Predicting Post One-year Durability of Glucose-lowering Monotherapies in Patients with Newly-diagnosed Type 2 Diabetes Mellitus – A MASTERMIND Precision Medicine Approach (UKPDS NN <number to be added on acceptance >)

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Abstract

Aims Predicting likely durability of glucose-lowering therapies for people with type 2 diabetes (T2D) could help inform individualised therapeutic choices.

Methods We used data from UKPDS patients with newly-diagnosed T2D randomised to first-line glucose-lowering monotherapy with chlorpropamide–glibenclamide–basal insulin or metformin. In 2,339 participants who achieved one-year HbA_{1c} values <7.5% (<59 mmol/mol)–we assessed relationships between one-year characteristics and time to monotherapy-failure (HbA_{1c} ≥7.5% or requiring second-line therapy). Model validation was performed using bootstrap sampling.

Results Follow-up was median (IQR) 11.0 (8.0–14.0) years. Monotherapy-failure occurred in 72%–82%–75% and 79% for those randomised to chlorpropamide–glibenclamide–basal insulin or metformin respectively–after median 4.5 (3.0–6.6)–3.7 (2.6–5.6)–4.2 (2.7–6.5) and 3.8 (2.6– 5.2) years. Time-to-monotherapy-failure was predicted primarily by HbA_{1c} and BMI values–with other risk factors varying by type of monotherapy–with predictions to within ±2.5 years for 55%–60%–56% and 57% of the chlorpropamide–glibenclamide–basal insulin and metformin monotherapy cohorts respectively.

Conclusions Post one-year glycaemic durability can be predicted robustly in individuals with newly-diagnosed T2D who achieve $HbA_{1c\ values}$ <7.5% one year after commencing traditional monotherapies. Such information could be used to help guide glycaemic management for individual patients.

Abbreviations

AFT	Accelerated failure time
CC	Complete case
eGFR	Estimated glomerular filtration rate
FPG	Fasting plasma glucose
MDRD	Modification of Diet in Renal Disease
MICD	Multiply-imputed complete data
T2D	Type 2 diabetes mellitus
UKPDS	UK Prospective Diabetes Study

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Introduction

The ADA/EASD Position Statement for the management of hyperglycaemia in type 2 diabetes (T2D) recommends a patient-centred approach to identifying the most appropriate glucose-lowering therapy for a given individual.[1] However–no specific guidance is provided as to how best to select the most durable glycaemic agent for any one individual. One strategy which could help make the most effective use of available glucose-lowering therapies is to target treatment to those who are most likely to respond to therapy–an approach known as stratified–or precision medicine.[2]

At a population level–mean HbA_{1c} levels in people with newly-diagnosed T2D decrease initially with therapy and then rise over time–necessitating multiple glucose-lowering therapies.[3] This biphasic pattern is sometimes referred to as the “Nike Curve” as it resembles the Nike "swoosh" trademark. While substantial research has been published investigating potential predictors of initial response to glucose lowering therapy–whether durability of individual therapies varies by participant characteristics and can be predicted has not been previously investigated. The MRC/APBI funded STratification and Extreme Response Mechanism IN Diabetes (MASTERMIND) consortium felt that the biphasic glucose curve in T2D would best be modelled by addressing the initial glycaemic drop with therapy and then–separately–its subsequent rise. This paper examines the development of models that predict the rise in glucose values during the second upward phase–taking into account the first-year response. Individual patient upward HbA_{1c} trajectories are difficult to predict given their often apparently random variation–although a DIRECT study of the clinical and genetic determinants of glycaemic progression in patients with T2D suggested that increased triglyceride and low HDL-cholesterol levels were independently associated with an increased rate of progression of diabetes.[4] In clinical practice, however, it remains unclear at an individual patient level which factors most affect durability of glycaemic response to glucose-lowering therapies.

Potential predictors were investigated for the post one-year glycaemic durability of the glucose-lowering monotherapies allocated at random as first-line therapy to patients with

newly-diagnosed T2D enrolled into the UK Prospective Diabetes Study (UKPDS).[5] UKPDS participants were assigned at random to monotherapy with chlorpropamide, glibenclamide, basal insulin or metformin (only if >120% ideal body weight). In those who achieved acceptable HbA_{1c} values at one year, we sought to predict the time at which their glycaemic control would worsen to the point when the addition of second-line glucose-lowering therapy would likely be indicated by many guidelines.

Subjects

We used data from UKPDS patients. Details of UKPDS recruitment, inclusion and exclusion criteria, protocol and trial results have been published.[5-7] Briefly, patients with newly-diagnosed T2D who were allocated to the UKPDS intensive glucose control arm were randomised to first-line glucose-lowering monotherapy with chlorpropamide (a first-generation sulfonylurea), glibenclamide (a second generation sulfonylurea), basal insulin or metformin (only if >120% ideal body weight). The aim of the intensive glucose control arm was to achieve and maintain fasting plasma glucose (FPG) levels <6.0 mmol/l by increasing monotherapy doses as necessary to the maximum permitted or tolerated, based on 3-monthly FPG measurements. Glycaemic rescue, with the addition of a second protocol-specified glucose-lowering agent, was only permitted if repeated FPG values were >15.0 mmol/l or if hyperglycaemic symptoms had become unacceptable. The participants selected for this study were those at one-year who remained on their allocated monotherapy, had an HbA_{1c} <7.5% (<59 mmol/mol) at 1 year, and who had the requisite analytic data available.

Materials and Methods

For the purposes of this analysis monotherapy failure, *i.e.* the need for a second line glucose-lowering therapy, was defined as an HbA_{1c} ≥7.5% (≥59 mmol/mol) or the UKPDS protocol-driven requirement for glycaemic rescue. Post one-year time-to-monotherapy-failure times were calculated as the interval between the one-year visit and the time when either of the indications for monotherapy failure were met. As HbA_{1c} values were only

measured annually,[5] we used linear interpolation to estimate time points between visits when values likely became ≥7.5% (≥59 mmol/mol).

The two outcomes of interest for each monotherapy were: 1) The median post one-year time-to-monotherapy-failure; 2) The degree to which this time point could be predicted from the one-year demographic, phenotypic and laboratory data available. We developed a BASIC model using only those variables likely to be available in routine clinical practice, *i.e.* HbA_{1c}, age, sex, ethnicity, smoking, body mass index (BMI), plasma creatinine, total cholesterol, LDL-cholesterol (LDL-C), HDL-cholesterol (HDL-C), plasma triglycerides and estimated glomerular filtration rate (eGFR), and an EXTENDED model that included additional variables collected as part of the UKPDS protocol, *i.e.* fasting plasma glucose (FPG), fasting plasma insulin (FPI), HOMA2_%B, HOMA2_%S and urinary creatinine.

Statistical Analysis

Complete case (CC) and multiple-imputed complete data (MICD) datasets were used to construct the BASIC and the EXTENDED models, with missing data imputed by multiple imputation function in R (aregImpute). The mechanisms and patterns of missing data were investigated by employing further R functions (naclus and naplot) for a cluster analysis investigating missing values status and graphical representation of missing patterns. CC and MICD datasets from each monotherapy cohort were used to develop models and validated using a bootstrapping procedure. MICD sensitivity analyses were used to check that any missing data did not bias complete case model estimates. HOMA2_%B and HOMA2_%S values were derived from FPG and FPI levels using the HOMA2 Calculator,[8] and eGFR values were calculated using the Modification of Diet in Renal Disease (MDRD) formula.[9]

Univariate accelerated failure time (AFT) regression modelling was used to investigate the relationship between variables measured at one year and the subsequent time-to-monotherapy-failure, based on a log-logistic three-parameter distribution. We optimised potential associations by examining alternative distributions, *e.g.* log, square, square root, *etc*., and the best fit with the simplest form for clinical interpretation chosen. A

statistical significance level of p≤0.1 was used in univariate AFT regression analyses to select which variables would be included in multivariate AFT regression analyses.

A multivariable AFT regression was performed in separate prognostic models for each monotherapy cohort to assess independent associations between one-year covariates and subsequent time-to-monotherapy-failure. The final model variables were decided by backward selection procedures during which individual model outputs (regression coefficients, p-values, Akaike information criterion (AIC), Bayesian information criterion (BIC), and log likelihood value were monitored. All models were validated internally for their discrimination and predictive abilities using bootstrap sampling. In addition, the relative performance of the basic and extended models was evaluated by comparing their estimated information criteria (AIC and BIC).

All statistical analyses were performed with Regression Modelling Strategies (RMS) Package (Version 5.0-0, 2016-10-31), R-3.4.3 for Windows (Copyright© 2015, The R Foundation for Statistical Computing) and STATA version 15.0 (StataCorp LP 4905 Lakeway Drive College Station, Texas 77845-4512 USA).

Results

Of the 5102 patients enrolled into the UKPDS, 2110 (41%) were included in the MICD dataset who fulfilled our criteria for this analysis and who had achieved an HbA1c <7.5% (<59 mmol/mol) at one year. They had been assigned at random to chlorpropamide (N=573, 27%), glibenclamide (N=462, 22%), basal insulin (N=828, 39%) or metformin (N=247, 18%) with a median (IQR) post one-year follow-up of 11.0 (8.0, 14.0) years (**Supplementary Appendix Fig. S1)**. There were too few patients allocated to glipizide (N=170) in UKPDS Glucose Study II[5] to be included in this analysis. **Table 1** lists the one-year variables utilised, their summary statistics, the proportions of missing data and the modelling approaches used. There were no missing values for age, sex, race or smoking, whilst the proportions of missing data for total cholesterol, LDL-C, HDL-C, triglycerides, creatinine,

fasting plasma glucose, insulin, eGFR, HOMA2_%B and HOMA2_%S ranged from 9% to 27%.

In the MICD data set, post one-year monotherapy-failure occurred in 76% (1607/2110) participants, comprising 72% (415/573) for chlorpropamide, 82% (378/462) for glibenclamide, 75% (620/828) for basal insulin, and 79% (194/247) for metformin. The overall proportion of these participants requiring glycaemic rescue *per* protocol was 4.7% (99/2110), being 7.7% (44/573) for chlorpropamide, 9.7% (45/462) for glibenclamide, 0.2% (2/828) for basal insulin and 3.2% (8/247) for metformin.

The number of patients in the complete case data set was 1438 (82% of the MICD dataset) with the proportions randomised to each glucose-lowering monotherapy being 70% (399/573) for chlorpropamide, 67% (318/462) for glibenclamide, 67% (557/828) for basal insulin and 66% (164/247) for metformin.

BASIC model predictors of time-to-monotherapy-failure using routinely available data

Overall, the median (IQR) time-to-monotherapy-failure was 4.0 (2.0, 8.0) years. This time differed by monotherapy being 4.5 (3.0, 6.6) years for chlorpropamide, 3.7 (2.6, 5.6) years for glibenclamide, 4.2 (2.7, 6.) years for basal insulin and 3.8 (2.6, 5.2) years for metformin. In univariate analyses, time-to-monotherapy-failure increased with higher age, lower BMI, male sex and being White Caucasian. (**Supplementary Appendix Table S1**).

In the CC multivariate BASIC model, one-year HbA_{1c} and BMI were predictive factors for all monotherapies, with higher values associated with a shorter time-to-monotherapy-failure (**Table 2**). Additional factors by monotherapy cohort were: chlorpropamide (age, sex, ethnicity, smoking, LDL-C and triglycerides; glibenclamide (age and triglycerides); basal insulin (age, total cholesterol and HDL-C); metformin (none). The magnitude and direction of the different effect sizes are listed in **Table 2** as failure time ratios with 95% confidence limits. The findings for the equivalent BASIC MICD multivariate model analyses were all similar (**Supplementary Appendix Table S2**).

EXTENDED model predictors of time-to-monotherapy-failure

The median time-to-monotherapy-failure predicted by the *extended* model with additional variables for each monotherapy cohort was 4.7 (3.0, 6.9) years for chlorpropamide, 4.0 (2.6, 6.0) years for glibenclamide, 3.9 (2.6, 6.1) years for insulin, and 3.8 (2.6, 5.2) years for metformin. (**Table 2**).

In the CC multivariate EXTENDED model, one-year HbA_{1c} and BMI were predictive factors for all monotherapies, with higher values of both associated with a shorter time-to-monotherapy-failure. Additional factors by monotherapy cohort were: chlorpropamide (age, ethnicity, smoking, LDL-C, FPG and HOMA2_%B); glibenclamide (age, ethnicity and FPG); basal insulin (age, smoking, FPI, HOMA2_%B and HOMA2_%S); metformin (none). The magnitude and direction of the different effect sizes are listed in **Table 2**. The findings for the equivalent EXTENDED model MICD analyses were all similar (**Supplementary Appendix Table S2**).

The results of the internal validation, the discrimination and calibration bootstrap corrected indices (Nagelkerke R^2, Somers' D[Dxy], and shrinkage factor [Slope]) are shown in **Table 2**. The discrimination indices, R^2 and Dxy, range from 15.0%–29.3% and 0.3058-0.4062 across cohorts and models, respectively. The bootstrap corrected slopes were greater than 90% across cohorts and models. Similar results were obtained for the MICD models (**Supplementary Appendix Table S2**).

The smaller AIC and BIC values for the *extended* models show that they fit the data better for all the monotherapies than the *basic* models, except for metformin.

Predictive equations

The predictive equations for individual patient time-to-monotherapy-failure derived from the BASIC and EXTENDED models are shown in **Supplementary Appendix Figures S2 and S3** respectively. The performance of these equations for the BASIC and EXTENDED models are depicted in **Fig. 1 and Supplementary Appendix Fig. S4**, comparing the differences

between predicted and observed time-to-monotherapy-failure with the observed time-to-monotherapy-failure for each monotherapy cohort. For the BASIC model, the post one-year time-to-monotherapy-failure was predictable to within ±2.5 years for 55%, 60%, 56% and 57% of individuals allocated to chlorpropamide, glibenclamide, basal insulin and metformin monotherapy respectively. The corresponding proportions for the EXTENDED model were 56%, 61%, 59% and 57% respectively.

Median time-to-monotherapy-failure predictions, calculated for each monotherapy for five example patients using the BASIC model, are illustrated in **Table 3**, showing a different rank order for monotherapy durability depending on patient's one-year characteristics. The equivalent predictions for the EXTENDED models are shown in **Supplementary Appendix Fig. S5**.

Discussion

These analyses show that the post one-year durability of glycaemic control for the majority of individuals with newly-diagnosed T2D who have an HbA_{1c} <7.5% one year after commencing treatment with chlorpropamide, glibenclamide, basal insulin or metformin monotherapies, can be estimated to within ±2.5 years for around half of the patients in each monotherapy cohort. Application of the predictive equations showed that a hierarchy of glycaemic durability can be derived using routinely available clinical information. Such information could be used in the management of tyT2D to help guide therapeutic choices for individual patients.

It is of interest that for most of the monotherapies studied it is largely the same factors that predict glycaemic durability, with a lower one-year HbA_{1c}, lower one-year BMI and higher age of diabetes diagnosis onset favouring greater durability. This fits with the previous paper by Zhou *et al* [4] that showed higher BMI, HbA_{1c} and a younger age of diagnosis were associated with more rapid progression to insulin. A key finding of our study is that these factors have a different quantitative impact on different therapies explaining why there is overall a difference in durability between therapies. Previous studies have

compared glycaemic durability with different agents [11] but have not examined the factors which are predictive for individuals.

The strengths of these analyses include the randomised allocation of therapies from diagnosis of T2D and the unusually long follow-up period as a consequence of the UKPDS protocol requirement for glycaemic rescue only when FPG values became >15.0 mmol/l or hyperglycaemic symptoms became unacceptable. Limitations include the lack of data for other indicators possibly related to the modes of action of the therapies examined, *e.g.* fasting and postprandial C-peptide levels which were not collected in the UKPDS, as well as the relatively small sample sizes. The proportions of missing data could also be a concern but these were either missing completely at random, or missing at random, with the MICD sensitivity analyses showing no evidence of missing data biasing the results. The two sulfonylureas (chlorpropamide and glibenclamide) analysed here are no longer recommended in routine clinical practice but the methodology we have used could be applied to more contemporaneous datasets to estimate the likely durability of newer glucose-lowering agents.

Routinely available phenotypic and laboratory data in people with newly-diagnosed T2D, who have achieved an HbA_{1c} <7.5% (<59 mmol/mol) on monotherapy with chlorpropamide, glibenclamide, basal insulin or metformin at one year after diagnosis, can be used to estimate the likely glycaemic durability of continued monotherapy. Such information could be used to help guide individualised patient management.

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Duality of Interest.

No potential conflicts of interest relevant to this article were reported.

Author Contributions.

O. F. A. and R.R.H conceived the study and wrote the manuscript.

O. F. A. and R.L.C carried out the analyses.

O. F. A., R.L.C., A.T.H., A.G.J., E.R.P., B.M.S. and R.R.H contributed to the discussion and reviewed or edited the manuscript.

R.R.H. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Figure Legend

Fig. 1. Comparison of the differences between the complete case *basic* model predicted and the observed time-to-monotherapy-failure (observed minus predicted), with the observed time-to-monotherapy-failure. Panel A: Chlorpropamide, Panel B: Glibenclamide, Panel C: Basal insulin, Panel D: Metformin. The dotted horizontal lines depict ±2.5 years.

Table 1. Variables included in the *basic* and *extended* models.

Variable	Summary statistics*	Number with missing data n (%) Chlorpropamide [573]	Glibenclamide [462]	Insulin [828]	Metformin [247]	Modelling methodology
HbA_{1c} (%)	5.9 (0.8)	573 (0%)	462 (0%)	828 (0%)	247 (0%)	Linear
Age (years)	54 (47.859.7)	573 (0%)	462 (0%)	828 (0%)	247 (0%)	Categorical
Sex		573 (0%)	462 (0%)	828 (0%)	247 (0%)	Categorical
Male	1128 (61.3%)					
Female	712 (38.7%)					
Ethnicity		573 (0%)	462 (0%)	828 (0%)	247 (0%)	Categorical
Caucasian	1554 (84.5%)					
Non-Caucasian	286 (15.5%)					
Smoking		573 (0%)	462 (0%)	828 (0%)	247 (0%)	Categorical
Non-Smoker	640 (34.8%)					
Ex-Smoker	647 (35.2%)					
Smoker	553 (30.0%)					
BMI (kg/m^2)	27.3 (24.7–30.8)	521 (9%)	409 (11%)	751 (9%)	214 (13%)	Logarithm
Plasma creatinine (µmol/L)	83.8 (17.2)	444 (23%)	370 (20%)	645 (22%)	189 (23%)	Linear
Total cholesterol (mmol/L)	5.4 (1.1)	439 (23%)	353 (24%)	632 (24%)	179 (28%)	Linear
LDL-cholesterol (mmol/L)	3.5 (1)	433 (24%)	347 (25%)	616 (26%)	175 (29%)	Linear
HDL-cholesterol (mmol/L)	1.1 (0.3)	434 (24%)	350 (24%)	623 (25%)	176 (29%)	Linear
Plasma triglycerides (mmol/L)	1.5 (1.1–2.1)	436 (24%)	345 (25%)	624 (25%)	181 (27%)	Logarithm
eGFR ($ml/min/1.73m^2$)	79.5 (18.1)	444 (23%)	370 (20%)	645 (22%)	189 (23%)	Linear
Extended Model (additional variables)						
Fasting plasma glucose (mmol/l)	6.8 (1.5)	516 (10%)	407 (12%)	747 (10%)	212 (14%)	Linear
Fasting plasma insulin (mu/l)	13.9 (9.6–19.6)	440 (23%)	355 (23%)	618 (25%)	183 (26%)	Logarithm
HOMA2_%B	80.9 (57.8–112.3)	430 (25%)	349 (24%)	601 (27%)	180 (27%)	Logarithm
HOMA2_%S	53.5 (37.8–76.2)	430 (25%)	349 (24%)	601 (27%)	180 (27%)	Logarithm
Urinary creatinine (µmol/l)	10.3 (5.9)	447 (22%)	365 (21%)	640 (23%)	189 (23%)	Linear

**Summary statistics are mean (SD) or median (IQR) for continuous variables, and number (%) for categorical variables*

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Table 2. Complete case (CC) multivariate analyses showing monotherapy failure time ratios and 95% confidence intervals.

	Chlorpropamide		Glibenclamide		Insulin		Metformin	
Basic Model Variables	**TR [95% CI]**	**P-Value**	**TR [95% CI]**	**P-Value**	**TR [95% CI]**	**P-Value**	**TR [95% CI]**	**P-Value**
HbA_{1c} (%)	0.65 [0.57–0.74]	0.000	0.56 [0.49–0.65]	0.000	0.54 [0.48–0.61]	0.000	0.56 [0.46–0.69]	0.000
Age (years)								
<40	1		1		1		1	
40-44	1.32 [0.82–2.14]	0.256	1.45 [0.76–2.77]	0.254	1.17 [0.71–1.93]	0.536	-	-
45-49	1.39 [0.88–2.20]	0.160	1.58 [0.86–2.88]	0.139	1.10 [0.70–1.72]	0.694	-	-
50-54	1.68 [1.12–2.52]	0.012	1.89 [1.05–3.40]	0.035	1.56 [1.00–2.42]	0.049	-	-
55-59	1.60 [1.07–2.40]	0.023	2.06 [1.15–3.69]	0.015	1.81 [1.16–2.82]	0.009	-	-
60-64	1.95 [1.30–2.91]	0.001	2.14 [1.21–3.80]	0.009	1.99 [1.27–3.11]	0.003	-	-
>64	2.02 [1.15–3.53]	0.014	2.31 [1.15–4.66]	0.019	1.82 [1.09–3.05]	0.022	-	-
Sex								
Male	1		1		1		1	
Female	1.18 [0.95–1.48]	0.136	-	-	-	-	-	-
Race								
Caucasian	1		1		1		1	
Non-Caucasian	0.71 [0.53–0.94]	0.016	-	-	-	-	-	-
Smoking								
Non-Smoker	1		1		1		1	
Ex-Smoker	1.36 [1.04–1.79]	0.027	-	-	-	-	-	-
Smoker	0.97 [0.75–1.26]	0.838	-	-	-	-	-	-
Log BMI (kg/m^2)	0.27 [0.15–0.49]	0.000	0.24 [0.12–0.46]	0.000	0.37 [0.22–0.62]	0.000	0.31 [0.11–0.93]	0.037
Plasma creatinine (μmol/L)	-	-	-	-	-	-	-	-
Total cholesterol (mmol/L)	-	-	-	-	0.93 [0.86–1.02]	0.112	-	-
LDL-C (mmol/L)	0.90 [0.81–1.01]	0.067	-	-	-	-	-	-
HDL-C (mmol/L)	-	-	-	-	1.36 [0.96–1.92]	0.085	-	-
Log Triglycerides (mmol/L)	0.80 [0.65–1.00]	0.047	0.86 [0.70–1.06]	0.169	-	-	-	-
eGFR ($ml/min/1.73m^2$)	-	-	-	-	-	-	-	-
Information criteria								
AIC	1068.193		894.8231		1564.809		573.8394	
BIC	1013.907		1022.962		1512.145		573.8394	
Bootstrap internal validation corrected-index								
R^2	*0.1983*		*0.2359*		*0.2019*		*0.1503*	
Somers' Dxy	*0.3420*		*0.3655*		*0.3518*		*0.3058*	
Calibration slope	*0.9074*		*0.9377*		*0.9427*		*0.9948*	
Model estimated failure time Median[IQR]	*4.5 [3.0–6.6]*		*3.7 [2.6–5.6]*		*4.2 [2.7–6.5]*		*3.8 [2.6–5.2]*	

Extended Model Variables	-	-	-	-	-	-	-	-
HbA_{1c} (%)	0.71 [0.62–0.81]	0.000	0.65 [0.58–0.74]	0.000	0.56 [0.50–0.63]	0.000	0.56 [0.46–0.69]	0.000
Age (years)								
<40	1		1		1		1	
40-44	1.21 [0.76–1.91]	0.422	1.39 [0.80–2.42]	0.240	1.21 [0.75–1.95]	0.461	-	-
45-49	1.31 [0.85–2.03]	0.218	1.62 [0.97–2.70]	0.063	1.18 [0.77–1.82]	0.533	-	-
50-54	1.54 [1.04–2.26]	0.029	1.55 [0.94–2.55]	0.084	1.64 [1.08–2.51]	0.031	-	-
55-59	1.54 [1.04–2.26]	0.031	1.62 [0.99–2.65]	0.053	1.82 [1.19–2.77]	0.010	-	-
60-64	1.86 [1.26–2.74]	0.002	1.65 [1.02–2.68]	0.043	1.96 [1.28–3.01]	0.004	-	-
>64	1.77 [1.04–3.03]	0.037	1.66 [0.93–2.99]	0.089	1.88 [1.15–3.07]	0.019	-	-
Sex								
Male	1		1		1		1	
Female	-	-	-	-	-	-	-	-
Race								
Caucasian	1		1		1		1	
Non-Caucasian	0.70 [0.54–0.92]	0.010	0.69 [0.53–0.89]	0.005	-	-	-	-
Smoking								
Non-Smoker	1		1		1		1	
Ex-Smoker	1.15 [0.90–1.47]	0.269	-	-	0.91 [0.74–1.12]	0.399	-	-
Smoker	0.84 [0.66–1.07]	0.151	-	-	0.77 [0.63–0.95]	0.014	-	-
Log-BMI (kg/m^2)	0.26 [0.14–0.47]	0.000	0.26 [0.15–0.46]	0.000	0.41 [0.24–0.70]	0.001	0.31 [0.11–0.93]	0.037
Plasma creatinine (µmol/L)	-	-	-	-	-	-	-	-
Total cholesterol (mmol/L)	-	-	-	-	-	-	-	-
LDL-C (mmol/L)	0.92 [0.83–1.01]	0.088	-	-	-	-	-	-
HDL-C (mmol/L)	-	-	-	-	-	-	-	-
Log Triglycerides (mmol/L)	-	-	-	-	-	-	-	-
eGFR ($ml/min/1.73m^2$)	-	-	-	-	-	-	-	-
Fasting plasma glucose (mmol/l)	0.81 [0.74–0.88]	0.000	0.80 [0.75–0.86]	0.000				
Log HOMA2_%B	0.79 [0.61–1.04]	0.093	-	-	1.23 [1.01–1.50]	0.011	-	-
Log HOMA2_%S	-	-	-	-	1.44 [1.17–1.77]	0.033	-	
Urinary creatinine (µmol/l)	-	-	-	-	-	-	-	
Information criteria								
AIC	1133.0270		936.9738		1514.873		587.3033	
BIC	1078.3590		1071.0390		1576.360		587.3033	
Bootstrap internal validation corrected-index								
R^2	0.2463		0.2931		0.2251		0.1503	
Somers' Dxy	0.3640		0.4062		0.3675		0.3058	
Calibration slope	0.9273		0.9540		0.9434		0.9948	
Model estimated failure time								
Median[IQR]	4.7 [3.0–6.9]		4.0 [2.6–6.0]		3.9 [2.6–6.1]		3.8 [2.6–5.2]	

R^2 = Nagelkerke R^2 Somers' D = Dxy–Slope = shrinkage factor–AIC = Akaike information criterion–BIC = Bayesian information criterion

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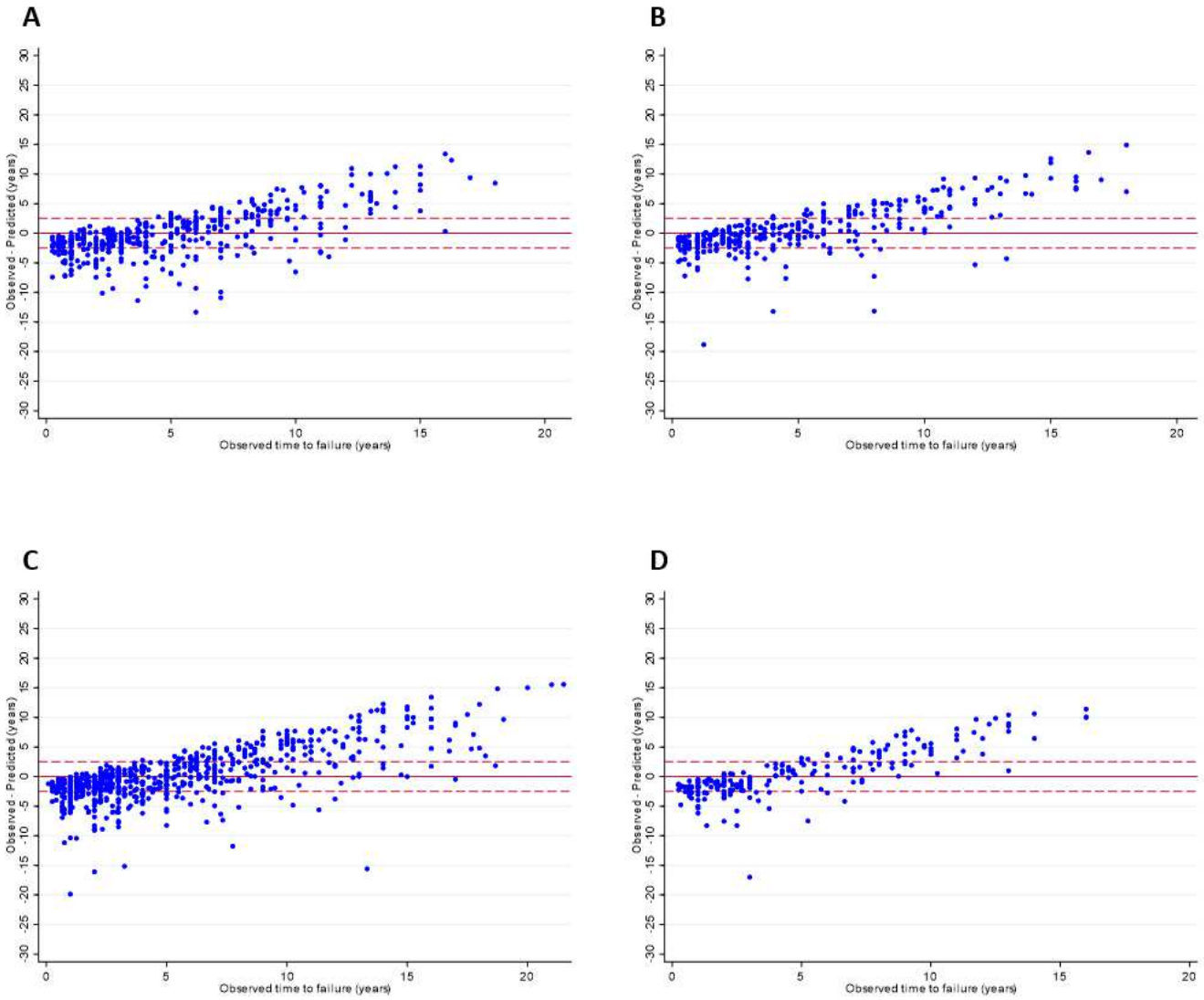
Table 3. Median time-to-failure (durability) calculated using the *basic* model equations and shown in rank order for six examplar cases.

	Case 1	**Case 2**	**Case 3**	**Case 4**	**Case 5**	**Case 6**
HbA_{1c} (%)	5.0	5.5	6	6.5	7	7.5
Age (years)	65	60	55	50	45	40
BMI (kg/m^2)	25.0	27.0	29.0	31.0	33.0	35.0
Sex	Male	Female	Male	Female	Male	Male
Race	Caucasian	Non Caucasian	Caucasian	Non Caucasian	Caucasian	Non Caucasian
Time-to-failure (years)						
	Chlorpropamide 13.1	Basal Insulin 8.3	Chlorpropamide 5.6	Chlorpropamide 3.6	Chlorpropamide 2.7	Chlorpropamide 1.6
	Basal Insulin 10.7	Chlorpropamide 7.7	Basal Insulin 5.0	Basal Insulin 3.0	Metformin 1.9	Metformin 1.4
	Glibenclamide 9.2	Metformin 5.8	Metformin 4.0	Metformin 2.8	Basal Insulin 1.4	Basal Insulin 1.1
	Metformin 8.5	Glibenclamide 5.7	Glibenclamide 3.7	Glibenclamide 2.4	Glibenclamide 1.3	Glibenclamide 0.9

354 **Fig. 1**


A
B
C
D
Observed - Predicted (years)
Observed time to failure (years)
-30
-25
-20
-15
-10
-5
0
5
10
15
20
25
30
0
5
10
15
20

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