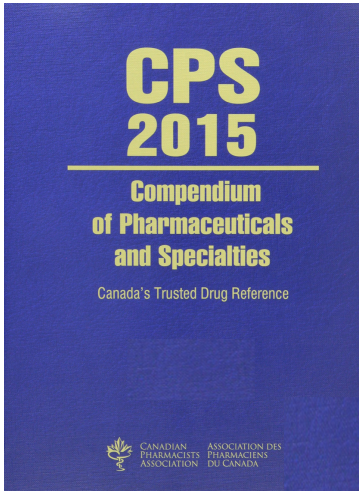
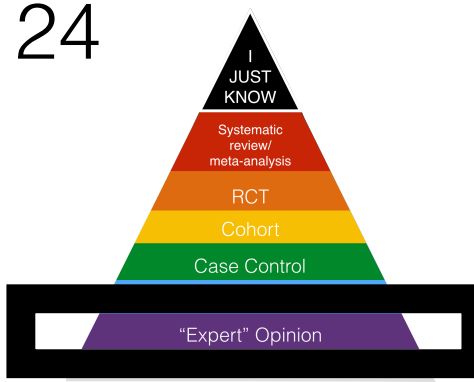

Metformin:
Fights sugars but is
it really still sweet ?
Gallega officinalis



Metformin is contraindicated…

"…in the presence of renal impairment or when renal function is not known, and also in patients with serum creatinine levels above the upper limit of normal range. Renal disease or renal dysfunction (e.g., as suggested by serum creatinine levels ≥136 µmol/L (males), ≥124 µmol/L (females) or abnormal creatinine clearance <60 mL/min))"

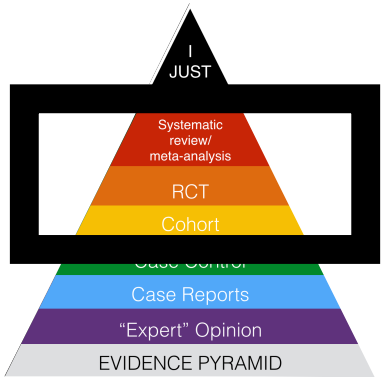


Metformin in Patients With Type 2 Diabetes and Kidney Disease
A Systematic Review

"The risk of lactic acidosis is essentially nil in the context of clinical trials, including those that did not specify kidney disease as an exclusion criterion."
347 studies - 70,490 pt/yrs - no cases

"Data from observational clinical practice data sets are conflicting, with most appearing to confirm the drug's overall safety profile, finding lactic acidosis rates not different from those in the general population of patients with diabetes treated with other agents."

~10 per 100,000 pt years



JAMA 2014;312:2668-75

Clinical Toxicology (2014), **52**, 85–87

ISSN: 1556-3650 print / 1556-9519 online
DOI: 10.3109/15563650.2014.880174

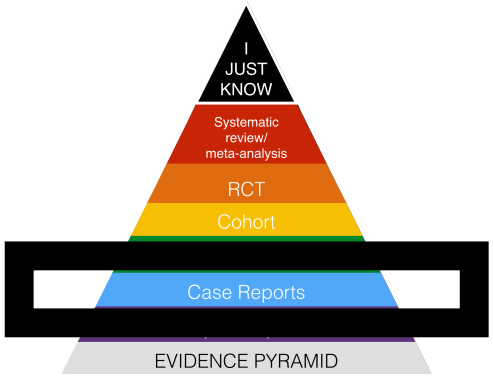
informa
healthcare

COMMENTARY

The enigma of metformin-associated lactic acidosis

D. N. JUURLINK[1] and D. M. ROBERTS[2]

"Metformin is clearly capable of causing profound acidemia on its own, as evidenced by case reports of deliberate overdose"



Metformin Dose Adjustments

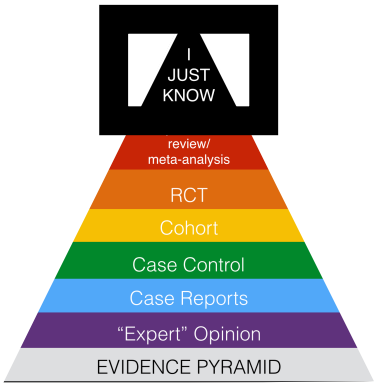
It's 95% renally eliminated

<u>Estimated glomerular filtration rates (eGFRs)</u>

>60 mL/min/1.73 m - no change

30-60 - reduce dose by 50%

15-30 - reduce dose by 75%



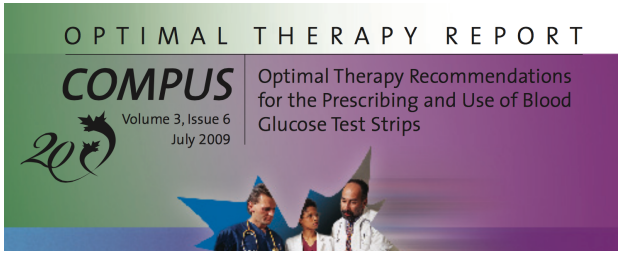
Quantifying the Effect of Metformin Treatment and Dose on Glycemic Control

Jennifer A. Hirst, msc[1]
Andrew J. Farmer, md[1]
Raghib Ali, msc[2,3]
Nia W. Roberts, msc[4]
Richard J. Stevens, phd[1]

metformin monotherapy reduces A1c ~1.1%

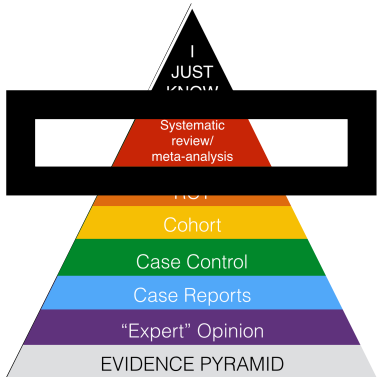
doubling dose from 1000 to 2000 mg/day adds ~0.25-0.3% additional change in A1c

Diabetes Care 2012;35:446–54



A1c reduction of 0.75%-1% is considered the “minimal clinically important difference”

To reduce “problems” maybe no one should be on >1000 mg a day anyway?



Diabetes Prevention Program - 3 year trial - 15 year follow up
Baseline A1c 5.9 - used OGTT and FPG for diagnosis

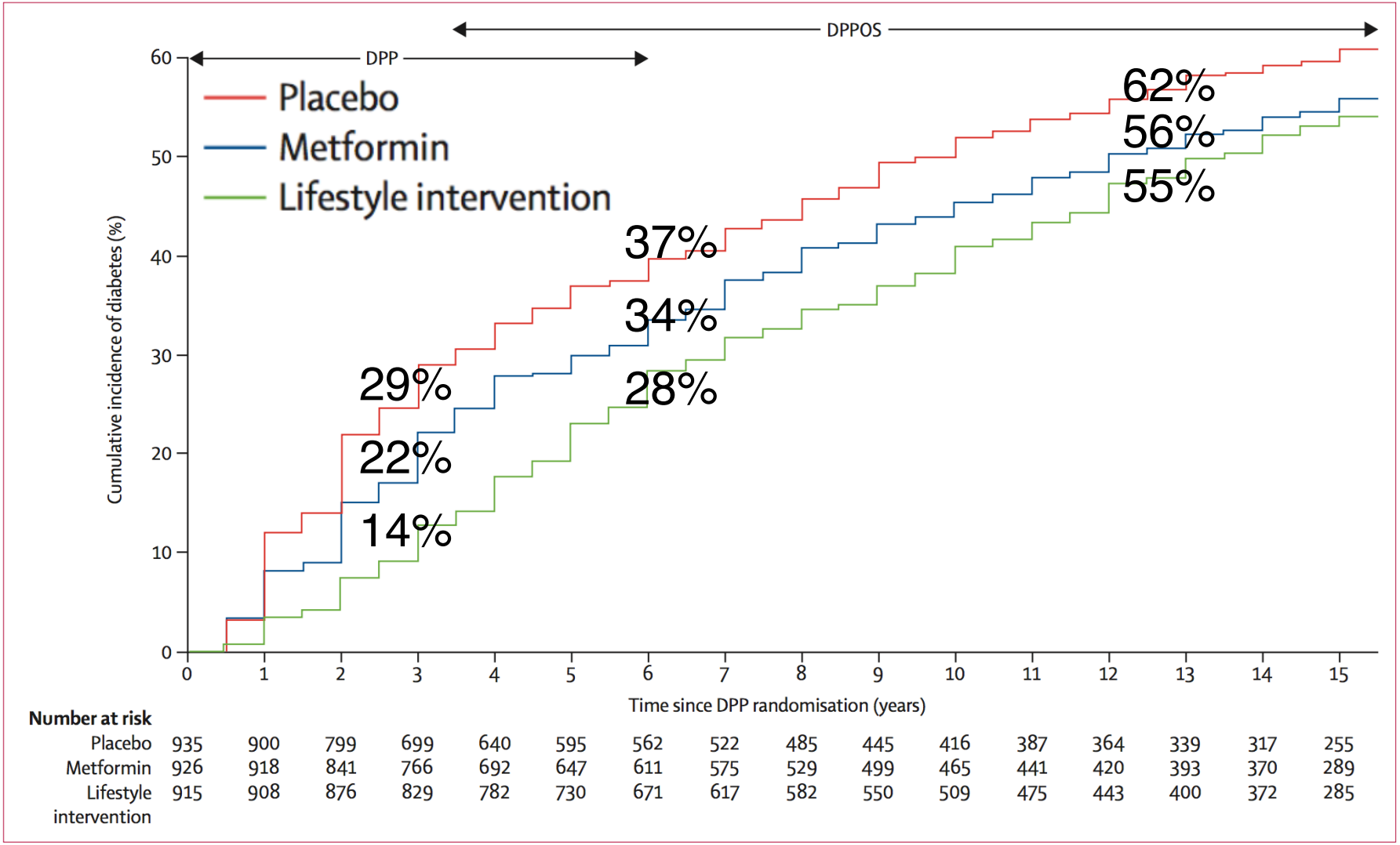
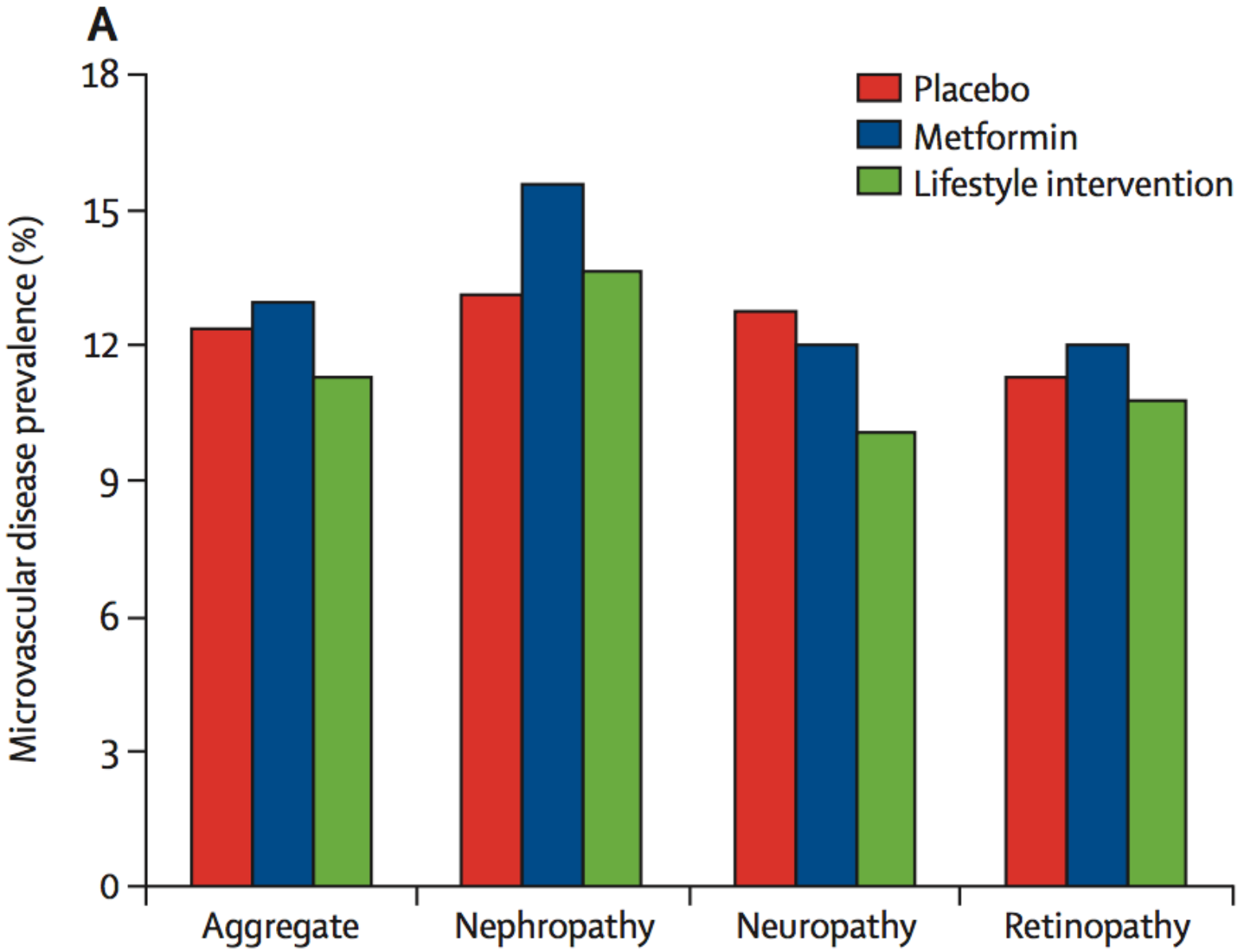


Figure 2: **Cumulative incidence of diabetes by treatment group in the 2776 DPP–DPPOS participants**
The Diabetes Prevention Program (DPP) and DPP Outcomes Study (DPPOS) periods, and the overlap between them, are shown. Over the entire study, the cumulative incidence was 27% lower for the lifestyle group than for the placebo group (p<0·0001) and 18% lower for the metformin group than for the placebo group (p<0·0001). The difference between the lifestyle and metformin groups was not significant (p=0·10).

Microvascular outcomes



Reverse Logic

Assume “a drug” reduces the chance of a person going from a “pre-diabetic” to a “real-diabetic” by an absolute 7%

This means you have to give
100% of people with pre-diabetes
a drug every day

to prevent 7% of them from getting diabetes
for which they would need to take
a drug every day

“Pre-diabetes could be defined as a risk factor for developing a risk factor.”

Yudkin J, Montori V

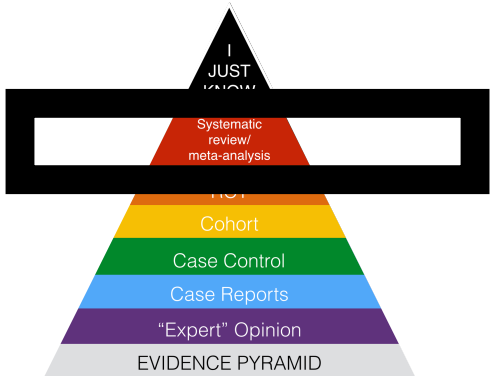
ALL LOWER GLUCOSE							
RED - no effect on clinical outcomes	Key RCTs (patients/years)		MA (# of studies)				
METFORMIN - Glucophage, Glumetza, generic	700/11	7%	13				
SULFONLYUREAS - Gliclazide (Diamicron, generic), Glimepiride (Amaryl), Glyburide (Diabeta, Euglucon, generic)	4,000/10	UKPDS COMBO	4-11		3%		
INSULIN	12,000/6 4,000/10	UKPDS COMBO	None done				
DPP4s - Sitagliptin (Januvia), Saxagliptin (Onglyza), Linagliptin (Trajenta), Alogliptin (Nesina)	5,000/1.5 16,000/2 1,500/2	vs glimiperide	None done				
GLITAZONES - Pioglitazone (Actos), Rosiglitazone (Avandia)	4,400/4 5,200/3	?	42	?CHF harm	?	?	?
GLPs - Exenatide (Byetta) Liraglutide (Victoza), Dulaglutide (Trulicity)	? - not studied		?		?	?	?
MEGLITINIDES - Nateglinide (Starlix), Repaglinide (GlucoNorm)	? - not studied		?		?	?	?
SGLT2 - Canagliflozin (Invokana), Dapagliflozin (Farxiga), Empagliflozin (Jardiance)	7000/3.1 Empag Others?	1.6%	?		?	?	?
Tight control	10,000/3.5 1,800/5.5 11,000/5	?Mortality harm	3		2%	2%	2%

Review

Effects of pharmacological treatments on micro- and macrovascular complications of type 2 diabetes: What is the level of evidence?

R. Boussageon [a,*], F. Gueyffier [b,c], C. Cornu [b,c,d]

"In 2013, the level of evidence for the clinical efficacy of antidiabetic drugs is disappointing and does not support the millions of prescriptions being written for them"

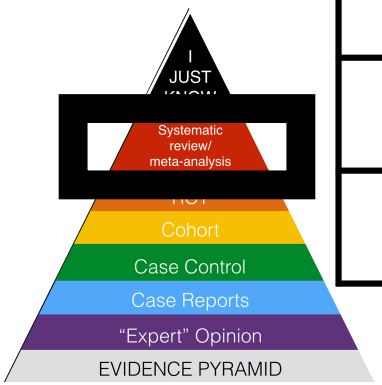


Diabetes Metab 2014 Feb 3. pii: S1262-3636

Reappraisal of Metformin Efficacy in the Treatment of Type 2 Diabetes: A Meta-Analysis of Randomised Controlled Trials

13 studies - 9,500 metformin/3,500 conventional or placebo - 5 years

	RR	CI
Mortality	0.99	0.75-1.31
CVD mortality	1.05	0.67-1.64
MIs	0.90	0.74-1.09
Strokes	0.76	0.51-1.14
Heart failure	1.03	0.67-1.59
PVD	0.90	0.46-1.78
Amputation	1.04	0.44-2.44
Microvascular	0.83	0.59-1.17



PLoS Medicine 2012;9:e1001204

Is HbA_{1c} a valid surrogate for macrovascular and microvascular complications in type 2 diabetes?

T. Bejan-Angoulvant [a,b,c], C. Cornu [d,e,f,g], P. Archambault [h], B. Tudrej [h], P. Audier [h], Y. Brabant [h], F. Gueyffier [d,e,f,g], R. Boussageon [h,*]

"Meta-regression analysis could find no significant association between HbA1c-lowering and a decrease in clinical outcomes, thereby questioning the use of HbA1c as a surrogate outcome for T2D-related complications."

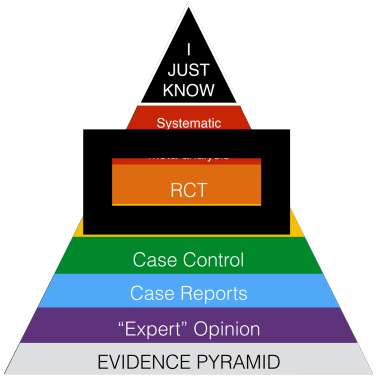
Diabetes Metab 2015, http://dx.doi.org/10.1016/j.diabet.2015.04.001

UKPDS 34 – 10 year follow up

10 year post UKPDS trial: 17 year total

3277 patients (1525 completed - only 136 on metformin)

	Any diabetes related end-point	Deaths related to diabetes	All cause mortality	MI	Stroke
Conventional/ Baseline	~50	~20	~30	~20	~5
Metformin 342 pts started!!!!!	8%↓	5%↓	7%↓	6%↓	NS
Sulfonylurea/ insulin	4%↓	3%↓	3%↓	3%↓	NS



↓ - refers to ARR NEJM 2008;359 - Sep 10

Don't forget that in UKPDS 34 metformin when added to sulfonylureas increased overall mortality by 60% - 6% absolute

Things that make me worry about the UKPDS 34

342 patients got metformin - 136 in the follow-up

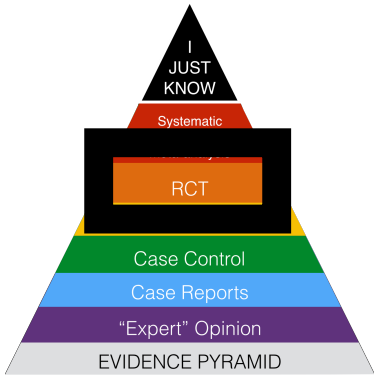
Unblinded

Multiple outcomes added during the study

Only 78% of people initially entered were analyzed

It's never been reproduced

In the same study the addition of metformin to sulfonylureas increased mortality



ORIGINAL ARTICLE

Glycemic Durability of Rosiglitazone, Metformin, or Glyburide Monotherapy

ADOPT - blinded RCT 4,360 patients - 4 years
A1c 7.4%, 57 y/o, 57% male

	Mortality (%)	CVD (%)	CHF (%)	GI (%)	Hypo-glycemia (%)	Edema (%)	Weight gain (%)	Fractures (women) (%)
Glyburide	2.2	2.8	0.6	22	39^	8.5	3.3**	3.5
Metformin	2.1	4.0	1.3	38	12	7.2	1.2	5.1
Rosiglitazone	2.3	4.3*	1.5*	23	10	14.1#	6.9**	9.3#

stat sig *compared to glyburide **compared to metformin
^ compared to metformin/rosiglitazone, # compared to glyburide/metformin

N Engl J Med 2006;355:2427-43

UKPDS vs ADOPT

	UKPDS 34	ADOPT
A1c	7.2%	7.4%
Duration of diabetes	Newly diagnosed	96% <2 years
Age	53	57
Male	46%	57%
Caucasian	86%	88%
SBP	140	133
DBP	86	80
BMI	31	32

EMPA-REG OUTCOME

3.1yr - 63 y/o, 71% male, 100% prev CVD, A1c 8.1%

	All deaths (%)	CVD death (%)	Death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke (%)	Genital infections (%)
Empagliflozin	5.7	3.7	10.5	6.4
Placebo	8.3	5.9	12.1	1.8
RR	31	38	14	260
ARR	2.6	2.2	1.6	4.6
NNT	39	45	61	22

NEJM 2015;DOI: 10.1056/NEJMoa1504720