Determinants of monotherapy failure in ADOPT (A Diabetes Outcome Progression Trial)

R. R. Holman, S. E. Kahn, S. M. Haffner, B. Zinman, G. F. Viberti, W. H. Herman, J. M. Lachin, B. G. Kravitz, M. A. Heise

Diabetologia (2007); **50**: Suppl 1: S356

Background and Aims: ADOPT (A Diabetes Outcome Progression Trial), a double-blind, randomised clinical trial in 4360 recently diagnosed type 2 diabetic patients, assessed the efficacy of rosiglitazone (RSG), glyburide (GLY) and metformin (MET) as initial therapy. This 4-year study showed that, compared with GLY or MET, RSG slowed progression to monotherapy failure (MTF), defined as the time to the first of two successive fasting plasma glucose (FPG) values >180 mg/dl. To address whether tailoring glucose-lowering medication based on individual phenotypes would promote the achievement and maintenance of glycemic targets, data from ADOPT were analysed to assess which phenotypic features at baseline most influenced time to MTF.

Materials and Methods: Patient demographic and baseline characteristics by allocated therapy were analysed using a multivariate proportional hazards model.

Results: Significant factors ($p<0.05$) with hazard ratios (HR), 95% confidence intervals and Madalla R^2 values were:

	Rosiglitazone		**Metformin**		**Glyburide**	
	HR	R^2%	HR	R^2%	HR	R^2%
Age (per year)	0.92 (0.90-0.94)	4.7	0.96 (0.94-0.97)	2.1	0.96 (0.95-0.97)	3.6
HbA_{1c} (per 1%)	1.50 (1.21-1.86)	1.1	1.46 (1.25-1.71)	1.7	1.25 (1.09-1.44)	0.8
FPG (per mg/dl)			1.01 (1.00-1.02)	0.6	1.01 (1.01-1.02)	1.7
HOMA%B (per unit)	0.98 (0.97-0.99)	1.1				
HOMA%S (per unit)	1.01 (1.006-1.014)	1.5			0.99 (0.98-1.00)	0.3
Proinsulin:insulin (per unit)					2.06 (1.37-3.09)	1.0

For all therapies, increasing age was associated with decreasing risk of MTF, with time to MTF increasing; the greatest effect of age (R^2) was seen in the RSG group ($p<0.05$). High levels of HbA_{1c} and FPG were the next greatest influences in the MET and GLY treatment groups, with both reducing the time to MTF. In the RSG group, HOMA%S had the next greatest impact, with higher levels increasing time to MTF. Lower HOMA%B levels and higher HbA_{1c} levels reduced time to MTF in the RSG group. For GLY, a higher proinsulin: insulin ratio (another measure of beta-cell function) increased time to MTF, and higher HOMA%S levels reduced time to MTF.

Conclusion: Hyperglycaemic progression is slower in older patients. The next most important determinants for the rate of progression to MTF were initial hyperglycaemia in the MET and GLY groups, and lower insulin resistance (assessed by HOMA%S) in the RSG group.