Received: 7 November 2021 | Revised: 11 March 2022 | Accepted: 30 March 2022

DOI: 10.1111/dom.14705

ORIGINAL ARTICLE

WILEY

Early and ongoing stable glycaemic control is associated with a reduction in major adverse cardiovascular events in people with type 2 diabetes: A primary care cohort study

Martin B. Whyte PhD[1] | Mark Joy PhD[2] | William Hinton BSc[1,2] | Andrew McGovern MD[1] | Uy Hoang PhD[1] | Jeremy van Vlymen BSc[1] | Filipa Ferreira BSc[2] | Julie Mount PhD[3] | Neil Munro DPhil[1] | Simon de Lusignan MD[1,2]

[1]Department of Clinical and Experimental Medicine, University of Surrey, Guildford, UK

[2]Nuffield Department of Primary Care Health Sciences, University of Oxford, Oxford, UK

[3]Eli Lilly and Company, Hampshire, UK

Correspondence
Martin B. Whyte, PhD, Department of Clinical & Experimental Medicine, Leggett Building, University of Surrey, Guildford GU2 7WG, UK.
Email: m.b.whyte@surrey.ac.uk

Funding information
Eli Lilly and Company

Abstract

Aim: To determine whether achieving early glycaemic control, and any subsequent glycaemic variability, was associated with any change in the risk of major adverse cardiovascular events (MACE).

Materials and Methods: A retrospective cohort analysis from the Oxford-Royal College of General Practitioners Research and Surveillance Centre database—a large, English primary care network—was conducted. We followed newly diagnosed patients with type 2 diabetes, on or after 1 January 2005, aged 25 years or older at diagnosis, with HbA1c measurements at both diagnosis and after 1 year, plus five or more measurements of HbA1c thereafter. Three glycaemic bands were created: groups A (HbA1c < 58 mmol/mol [<7.5%]), B (HbA1c ≥ 58 to 75 mmol/mol [7.5%-9.0%]) and C (HbA1c ≥ 75 mmol/mol [≥9.0%]). Movement between bands was determined from diagnosis to 1 year. Additionally, for data after the first 12 months, a glycaemic variability score was calculated from the number of successive HbA1c readings differing by 0.5% or higher (≥5.5 mmol/mol). Risk of MACE from 1 year postdiagnosis was assessed using time-varying Cox proportional hazards models, which included the first-year transition and the glycaemic variability score.

Results: From 26 180 patients, there were 2300 MACE. Compared with group A->A transition over 1 year, those with C->A transition had a reduced risk of MACE (HR 0.75; 95% CI 0.60-0.94; $P = .014$), whereas group C->C had HR 1.21 (0.81-1.81; $P = .34$). Compared with the lowest glycaemic variability score, the greatest variability increased the risk of MACE (HR 1.51; 1.11-2.06; $P = .0096$).

Conclusion: Early control of HbA1c improved cardiovascular outcomes in type 2 diabetes, although subsequent glycaemic variability had a negative effect on an individual's risk.

KEYWORDS
computerized, diabetes complications, macrovascular, medical record systems, primary care, type 2 diabetes

1 | INTRODUCTION

Cardiovascular disease (CVD) is a major cause of death and disability in people with diabetes[1] and CVD risk is associated with higher HbA1c.[2] The UK Prospective Diabetes Study (UKPDS) showed that, even after subsequent deterioration in glycaemia, early tight glycaemic control was associated with a reduced number of macrovascular events.[3] Glycaemic control achieved soon after the diagnosis of type 2 diabetes has been associated with a reduction in the risk of subsequent macrovascular events,[4,5] whereas a deteriorating HbA1c pattern after diagnosis is associated with an increased risk of long-term co-morbidities and death.[6] These findings led to the concept of a 'legacy effect' (i.e. metabolic memory) of early glycaemic control.[7] The mechanisms(s) underpinning the legacy effect are unresolved but may relate to epigenetic processes such as persistence of post-translational histone methylation and changes in microRNA after normalization of glucose,[8] or the prevention of glycation of the protein matrix in arterial walls, thereby curbing the development of atherosclerotic lesions.[9]

Conversely, the introduction of tight glycaemic control only later in the disease course—several years after the diagnosis of type 2 diabetes—may lead to adverse cardiovascular outcomes.[10-12] Greater glycaemic variability has been implicated as a pathophysiological mechanism.[13] Fluctuation in daily glucose values,[14-16] or longer term swings (visit-to-visit HbA1c),[13,17-21] may lead to oxidative stress, promoting inflammation, endothelial dysfunction and greater macrovascular risk and death.[13-15,21] The importance of glycaemic variability on vascular outcomes in type 2 diabetes has been challenged.[22] It is unclear whether glycaemic variability affects future macrovascular risk once the early period of glycaemic control (relating to the legacy effect) has been accounted for. To date, few studies have distinguished between the metabolic flux needed to achieve early glycaemic control, from later glycaemic variability.[17,20] We used the Royal College of General Practitioners (RCGP) Research and Surveillance Centre (RSC) database to perform a comprehensive examination of glycaemic control achieved within the first year of diagnosis and subsequent HbA1c variability, with incident CVD.

2 | MATERIALS AND METHODS

2.1 | Source population

This was a retrospective cohort analysis of adults with type 2 diabetes identified from the RCGP RSC database. This comprises primary care data from a sentinel network of general practices distributed across England. The clinical computing systems that the contributing practices use are EMIS Web, INPS Vision and TPP SystmOne. At the time of analysis, the database contained primary care records collected from 1 595 170 people registered with 164 practices (2.9% of the population of England). The database included all recorded clinical codes with associated values and dates for the population up to 31 December 2016. At the time of the study, clinical codes were recorded using the Read code 5-byte version 2 and Clinical Terms Version 3 coding hierarchies and included diagnosis codes, medication codes, investigation codes, process of care codes and laboratory data. Since 2018, this has been replaced by Systematized Nomenclature of Medicine—Clinical Terms (SNOMED-CT). The RCGP RSC has been shown to be representative of the national population with regards to demographic composition, geographical coverage and prevalence of chronic disease.[23]

UK general practice is a registration-based system with citizens registering with a single general practitioner. Care is free and nearly all care and prescribing for type 2 diabetes is carried out in primary care.

Patients with type 2 diabetes are identified through an algorithm as previously reported.[24] The first step identifies all people with diabetes (of any type) through (i) diagnostic code (diagnosis of diabetes), (ii) clinical investigations (two or more fasted, random or glucose tolerance test values or HbA1c measurements consistent with diagnosis), or (iii) medication use (two or more prescriptions for oral diabetes medications, excluding metformin or injectable therapies). These people were then categorized by diabetes type using a clinically based seven-step algorithm, centred on, but not limited to, the duration of preceding oral glucose lowering medication use.[24]

2.2 | Design

We constructed a time-varying Cox proportional hazards model for time to major adverse cardiovascular events (MACE). A priori we had considered that it was more appropriate to consider HbA1c fluctuation as being time-dependent (i.e. the variance of HbA1c would not be expected to be uniform throughout the follow-up period). The measurement of time was the number of years since diabetes diagnosis.

2.3 | Inclusion and exclusion

We excluded patients who did not have any HbA1c results within 3 months either before or after diagnosis and who did not have a second HbA1c result during the first year after diagnosis because we were unable to classify their levels of early HbA1c exposure. We also excluded individuals with less than five HbA1c measurements

thereafter, as this was required for assessment of HbA1c variability. MACE within the first 12 months of diagnosis of type 2 diabetes were excluded as they were considered to not represent the effectiveness, or otherwise, of any legacy effect.

2.4 | Exposure

We followed newly diagnosed patients with type 2 diabetes (first entry of diabetes indicator at any time on or after 1 January 2005 to 31 December 2016). To be included, patients had to be aged 25 years or older at diagnosis and have HbA1c measurements at both diagnosis and 1 year after (a leeway of 3 months was applied either side of diagnosis and at the 1-year follow-up time point). Furthermore, all patients had to have an additional five or more measurements of HbA1c, after the first year, to be included.

The first registered HbA1c measurement within 3 months either side of first indicator code for diabetes was used as the index value. The HbA1c measurement 12 months after the first measurement (±3 months) was used as the '1-year' HbA1c. If an individual had more than one measurement of HbA1c in the 9-15 months period after the first measurement, the latest registered measurement in that time span was used as the 1-year value.

We constructed an indicator variable for glycaemic transition over the first year by banding the cohort into three groups based upon their initial HbA1c level (mmol/mol). Categories of HbA1c were chosen from reports of a J-shaped relationship of HbA1c with macrovascular risk with a broadly comparative risk for HbA1c from 7.5% to 9.0%.[25-27] The categories used were: group A (HbA1c < 58 mmol/mol [<7.5%]), group B (HbA1c ≥ 58 and < 75 mmol/mol [7.5%-9.0%]) and group C (HbA1c ≥ 75 mmol/mol [≥9.0%]).

We then also recorded the group status, per individual, at the end of the first year and categorized the glycaemic transition that had occurred. For example, a person with status A->A had an HbA1c level below 57 mmol/mol at their first measurement and at 1 year. A person with status C->A would initially have had an HbA1c level above 75 mmol/mol, but then reduced this at the end of year 1 to be lower than 57 mmol/mol.

The models also included a glycaemic variability score based upon the method reported by Forbes et al.,[28] which we modified by using time-varying covariates. In the sensitivity analysis, HbA1c was treated as a time-fixed approach, whereby the covariate is considered to be more constant through the follow-up period. In brief, to calculate a glycaemic variability score using HbA1c values, the number of times successive HbA1c readings differed by 0.5% or more (≥5.5 mmol/mol) were counted. This number was divided by the number of comparisons, then multiplied by 100. For example, if a person had a sequence of HbA1c values of 6.7%, 7.0%, 7.8%, 7.4%, 8.0% and 7.9%, the number of times that a difference of 0.5% or more was noted would be two and the score would be 40 (i.e. [100 × 2]/5). As with Forbes et al.,[28] for analysis purposes, we grouped the scores into five categories: 0-20, 21-40, 41-60, 61-80 and 81-100.

Measurements during the first 12 months were excluded from the variability score to distinguish the effect of early glucose normalization from later glucose variability.

2.5 | Outcomes

The outcomes of interest were the first occurrence of MACE, defined as myocardial infarction (MI), coronary intervention, stroke and amputation/limb revascularizations. All patients were followed for outcomes until the earliest date of the following: death, deregistration from practice, practice leaving the RCGP RSC network or 31 December 2016.

2.6 | Covariates

We adjusted for potentially confounding variables using the most recently recorded measurement at the time of diagnosis of type 2 diabetes. Baseline covariates in the model were age (banded into the following categories: 25-44, 45-64, 65-74, 75-84 and ≥85 years), smoking status, body mass index (BMI), total cholesterol, HDL-cholesterol and LDL-cholesterol. When there were issues with missing data, the last observation was carried forward. Co-morbidities were defined using codes for diagnosis, investigation and process of care (Table S1).

2.7 | Statistical analysis

We summarized data for patient characteristics using means and standard deviations (SDs) for continuous variables and counts and percentages for categorical variables. We used the chi-squared test for bivariate statistics for categorical variables and the Mann–Whitney *U* test or *t*-test for non-parametric or parametric, continuous variables, respectively.

Analyses addressing either change in HbA1c over the first year, or HbA1c variability, were adjusted for the other. HbA1c was treated as a time-dependent variable in the model with variability based on prior data and the hazard ratio interpreted as giving an instantaneous hazard of MACE. Each person was followed until death, leaving the RCGP RSC database, for instance, by emigration (censoring), or 31 December 2016, whichever came first. This was a complete-case analysis. Missing data were handled by multiple imputation and the multiple results then combined into one inference using Rubin's rules.

A sensitivity analysis was performed that used HbA1c as a time-fixed variable.

Estimates are presented with hazard ratios (HR) and 95% confidence intervals. A two-sided *P* of less than .05 was considered statistically significant for all analyses. All analyses were performed using R statistical software version 3.5.3.

2.8 | Compliance with ethics guidelines

All data were pseudonymized at the point of data extraction. No clinically identifiable information was available to researchers. National Research Ethics Committee approval was obtained on 30 September

TABLE 1 The characteristics of the type 2 diabetes adult population at data extraction (31 December 2016; n = 26 180)

Characteristic	Number (%)
Gender	
Male	14 429 (55.1)
Female	11 751 (44.9)
Ethnicity	
White	18 590 (71.0)
Asian	1730 (6.6)
Black	865 (3.3)
Mixed	164 (0.6)
Other	161 (0.6)
None recorded	4670 (17.8)
Socioeconomic status	
IMD quintile 1 (most deprived)	4853 (18.5)
IMD quintile 2	4330 (16.5)
IMD quintile 3	5170 (19.7)
IMD quintile 4	5548 (21.2)
IMD quintile 5 (least deprived)	6222 (23.8)
None recorded	57 (0.2)
Body mass index	
Underweight	227 (0.9)
Normal	4212 (16.1)
Overweight	8640 (33.0)
Obesity class I	7212 (27.5)
Obesity class II	3494 (13.3)
Obesity class III	2196 (8.4)
None recorded	199 (0.8)
Smoking status	
Never	6332 (24.2)
Active	4186 (16.0)
Ex-smoker	14 936 (57.1)
Unknown	726 (2.8)
Duration of diabetes (y)	
1-3	9398 (35.9)
4-6	6923 (26.4)
7-9	5970 (22.8)
≥10	3889 (14.9)
HbA1c (mmol/mol; % DCCT units)	
<48 (6.5)	5084 (19.4)
48-57 (6.5-7.4)	10 839 (41.4)
58-74 (7.5-8.9)	4399 (16.8)
≥75 (9.0)	5858 (22.4)
Systolic blood pressure (mmHg)	
<120	4620 (17.6)
120-139	14 759 (56.4)
140-159	5847 (22.3)
≥160	950 (3.6)
Missing	4 (0.0)
Diastolic blood pressure (mmHg)	
<80	17 035 (65.1)
80-89	7422 (28.3)
90-99	1436 (5.5)
≥100	283 (1.1)
Missing	4 (0.0)
eGFR (ml/min)	
<15	46 (0.2)
15-29	309 (1.2)
30-44	1270 (4.9)
45-59	2672 (10.2)
≥60	21 833 (83.4)
Missing	50 (0.2)
Co-morbidity	
Retinopathy	13 103 (50.0)
Amputation	248 (0.9)
Angina	2661 (10.2)
Atrial fibrillation	2822 (10.8)
Congestive cardiac failure	1646 (6.3)
Hypertension	16 091 (61.5)
Stroke or transient ischaemic attack	2148 (8.2)
Peripheral artery disease	1061 (4.1)
Chronic kidney disease	5885 (22.5)
Renal replacement	56 (0.2)
Acute myocardial infarction	2063 (7.9)

Abbreviations: DCCT, diabetes control and complications trial; eGFR, estimated glomerular filtration rate; IMD, index of multiple deprivation.

2016 (REF: 16/WM/0425) and subsequently approved by the RCGP RSC approvals committee.

3 | RESULTS

3.1 | The diabetes cohort

A total of 1 595 170 people were included from 164 primary care practices. Within this total population, a cohort of 90 730 (5.7%) adults were identified as having diabetes. Of these, 84 378 (93.0%) individuals were categorized as having type 2 diabetes. Within this cohort we only included individuals who had diabetes diagnosed on or after 1 January 2005, with HbA1c measurements at diagnosis and 1 year after, plus at least five other times thereafter (n = 26 180) (Table 1). Most exclusions were a result of pre-existing diabetes (prior to 2005). The characteristics of the other excluded patients (n = 4280) are listed in Table S2. The median duration of follow-up was 1583 (IQR 987-1737) days.

TABLE 2 Adjusted hazard ratios for MACE in people with type 2 diabetes

	HR	95% CI	*P* value
HbA1c group change over first 12 mo			
A to A	REF	REF	—
A to B	0.81	0.59-1.11	.18
A to C	1.07	0.58-1.97	.83
B to A	0.86	0.72-1.04	.12
B to B	0.95	0.72-1.27	.75
B to C	1.07	0.67-1.70	.78
C to A	0.75	0.60-0.94	**.014**
C to B	0.83	0.61-1.14	.26
C to C	1.21	0.81-1.81	.34
Glycaemic variability after 12 mo			
0-20	REF	REF	—
21-40	1.05	0.88-1.26	.61
41-60	1.09	0.88-1.34	.43
61-80	1.14	0.88-1.46	.32
81-100	1.51	1.11-2.06	**.0096**
Female gender	0.73	0.63-0.85	**<.001**
Smoking			
Ex-smoker	REF	REF	—
Non-smoker	0.67	0.57-0.79	**<.001**
Active smoker	0.99	0.84-1.17	.93
Age (y)			
25-44	0.54	0.41-0.72	**<.001**
45-64	REF	REF	—
65-74	1.75	1.50-2.05	**<.001**
75-84	3.01	2.50-3.63	**<.001**
≥85	4.84	3.26-7.17	**<.001**
Systolic BP (mmHg)	0.99	0.99-1.00	**.0011**
Cholesterol (mmol/L)			
Total cholesterol	1.00	0.93-1.07	.98
HDL-cholesterol	0.75	0.60-0.94	**.014**
LDL-cholesterol	0.92	0.85-1.00	**.049**
BMI (kg/m^2)	1.02	1.00-1.03	**.0062**

Abbreviations: BMI, body mass index; BP, blood pressure; CI, confidence interval; HR, hazard ratio; MACE, major adverse cardiovascular events. Group A: HbA1c < 58 mmol/mol (<7.5%); group B: HbA1c ≥ 58 and <75 mmol/mol (7.5%-9.0%); group C: HbA1c ≥ 75 mmol/mol (≥9.0%). Bold type represents *P* < .05.

At the time of data extraction (31 December 2016), the mean age of people with type 2 diabetes was 68.7 ± 12.6 years. Less than half of these were female (43.9%). There were 3207 in the 25-44 years age category (12%), 12 110 aged 45-64 years (26%), 6407 aged 65-74 years (25%), 3639 aged 75-84 years (14%) and 817 aged 85 years or older (3.1%). Mean BMI was 31.72 (6.64) kg/m^2. Mean systolic blood pressure (BP) was 138.5 (17.4) mmHg and diastolic BP was 81.0 (10.7) mmHg. Ethnicity was identified in 85.5% of the diabetes cohort. People of Asian (6.6%) and Black (3.3%) ethnicity were representative of the general RCGP RSC population (5.8% and 3.5%, respectively).

The majority of the type 2 diabetes cohort (n = 26 180; 98.9%) had at least one measurement of BMI. The mean BMI was 30.7 ± 6.4 kg/m^2. The mean HbA1c measurement (most recent) for the cohort was 57.5 ± 16.5 mmol/mol [7.4% ± 1.5%]. The mean systolic BP was 139.0 (median: 138.0 [IQR: 129-148]) mmHg and the mean diastolic BP was 81.4 (median: 80.0 [IQR: 75-88]) mmHg. The mean estimated glomerular filtration rate was 81.4 (median: 82.2 [IQR: 68.2-94.9]) ml/min.

The numbers and percentages of individuals in the nine transition groups over the first 12 months were: A->A, n = 12 559 (48%); A->B, n = 1439 (5.5%); A->C, n = 388 (1.5%); B->A, n = 3822 (14.6%); B->B, n = 898 (3.4%); B->C, n = 451 (1.7%); C->A, n = 4223 (16.1%); C->B, n = 1736 (6.6%); and C->C, n = 664 (2.5%). The numbers and percentages of individuals in the five glycaemic variability groups were: score 0-20, n = 13 477 (51.5%); score 21-40, n = 4929 (18.8%); score 41-60, n = 4208 (16.1%); score 61-80, n = 2557 (9.8%); and score 81-100, n = 1009 (3.9%).

3.2 | Major adverse cardiovascular events

From the 26 180 patients in the cohort, 4179 MACE were recorded prior to the diagnosis of type 2 diabetes. Within the first 12 months after diagnosis of diabetes, there were a further 1457 MACE, and from 12 months after the diagnosis of diabetes onwards, there were 2300 MACE. The median time to MACE after diagnosis was 635 (IQR 164-1539) days. Inclusive within the category of MACE was MI, of which there were 1424 events prior to the diagnosis of diabetes, 289 within 12 months of the diagnosis of diabetes, and a further 513 after 12 months of diabetes. The cumulative burden of disease in the cohort, at the end of follow-up, is shown in Table 1.

The modelling of the effect of change from baseline HbA1c to 12-month HbA1c suggested that those who moved from the highest category to the lowest category (C->A) had a reduced hazard for subsequent MACE (Table 2).

Increased glycaemic variability was associated with an increased risk of MACE; this risk increased across the categories of glycaemic variability, but was significant only for those in the highest category (81-100) (Table 2). Increasing BMI was associated with an increased risk of MACE (HR 1.02 [1.00-1.03] per kg/m^2; *P* = .0062).

Female gender (HR 0.73 [0.63-0.85]; *P* < .001), higher HDL-cholesterol (HR 0.75 [0.60-0.94] per mmol/L; *P* = .014), and individuals who had never smoked (HR 0.702 [0.611-0.807]; *P* < .001), had a lower risk of MACE. The concordance of the (time-varying) model was 0.729. The relationships did not change appreciably with the sensitivity analysis (Table S3).

The characteristics of those whose control normalized from poor to good over the first 12 months were compared with those whose control remained poor (Table 3). There were no differences by gender, BP or cholesterol. However, there were more individuals aged 65-74 years in the changing (C->A) group, and more aged 25-44 years in the no-change group (C->C). There were more ex-smokers in the changing (C->A) group and more active smokers in the no-change (C->C) group.

TABLE 3 Characteristics of people who remain with HbA1c ≥ 75 mmol/mol (≥9.0%) (C to C transition), or change from HbA1c ≥ 75 mmol/mol (≥9.0%) to HbA1c < 58 mmol/mol (<7.5%) (C to A transition), over 12 months

	Year 1 change: C to C	Year 1 change: C to A	*P* value
Gender			
Male	346 (64.7)	2197 (64.0)	1.0
Female	194 (35.9)	1236 (36.0)	
Age band (y)			
25-44	155 (28.7)	590 (17.2)	<.001
45-64	213 (67.8)	1836 (54.8)	
65-74	51 (9.4)	669 (19.5)	
75-84	18 (3.3)	257 (7.49)	
≥85	4 (0.74)	31 (0.9)	
Smoking status			
Ex-smoker	156 (29.7)	1470 (43.9)	<.001
Non-smoker	187 (35.6)	1098 (32.8)	
Active smoker	182 (34.7)	778 (23.3)	
Systolic BP (mmHg)			
Mean	137.9	138.4	.68
IQR	126-148	127-148	
Total cholesterol (mmol/L)			
Mean	5.61	5.59	.59
IQR	4.6-6.4	4.7-6.4	
HDL cholesterol (mmol/L)			
Mean	1.14	1.18	.80
IQR	0.9-1.3	0.9-1.3	
LDL cholesterol (mmol/L)			
Mean	3.12	3.08	.61
IQR	2.23-3.8	2.3-3.8	
BMI (kg/m^2)			
Mean	32.1	31.2	.04
IQR	26.7-35.9	26.7-34.4	

Abbreviations: BMI, body mass index; BP, blood pressure; IQR, interquartile range.
Group A: HbA1c < 58 mmol/mol (<7.5%); group B: HbA1c ≥ 58 and <75 mmol/mol (7.5%-9.0%); group C: HbA1c ≥ 75 mmol/mol (≥9.0%).

4 | DISCUSSION

We have shown that improvement of glycaemic control, within the first year following diagnosis of type 2 diabetes, was associated with a reduced risk of subsequent MACE. Furthermore, we found that the greatest glycaemic variability (i.e. after the initial 12 months of glycaemic trajectory) also conferred a higher risk of MACE. These data are in keeping with the concept of a legacy effect, but with subsequent glycaemic variability contributing to an individual's risk profile.

4.1 | Trajectory/metabolic memory

Following the landmark trials of glucose regulation in type 2 diabetes (UKPDS, The Action to Control Cardiovascular Risk in Diabetes Study [ACCORD], Veterans Affairs Diabetes Trial [VADT], Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation [ADVANCE]),[3,10-12] trajectories of control have gained prominence. The effect of the metabolic memory may depend on the absolute reduction in HbA1c, the achievement below a 'threshold value', the speed at which that is obtained, and/or the duration for which it is maintained. Our data, of benefits associated with early control (by 1 year after diagnosis), concord with those of other groups.[4,5] Conversely, glycaemic control attained later than 1 year may lose benefit. Correction of high HbA1c over a prolonged period of 4-5 years was associated with either no benefit or worse outcomes.[6,29]

Delaying the institution of glycaemic control until several years after diagnosis of type 2 diabetes is also of limited benefit to macrovascular reduction. A randomized controlled trial (RCT) of multifactorial cardiovascular risk management (including normalization of HbA1c from 8.0% to 6.8%), found little benefit in type 2 diabetes of (mean) 8.5 years' duration, although this study was underpowered, as the HbA1c in the control group also decreased (to 7.1%).[30] Absence of benefit was also reported in ADVANCE, VADT and ACCORD, with

durations of diabetes of 7.9-11.5 years.[10-12] Analysis of 10- versus 15-year follow-up of VADT suggests that the metabolic memory in intensively treated patients is time-limited, with any effect dissipating over prolonged follow-up.[31] The duration of follow-up in our data was 12 years, and it might be that benefits of early control would become blunted thereafter.

4.2 | Variability

HbA1c variability has been increasingly recognized as an adverse prognosticator in type 2 diabetes.[17,19-22] Our data show that this effect was independent of the baseline HbA1c and trajectory of HbA1c change over the first year. Long-term variability, based on HbA1c, may represent poor adherence to dietary and pharmacological regimes, rather than having the same interpretation as short-term (daily) variability.[31] Even so, ADVANCE showed that in a RCT (with the ability to monitor treatment adherence), greater HbA1c variability remained associated with an increased risk of vascular events and mortality.[16]

HbA1c variability may be a surrogate for the overall quality of care.[32] Therefore, we adjusted for baseline cardiovascular risk factors, although we did not have data for the transitioning of these factors over the follow-up period. Alternatively, the adverse effects of glycaemic variability may relate to sympathoadrenal activation from hypoglycaemia, causing myocellular irritability.[33] However, mortality risk persists for months after hypoglycaemia.[34] Hypoglycaemia, although considered under-reported, is highly prevalent among people with type 2 diabetes, particularly in late disease.[34] Visit-to-visit variability in fasting glucose has also been linked to all-cause mortality.[35]

We found that younger adults, aged 25-44 years, were more probable to remain in the high HbA1c category over the first year. This is concerning, as these patients may be more probable to benefit from a later pay-off from a legacy effect.[36] This observation should be explored in future studies.

There is currently no standardized definition for HbA1c variability. Studies have expressed variability as the SD or coefficient of variation for all HbA1c measurements.[18] However, in view of the progressive nature of type 2 diabetes and the tendency of HbA1c to increase over time,[3] the SD would be inflated relative to the mean without representing fluctuation in HbA1c. We considered an absolute change in HbA1c of at least 0.5% as being clinically meaningful, but modified the method of Forbes et al. to give greater statistical weight to more recent variability in HbA1c.[28]

4.3 | Strengths and limitations

The large size of the cohort and the robust nature of the diabetes case finding and classification algorithm are major advantages of our approach. Most type 2 diabetes in the UK is treated within primary care, meaning that it is improbable that any measurements of HbA1c would not have been recorded, and thus the results are translatable to the wider population.[17,19] Other studies of variability have been made from secondary care, with the potential for bias.[13,20,22] Only one other study has used primary care data in newly diagnosed type 2 diabetes,[19] and no studies have addressed the twin components of early control plus later variability, using primary care data.

Relationships of glycaemic patterns with mortality were not possible because of incomplete mortality data. Our primary endpoint was MACE, identified from primary care records. It is possible that some events, resulting in acute hospitalization, may not have been entered into the primary care record. However, we have shown that CVD is well recorded in the RCGP RSC.[37] Analysis of long-term VADT data [38] showed that intensive glycaemic control reduces the relative risk of non-fatal MI and coronary heart disease events, but without an effect on mortality. However, those analyses were not restricted to early onset of intensive therapy. We did not include diabetes medications as a covariate, as the relationship between HbA1c and diabetes medications is not unidirectional.[29] The BMI may modify the relationship between HbA1c and mortality in patients with type 2 diabetes[39] and so we adjusted for BMI at baseline, but BMI was not recorded sufficiently frequently to allow time-varying adjustment. Prediagnosis glucose exposure (duration and concentration) may have a bearing on subsequent outcomes, but—as with most studies of type 2 diabetes—we were unable to quantify the exposure to prolonged hyperglycaemia prior to the diagnosis of diabetes, although we did adjust for initial HbA1c.

Newer glucose-lowering agents (sodium-glucose co-transporter-2 inhibitors [SGLT2is] and glucagon-like peptide-1 receptor agonists [GLP-1 RAs]) have the added attribute of cardiovascular risk reduction and may also reduce glycaemic variability.[40,41] The use of SGLT2is and GLP-1RAs, at the time of data extraction (31 December 2016), was less than 5% among individuals with type 2 diabetes in our cohort.[24] The numbers in some of the first-year transition groups were less than 2% of the total cohort, consequently confidence intervals were wide. We excluded patients who did not have HbA1c measurements at both diagnosis and 1 year after (±3 months either side of diagnosis and at 1-year follow-up), plus at least five measurements of HbA1c thereafter. This may affect interpretation as to whether these results are representative of most patients with type 2 diabetes.

For the variability analysis, we used time-updated analyses, as greater weight is placed on more recent glycaemic exposure; however, with this approach there is a greater risk of reverse causality. Nevertheless, analysis of data using a time-fixed approach did not appreciably change the outcome. Transitioning from C to A categories within the first year was associated with reduced hazard for MACE, and therefore further research into the value of early intensification is needed, to establish whether benefits are therapy-related, and the appropriateness for more frail individuals.

In conclusion, we found that (i) transitioning to an HbA1c of less than 7.5% (<59 mmol/mol) in the first year after diagnosis of type 2 diabetes was associated with reduced MACE, and (ii) thereafter, lack of substantial variability also lowered the risk for MACE. Our findings support the concept that effort must be made to achieve rapid metabolic normalization after the diagnosis of diabetes in those with a low propensity to hypoglycaemia.

ACKNOWLEDGEMENTS

Rachel Byford and Julian Sherlock, SQL developers, for database management and data extraction; and the participating practices and patients for providing the data for this cohort. Collaboration with the GP computer system/data suppliers: EMIS, InPractice Systems, TPP and Wellbeing; and Eli Lilly and Company as funders for this work.

CONFLICT OF INTEREST

MBW has received investigator-led grant funding from AstraZeneca, Sanofi, Eli Lilly and speaker fees from AstraZeneca and MSD. AMcG has received research funding from Eli Lilly, AstraZeneca, Boehringer-Ingelheim and Pfizer. NM has received fees for serving as a speaker, a consultant or an advisory board member for Allergan, Bristol-Myers Squibb-Astra Zeneca, GlaxoSmithKline, Eli Lilly, Lifescan, MSD, Metronic, Novartis, Novo Nordisk, Pfizer, Sankio, Sanofi, Roche, Servier and Takeda. SdeL has held grants through his University for investigator-led studies from AstraZeneca, Eli Lilly Company (which funded academic time including part of WHs to work on this project), GlaxoSmithKline, MSD, Takeda and Novo Nordisk Limited. JM is an employee of Eli Lilly Company. WH, JvV, FF, MJ, UH report no conflicts of interest.

AUTHOR CONTRIBUTIONS

MBW: conceptualization, formal analysis, writing original draft. MJ: methodology, formal analysis. WH: formal analysis, writing – review & editing. AMcG: formal analysis, writing – review & editing. UH: formal analysis, writing – review & editing. JvV: methodology, formal analysis. FF: data curation, project administration. JM: project administration; writing original draft; writing – review & editing. NM: conceptualization, data interpretation, writing original draft. SdL: conceptualization, writing original draft, oversight and leadership responsibility for the research activity planning and execution.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/dom.14705.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ORCID

Martin B. Whyte https://orcid.org/0000-0002-2897-2026
Simon de Lusignan https://orcid.org/0000-0002-8553-2641

REFERENCES

1. Rawshani A, Rawshani A, Franzen S, et al. Risk factors, mortality, and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2018;379(7):633-644.
2. de Jong M, Woodward M, Peters SAE. Diabetes, glycated hemoglobin, and the risk of myocardial infarction in women and men: a prospective cohort study of the UKbiobank. *Diabetes Care*. 2020;43:2050-2059.
3. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med*. 2008;359(15):1577-1589.
4. Kerr D, Partridge H, Knott J, Thomas PW. HbA1c 3 months after diagnosis predicts premature mortality in patients with new onset type 2 diabetes. *Diabet Med*. 2011;28(12):1520-1524.
5. Laiteerapong N, Ham SA, Gao Y, et al. The legacy effect in type 2 diabetes: impact of early glycemic control on future complications (the Diabetes & Aging Study). *Diabetes Care*. 2019;42(3):416-426.
6. Luo M, Lim WY, Tan CS, et al. Longitudinal trends in HbA1c and associations with comorbidity and all-cause mortality in Asian patients with type 2 diabetes: a cohort study. *Diabetes Res Clin Pract*. 2017;133:69-77.
7. Ceriello A, Ihnat MA, Thorpe JE. Clinical review 2: the "metabolic memory": Is more than just tight glucose control necessary to prevent diabetic complications?*J Clin Endocrinol Metab*. 2009;94(2):410-415.
8. Ling C, Ronn T. Epigenetics in human obesity and type 2 diabetes. *Cell Metab*. 2019;29(5):1028-1044.
9. Saremi A, Howell S, Schwenke DC, et al. Advanced glycation end products, oxidation products, and the extent of atherosclerosis during the VA diabetes trial and follow-up study. *Diabetes Care*. 2017;40(4):591-598.
10. Action to Control Cardiovascular Risk in Diabetes Study Group, Gerstein HC, Miller ME, et al. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med*. 2008;358(24):2545-2559.
11. Duckworth W, Abraira C, Moritz T, et al. Glucose control and vascular complications in veterans with type 2 diabetes. *N Engl J Med*. 2009;360(2):129-139.
12. Group AC, Patel A, MacMahon S, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2008;358(24):2560-2572.
13. Hirakawa Y, Arima H, Zoungas S, et al. Impact of visit-to-visit glycemic variability on the risks of macrovascular and microvascular events and all-cause mortality in type 2 diabetes: the ADVANCE trial. *Diabetes Care*. 2014;37(8):2359-2365.
14. Quagliaro L, Piconi L, Assaloni R, Martinelli L, Motz E, Ceriello A. Intermittent high glucose enhances apoptosis related to oxidative stress in human umbilical vein endothelial cells: the role of protein kinase C and NAD(P)H-oxidase activation. *Diabetes*. 2003;52(11):2795-2804.
15. Rizzo MR, Barbieri M, Marfella R, Paolisso G. Reduction of oxidative stress and inflammation by blunting daily acute glucose fluctuations in patients with type 2 diabetes: role of dipeptidyl peptidase-IV inhibition. *Diabetes Care*. 2012;35(10):2076-2082.
16. Slieker RC, van der Heijden A, Nijpels G, Elders PJM, Hart LM, Beulens JWJ. Visit-to-visit variability of glycemia and vascular complications: the Hoorn diabetes care system cohort. *Cardiovasc Diabetol*. 2019;18(1):170.
17. Critchley JA, Carey IM, Harris T, DeWilde S, Cook DG. Variability in glycated hemoglobin and risk of poor outcomes among people with type 2 diabetes in a large primary care cohort study. *Diabetes Care*. 2019;42(12):2237-2246.
18. Gorst C, Kwok CS, Aslam S, et al. Long-term glycemic variability and risk of adverse outcomes: a systematic review and meta-analysis. *Diabetes Care*. 2015;38(12):2354-2369.
19. Li S, Nemeth I, Donnelly L, Hapca S, Zhou K, Pearson ER. Visit-to-visit HbA1c variability is associated with cardiovascular disease and microvascular complications in patients with newly diagnosed type 2 diabetes. *Diabetes Care*. 2020;43(2):426-432.
20. Orsi E, Solini A, Bonora E, et al. Haemoglobin A1c variability is a strong, independent predictor of all-cause mortality in patients with type 2 diabetes. *Diabetes Obes Metab*. 2018;20(8):1885-1893.
21. Skriver MV, Sandbaek A, Kristensen JK, Stovring H. Relationship of HbA1c variability, absolute changes in HbA1c, and all-cause mortality

in type 2 diabetes: a Danish population-based prospective observational study. *BMJ Open Diabetes Res Care*. 2015;3(1):e000060.
22. Penno G, Solini A, Zoppini G, et al. Hemoglobin A1c variability as an independent correlate of cardiovascular disease in patients with type 2 diabetes: a cross-sectional analysis of the renal insufficiency and cardiovascular events (RIACE) Italian multicenter study. *Cardiovasc Diabetol*. 2013;12:98.
23. Correa A, Hinton W, McGovern A, et al. Royal College of general practitioners research and surveillance Centre (RCGP RSC) sentinel network: a cohort profile. *BMJ Open*. 2016;6(4):e011092.
24. Whyte MB, Hinton W, McGovern A, et al. Disparities in glycaemic control, monitoring, and treatment of type 2 diabetes in England: a retrospective cohort analysis. *PLoS Med*. 2019;16(10):e1002942.
25. Arnold LW, Wang Z. The HbA1c and all-cause mortality relationship in patients with type 2 diabetes is J-shaped: a meta-analysis of observational studies. *Rev Diabet Stud*. 2014;11(2):138-152.
26. Li FR, Zhang XR, Zhong WF, et al. Glycated hemoglobin and all-cause and cause-specific mortality among adults with and without diabetes. *J Clin Endocrinol Metab*. 2019;104(8):3345-3354.
27. Nichols GA, Joshua-Gotlib S, Parasuraman S. Glycemic control and risk of cardiovascular disease hospitalization and all-cause mortality. *J Am Coll Cardiol*. 2013;62(2):121-127.
28. Forbes A, Murrells T, Mulnier H, Sinclair AJ. Mean HbA1c, HbA1c variability, and mortality in people with diabetes aged 70 years and older: a retrospective cohort study. *Lancet Diabetes Endocrinol*. 2018;6(6):476-486.
29. Laiteerapong N, Karter AJ, Moffet HH, et al. Ten-year hemoglobin A1c trajectories and outcomes in type 2 diabetes mellitus: the Diabetes & Aging Study. *J Diabetes Complications*. 2017;31(1):94-100.
30. Ueki K, Sasako T, Okazaki Y, et al. Effect of an intensified multifactorial intervention on cardiovascular outcomes and mortality in type 2 diabetes (J-DOIT3): an open-label, randomised controlled trial. *Lancet Diabetes Endocrinol*. 2017;5(12):951-964.
31. Monnier L, Colette C, Schlienger JL, Bauduceau B, Owens DR. Glucocentric risk factors for macrovascular complications in diabetes: glucose 'legacy' and 'variability'-what we see, know and try to comprehend. *Diabetes Metab*. 2019;45(5):401-408.
32. Ceriello A, Rossi MC, De Cosmo S, et al. Overall quality of care predicts the variability of key risk factors for complications in type 2 diabetes: an observational, longitudinal retrospective study. *Diabetes Care*. 2019;42(4):514-519.
33. Reno CM, Daphna-Iken D, Chen YS, VanderWeele J, Jethi K, Fisher SJ. Severe hypoglycemia-induced lethal cardiac arrhythmias are mediated by sympathoadrenal activation. *Diabetes*. 2013;62(10):3570-3581.
34. International Hypoglycaemia Study Group. Hypoglycaemia, cardiovascular disease, and mortality in diabetes: epidemiology, pathogenesis, and management. *Lancet Diabetes Endocrinol*. 2019;7(5):385-396.
35. Xu D, Fang H, Xu W, Yan Y, Liu Y, Yao B. Fasting plasma glucose variability and all-cause mortality among type 2 diabetes patients: a dynamic cohort study in Shanghai, China. *Sci Rep*. 2016;6:39633.
36. Florez HJ. Glycaemic control and glycaemic variability in older people with diabetes. *Lancet Diabetes Endocrinol*. 2018;6(6):433-435.
37. Hinton W, McGovern A, Coyle R, et al. Incidence and prevalence of cardiovascular disease in English primary care: a cross-sectional and follow-up study of the Royal College of general practitioners (RCGP) research and surveillance Centre (RSC). *BMJ Open*. 2018;8(8):e020282.
38. Hayward RA, Reaven PD, Emanuele NV, et al. Follow-up of glycemic control and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2015;373(10):978.
39. Andersson C, van Gaal L, Caterson ID, et al. Relationship between HbA1c levels and risk of cardiovascular adverse outcomes and all-cause mortality in overweight and obese cardiovascular high-risk women and men with type 2 diabetes. *Diabetologia*. 2012;55(9):2348-2355.
40. Henry RR, Strange P, Zhou R, et al. Effects of dapagliflozin on 24-hour glycemic control in patients with type 2 diabetes: a randomized controlled trial. *Diabetes Technol Ther*. 2018;20(11):715-724.
41. Umpierrez GE, O'Neal D, DiGenio A, et al. Lixisenatide reduces glycaemic variability in insulin-treated patients with type 2 diabetes. *Diabetes Obes Metab*. 2017;19(9):1317-1321.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Whyte MB, Joy M, Hinton W, et al. Early and ongoing stable glycaemic control is associated with a reduction in major adverse cardiovascular events in people with type 2 diabetes: A primary care cohort study. *Diabetes Obes Metab*. 2022;24(7):1310-1318. doi:10.1111/dom.14705