Initial Mono Versus Combination Therapy for Type 2 Diabetes

The Case for Combination Therapy

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Medical Decision Making

- Expert Opinion: Aristotle reasoned the number of teeth in the jawbone of an ass.
- 2000 years later someone counted and found him to be wrong
- Aristotle also reasoned that a lighter object such as a feather would fall to earth more slowly than a heavier one such as a stone.
- 2000 years later Galileo proved him wrong.
- NASA does exact experiment on the Moon and finds Aristotle still wrong.

Scientific Experimentation

- Stepwise monotherapy was always the recommended therapy for type 2 diabetes.
- Tests of efficacy of mono versus combination therapy were not performed until the 1990's.
- Testing was done with metfomin and glyburide alone or in combination. Studies have been repeated later with metformin in combination with glipizide, rosiglitazone and sitagliptin.

Original Article:

Effect Of Metformin/Glyburide Tablets On HbA1c In First-Line Treatment Of Type 2 Diabetes

Diabetes. 49.5 (May 2000): pA107

Mean change in [HbA.sub.1c] (%) by Baseline [HbA.sub.1c] (%) at Week 20

Baseline [HbA.sub.1c]	Pbo n=147	Gly 2.5 mg n=142	Met 500 mg n=141	M/G 250/1.25 n=149	M/G 500/2.5 n=152
< 8.0	-0.10	-0.93	-0.73	-0.90	-0.92
8–8.9	-0.31	-1.27	-1.26	-1.31	-1.75
9–9.9	-0.46	-1.89	-1.50	-2.40	-2.37
≥ 10	0.09	-1.87	-1.28	-3.21	-2.78

n = Randomized subjects with available data.

Original Article:

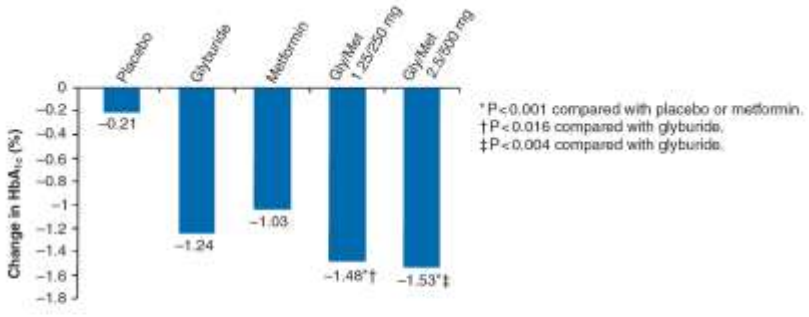
Simultaneous Glyburide/Metformin Therapy is Superior to Component Monotherapy as an Initial Pharmacological Treatment for Type 2 Diabetes

Diabetes, Obesity and Metabolism, 4, 2002, 201–208

Table 1 Baseline characteristics for all randomized patients

Characteristic	Placebo (n = 161)	Glyburide 2.5 mg (n = 161)	Metformin 500 mg (n = 161)	Gly/Met 1.25/250 mg (n = 158)	Gly/Met 2.5/500 mg (n = 165)
Age (years)					
Mean (s.d.)	55.4 (10.5)	56.5 (10.5)	56.0 (11.0)	56.9 (12.0)	56.1 (9.8)
Sex (n, %)					
Men	76 (47.2)	82 (50.9)	93 (57.8)	91 (57.6)	96 (58.2)
Women	85 (52.8)	79 (49.1)	68 (42.2)	67 (42.4)	69 (41.8)
Race (n, %)					
White	122 (75.8)	126 (78.3)	130 (80.7)	117 (74.1)	131 (79.4)
Black	18 (9.9)	15 (9.3)	7 (4.3)	20 (12.7)	10 (6.1)
Hispanic	17 (10.6)	14 (8.7)	20 (12.4)	18 (11.4)	16 (9.7)
Other	6 (3.7)	6 (3.7)	4 (2.5)	3 (1.9)	8, (4.9)
b.m.i. (kg/m^2)					
Mean (s.d.)	30.2 (4.6)	30.3 (3.9)	30.4 (4.3)	30.1 (4.0)	29.8 (4.5)
Body weight (kg)					
Mean (s.d.)	86.2 (16.6)	87.2 (15.3)	88.6 (14.9)	88.8 (15.4)	86.7 (17.5)
Duration of diabetes (years)					
Mean (s.d.)	2.76 (2.83)	2.81 (3.14)	2.98 (2.74)	3.52 (3.26)	3.30 (3.18)
FPG (mmol/l)*					
Mean (s.d.)	177 (51.2)	179 (48.4)	176 (43.9)	177 (45.4)	175 (46.7)
HbA_{1c} (%)					
Mean (s.d.)	8.21 (1.00)	8.21 (1.09)	8.26 (1.08)	8.25 (1.11)	8.18 (1.14)
Fasting plasma insulin (pmol/l)†					
Mean (s.d.)	136 (237)	119 (76)	119 (70)	117 (72)	105 (58)

Gly/Met = glyburide/metformin tablet; s.d. = standard deviation; FPG = fasting plasma glucose.
*To convert glucose from millimoles per litre to milligrams per decilitre, divide by 0.0555.
†To convert insulin from picomoles per litre to microunits per millilitre, divide by 6.945.



Mean final dose					
Glyburide (mg)	0	5.3	0	2.8	4.1
Metformin (mg)	0	0	1317	557	824

Fig. 1 Mean change in HbA_{1c} levels from baseline to final study visit (week 20 or last prior measurement) in patients receiving placebo, glyburide, metformin, glyburide/metformin 1.25/250 mg and glyburide/metformin 2.5/500 mg.

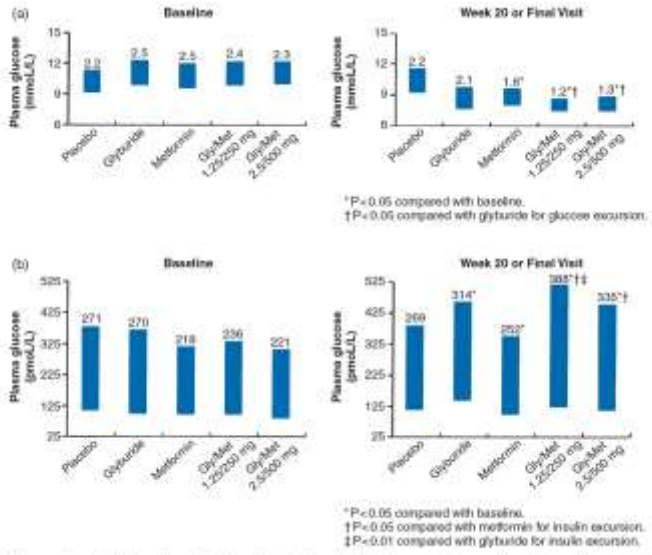


Fig. 2 Mean postprandial glucose (figure 2a, top) and insulin (figure 2b, bottom) excursions (mean change between fasting [bottom of each bar] and 2-h postprandial [top of each bar] concentrations) at baseline and final study visit [week 20 or last prior measurement] in patients receiving placebo, glyburide, metformin, glyburide/metformin 1.25/250 mg and glyburide/metformin 2.5/500 mg.

Table 2 Incidence of most common adverse events by the body system and discontinuation rates due to adverse events

Body system	Placebo (n = 161) (%)	Glyburide 2.5 mg (n = 160) (%)	Metformin 500 mg (n = 159) (%)	Gly/Met 1.25/250 mg (n = 158) (%)	Gly/Met 2.5/500 mg (n = 162) (%)
Respiratory	29	48	38	41	43
Nervous	25	32	25	30	31
Musculoskeletal	28	24	29	24	28
General	25	28	30	22	29
Gastrointestinal (total)†	24	24	43	32*	38
Diarrhoea	3.1	4.4	15.1	7.6	12.3
Nausea/vomiting	4.3	0.6	6.3	1.9	4.9
Abdominal pain	1.9	3.1	5.0	5.7	5.6
Dyspepsia	3.7	2.5	5.0	2.5	3.1
Discontinuations due to AE	1.9	6.9	6.3	3.8	11.1

Gly/Met = glyburide/metformin tablet.
*$p = 0.037$ vs. metformin.
†Drug-related gastrointestinal symptoms occurring in ≥ 5.0% of patients.

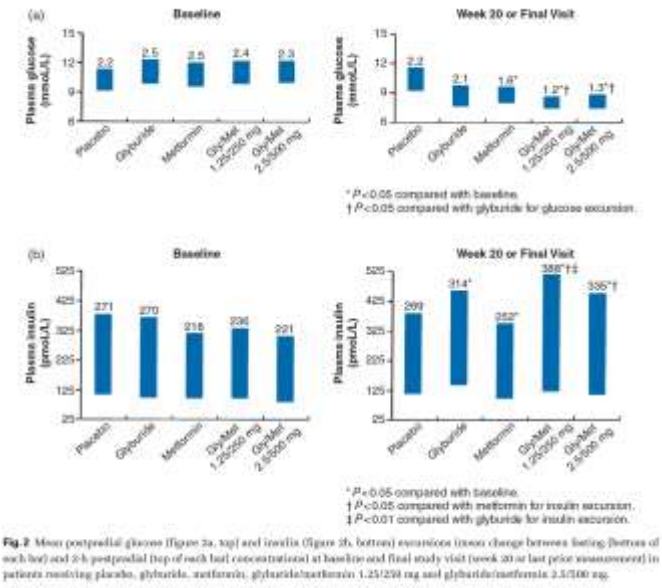


Fig. 2 Mean postprandial glucose (Figure 2a, top) and insulin (Figure 2b, bottom) excursions (mean change between fasting [bottom of each bar] and 2-h postprandial [top of each bar] concentrations) at baseline and final study visit (week 20 or last prior measurement) in patients receiving placebo, glyburide, metformin, glyburide/metformin 1.25/250 mg and glyburide/metformin 2.5/500 mg.

Original Article:

Initial Treatment with Rosiglitazone/Metformin Fixed-Dose Combination Therapy Compared with Monotherapy with Either Rosiglitazone or Metformin in Patients with Uncontrolled Type 2 Diabetes

Diabetes, Obesity and Metabolism, 8, 2006, 650–660

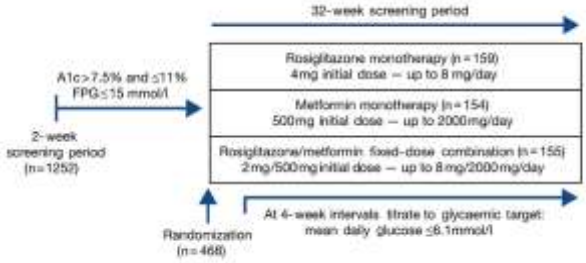


Fig. 1 Study design. A1c, glycated haemoglobin; FPG, fasting plasma glucose.

Table 1 Baseline demographical and clinical characteristics

Characteristic	RSG/MET (n = 155)	MET (n = 154)	RSG (n = 159)
Age in years, mean (s.d.)	50.1 (10.7)	51.5 (10.4)	50.6 (10.26)
Gender, n (%)			
Female	66 (43)	67 (44)	66 (42)
Male	89 (57)	87 (56)	93 (58)
Race, n (%)			
Caucasian	83 (54)	90 (58)	94 (59)
Latino	41 (26)	33 (21)	31 (19)
Asian	19 (12)	22 (14)	22 (14)
Black	10 (6)	8 (5)	8 (5)
Other	2 (1)	1 (<1)	4 (3)
BMI, mean (s.d.), kg/m^2	33.2 (7.7)	32.5 (7.0)	32.8 (7.1)
Duration of diabetes in years, mean (s.d.)	2.3 (2.7)	2.9 (3.7)	2.7 (3.0)
Median (25th, 75th percentile)	1.2 (0.2, 3.2)	1.2 (0.2, 3.8)	1.9 (0.2, 4.2)
A1c*, mean (s.d.), %	8.9 (1.1)	8.8 (1.0)	8.8 (1.0)
FPG*, mean (s.d.), mmol/l	11.2 (2.9)	11 (2.9)	10.7 (2.9)

A1c, glycated haemoglobin; BMI, body mass index; FPG, fasting plasma glucose; ITT, intent-to-treat; LOCF, last observation carried forward; MET, metformin monotherapy; RSG, rosiglitazone monotherapy; RSG/MET, rosiglitazone/metformin fixed-dose combination therapy; s.d., standard deviation.
*ITT with LOCF population.

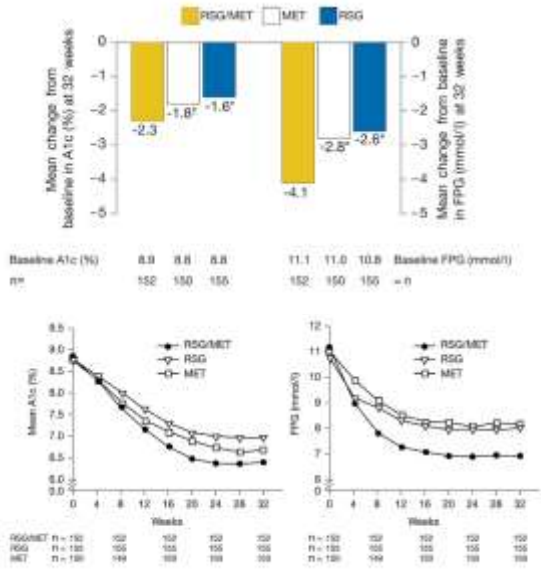


Fig. 2 Reductions in A1c and FPG to week 32. *$p < 0.0001$; †$p = 0.0008$. A1c, glycated haemoglobin; FPG, fasting plasma glucose; MET, metformin monotherapy; RSG, rosiglitazone monotherapy; RSG/MET, rosiglitazone/metformin fixed-dose combination therapy.

Fig. 3 Mean A1c (%) and FPG (mmol/l) concentrations over time. A1c, glycated haemoglobin; FPG, fasting plasma glucose; MET, metformin monotherapy; RSG, rosiglitazone monotherapy; RSG/MET, rosiglitazone and metformin fixed-dose combination therapy.

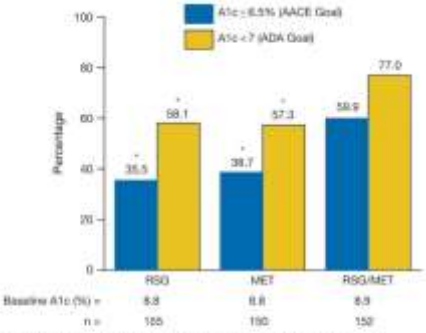


Fig. 4 Percentages of patients who reached A1c targets. ITT with LOCF. *RSG and MET are significantly different from RSG/MET. A1c, glycated haemoglobin; AACE, The American Association of Clinical Endocrinologists; ADA, The American Diabetes Association; ITT, intent-to-treat; LOCF, last observation carried forward; MET, metformin monotherapy; RSG, rosiglitazone monotherapy; RSG/MET, rosiglitazone and metformin fixed-dose combination therapy.

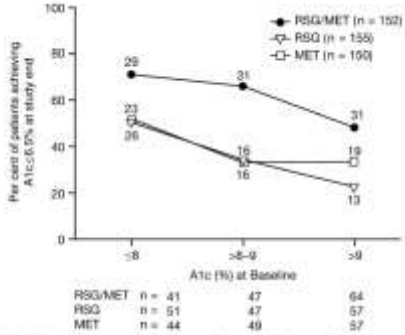


Fig. 5 Percentages of patients who reached A1c less than or equal to 6.5%, as stratified by baseline A1c levels. A1c, glycated haemoglobin; MET, metformin monotherapy; RSG, rosiglitazone monotherapy; RSG/MET, rosiglitazone and metformin fixed-dose combination therapy.

Table 2 Mean change from baseline to week 32 in lipid parameters

Lipid parameter (mg/dl)	RSG/MET (n = 155)	MET (n = 154)	RSG (n = 159)
Total cholesterol (n*)	132	117	128
Baseline (CV %)	200.4 (19.8)	201.6 (19.3)	198.4 (26.6)
Week 32 (CV %)	186.1 (19.8)	183.4 (20.3)	208.8 (27.9)
Per cent change from baseline (95% CI†)	−2.2 (−3.8, −0.5)	−9.1 (−10.5, −7.5)	5.3 (3.5, 7.2)
Per cent treatment difference‡	—	7.2 (2.6, 11.9)	−7.2 (−11.0, −3.1)
p value	—	0.009	0.0006
HDL cholesterol (n*)	132	117	128
Baseline (CV %)	42.6 (21.8)	42.9 (23.8)	42.8 (24.5)
Week 32 (CV %)	45 (25.5)	43 (23.0)	44.1 (27.0)
Per cent change from baseline (95% CI†)	5.8 (4.2, 7.3)	0 (−1.3, 1.3)	3.1 (1.4, 4.7)
Per cent treatment difference‡	—	5.4 (1.2, 9.7)	2.3 (−1.6, 6.4)
p value	—	0.0107	0.2530
LDL cholesterol (n*)	132	117	128
Baseline (CV %)	113.8 (32.5)	116 (33.9)	114.8 (40.5)
Week 32 (CV %)	113.5 (30.4)	103.6 (35.2)	119.7 (58.0)
Per cent change from baseline (95% CI†)	−0.2 (−2.8, 2.4)	−10.7 (−13.1, −8.2)	4.5 (0.8, 8.4)
Per cent treatment difference‡	—	10.4 (1.9, 19.7)	−5.5 (−12.7, 3.3)
p value	—	0.0161	0.1602
Triglycerides (n*)	132	117	128
Baseline (CV %)	180.3 (67.7)	175.7 (62.3)	166.6 (67.6)
Week 32 (CV %)	146.6 (68.6)	148.7 (58.3)	158.5 (74.8)
Per cent change from baseline (95% CI†)	−18.7 (−21.5, −15.8)	−15.4 (−18.4, −12.2)	−4.8 (−8.6, −0.9)
Per cent treatment difference‡	—	−3.3 (−12.4, 6.9)	−13 (−21.1, −4.1)
p value	—	0.5094	0.0052

A1c, glycated haemoglobin; ANCOVA, analysis of covariance; CI, confidence interval; CV, coefficient of variation; HDL, high-density lipoproteins; LDL, low-density lipoproteins; MET, metformin monotherapy; RSG, rosiglitazone monotherapy; RSG/MET, rosiglitazone/metformin fixed-dose combination therapy.

*Number of patients with a value at baseline and at week 32.

†Per cent change based on log-transformed data.

‡Per cent treatment difference between RSG/MET and monotherapy; ANCOVA model: log (value) − log (baseline) = log (baseline) + screening A1c + gender + country + treatment.

Table 3 Mean change from baseline to week 32 in FFA, CRP and adiponectin

Parameter	RSG/MET (n = 152)	MET (n = 150)	RSG (n = 155)
FFA, mmol/l (n*)	142	142	148
Baseline (CV %)	0.52 (39.8)	0.50 (39.9)	0.52 (37.5)
Week 32 (CV %)	0.41 (43.8)	0.45 (38.5)	0.38 (37.5)
Per cent change from baseline (95% CI†)	−23.3 (−25.8, −20.5)	−9.4 (−12.3, −6.5)	−26.1 (−28.6, −23.5)
Per cent treatment difference‡	—	−12.5 (−19.2, −5.3)	4.2 (−3.7, 12.6)
p value	—	0.0010	0.3057
CRP, µg/ml (n*)	119	112	120
Baseline (CV %)	4.5 (141.3)	3.6 (150.0)	3.8 (149.5)
Week 32 (CV %)	2.05 (188.5)	2.28 (181.6)	2.19 (186.3)
Per cent change from baseline (95% CI†)	−54.4 (−58.5, −49.8)	−36.7 (−40.9, −30.0)	−41.6 (−47.1, −35.5)
Per cent treatment difference‡	—	−23.8 (−40.3, −2.7)	−18.3 (−35.7, 3.9)
p value	—	0.0293	0.0991
Adiponectin, µg/ml (n*)	116	109	118
Baseline (CV %)	5.2 (58.9)	5 (57.2)	5 (55.9)
Week 32 (CV %)	12.9 (59.7)	5.5 (55.9)	13.4 (66.8)
Per cent change from baseline (95% CI†)	147.3 (138.0, 157.0)	8.6 (5.6, 11.7)	165.9 (155.3, 176.9)
Per cent treatment difference‡	—	131.1 (109.7, 154.6)	−5.55 (−14.1, 3.9)
p value	—	<0.0001	0.2388

A1c, glycated haemoglobin; ANCOVA, analysis of covariance; CI, confidence interval; CV, coefficient of variation; MET, metformin monotherapy; RSG, rosiglitazone monotherapy; RSG/MET, rosiglitazone/metformin fixed-dose combination therapy; CRP, C-reactive protein; FFA, free fatty acid.

*Number of patients with a value at baseline and at week 32.

†Per cent change based on log-transformed data.

‡Per cent treatment difference between RSG/MET and monotherapy; ANCOVA model: log (value) − log (baseline) = log (baseline) + screening A1c + gender + country + treatment.

Table 4 On-therapy adverse events reported by ≥10% of patients

Adverse event	Number (%) patients		
	RSG/MET (n = 155)	MET (n = 154)	RSG (n = 159)
Nausea/vomiting	25 (16)	20 (13)	13 (8)
Diarrhoea	22 (14)	32 (21)	11 (7)
Headache	17 (11)	18 (12)	16 (10)
Dyspepsia	15 (10)	12 (8)	14 (9)

MET, metformin monotherapy; RSG, rosiglitazone monotherapy; RSG/MET, rosiglitazone/metformin fixed-dose combination therapy.

Initial Combination Therapy with Metformin, Pioglitazone and Exenatide is More Effective Than Sequential Add-On Therapy in Subjects with New-Onset Diabetes.

Results from the Efficacy and Durability of Initial Combination Therapy for Type 2 Diabetes (EDICT): a randomized trial.

Diabetes Obes Metab. 2015 Mar;17(3):268-75. doi: 10.1111/dom.12417. Epub 2015 Jan 7.

Abstract: Aim

- To test our hypothesis that initiating therapy with a combination of agents known to improve insulin secretion and insulin sensitivity in subjects with new-onset diabetes would produce greater, more durable reduction in glycated haemoglobin (HbA1c) levels, while avoiding hypoglycaemia and weight gain, compared with sequential addition of agents that lower plasma glucose but do not correct established pathophysiological abnormalities.

Abstract: Methods

- Drug-naïve, recently diagnosed subjects with type 2 diabetes mellitus (T2DM) were randomized in an open-fashion design in a single-centre study to metformin/pioglitazone/exenatide (triple therapy; n = 106) or an escalating dose of metformin followed by sequential addition of sulfonylurea and glargine insulin (conventional therapy; n = 115) to maintain HbA1c levels at <6.5% for 2 years.

Abstract: Results

- Participants receiving triple therapy experienced a significantly greater reduction in HbA1c level than those receiving conventional therapy (5.95 vs. 6.50%; $p < 0.001$). Despite lower HbA1c values, participants receiving triple therapy experienced a 7.5-fold lower rate of hypoglycaemia compared with participants receiving conventional therapy. Participants receiving triple therapy experienced a mean weight loss of 1.2 kg versus a mean weight gain of 4.1 kg ($p < 0.01$) in those receiving conventional therapy.

Abstract: Conclusion

- The results of this exploratory study show that combination therapy with metformin/pioglitazone/exenatide in patients with newly diagnosed T2DM is more effective and results in fewer hypoglycaemic events than sequential add-on therapy with metformin, sulfonylurea and then basal insulin.

Conclusion

- Don’t be a jackass
- Use combination therapy where indicated for better and more rapid glycemic control