Modelling incremental benefits on complications rates when targeting lower HbA_{1c} levels in people with type 2 diabetes and cardiovascular disease

Running title: Incremental benefits of targeting lower HbA_{1c}

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Abbreviations:

TECOS = Trial Evaluating Cardiovascular Outcomes with Sitaglitpin

T2DM = Type 2 diabetes mellitus

UKPDS = United Kingdom Prospective Diabetes Study

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Novelty statement:

- Randomised controlled trials of glucose lowering in type 2 diabetes mellitus have demonstrated benefits on reducing micro- and macro-vascular complication rates. Few data, however, exist to quantify the degree of benefit that might be gained from targeting different HbA1c reductions.
- We have simulated complication rates using a validated clinical prediction model to estimate the benefits of targeting progressively lower HbA1c levels, starting from a baseline of 10.0%.
- These simulated results demonstrate the independent contribution that HbA1c exerts on microvascular and macrovascular complications, and estimate what degree of benefit might be gained by targeting specific HbA1c reductions.

Abstract

Aims

Glucose-lowering interventions in type 2 diabetes mellitus (T2DM) have demonstrated reductions in microvascular complications and modest reductions in macrovascular complications. However, the degree to which targeting different HbA_{1c} reductions might reduce risk is unclear.

Methods

Participant-level data for Trial Evaluating Cardiovascular Outcomes with Sitagliptin participants with established cardiovascular disease were used in a T2DM-specific simulation model to quantify the likely impact of different HbA_{1c} decrements on complication rates. Ten-year microvascular and macrovascular rates were estimated with HbA_{1c} levels fixed at 86, 75, 64, 53 and 42 mmol/mol (10%, 9%, 8%, 7% and 6% respectively) whilst holding other risk factors constant at their baseline levels. Cumulative relative risk reductions (cRRRs) for each outcome were derived for each HbA_{1c} decrement.

Results

Of 5,717 participants studied, 72.0% were men and 74.2% White European, with mean (SD) age 66.2 (7.9) years, systolic blood pressure 134 (16.9) mmHg, LDL-cholesterol 2.3 (0.9) mmol/l, HDL-cholesterol 1.13 (0.3) mmol/l and median T2DM duration 9.6 (5.1-15.6) years. 10-year cRRRs for modelled HbA_{1c} values of 75, 64, 53 and 42 mmol/mol, relative to 86 mmol/mol, were 4.6%, 9.3%, 15.1% and 20.2% for myocardial infarction; 6.0%, 12.8%, 19.6% and 25.8% for stroke; 14.4%, 26.6%, 37.1% and 46.4% for diabetes-related ulcer; 21.5%, 39.0%, 52.3% and 63.1% for amputation; 13.6%, 25.4%, 36.0% and 44.7 for single-eye blindness.

Conclusions

These simulated complication rates might help inform the degree to which complications might be reduced by targeting particular HbA_{1c} reductions in T2DM.

Introduction

People with type 2 diabetes mellitus (T2DM) experience higher morbidity and mortality rates than individuals without diabetes (1). Control of modifiable risk factors, including blood pressure, lipid levels and levels of glycaemia can ameliorate some, but not all, of the excess disease burden (2-4). Randomised controlled trials of glucose lowering in T2DM have demonstrated benefits on reducing micro- and macrovascular complication rates (3-5). Few data, however, exist to quantify the relative benefit gained from glucose lowering for these complications. Also, the effect size attributable to glucose lowering can be difficult to determine because randomised trials report effects according to the observed glycated haemoglobin (HbA_{1c}) reduction between intervention and control arms (4-7), rather than by specific HbA_{1c} decrements.

The benefits of glucose lowering can be modelled (8-10). Although these simulated benefits may not represent true patient outcomes, modelling exercises have certain advantages of (1) pre-selecting standardised interval reductions of glucose lowering (e.g. estimating the outcome benefits per 1% HbA_{1c} reduction) to be achieved over a specified time period, (2) allowing independent examination that HbA_{1c} contributes towards developing T2D complications, without having to account for contributions from many other risk factors and (3) allowing examination of multiple target HbA_{1c} levels.

Here, we have used a T2DM-specific simulation model to estimate the 10-year incremental impact on micro- and macro-vascular events of T2DM of targeting progressively decremented HbA_{1c} levels (11).

Methods

Simulation Model

The modelling exercise was performed using the UKPDS Outcomes Model version 2.0, a second-generation lifetime simulation model designed to assess the total burden of disease over an extrapolated lifetime for people with T2DM (11). Model equations are based on a median of 17.6 years follow-up with up to 89,760 patient-years of data, and are internally valid over 25 years (4). External validation of this model has shown similar results to version 1.0 and that model performed well when evaluated in modern T2DM patient cohorts (12-13).

Contemporaneous T2DM population

We used baseline data from participants in the Trial Evaluating Cardiovascular Outcomes with Sitaglitpin (TECOS; clinical trials.gov registration number NCT00790205), with recruitment between 2008 and 2012 and the study finishing in 2015 (14-16). These data provide representative real world risk factor variables of a modern cohort of people with T2DM and established cardiovascular disease. TECOS has been described elsewhere (15-16). No TECOS follow-up data were included in this analysis.

Simulation

Baseline risk factor variables required for the simulation model are age, sex, ethnic group (White European, Afro-Caribbean or Asian), T2DM duration, weight, height, HDL-cholesterol, LDL-cholesterol, systolic blood pressure, HbA_{1c}, heart rate, haemoglobin, eGFR, white blood cell count, smoking status (current smoker *vs.* combined ex- and non-smoker) and prior history of ischaemic heart disease (defined as angina, atherosclerosis, acute coronary syndrome), peripheral vascular disease (atherosclerosis of an artery in the extreme, intermittent claudication, ulceration, gangrene or any interventional repair), atrial fibrillation, albuminuria, myocardial infarction, stroke, amputation (any digit or limb), heart failure, single-eye blindness, renal failure (doubling of serum creatinine level, macroalbuminuria or renal replacement therapy) and diabetes-related ulcer. The baseline risk factor variables entered

into the model were all held constant for 10 years whilst the model was run with five different fixed HbA_{1c} values of 86, 75, 64, 53 and 42 mmol/mol (10%, 9%, 8%, 7% and 6% respectively) (to produce HbA_{1c}-specific estimates (with 95% Confidence Intervals) of macrovascular (myocardial infarction, stroke, cardiovascular death, all-cause mortality) and microvascular (single eye blindness, amputation, diabetes-related ulcer) event rates. We did not investigate outcomes for renal failure or chronic heart failure as previous research conducted to create the model did not find HbA_{1c} to be a statistically significant independent risk factor for either condition, therefore no clinically meaningful differences would be expected from modelling different HbA_{1c} levels (11).

As white blood cell count measures were not available, all participants were allocated a mid-normal range value of 8.0×10^9 cells/L (17). All TECOS participants were required to have a baseline eGFR ≥30 mL/min/1.73m^2 and recent stable health. Accordingly, we assumed that none of them had prior renal failure and that any prior medical events had occurred greater than 12 months prior to study enrolment.

To obtain optimal precision of risk estimates and confidence intervals all simulations were performed using 5000 loops and 500 bootstraps in the model after first testing the model for stability in estimates (i.e. the lowest number of loops and bootstraps that led to convergence of risk estimates of up to two decimal places).

Statistical analyses

The distribution of continuous variables and 10-year risk estimates for all individual outcomes were inspected visually for normality using histograms and data were expressed as mean (standard deviation) or median (interquartile range) as appropriate. Ten-year risk estimates were used to calculate relative risk reductions at progressively 1% lower HbA_{1c} levels, relative to 86 mmol/mol (10%), expressed as percentages.

Analyses were conducted using Minitab 17 statistical Software (State College, PA, USA) and SPSS version 22.0 (SPSS Inc., Chicago, IL, USA). A two-sided p-value of <0.05 was

considered as statistically significant, with adjustments made for multiple comparisons using a Bonferroni correction.

Results

Of the 14,724 TECOS participants, 5,717 (38.8%) who had the requisite baseline variables were included in the analysis. Their baseline characteristics are listed in Table 1. Those excluded were 8,947 (60.1%) with one or more missing variables and 60 (1.0%) with a variable value outside the limits used by the model (11). Significant differences between those included and excluded in this analysis were respectively: proportion of men (72.0% vs 69.9%, p=0.005), history of smoking (53.7% vs 49.5%, p<0.001), White European origin (74.2% vs 75.2%, p=0.001), heart failure (15.4% vs 19.6%, p<0.001 and peripheral vascular disease (17.9% vs 15.7%, p<0.001) (Supplementary Table 1). A sensitivity analysis conducted for white blood cell count levels of 4.0 and 12.0 x 10^9 cells/L did not clinically alter the results and only the analysis including white blood cell count of 8.0 x 10^9 cells is reported here.

The median (95% CI) absolute point estimates for 10-year macrovascular and microvascular risks and mortality for each modelled HbA_{1c} level are listed in Table 2. For myocardial infarction, the 10-year absolute median estimate for a modelled constant HbA_{1c} of 86 mmol/mol (10%) was 22.3% (21.9, 22.6), with successively lower values for each modelled 1% HbA_{1c} decrement. Compared with the 86mmol/mol (10%) HbA_{1c} level, median relative risk reductions for myocardial infarction were 4.6% (4.4, 4.8) at 75 mmol/mol (9%) increasing to 15.1% (14.4, 15.7) at 53 mmol/mol (7%) (current guideline target,18), and 20.2% (19.3, 21.0) at 42 mmol/mol (6%).

Similar trends were noted for stroke, single eye blindness, diabetes-related ulcer, amputation and all-cause mortality. For microvascular complications, the absolute median estimates tended to be lower than for macrovascular complications at the same HbA_{1c} level, but cumulative relative risk reductions were greater. For amputation the 10-year absolute

median estimate for a modelled constant HbA_{1c} of 86 mmol/mol (10%) was 3.8% (3.7, 3.9), with successively lower values for each modelled 1% HbA_{1c} decrement. Compared with the 86 mmol/mol (10%) HbA_{1c} level, median relative risk reductions for amputation were 21.5% (21.1, 21.9) at 75 mmol/mol 9% increasing to 52.3% (52.0, 52.6) at 53 mmol/mol (7%).

Conclusions

There are few data available to estimate the likely incremental benefits of targeting progressively lower HbA_{1c} levels (4-7). This simulation exercise was designed to quantify the differential benefits in risk estimates of T2DM complications potentially attributable to targeting lower HbA_{1c} levels starting from a baseline of 86 mmol/mol (10%). Holding all other risk factor variables constant at their baseline values allowed us to examine the independent impact that HbA_{1c} reduction might contribute towards reducing T2DM complications.

Using monotonic 1% HbA_{1c} decrements allowed a detailed examination of T2DM outcomes for relative changes between targeted HbA_{1c} levels, in contrast to glucose lowering trials which report outcomes according to the observed HbA_{1c} reduction (4-6). Previous modelling simulation studies have reported outcomes on one or two targeted HbA_{1c} reductions or for microvascular outcomes only (8-10). To our knowledge this is the first study to report on multiple HbA_{1c} targets for both micro- and macrovascular complications. The use of version 2 of the UKPDS Outcomes Model, rather than version 1, allowed greater precision of risk estimates and modelling of additional outcomes including risk of developing a diabetes-related ulcer, second myocardial infarction and stroke events. The rate at which people develop complications may have changed over time; however, version 1.0 of outcomes model has been validated in modern cohorts (12-13).

Using baseline data from TECOS provided a contemporaneous cohort of over 5,000 people with T2DM and established cardiovascular disease and therefore at high cardiovascular risk. While modelled absolute event rates may not be entirely accurate, the purpose of this study was to examine the relative differences in modelled outcomes that likely to apply to more generally to a T2DM population.

Regarding the 10-year risk estimates, greater estimated risk reductions were seen with HbA_{1c} lowering for micro- than macrovascular complications, as expected from the findings of glucose lowering trials (3-6).

Relative risk reductions in microvascular and macrovascular complications for each 1% HbA1c reduction were similar for each decrement. The exception was all-cause mortality, where the relative risk reductions for 1% HbA1c decrements were greater at higher baseline HbA1c levels. These simulated outcomes differ from the DCCT outcome in people with type 1 diabetes, where lowering HbA1c from higher baseline HbA1c levels had a larger impact on microvascular risk reduction (19).

There are some limitations. The generated results of this modelling exercise suggest what may be achieved by glucose lowering alone, and do not take into account changes in other risk factors such as possible lipid profile improvements secondary to glucose lowering. Although, risk estimates for microvascular disease were generated for end-stage events, only diabetes-related ulcer development was modelled to represent an earlier stage complication. The use of the TECOS data limits our findings to people with T2DM and established cardiovascular disease.

The current analysis demonstrates the potential benefits of targeting lower HbA_{1c} levels. Such benefits must be balanced against potential adverse effects, which cannot be accounted for in the simulation model. One example is hypoglycaemia, which can impair quality of life and increases financial costs (20-21). The annual total hypoglycaemia rate of people with T2DM has been reported as 2.5%, more common in those people with an HbA_{1c} less than 53mmol/mol (7%) (5.2%), particularly in those administering insulin (22). Severe and non-severe symptomatic hypoglycaemia rates are reported as 1.0% and 9.8% respectively with use of a basal insulin, when HbA_{1c} levels were between 41 to 46mmol/mol (5.9 to 6.4% respectively) (23). Finally, the Action to Control Cardiovascular Risk in Diabetes trial demonstrated an increased mortality of 22% (hazard ratio, 1.22; 95% CI, 1.01 to 1.46) in people randomised to the intervention treatment target of HbA_{1c} 42mmol/mol (6.0%) (24).

However, these findings remain contentious as there was no explanation for the observed excess mortality, except that it occurred predominantly in individuals with renal disease at baseline (25). Overall, the potential benefits of targeting lower HbA_{1c} must be balanced against the possible risks.

In conclusion, targeting progressively lower HbA_{1c} levels has the potential for greater reduction of estimated risk of T2DM complications, more pronounced in microvascular than macrovascular complications.

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Declarations

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Other authors have no declarations.

Contributions

SAM – designed the study, wrote the manuscript and performed the data modelling.

RLC – supervised the statistical analysis and data modelling, revised the manuscript

OFA – supervised the statistical analysis and data modelling, revised the manuscript

AMG - revised the manuscript

RRH – designed the study, revised the manuscript, provided material support

MAB - designed the study, revised the manuscript and is guarantor of this paper.

Table 1. Baseline characteristics of variables used in the model (n=5717)

Variable	Response
Age (years)	66.2 (7.9)
Male (n, %)	4119 (72.0)
White European (n, %)	4241 (74.2)
Diabetes duration (years)	9.6 (5.1 – 15.6)
Ever smoked (n, %)	3068 (53.7)
Weight (kg)	85.2 (19.3)
Height (m)	1.68 (0.1)
HDL-C (mmol/l)	1.13 (0.3)
LDL-C (mmol/l)	2.28 (0.9)
Systolic BP (mmHg)	134.1 (16.9)
HbA_{1c} (mmol/mol, %)	56, 7.3 (0.6)
Heart rate (bpm)	71.6 (11.1)
Haemoglobin (g/dl)	13.6 (1.5)
eGFR (ml/min/1.73m^2)	75.1 (21.1)
Albuminuria (n, %)	1378 (24.1)
Myocardial infarction (n, %)	2428 (40.1)
Heart failure (n, %)	880 (15.4)
Stroke (n, %)	965 (16.9)
Atrial Fibrillation (n, %)	478 (8.4)
Peripheral vascular disease (n, %)	1022 (17.9)
Renal failure (n, %)	0 (0)
Blindness (n, %)	97 (1.7)
Diabetes-related ulcer (n, %)	158 (2.8)
Amputation (n, %)	138 (2.4)

Data expressed as mean (standard deviation) or median (interquartile range) for continuous variables and n (%) for category variables. Key: BP = blood pressure, bpm = beats per minute, eGFR = estimated glomerular filtration rate

Table 2. 10-year estimated absolute risks and 95% confidence intervals for individual macrovascular and microvascular events and mortality at different imposed HbA_{1c} levels and corresponding relative risk reductions from an HbA_{1c} of 86mmol/mol (10%)

HbA_{1c}:	10.0% (86mmol/mol)	9.0% (75mmol/mol)	8.0% (64mmol/mol)	7.0% (53mmol/mol)	6.0% (42mmol/mol)
Macrovascular:					
Myocardial infarction (%)	22.3 (21.9-22.6)	21.5 (21.2-21.8)	20.7 (20.5-21.0)	20.0 (19.8-20.3)	19.4 (19.2-19.6)
RRR (%)	Reference	4.6 (4.4- 4.8)	4.5 (4.3- 4.8)	4.7 (4.4- 4.9)	4.8 (4.5-5.1)
Cumulative RRR (%)	Reference	4.6 (4.4 - 4.8)	9.3 (8.9 - 9.7)	15.1 (14.4-15.7)	20.2 (19.3-21.0)
Stroke (%)	13.0 (12.7-13.3)	12.1 (11.8-12.4)	11.3 (11.1-11.6)	10.4 (10.2-10.7)	9.7 (9.4-10.0)
RRR (%)	Reference	6.0 (5.8 - 6.2)	6.0 (5.7 - 6.2)	6.1 (5.8 - 6.4)	6.0 (5.7 - 6.2)
Cumulative RRR (%)	Reference	6.0 (5.8 - 6.2)	12.8 (12.5-13.1)	19.6 (19.3-19.9)	25.8 (25.5-26.0)
Cardiovascular mortality (%)	21.7 (21.2-22.1)	20.6 (20.2-21.0)	19.7 (19.2-20.1)	18.7 (18.3-19.1)	17.9 (17.5-18.3)
RRR (%)	Reference	4.2 (4.0 - 4.3)	4.2 (4.0 - 4.3)	4.3 (4.1-4.4)	4.1 (3.9-4.2)
Cumulative RRR (%)	Reference	4.2 (4.0 - 4.3)	8.0 (7.8 - 8.2)	11.5 (11.2-11.8)	14.7 (14.2-15.1)
All-cause mortality (%)	53.4 (52.3-54.3)	52.1 (51.2-53.2)	51.2 (50.3-52.2)	50.3 (49.4-51.2)	49.4 (48.5-50.3)
RRR (%)	Reference	1.4 (13.4-14.8)	1.3 (1.3 - 1.4)	1.3 (1.2 - 1.3)	1.1 (1.1 - 1.2)
Cumulative RRR (%)	Reference	1.4 (13.4-14.8)	2.7 (2.6 - 2.8)	3.9 (3.8 - 4.1)	5.0 (4.7 - 5.1)
Microvascular					
Single eye blindness (%)	6.4 (6.3 - 6.5)	5.5 (5.4 - 5.5)	4.6 (4.6-4.7)	4.0 (3.9 - 4.0)	3.4 (3.3 - 3.4)
RRR (%)	Reference	14.4 (14.2-14.7)	14.4 (14.1-14.7)	14.4 (14.1-14.7)	14.8(14.4 -15.1)
Cumulative RRR (%)	Reference	14.4 (14.2-14.7)	26.6 (26.4-26.8)	37.1 (37.0- 37.3)	46.4 (46.3 -46.6)
Amputation (%)	3.8 (36.6 - 38.6)	2.9 (28.4 - 30.0)	2.3 (22.0 - 23.2)	1.8 (17.2 - 18.2)	1.4 (13.2- 14.0)
RRR (%)	Reference	21.5 (21.1-21.9)	21.5 (20.3-21.2)	21.2 (20.7-21.8)	21.6 (21.1- 22.1)
Cumulative RRR (%)	Reference	21.5 (21.1-21.9)	39.0 (39.0 - 39.3)	52.3 (52.0-52.6)	63.1 (62.9 -63.4)
Diabetes-related ulcer (%)	2.1 (21.0 - 21.6)	1.8 (18.00-18.8)	1.6 (15.4- 16.2)	1.4(13.4-14.0)	1.2(11.4 - 12.0)
RRR (%)	Reference	13.6 (13.3- 4.1)	13.5 (13.0-14.0)	14.0 (13.4 -14.6)	13.8 (13.3 -14.3)
Cumulative RRR (%)	Reference	13.6 (13.3-14.1)	25.4 (25.0-25.8)	36.0 (35.7 -36.4)	44.7 (44.4- 45.1)

Data are expressed as median absolute point risk estimates for events with 95% confidence intervals, with Bonferroni corrections applied to p-values to account for multiple comparisons. Myocardial infarction and stroke include both fatal and non-fatal events. All-cause mortality is included here for comparison which is a composite of microvascular, macrovascular and non-vascular causes of death. Key: RRR = relative risk reduction