

SUPPLEMENTARY MATERIAL

CONTENT

SUPPLEMENTARY SECTION 1: FURTHER DETAILS ON METHODS	2
SUPPLEMENTARY TABLES	6
Table A1: Baseline characteristics of patients with Type 2 diabetes used in analysis in deciles of GP practices based on percentage of patients achieving the HbA1c, total cholesterol and blood pressure targets.....	6
Table A2: Odds ratios from multivariable beta regression models for 10-year risks of mortality and first-occurrence of complications.....	7
Table A3: Proportional effects on health outcomes (LYs, QALYs) and complication costs from multivariable generalized linear regression models (Gaussian; log link).....	8
Table A4: Average effects of achieving each additional treatment target over Type 2 diabetes patient's lifetime	9
Table A5: Baseline characteristics of patients used in analysis, by number of treatment targets achieved	10
SUPPLEMENTARY FIGURES	11
Figure A1: Average impacts on 10-year risk of mortality and complications for patients with Type 2 diabetes in GP practice in the lowest performing decile following improvements in treatment target achievement rates.....	11
Figure A2: Average impacts on health outcomes and healthcare costs over 10 years per patient with Type 2 diabetes achieving one to three of the HbA1c, total cholesterol and blood pressure targets compared to achieving none	12
Figure A3: Average impacts on health outcomes and healthcare costs over lifetime per patient with Type 2 diabetes in GP practice in the lowest performing decile following improvements in treatment target achievement rates	13

SUPPLEMENTARY SECTION 1: FURTHER DETAILS ON METHODS

GP practices included in analysis

6609 (82%) out of 8021 GP practices across England and Wales submitted diabetes data for the 2015-2016 National Diabetes Audit (NDA).¹ The NDA GP practice-level summary data we received from Healthcare Quality Improvement Partnership (HQIP) consisted of data from 5900 GP practices (89% of practices which submitted), after excluding GP practices with low numbers of diabetes patients to ensure anonymity and confidentiality of patients. Finally, 5472 GP practices (83% of practices which submitted) with data in both the HQIP dataset and the published NDA dataset² were included for analysis.

Sampling hypothetical patients within each decile of GP practices by performance

The NDA GP practice-level summary data on baseline characteristics of patients with T2D was stratified by gender and history of IHD. This was with the exception of smoking status and ethnicity, which were aggregated at GP practice-level without stratification. The proportion of current smokers in each GP practice was assumed to be the same within each stratum. All patient characteristics were then summarised within each decile (approximately equal-sized groups based on achievement of all three treatment targets), stratified by gender and history of IHD, with GP practice-level summary characteristics weighted by the number of patients with T2D in each GP practice. For each decile, 2500 patients were sampled for each ethnicity (White Caucasian, Afro-Caribbean, and South Asians, as in the UKPDS) in each stratum. So a total of 30 000 patients (2 for gender X 2 for history of IHD X 3 for ethnicity X 2500 patients) were sampled for each decile. Ethnicity was sampled separately instead of proportionately within each stratum because ethnicity was an important predictor of several complications and mortality.³ Furthermore, the proportion of Afro-Caribbean and South Asians are often small, so heterogeneity between ethnic patients may not be well accounted for if they were sampled proportionately in each strata unless an even larger sample size is used.

For each patient, we first sampled duration of diabetes from a gamma distribution. A gamma distribution was chosen because duration of diabetes is bounded below by 0, which is about 1 standard deviation away from the mean. Further patient characteristics and risk factors were then sampled assuming multivariate normality using the Cholesky decomposition method to retain correlation.⁴ The full list of variables sampled can be found in Table S1 below. For characteristics required by the UKPDS-OM2 but not available from the NDA, we use the means and standard deviations obtained from the UKDPS patient data, stratified by gender and history of IHD, conditional on the sampled duration of diabetes. Correlation between variables are also obtained from the UKPDS patient data, stratified by gender and conditional on duration of diabetes. BMI, white blood cell count, and HbA1c which were found to be skewed in the UKPDS patient data were sampled on a log scale.

Table S1. List of patient characteristics sampled and source of summary statistics

Patient characteristic	Source	Note
Ethnicity	NDA	White Caucasian, Afro-Caribbean, and South Asians.
Gender	NDA	
Age	NDA	
Duration of diabetes	NDA	
Weight	NDA	BMI used instead (BMI used in the UKPDS-OM2 risk equations).
Height	-	
Atrial fibrillation	UKPDS	
Peripheral vascular disease	UKPDS	

Patient characteristic	Source	Note
Current smoker	NDA	
Albuminuria	NDA	
HDL cholesterol	UKPDS	
LDL cholesterol	NDA + UKPDS	Total cholesterol given in NDA; sampled values transformed into LDL cholesterol using linear equation describing relationship between total cholesterol and LDL cholesterol derived using UKPDS patient data.
Systolic blood pressure	NDA	
HbA1c	NDA	
Heart rate	UKPDS	
White blood count	UKPDS	
Haemoglobin	UKPDS	
eGFR	NDA	Creatinine given in NDA; eGFR calculated using the 186-MDRD equation (as in UKPDS).
History of complications		
Ischaemic heart disease	NDA	
Heart failure	UKPDS	
Blindness	UKPDS	
Renal failure	UKPDS	
Stroke	UKPDS	
Myocardial infarction	UKPDS	
Ulcer	UKPDS	

NDA, summary statistics provided in 2015-16 National Diabetes Audit data obtained from Healthcare Quality Improvement Partnership (HQIP); UKPDS, summary statistics obtained from UK Prospective Diabetes Study patient-level data. HDL, high-density lipoprotein; LDL, low-density lipoprotein; HbA1c, glycated haemoglobin; eGFR, estimated glomerular filtration rate; BMI, body mass index.

Simulating healthcare costs and health outcomes for sampled patients

Simulation was performed using the UKPDS-OM2. All risk factors were assumed to remain constant over lifetime of patients. 10 000 loops per patient were used to reduce stochastic error and to ensure convergence of event rates (particularly for low incidence events). 1000 bootstrap runs were performed to account for parameter uncertainty for lifetime costs, QALYs, and LYs.

Regression models

The regression models were estimated using only data on simulated patients with values of sampled continuous variables (current age, age at diagnosis, body mass index, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, systolic blood pressure (SBP), estimated glomerular filtration rate (eGFR), and glycated haemoglobin (HbA1c)) within the central 95% of respective distributions (Table S2). All subsequent analyses were performed in this subset of patients.

Table S2. Percentiles of continuous variables

Percentile	Min.	2.5%	25%	Median	75%	97.5%	Max.
Current age (years)	4.2	42.4	60.3	68.9	77.1	91.5	100.0
Age at diagnosis (years)	0.2	30.7	51.4	61.1	70.1	85.8	99.9
HbA1c (mmol/mol)	14.2	32.0	45.4	54.6	65.7	93.5	193.9
HDL cholesterol (mmol/L)	0.0	0.6	0.9	1.0	1.2	1.7	2.9
LDL cholesterol (mmol/L)	0.0	0.9	2.0	2.6	3.1	4.2	6.5
Systolic blood pressure (mm Hg)	53.7	103.8	122.4	132.1	141.9	160.8	212.4

Percentile	Min.	2.5%	25%	Median	75%	97.5%	Max.
eGFR (mL/min/1.73m ²)	14.8	30.6	50.2	68.2	96.4	175.0	200.0
Body mass index (kg/m ²)	11.4	20.4	26.5	30.3	34.6	45.2	80.0

HbA1c, glycated haemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; eGFR, estimated glomerular filtration rate. Values within the shaded area (central 95% percentile) retained for use in analysis.

Quantifying uncertainty

Due to the large sample size and the large number of Monte Carlo loops required, bootstrap runs are extremely computationally intensive. Hence, we only quantified uncertainties around lifetime costs, QALYs, and LYs to provide a gauge of the extent of uncertainty around these results. The regression models were re-fitted with each set of bootstrapped outcomes, and the within-bootstrap-variance and between-bootstrap-variance were combined using Rubin's rule.

Quantifying healthcare costs and health outcomes for different scenarios

To illustrate the absolute effects of achieving different numbers of treatment targets, we present three perspectives:

- (A) Outcome for individual patient by achieving different combinations of treatment targets:
Given an individual patient's defined characteristics and risk factor profile, we predict this patient's outcomes using the respective regression equations for achieving different combinations of treatment targets.
- (B) Average outcome per patient for patients with T2D across the NDA population by achieving different numbers/combinations of treatment targets:
For all patients used in the analysis, we predict the outcomes using the respective regression equations under different scenarios of achieving different treatment targets. The results are aggregated and weighted based on the distribution of patients by gender, history of IHD, and ethnicity, as well as by the distribution of patients achieving different combinations of treatment targets across the entire population observed in the NDA.
- (C) Average outcome from GP practice's perspective when different proportions of patients with T2D achieving different numbers/combinations of treatment targets:
Given a GP practice's distribution of patients achieving different combinations of treatment targets, the GP practice is assigned to its corresponding decile based on the percentage that achieves all three targets. For all sampled patients within the decile used in the analysis, we predict the outcomes using the respective regression equations under different scenarios of achieving different treatment targets. The results are aggregated and weighted based on the distribution of patients based on their gender, history of IHD, and ethnicity, as well as the distribution of patients achieving different combinations of treatment targets in the GP practice under different scenarios.

In the main analysis, we illustrated the average outcome per patient for patients with T2D across the NDA population by achieving different numbers of treatment targets (B), and the average outcome for GP practice in the lowest performing decile in different scenarios of performance (C). Assumptions were made with regards to the distribution of patients achieving different combinations of treatment targets (Table S3). The distribution was chosen subjected to information from the NDA on the total percentage of patients achieving individually each target and all the three targets under each scenario.

This constraint restricts the solution space from which the distribution can be chosen, and the results are robust to this choice.

Table S3. Assumptions on distribution of patients achieving each treatment target, by performance decile across GP practices

Decile of GP practice, by performance	01 (worst)	05	10 (best)	ALL
% achieving specified treatment target (assumed)				
No targets	8	7	1	5
One target only	20	10	12	13
HbA1c only	6	2	0	4
Total cholesterol only	11	3	0	2
Blood pressure only	3	5	12	7
Two targets only	45	44	33	42
HbA1c and total cholesterol only	15	15	15	15
HbA1c and blood pressure only	10	9	5	7
Total cholesterol and blood pressure only	20	20	13	20
All three targets	27	39	54	40
% achieving individually each target (from National Diabetes Audit)				
HbA1c	58	65	74	66
Total cholesterol	73	77	82	77
Blood pressure	60	73	84	74

HbA1c, glycated haemoglobin. Assumption on distribution of patients achieving each treatment target is made to match percentage of patients achieving individually each target and all three targets in the National Diabetes Audit.

The outcomes of achieving different combinations of treatment targets from the patient-level perspective (A) and from the GP practice-level perspective (C) presented above are implemented in the accompanying Excel workbook.

References

1. Health and Social Care Information Centre. National Diabetes Audit – 2015–2016 Audit Participation: Primary Care <https://digital.nhs.uk/data-and-information/publications/statistical/national-diabetes-audit/national-diabetes-audit-2015-2016-audit-participation-primary-care2016>. Accessed 03/05/2019.
2. Health and Social Care Information Centre. National Diabetes Audit Report 1, England – CCG/GP Level Spreadsheet 2014-16 <https://digital.nhs.uk/catalogue/PUB232412017>. Accessed 10/12/2017.
3. Hayes AJ, Leal J, Gray AM, et al. UKPDS outcomes model 2: a new version of a model to simulate lifetime health outcomes of patients with type 2 diabetes mellitus using data from the 30 year United Kingdom Prospective Diabetes Study: UKPDS 82. *Diabetologia* 2013;56(9):1925-33. doi: 10.1007/s00125-013-2940-y
4. Briggs A, Claxton K, Sculpher M. Decision Modelling for Health Economic Evaluation. Oxford: Oxford University Press 2006.

SUPPLEMENTARY TABLES

Table A1: Baseline characteristics of patients with Type 2 diabetes used in analysis in deciles of GP practices based on percentage of patients achieving the HbA1c, total cholesterol and blood pressure targets

Decile	01	02	03	04	05	06	07	08	09	10	ALL
Current age (years)	65.5 (10.6)	65.8 (10.4)	66.0 (10.6)	65.9 (10.4)	65.9 (10.4)	65.9 (10.3)	66.2 (10.4)	66.2 (10.5)	66.5 (10.4)	66.4 (10.3)	66.0 (10.4)
Duration of diabetes (years)	6.8 (6.1)	6.9 (6)	6.8 (6)	6.9 (6.1)	6.9 (6)	6.9 (5.9)	6.9 (6.1)	6.8 (6)	6.8 (6)	6.8 (6.1)	6.9 (6)
HbA1c (mmol/mol)	58.2 (14)	56.9 (13.5)	57.1 (13.7)	57.0 (13.5)	56.4 (13.8)	56.1 (13.3)	56.1 (13.4)	55.4 (13.2)	55.2 (13.1)	54.4 (12.8)	56.2 (13.5)
Total cholesterol (mmol/L)	4.4 (0.9)	4.3 (0.9)	4.3 (0.9)	4.3 (0.9)	4.3 (0.9)	4.3 (0.9)	4.3 (0.9)	4.3 (0.9)	4.2 (0.9)	4.2 (0.9)	4.3 (0.9)
Systolic blood pressure (mm Hg)	134.4 (12.8)	133.6 (12.6)	133.1 (12.4)	132.9 (12.4)	132.7 (12.3)	132.1 (12.1)	132.1 (12.2)	131.8 (12)	131.4 (11.6)	130.5 (11.6)	132.4 (12.3)
eGFR (mL/min/1.73m ²)	76.0 (31.6)	76.8 (32)	76.0 (31.4)	76.8 (31.5)	77.1 (32.1)	75.9 (31.2)	76.7 (31.1)	76.5 (31.3)	76.3 (31.2)	76.3 (31.6)	76.5 (31.5)
Body mass index (kg/m ²)	31.0 (5.4)	30.6 (5.3)	30.9 (5.4)	30.9 (5.4)	31.0 (5.4)	30.9 (5.4)	30.9 (5.3)	30.9 (5.3)	30.8 (5.4)	30.8 (5.4)	30.9 (5.4)
% Smoker	16.7	14.4	15.0	14.7	14.8	13.6	14.0	14.1	14.2	14.7	14.6
% Albuminuria	15.3	16.3	16.7	16.8	15.0	16.0	16.3	16.5	15.5	15.3	16.0
% of patients with history of complication											
Peripheral vascular disease	15.1	15.2	15.2	15.5	15.6	15.8	15.9	15.7	15.6	15.7	15.5
Atrial fibrillation	1.7	2.0	2.1	1.7	1.9	1.8	1.5	1.7	2.0	1.8	1.8
Myocardial infarction	6.4	5.9	5.5	6.5	6.3	6.3	6.5	6.2	6.4	5.9	6.2
Stroke	3.1	3.2	3.4	3.3	3.1	2.7	3.1	3.1	3.0	2.8	3.1
Heart failure	2.4	2.8	2.4	2.6	2.2	2.5	2.2	2.3	2.3	2.4	2.4
Blindness	3.1	3.1	3.4	3.3	3.3	3.2	3.2	3.3	3.3	3.0	3.2
Amputation	0.8	1.2	0.8	0.9	0.7	0.8	0.8	0.6	0.8	0.9	0.8
Ulcer	1.1	1.2	1.4	1.0	1.2	1.2	0.9	1.3	1.0	1.0	1.1
Renal failure	0.5	0.5	0.6	0.5	0.6	0.6	0.5	0.4	0.4	0.4	0.5

HbA1c, glycated haemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; eGFR, estimated glomerular filtration rate. Analysis dataset includes only sampled patients with continuous variables within 95% of sampled distribution. Equal number of patients sampled within each strata of gender, history of ischaemic heart disease, and ethnicity; these characteristics are thus not tabulated here.

Table A2: Odds ratios from multivariable beta regression models for 10-year risks of mortality and first-occurrence of complications

Targets achieved	Deaths	Macrovascular outcomes				Microvascular outcomes			
	CV Death	Myocardial infarction	Stroke	Heart failure	Other IHD	Blindness	Amputation	Ulcer	Renal failure
<i>None (Reference)</i>	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
HbA1c only	0.882	0.826	0.852	1.043	1.039	0.731	0.673	0.751	1.023
CHOL only	0.831	0.859	0.850	0.906	0.794	1.025	1.068	1.044	0.758
BP only	0.880	0.926	0.715	1.047	0.930	0.907	0.906	1.046	0.864
HbA1c & CHOL only	0.731	0.703	0.723	0.939	0.810	0.752	0.712	0.788	0.760
HbA1c & BP only	0.788	0.762	0.615	1.081	0.957	0.663	0.598	0.781	0.879
CHOL & BP only	0.720	0.785	0.602	0.947	0.723	0.927	0.943	1.091	0.646
All three	0.639	0.640	0.515	0.971	0.733	0.680	0.631	0.817	0.652

CV death, cardiovascular-related death; IHD, ischemic heart disease; HbA1c, glycated haemoglobin; CHOL, cholesterol; BP, blood pressure. For macro- and micro-vascular outcomes, models fitted using only patients who do not have history of respective complications (i.e. risk model for stroke fitted using patients who do not have history of stroke). All models are further adjusted for all other covariates (excludes HbA1c, cholesterol, and blood pressure) used in the UKPDS risk equations.

Table A3: Proportional effects on health outcomes (LYs, QALYs) and complication costs from multivariable generalized linear regression models (Gaussian; log link)

(A) 10-year

Targets achieved	Health outcomes		Total complication costs (£)
	LYs	QALYs	
<i>None (Reference)</i>	1.000	1.000	1.000
HbA1c only	1.015	1.020	0.962
CHOL only	1.020	1.023	0.975
BP only	1.020	1.024	0.972
HbA1c & CHOL only	1.036	1.044	0.947
HbA1c & BP only	1.032	1.039	0.957
CHOL & BP only	1.040	1.047	0.956
All three	1.053	1.062	0.943

(B) Lifetime

Targets achieved	Health outcomes				Total complication costs (£)	
	LYs		QALYs			
<i>None (Reference)</i>	1.000		1.000		1.000	
HbA1c only	1.035	(1.023, 1.047)	1.042	(1.029, 1.056)	0.975	(0.966, 0.984)
CHOL only	1.046	(1.031, 1.061)	1.049	(1.033, 1.065)	0.992	(0.983, 1.001)
BP only	1.038	(1.027, 1.050)	1.043	(1.031, 1.055)	0.980	(0.971, 0.989)
HbA1c & CHOL only	1.085	(1.065, 1.105)	1.095	(1.073, 1.117)	0.974	(0.963, 0.985)
HbA1c & BP only	1.070	(1.054, 1.086)	1.080	(1.063, 1.097)	0.976	(0.965, 0.987)
CHOL & BP only	1.087	(1.068, 1.106)	1.095	(1.075, 1.115)	0.982	(0.970, 0.994)
All three	1.120	(1.097, 1.144)	1.133	(1.108, 1.158)	0.976	(0.962, 0.990)

LYs, years of life; QALYs, quality adjusted life years; HbA1c, glycated haemoglobin; CHOL, cholesterol; BP, blood pressure. All models are further adjusted for all covariates (excludes HbA1c, cholesterol, and blood pressure) used in the UKPDS risk equations. 95% confidence intervals are included only for lifetime health outcomes and complication costs, and further details on this can be found in the Supplementary Section 1.

Table A4: Average effects of achieving each additional treatment target over Type 2 diabetes patient's lifetime

Outcome	No. of targets achieved	Effects with each additional target achieved
QALYs	1 vs 0	0.49 (0.38, 0.61)
	2 vs 1	0.55 (0.31, 0.79)
	3 vs 2	0.46 (0.11, 0.82)
LYs	1 vs 0	0.55 (0.41, 0.69)
	2 vs 1	0.65 (0.36, 0.94)
	3 vs 2	0.53 (0.10, 0.96)
Total cost (£)	1 vs 0	-859 (-1165, -553)
	2 vs 1	81 (-225, 387)
	3 vs 2	97 (-358, 552)

LYs, years of life; QALYs, quality adjusted life years.

Table A5: Baseline characteristics of patients used in analysis, by number of treatment targets achieved

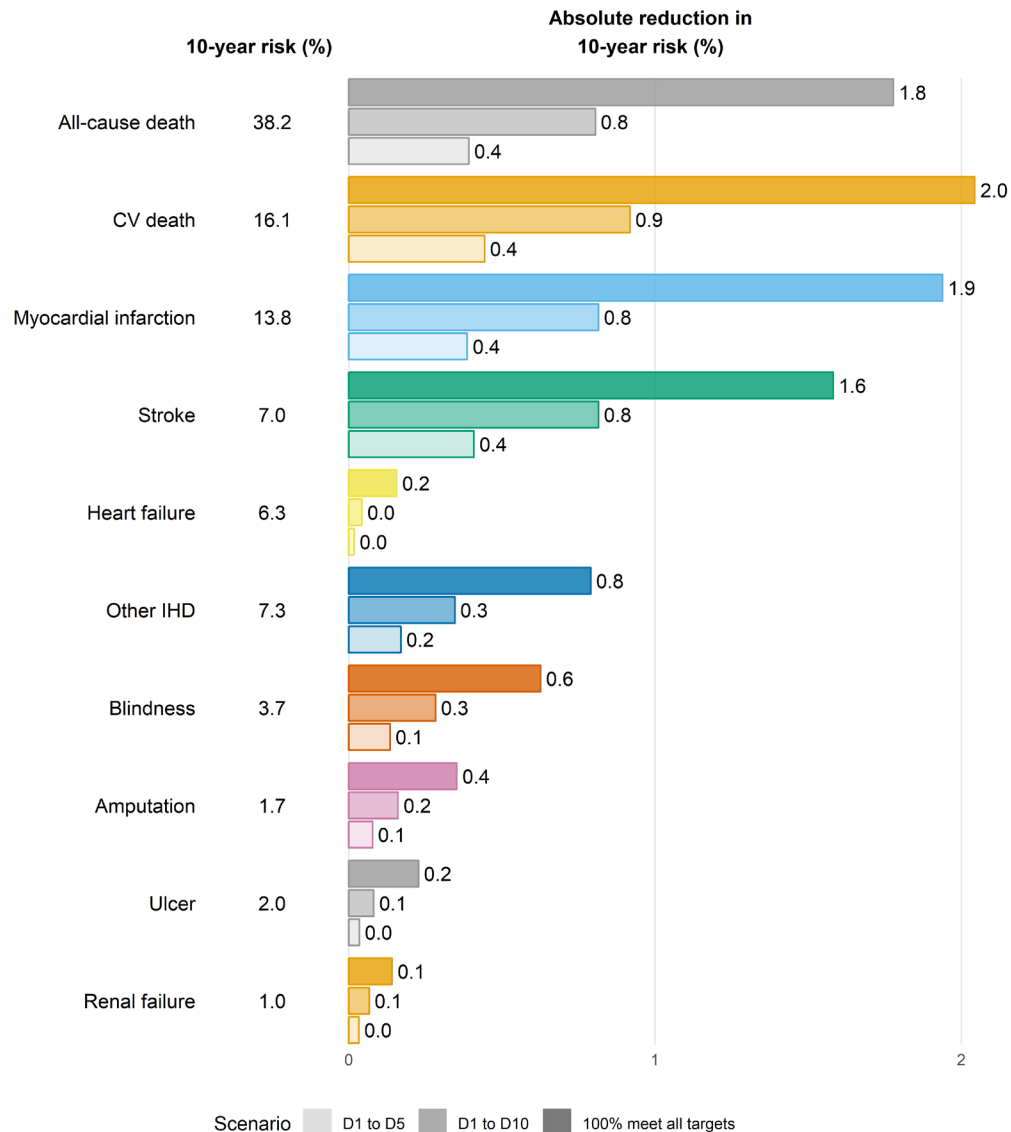
Number of targets achieved	0	1	2	3
Current age (years)	68.1 (9.8)	66.9 (10.5)	65.8 (10.6)	65.6 (10.2)
Duration of diabetes (years)	7.0 (6.3)	6.9 (6)	6.8 (5.9)	6.9 (6.1)
HbA1c (mmol/mol)	69.5 (8.7)	64.3 (12.7)	58.4 (13.7)	47.1 (6.7)
Total cholesterol (mmol/L)	5.5 (0.4)	4.9 (0.9)	4.2 (0.9)	3.9 (0.7)
Systolic blood pressure (mm Hg)	147.4 (5.4)	139.4 (12.1)	132.5 (12.4)	126.7 (8.6)
eGFR (mL/min/1.73m ²)	73.3 (31.8)	74.0 (30.7)	76.7 (31.6)	77.9 (31.8)
Body mass index (kg/m ²)	32.5 (5.5)	31.6 (5.5)	30.9 (5.4)	30.1 (5.2)
% Smoker	14.4	15.2	15.0	13.7
% Albuminuria	26.5	20.8	16.4	11.6
% of patients with history of complication				
Peripheral vascular disease	21.1	18.0	15.8	13.2
Atrial fibrillation	1.4	1.9	1.8	1.8
Myocardial infarction	6.8	6.6	6.1	5.9
Stroke	3.3	3.4	3.1	3.0
Heart failure	2.4	2.2	2.4	2.5
Blindness	3.8	3.5	3.2	3.1
Amputation	0.7	0.9	0.8	0.9
Ulcer	1.5	1.3	1.2	0.9
Renal failure	0.6	0.6	0.5	0.4

Values presented are means (SD) or percentages. HbA1c, glycated haemoglobin; eGFR, estimated glomerular filtration rate.

Analysis dataset includes only sampled patients with continuous variables within 95% of sampled distribution. Equal number of patients sampled within each strata of gender, history of ischaemic heart disease, and ethnicity; these characteristics are thus not tabulated here.

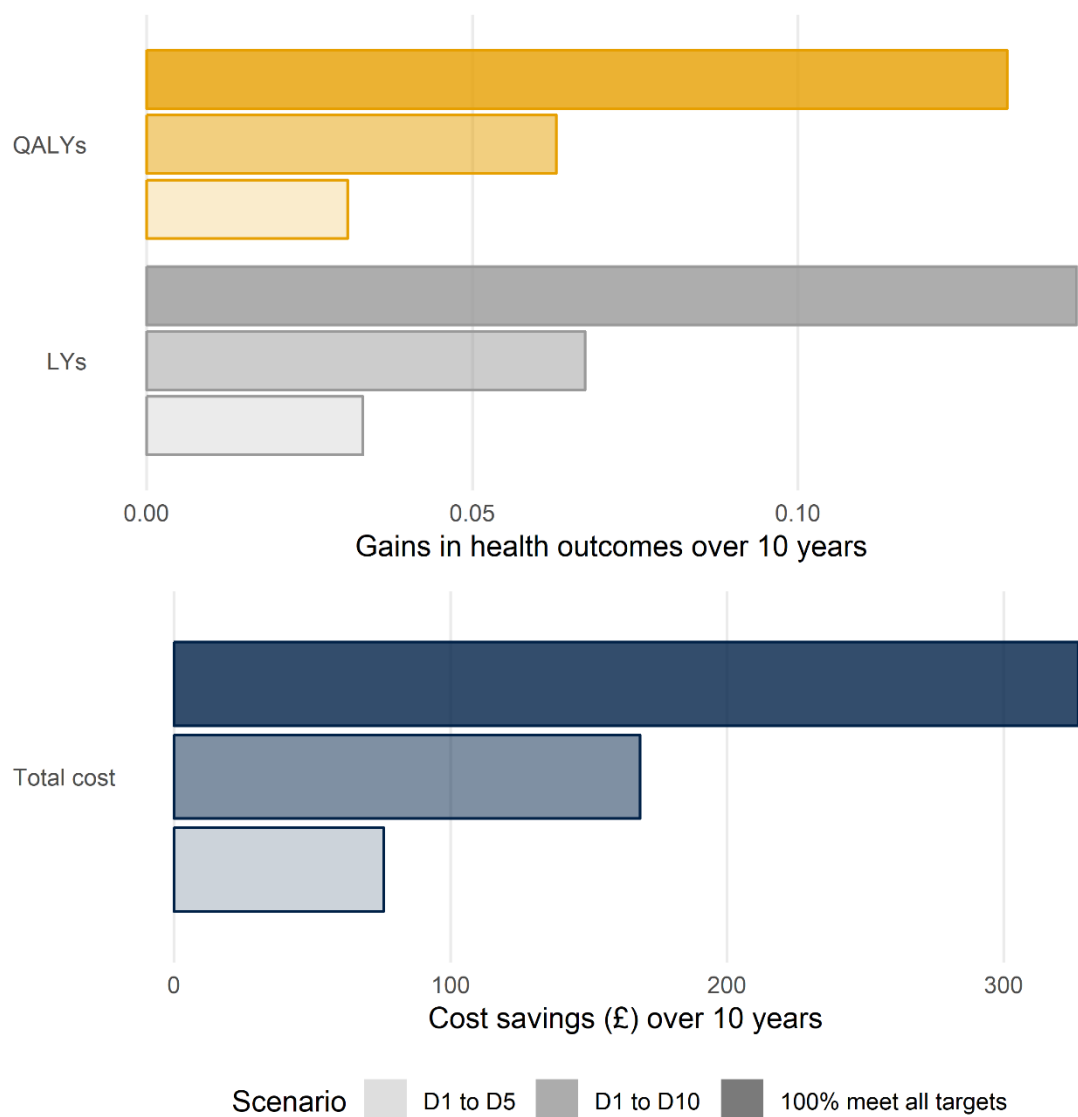
SUPPLEMENTARY FIGURES

Figure A1: Average impacts on 10-year risk of mortality and complications for patients with Type 2 diabetes in GP practice in the lowest performing decile following improvements in treatment target achievement rates



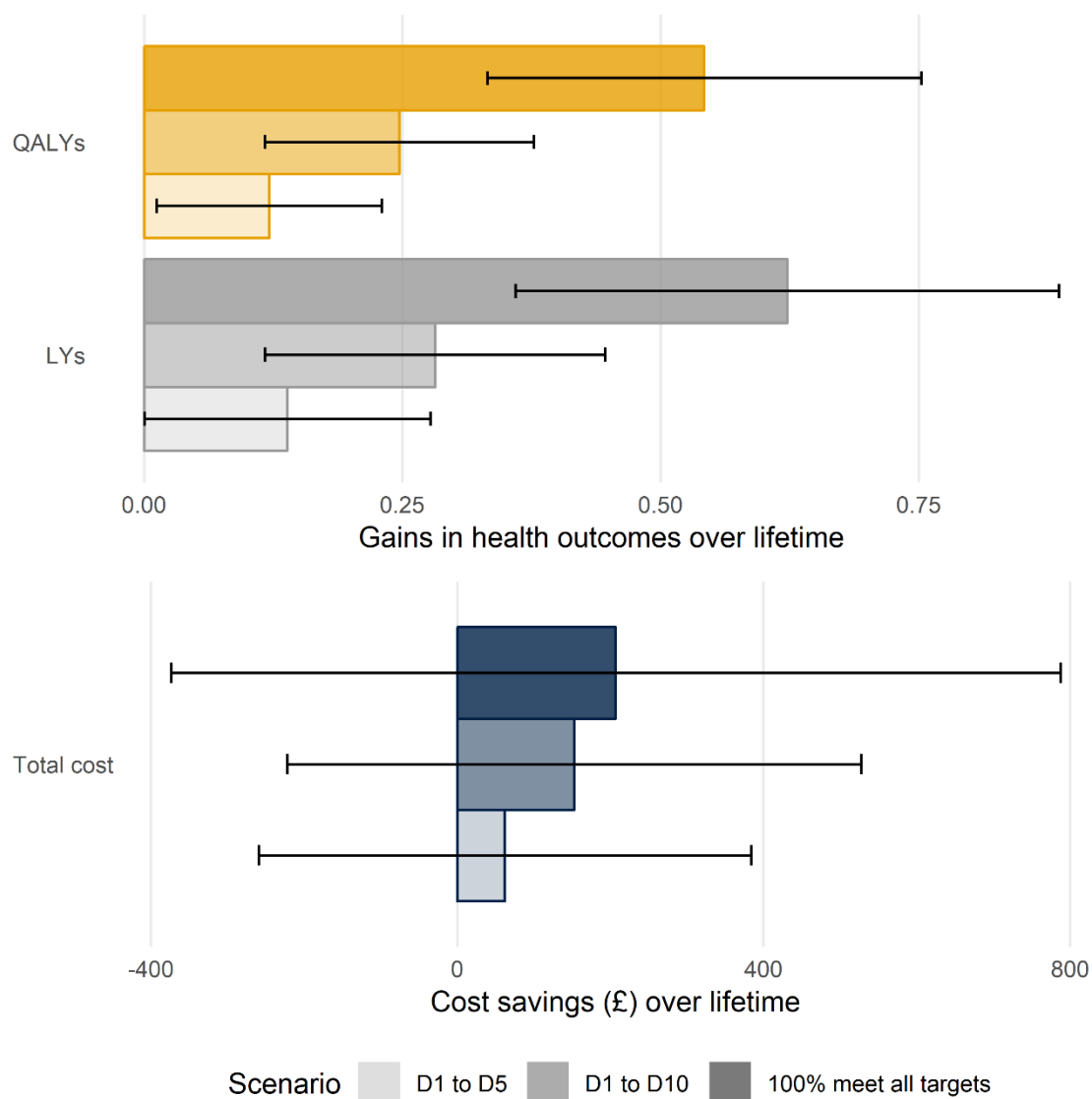
CV death, cardiovascular-related death; IHD, ischaemic heart disease. Absolute risk refers to average risk of first occurrence of complication for patients in GP practice in the lowest performing decile (D1), who do not have a history of respective complication (i.e. risk of stroke for patient who does not have history of stroke). D1 to D5, improving performance to that equivalent of GP practices in middle decile (D5); D1 to D10, improving performance to that equivalent of GP practices in highest performing decile (D10); 100% achieve all targets, improving performance such that all patients achieve all three treatment targets.

Figure A2: Average impacts on health outcomes and healthcare costs over 10 years per patient with Type 2 diabetes achieving one to three of the HbA1c, total cholesterol and blood pressure targets compared to achieving none



LYs, years of life; QALYs, quality-adjusted life years.

Figure A3: Average impacts on health outcomes and healthcare costs over lifetime per patient with Type 2 diabetes in GP practice in the lowest performing decile following improvements in treatment target achievement rates



LYs, years of life; QALYs, quality adjusted life years. All effects relative to scenario where GP practice remain in lowest performing decile (D1). D1 to D5, improving performance to that equivalent of GP practices in middle decile (D5); To D10, improving performance to that equivalent of GP practices in highest performing decile (D10); 100% achieve all targets, improving performance such that all patients achieve all three treatment targets.