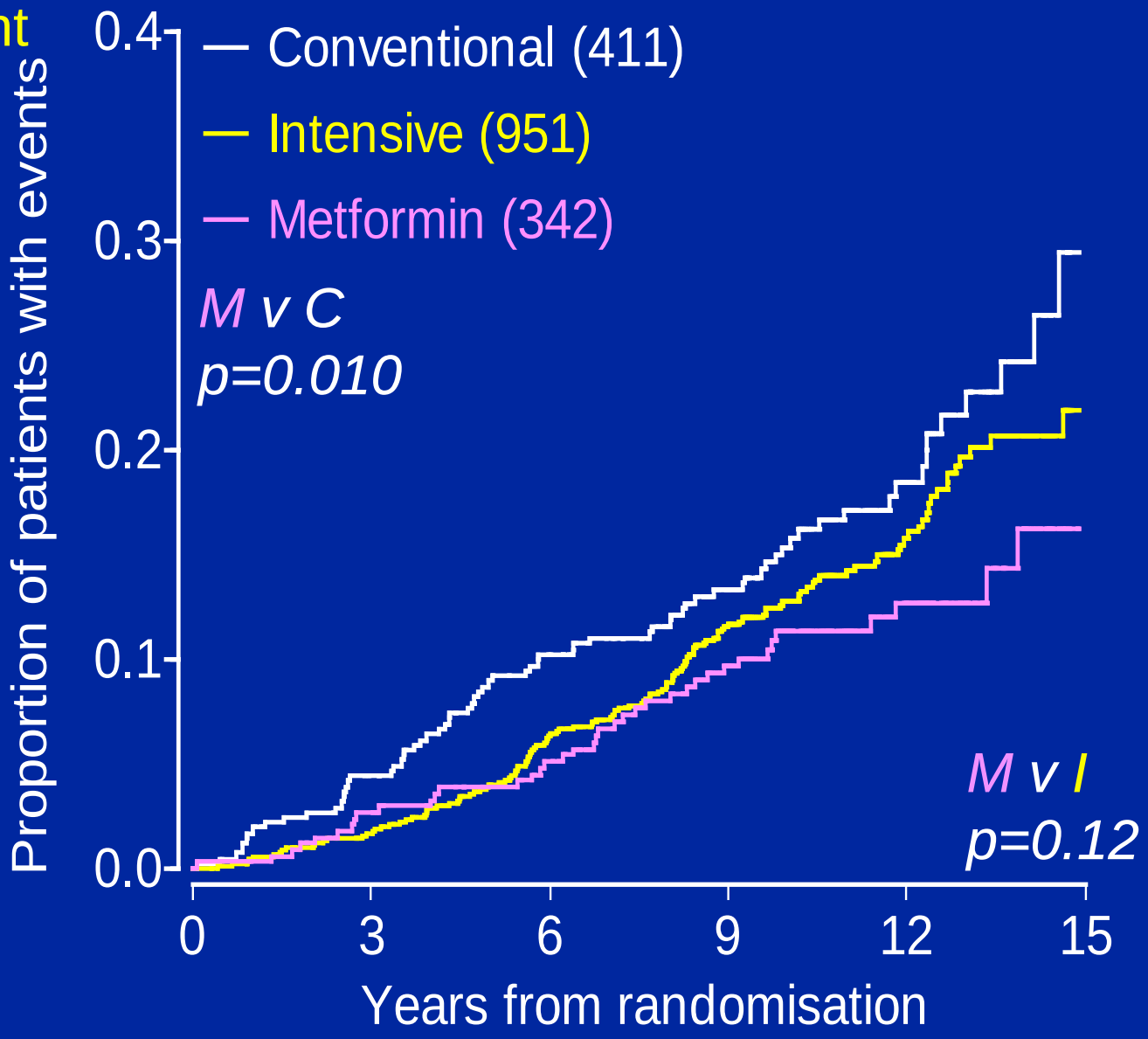
Myocardial Infarction

overweight patients



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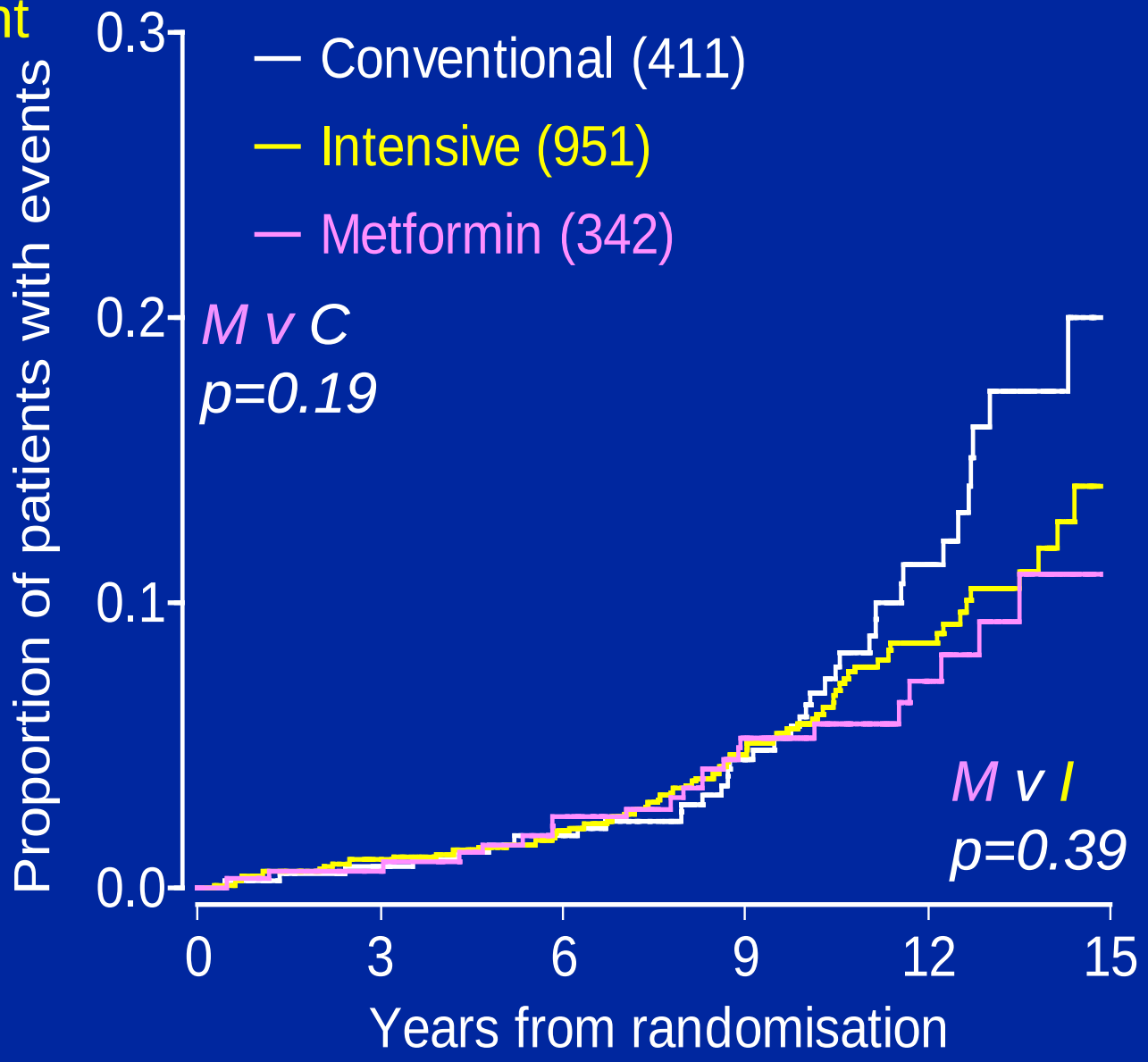
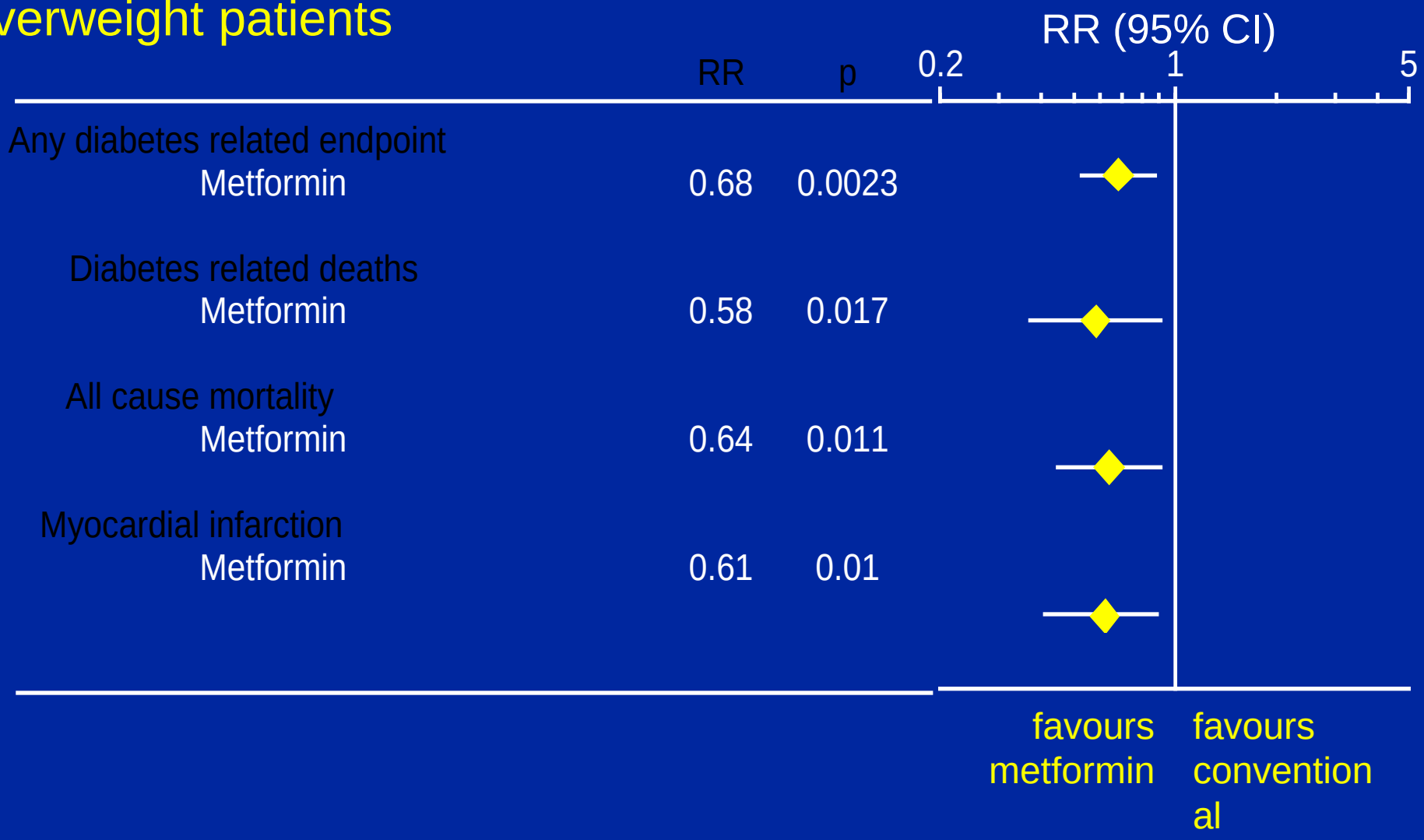
Microvascular endpoints

overweight patients



Metformin Comparisons

overweight patients



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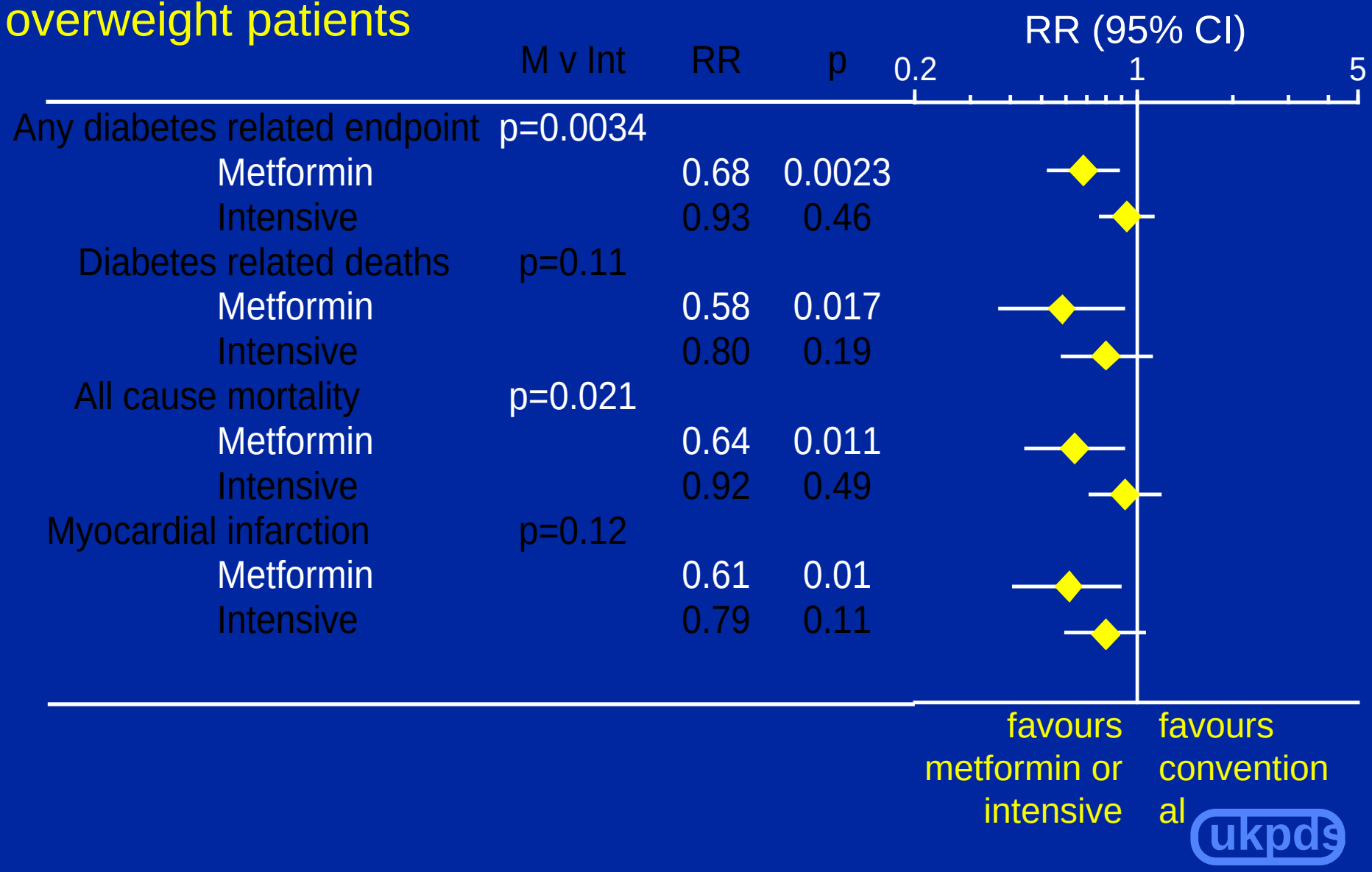
Metformin Comparisons

overweight patients



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Metformin in Overweight Patients

compared with conventional policy

32% risk reduction in any diabetes-related endpoints	p=0.0023
42% risk reduction in diabetes-related deaths	p=0.017
36% risk reduction in all cause mortality	p=0.011
39% risk reduction in myocardial infarction	p=0.01

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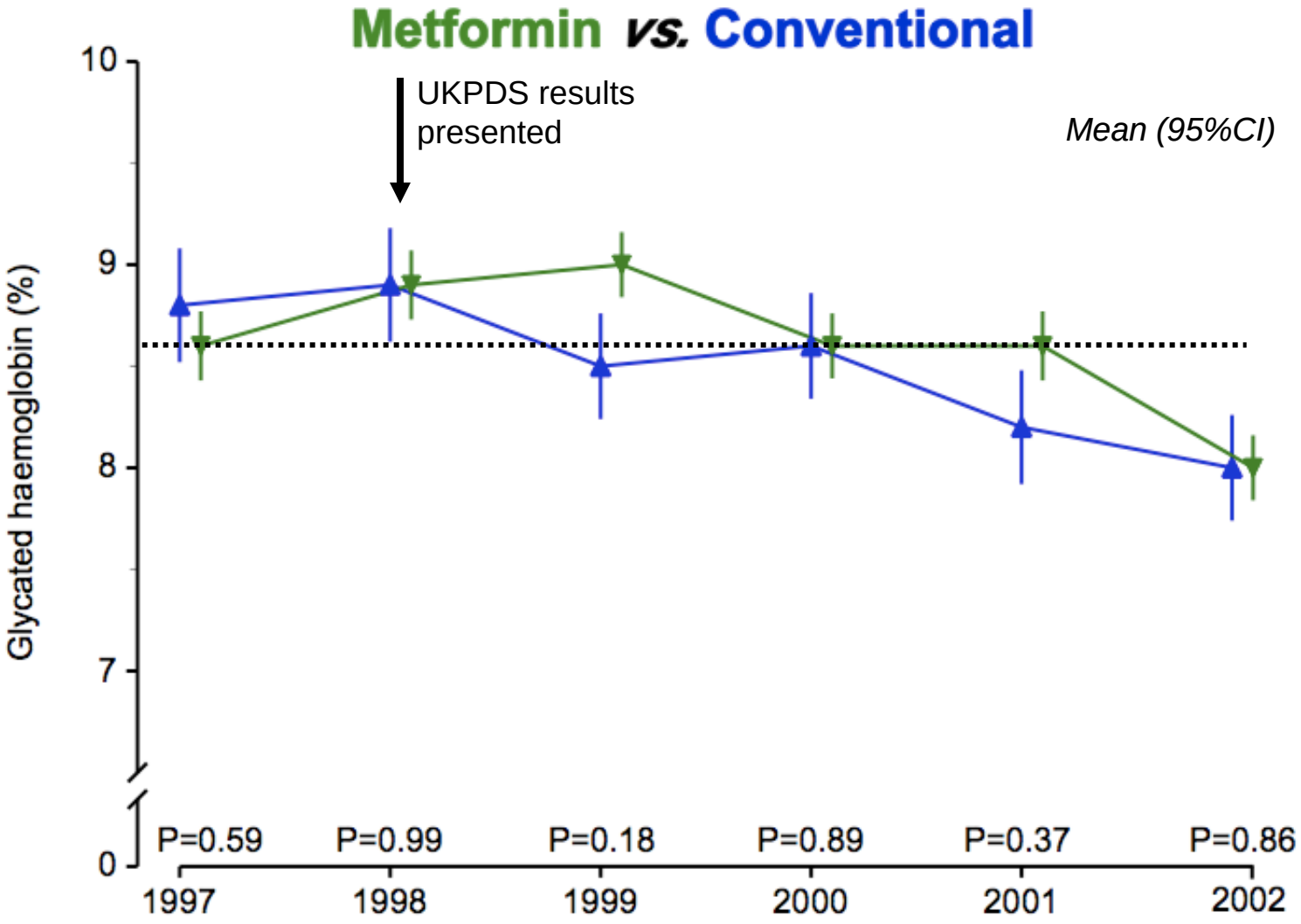
Post-Trial Changes in HbA_{1c}



UKPDS 80. N Eng J Med 2008; ***359****:*

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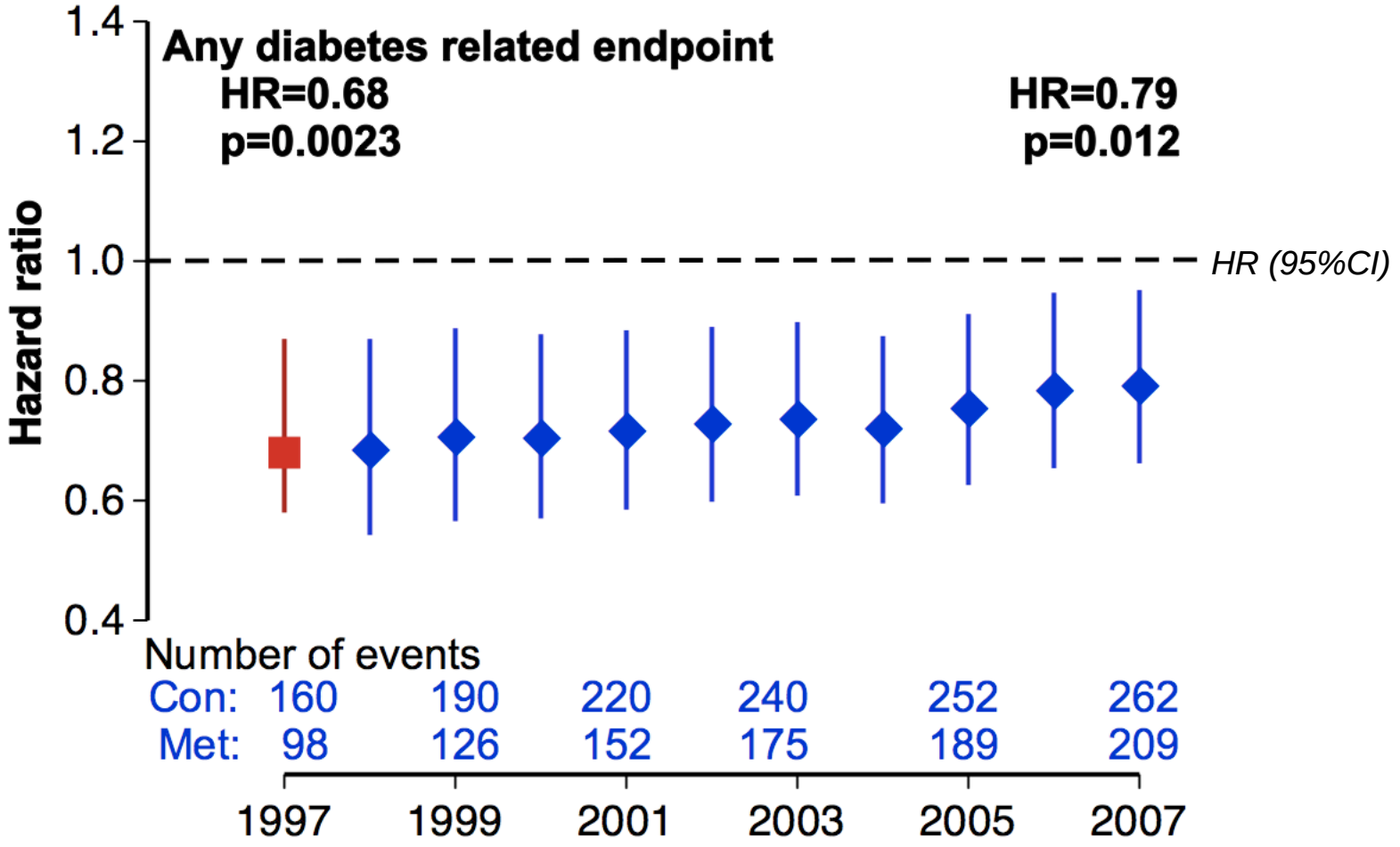
Any Diabetes Related Endpoint Hazard Ratio

Intensive (metformin) *vs.* Conventional glucose control



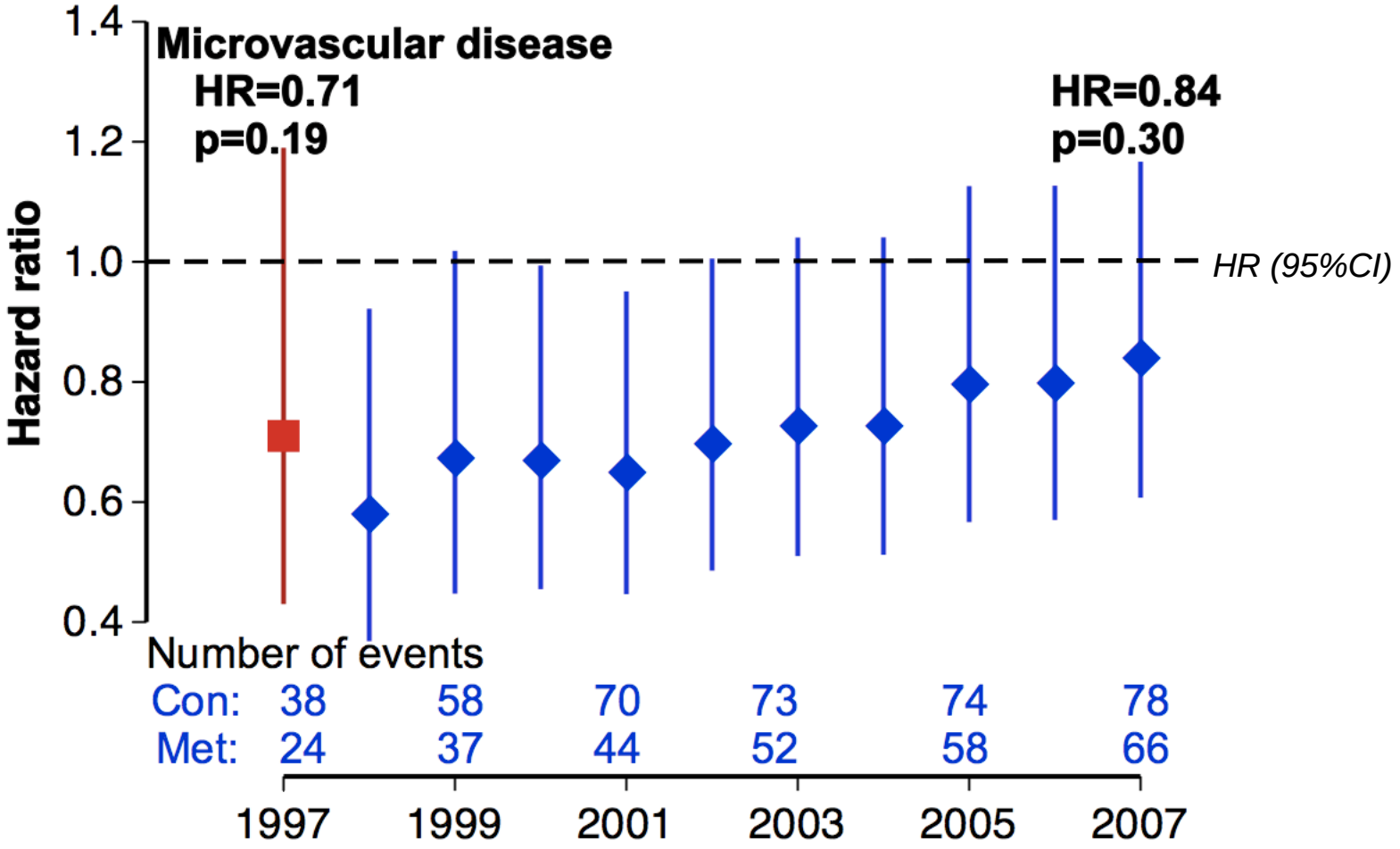
UKPDS 80. N Eng J Med 2008; ***359****:*

ukpds~ptm

Microvascular Disease Hazard Ratio

(photocoagulation, vitreous haemorrhage, renal failure)

Intensive (metformin) *vs.* Conventional glucose control



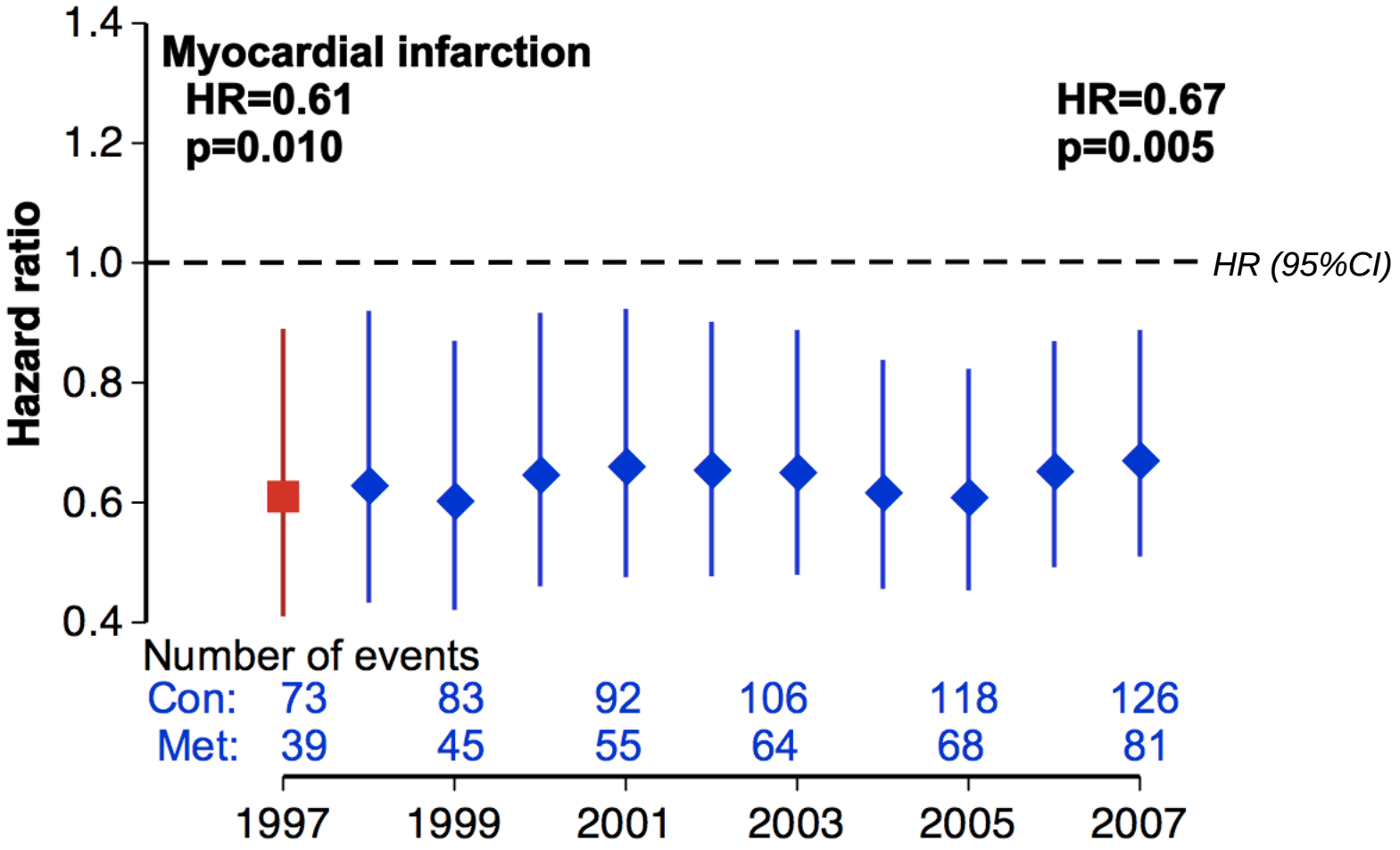
UKPDS 80. N Eng J Med 2008; ***359****:*

ukpds~ptm

Myocardial Infarction Hazard Ratio

(fatal or non-fatal myocardial infarction or sudden death)

Intensive (metformin) *vs.* Conventional glucose control

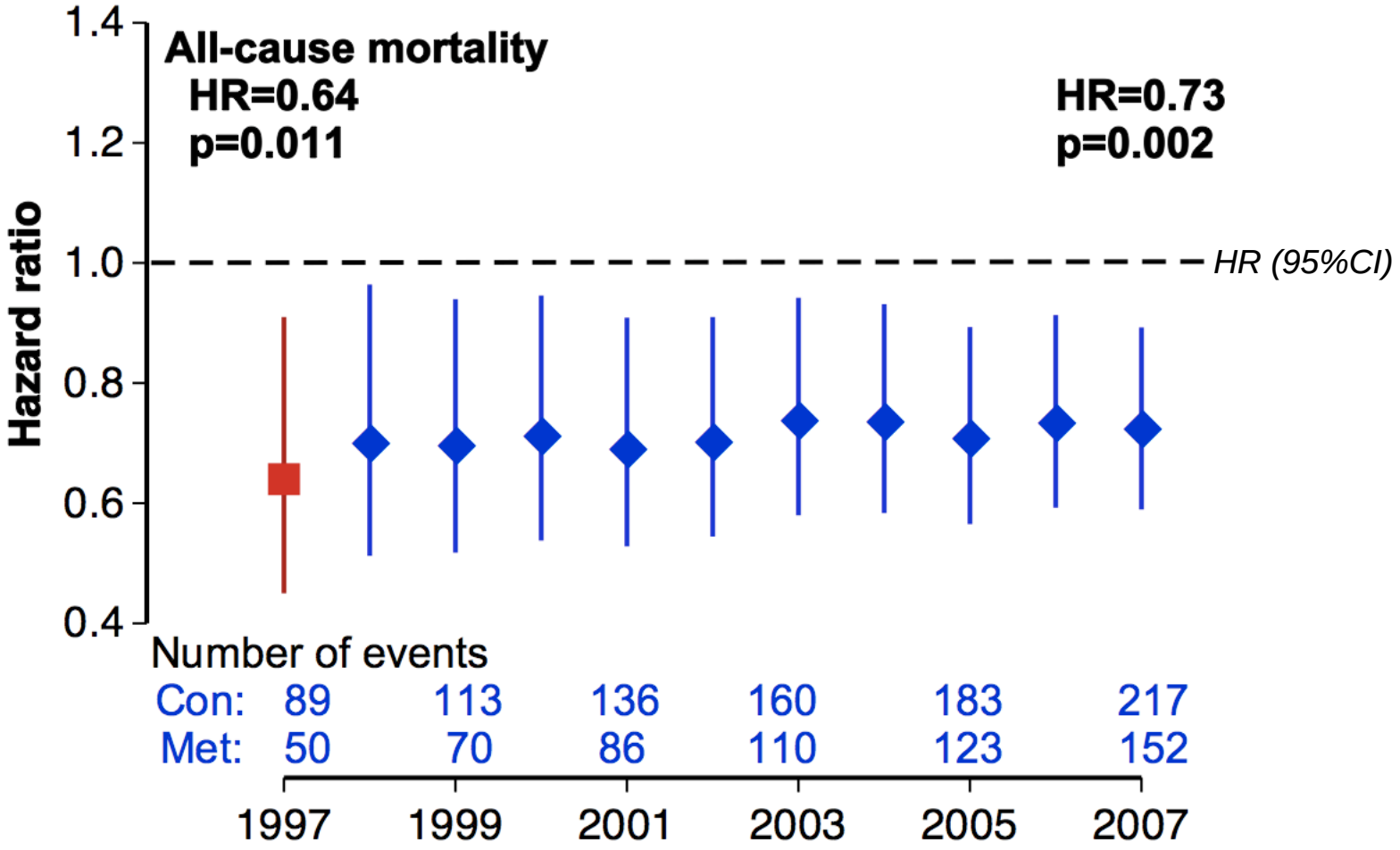


UKPDS 80. N Eng J Med 2008; ***359****:*

ukpds~ptm

All-cause Mortality Hazard Ratio

Intensive (metformin) *vs.* Conventional glucose control



UKPDS 80. N Eng J Med 2008; ***359****:*

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Legacy Effect of Earlier Metformin Therapy

After median 8.8 years post-trial follow-up

Aggregate Endpoint		1997	2007
Any diabetes related endpoint	*RRR:*	32%	**21%**
	P:	0.0023	**0.013**
Microvascular disease	*RRR:*	29%	**16%**
	P:	0.19	**0.31**
Myocardial infarction	*RRR:*	39%	**33%**
	P:	0.010	**0.005**
All-cause mortality	*RRR:*	36%	**27%**
	P:	0.011	**0.002**

RRR = Relative Risk Reduction, P = Log Rank

UKPDS 80. N Eng J Med 2008; ***359****:*

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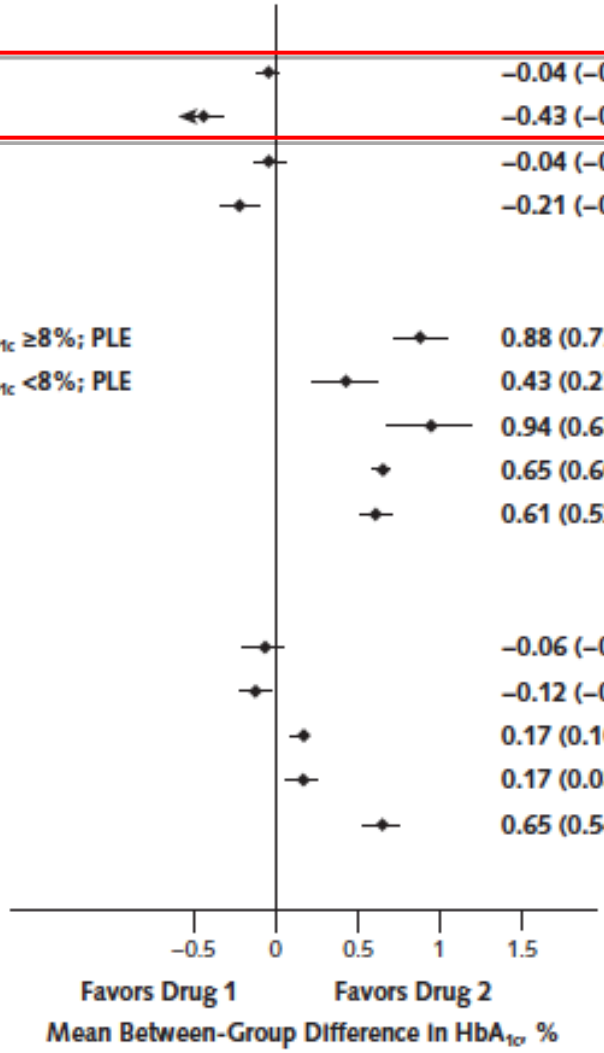
Diabetes Medications as Monotherapy or Metformin-Based Combination Therapy for Type 2 Diabetes

A Systematic Review and Meta-analysis

Nisa M. Maruthur, MD, MHS; Eva Tseng, MD, MPH; Susan Hutfless, PhD; Lisa M. Wilson, ScM; Catalina Suarez-Cuervo, MD; Zackary Berger, MD, PhD; Yue Chu, MSPH; Emmanuel Iyoha, MBChB, MPH; Jodi B. Segal, MD, MPH; and Shari Bolen, MD, MPH

HbA1c

Comparison (Drug 1 vs. Drug 2)	Studies, *n*	Participants, *n*	Study Characteristics	Effect Size (95% CI)	Strength of Evidence
Monotherapies					
Met vs. TZD	23	6733	≤52 wk	−0.04 (−0.11 to 0.03)	High
Met vs. DPP-4	6	2813	≤52 wk	−0.43 (−0.55 to −0.31)	High
TZD vs. SU	15	5986	≤52 wk	−0.04 (−0.13 to 0.06)	High
SU vs. DPP-4	3	769	≤52 wk	−0.21 (−0.32 to −0.09)	Moderate
Metformin vs. metformin-based combinations					
Met vs. Met + TZD	7	1718	≤52 wk; BL HbA_{1c} ≥8%; PLE	0.88 (0.73 to 1.04)	High
Met vs. Met + TZD	7	2022	≤52 wk; BL HbA_{1c} <8%; PLE	0.43 (0.23 to 0.63)	High
Met vs. Met + SU	15	3756	≤52 wk	0.94 (0.68 to 1.19)	High
Met vs. Met + DPP-4	26	11 285	≤52 wk	0.65 (0.60 to 0.70)	High
Met vs. Met + SGLT-2	9	2399	≤52 wk	0.61 (0.52 to 0.71)	High
Metformin-based combinations					
Met + TZD vs. Met + SU	8	3063	≤52 wk	−0.06 (−0.19 to 0.06)	Moderate
Met + TZD vs. Met + DPP-4	5	926	≤52 wk	−0.12 (−0.21 to −0.02)	Moderate
Met + SU vs. Met + SGLT-2	3	2933	104 wk	0.17 (0.10 to 0.20)	Moderate
Met + DPP4 vs. Met + SGLT-2	4	1278	≤52 wk	0.17 (0.08 to 0.26)	Moderate
Met + DPP4 vs. Met + GLP-1	3	1385	≤52 wk	0.65 (0.54 to 0.75)	Moderate



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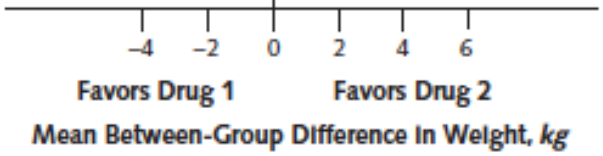
Peso

Comparison (Drug 1 vs. Drug 2)	Studies, *n*	Participants, *n*	Study Characteristics	Effect Size (95% CI)	Strength of Evidence
Monotherapies					
Met vs. DPP-4	6	2774	≤52 wk	−1.3 (−1.6 to −1.0)	High
TZD vs. SU	7	664	≤52 wk	1.2 (0.6 to 1.8)	High
SU vs. GLP-1	4	1710	≤52 wk; PLE	2.3 (1.2 to 3.3)	Moderate
Metformin vs. metformin-based combinations					
Met vs. Met + TZD	6	2860	≤52 wk	−2.2 (−2.6 to −1.9)	High
Met vs. Met + SU	5	1169	≤52 wk; BL wt ≥90 kg; PLE	−3.2 (−4.6 to −1.6)	High
Met vs. Met + SU	5	846	≤52 wk; BL wt <90 kg	−1.2 (−1.6 to −0.6)	High
Met vs. Met + DPP-4	20	10 564	≤52 wk	−0.1 (−0.3 to 0.01)	High
Met vs. Met + SGLT-2	7	2297	≤52 wk	2.0 (1.5 to 2.5)	High
Met vs. Met + GLP-1	5	1013	≤52 wk	2.0 (1.3 to 2.7)	Moderate
Metformin-based combinations					
Met + TZD vs. Met + SU	6	2572	≤52 wk	0.9 (0.4 to 1.3)	Moderate
Met + TZD vs. Met + DPP-4	4	674	≤52 wk	2.7 (0.8 to 4.5)	Moderate
Met + SU vs. Met + DPP-4	4	2373	≤52 wk	2.2 (1.8 to 2.5)	High
Met + DPP4 vs. Met + SGLT-2	3	2948	52–104 wk	4.7 (4.4 to 5.0)	High
Met + DPP4 vs. Met + GLP-1	3	1382	≤52 wk	1.8 (1.1 to 2.5)	Moderate



Metformina e acidosi lattica

Study, Reference, Year	Incidence of Metformin-associated Lactic Acidosis (Cases/100,000 Patient Years)
Wiholm & Myrhed,[48] 1993	2.4 (1987–1991)
DeFronzo et al,[49] 1995	0
Brown et al,[50] 1998	9.7
Misbin et al,[51] 1998	5
UKPDS 34,[17] 1998	0
Salpeter et al,[52] 2003	8.1–9.9
Stang et al,[53] 1999	9
Cryer et al,[54] 2005	0
Bodmer et al,[55] 2008	3.3
Salpeter et al,[56] 2010	4.3
Eppenga et al,[57] 2014	7.4
Richy et al,[58] 2014	10.4
Huang et al,[59] 2015	2.3

Than HM, Endocrinol Metab Clin N Am , 2016

Metformina e funzione renale

Estimated Glomerular Filtration Rate (mL/min per 1.73 m^2)	Recommendation	Recommendation
—	Lipska et al,[67] 2011 and ADA/ EASD position paper	NICE
≥60	No renal contraindication for metformin use Monitor renal function annually.	Step up metformin over weeks to minimize risk for GI side-effects. Try metformin ER if GI intolerance is a problem.
<60 and ≥45	Continue metformin use if tolerated. Monitor renal function every 3–6 mo.	
<45 and >30	Prescribe metformin with caution. Use lower dose (50% maximal dose). Monitor renal function every 3 mo.	Review metformin dose if eGFR <45 mL/min/1.73 m^2.
<30	Stop metformin.	Stop metformin if eGFR <30 mL/min/1.73 m^2.
Caution	"Required in those at risk of for acute kidney injury or with anticipated fluctuations in renal status."	"Prescribe metformin with caution for those at risk of a sudden deterioration in kidney function."

Than HM, Endocrinol Metab Clin N Am , 2016

14 ottobre 2016

Use of metformin to treat diabetes now expanded to patients with moderately reduced kidney function

Recommendations for patients with kidney impairment updated in product information

The European Medicines Agency (EMA) has concluded that metformin-containing medicines can now be used in patients with moderately reduced kidney function (GFR [glomerular filtration rate]=30–59 ml/min) for the treatment of type 2 diabetes. The product information for these medicines will be updated to revise the current contraindication and give information about doses, monitoring and precautions in patients with reduced kidney function.

The recommendations are the result of a review by EMA of metformin-containing medicines following concerns that current scientific evidence does not justify a contraindication in patients with moderate reduction of kidney function. The current product information also varies between countries and products in the EU and is no longer consistent with clinical guidelines.

Metformin may increase the risk of a rare but serious complication called lactic acidosis, which occurs when naturally produced lactic acid builds up in the blood faster than it can be removed. Currently, the product information states that metformin must not be used in patients with reduced kidney function because these patients are considered to be at a higher risk of developing lactic acidosis as their kidneys do not remove metformin efficiently enough.

However, after considering the scientific literature, clinical data, epidemiological studies and clinical guidelines from medical bodies, EMA concluded that the large patient population with moderately reduced kidney function can benefit from use of metformin. Clear dosing recommendations and monitoring before and during treatment aim to minimise any possible increased risk in these patients. The contraindication for patients with severely reduced kidney function will remain (GFR less than 30 ml/min).

Soggetti trattati con farmaci antidiabetici, e relativa spesa

Soggetti con diabete 548.735	N. soggetti trattati con antibiabetici: 458.533	Spesa per farmaci antidiabetici: € 104.795.988	Pezzi prescritti di antidiabetici: 7.495.184

ATC	Principio attivo	Trattati		% Spesa	Spesa media per trattato €	Spesa media pro capite €
		N	%			
A10BA02	Metformina	278.768	60,8	10,1	38,1	19,3
A10BB09	Gliclazide	50.437	11,0	3,0	62,3	5,7
A10BD02	Metformina e sulfonamidi	49.658	10,8	2,8	59,6	5,4
A10BX02	Repaglinide	47.127	10,3	3,7	81,4	7,0
A10BB12	Glimepiride	38.976	8,5	1,1	28,4	2,0
A10BF01	Acarbosio	13.650	3,0	1,0	79,7	2,0
A10BH01	Sitagliptin	11.369	2,5	4,0	364,6	7,6
A10BG03	Pioglitazone	9.680	2,1	1,5	157,6	2,8
A10BX07	Liraglutide	5.439	1,2	4,2	817,1	8,1
A10BB01	Glibenclamide	3.736	0,8	0,1	35,9	0,2
A10BH02	Vildagliptin	3.313	0,7	1,2	374,2	2,3
A10BH05	Linagliptin	2.901	0,6	0,5	194,3	1,0
A10BH03	Saxagliptin	2.194	0,5	0,7	353,0	1,4
A10BX04	Exenatide	2.029	0,4	1,2	632,8	2,3
A10BX10	Lixisenatide	370	0,1	0,1	385,1	0,3

Osservatorio Arno Diabete, Rapporto 2015

Conclusioni

- **La metformina è:**
  - **efficace**
  - **sicura (basso rischio di ipoglicemia)**
  - **riduce la mortalità cardiovascolare, rispetto alle sulfoniluree**
  - **costa poco**

- **L'acidosi lattica indotta da metformina è rara e spesso causata da altri fattori**

- **Le linee guida sull'uso della metformina nell'insufficienza renale lieve/moderata sono cambiate**

- **La metformina è oggi utilizzata anche per ritardare lo sviluppo del diabete di tipo 2, nel diabete gestazionale e nella PCOS.**

La prossima sfida per la Diabetologia:

La "Precision Medicine"

"Tonight, I'm launching a new Precision Medicine Initiative to bring us closer to curing diseases like cancer and diabetes — and to give all of us access to the personalized information we need to keep ourselves and our families healthier."

— President Barack Obama, State of the Union Address, January 20, 2015

N ENGL J MED 372;9 NEJM.ORG FEBRUARY 26, 2015

The Impact of Precision Medicine in Diabetes: A Multidimensional Perspective

Stephen S. Rich[1] and William T. Cefalu[2]

Diabetes Care 2016;39:1854–1857 | DOI: 10.2337/dc16-1833

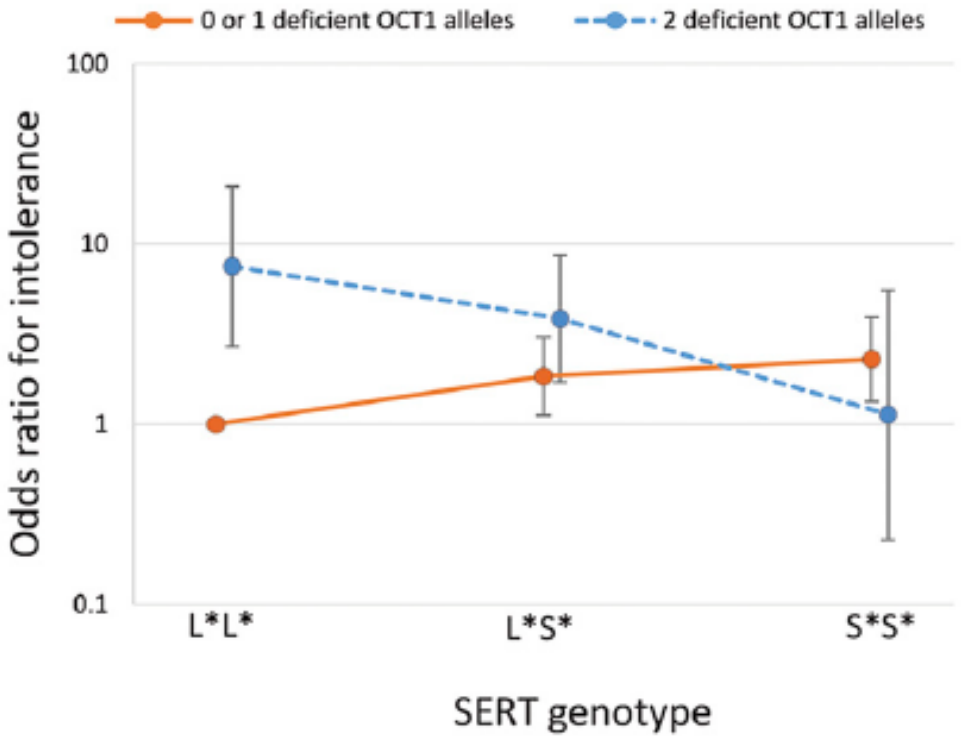
Farmacogenomica e risposta alla metformina

Metformin					
Pharmacokinetic	*SLC22A1*	HbA_{1c} response	102	0.3% absolute lower reduction in HbA_{1c} (per variant allele)	166
		HbA_{1c} response	371	1.1% absolute lower reduction in HbA_{1c} (per variant allele)	77
		On treatment HbA_{1c} <7%	1,531	No association	76
		Drug intolerance	2,166	OR 2.4 for discontinuation (homozygous for variant alleles)	73
	SLC47A1	HbA_{1c} response	116	0.3% absolute lower reduction in HbA_{1c} (per variant allele)	167
		HbA_{1c} response	371	No association	77
		Risk of type 2 diabetes	2,994	Less reduction in diabetes risk	
	SLC47A2	HbA_{1c} response	253	0.1% absolute lower reduction in HbA_{1c} (any variant allele)	168
		HbA_{1c} response	371	No association	77
GWA studies	*ATM*	HbA_{1c} response, on treatment HbA_{1c} <7%	2,896	0.1% absolute greater reduction in HbA_{1c} and OR 1.4 for treatment success (per variant allele)	80
		HbA_{1c} response, on treatment HbA_{1c} <7%	1,366	No association with HbA_{1c} response, OR 1.2 for treatment success (per variant allele)	81

Effect of Serotonin Transporter 5-HTTLPR Polymorphism on Gastrointestinal Intolerance to Metformin: A GoDARTS Study

Tanja Dujic,[1,2] Kaixin Zhou,[2] Roger Tavendale,[2] Colin N.A. Palmer,[2] and Ewan R. Pearson[2]

DOI: 10.2337/dc16-0706



Numbers of intolerant/tolerant individuals

	SERT genotype		
OCT1 genotype	L*L*	L*S*	S*S*
0 or 1 deficient OCT1 allele	26/362	68/605	47/298
2 deficient OCT1 alleles	8/20	13/51	2/20

Changing how drugs are delivered

Identify non-responders and safety issues before prescribing or treating