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The frequency of testing for glycated hemoglobin, HbA1c, is linked to the probability of achieving target levels in patients with sub-optimally controlled diabetes mellitus.

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Abbreviations. HbA1c: Glycated hemoglobin **,** DM: diabetes mellitus, NICE: National Institute for Health and Care Excellence, UHNM: University Hospital of North Midlands NHS Trust, RWT: Royal Wolverhampton NHS Trust, SRFT: Salford Royal NHS Foundation Trust.

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ABSTRACT

Introduction:

We previously showed, in patients with diabetes, that >50% of monitoring tests for glycated hemoglobin (HbA1c) are outside recommended intervals and that this is linked to diabetes control. Here, we examined the impact of tests/year on achievement of commonly-utilised HbA1c targets and on HbA1c changes over time.

Subjects & Methods:

Data on 20,690 adults with diabetes with a baseline HbA1c of >53 mmol/mol (7%) were extracted from Clinical Biochemistry Laboratory records at three UK hospitals. We examined the impact of HbA1c tests/year on: (i) probability of achieving targets of ≤53mmol/mol (7%) and ≤48mmol/mol (6.5%) in a year using multi-state modelling and (ii) changes in mean HbA1c using a linear mixed-effects model.

Results:

The probabilities of achieving ≤53mmol/mol (7%) and ≤48mmol/mol (6.5%) targets within 1 year were 0.20 (95% confidence interval:0.19-0.21) and 0.10 (0.09-0.10), respectively. Compared with 4 tests/year, having 1 test or >4 tests/year were associated with lower likelihoods of achieving either target; 2-3 tests/year gave similar likelihoods to 4 tests/year. Mean HbA1c levels were higher in patients who had 1 test/year compared to those with 4 tests/year (mean difference: 2.64mmol/mol [0.24%], p<0.001).

Conclusions:

We showed that ≥80% of patients with sub-optimal control are not achieving commonly recommended HbA1c targets within 1 year, highlighting the major challenge facing healthcare services. We also demonstrated that, while appropriate monitoring frequency is important, 6-monthly testing is as effective as quarterly testing, supporting international recommendations. We suggest that the importance HbA1c monitoring frequency is being insufficiently recognised in diabetes management.

INTRODUCTION

Achieving and maintaining adequate glycaemic control, as measured by glycated hemoglobin (HbA1c), is the focus of management strategies for patients with diabetes mellitus (DM). Guidance from many professional bodies worldwide recommends regular HbA1c monitoring to optimise the chances of attaining treatment goals for these patients. American Diabetes Association guidelines recommend testing '*at least two times a year in patients who are meeting treatment goals (and who have stable glycemic control)'* and *'quarterly in patients whose therapy has changed or who are not meeting glycaemic goals*' (1), while UK National Institute for Health and Care Excellence (NICE) guidance recommends measuring HbA1c at '*3–6-monthly intervals…, until the HbA1c is stable on unchanging therapy'* and '*6-monthly intervals once the HbA1c level and blood glucose lowering therapy are stable*' (2-3).

While guidance on monitoring frequency is clear, studies have shown that many patients do not have tests at the recommended frequency (4-11). For example, a Australian study (10) showed that, of patients with HbA1c >53 mmol/mol (>7%), only 22.9% received a follow-up test within the recommended 3-monthly interval over the 24 month study period, while we showed that >50% of all tests are requested outside recommended monitoring intervals (21% too soon; 30% too late) (7). We have observed this phenomenon in other cases where scheduled testing is required (12). This raises questions as to the implications of inadequate, excessive or inappropriate monitoring, on both clinical and economic endpoints (11). In an attempt to provide some validation of recommended intervals, Parcero et al (13), in a study of 193 patients with diabetes in general practice, found that median HbA1c values in patients who were tested at recommended intervals were significantly lower than those in

patients with intervals that did not adhere to guidelines. Furthermore, we have previously shown that HbA1c monitoring interval is associated with changes in diabetes control, as measured by difference in HbA1c levels between consecutive tests (11) while Phan et al (14) showed that excessive or infrequent testing was associated with a higher proportion of patients with worsening glycaemic control. Fu et al (15) also studied the relationship between patient-reported HbA1c testing frequency and optimal glycaemic control defined as a target HbA1c of <53 mmol/mol (<7%). They showed that, after adjusting for age, gender, education level and lifestyle factors, patients with ≥2 tests/year were more likely to have an HbA1c below target than those with either one or no tests during that period.

With regard to patient management, the most important decision is how frequently to test in order to achieve the patient treatment goal. While Fu et al (15) sought to address this, their analysis was cross-sectional and did not sub-classify patients with ≥2 tests/year. Loh et al (16) indicated that testing more frequently than every 4 weeks was not justified while Phan et al (14) indicated that, in young patients with type 1 diabetes, four tests/year was least likely to result in worsening control. Nevertheless, the wider question of optimum number of test/year to attain the target HbA1c remains elusive.

In this study, we hypothesised that requesting HbA1c tests at recommended frequcny would result in a higher proportion achieving target and reduced overall HbA1c levels within 1 year. We analysed four years of HbA1c records from a cohort of patients with HbA1c levels >53 mmol/mol (7%) at baseline from a dataset of 39,138 patients with DM across three UK centres. We developed dynamic modelling based on multistate models to examine the impact of number of tests/year on the probability of achieving targets of 53 mmol/mol (7%)

and 48 mmol/mol (6.5%), as suggested in most guidance (1-3). Additionally, we examined the impact of frequency of testing on HbA1c levels over the course of the 4 years using longitudinal modelling.

RESEARCH DESIGN AND METHODS

Patients

This study involved patient level data collected as part of routine clinical practice from clinical laboratory databases. Data on all HbA1c test requests from 39,138 patients >16 years old collected from 2007 to 2011 were extracted from the Clinical Biochemistry Laboratory Information Management Systems at the University Hospital of North Midlands NHS Trust (UHNM), Royal Wolverhampton NHS Trust (RWT) and Salford Royal NHS Foundation Trust (SRFT) (7,11). HbA1c concentrations were obtained using either cation-exchange high performance liquid chromatography (Tosoh G8; UHNM and RWT) or borate affinity high performance liquid chromatography (Menarini Hb9210; SRFT) methodology, with a between batch coefficient of variation of <2%. In each laboratory, external quality assurance was provided by membership of the UK National External Quality Assurance Scheme (NEQAS). From this data set, we examined the cohort of patients who had a baseline HbA1c test above 53 mmol/mol (7%) and at least one further HbA1c requested on an annual anniversary (i.e. at intervals of 365 days ± 30 days) during the study period. These comprised 20,836 individuals, 53.2% of the original dataset; 146 were excluded due to missing HbA1c levels. This left a core dataset of 20,690 participants (3483 from SRFT, 9502 from UHNM and 7705 from RWT), including information on dates of requested tests in the course of four years, HbA1c levels, age, sex and centre.

Model development and study design

Rates of transition and probability of achieving HbA1c targetThe main objective was to examine the impact of frequency of testing on the probability of achieving a target HbA1c level (≤53 mmol/mol [≤7%] or ≤48 mmol/mol [≤6.5%]) for patients with sub-optimal control

at baseline. Each patient had 1-4 HbA1c records on the annual anniversaries after baseline. For each patient, at each of their yearly test dates, we defined two possible *states*: "HbA1c level >target", if the HbA1c level was above the set threshold, or "HbA1c level ≤target" if the target was achieved. Every patient occupied the "HbA1c level >target" state (for the 53 mmol/mol [7%] threshold) at baseline. Over time, at each yearly test request, a patient either remained in their current state or moved to the other state, generating a sequence of *transitions* from one state to the other. A multi-state model (17) was developed, for each threshold value (53 mmol/mol [7%] and 48 mmol/mol [6.5%]), to model these transitions.

A time-varying categorical variable "frequency of testing" was created to indicate the number of tests a patient had within his/her previous year's record (excluding the baseline test), with value "1" if the patient had just one additional test, "2", "3", "4" and ">4" if the patient had 2, 3, 4, or 5 or more additional tests, respectively.

The hazard functions of transition were modelled in terms of frequency of testing, sex, age and centre. In addition, the model was stratified by baseline HbA1c category (53-64, 64-75, 75-86,86-108,>108 mmol/mol [7-8%, 8-9%, 9-10%, 10-12% >12%]) to give an indication of the initial degree of sub-optimal control.

The focus of the analysis was the rate of transition from "HbA1c level >target" to "HbA1c level ≤target"; this provides a dynamic assessment of glycaemic control. Estimates of the hazard ratios are reported for each explanatory variable. For a categorical variable (e.g. frequency of testing), the hazard ratio represents the ratio of transition rates for each category compared to a reference category. For a continuous variable (e.g. age), the hazard

ratio is the ratio of transition rates for two individuals with one unit difference. A hazard ratio value of one indicates no difference in rates. Finally, from this model the probability of moving from the state "HbA1c level >target" to the state "HbA1c level ≤target" during one year was calculated overall and by frequency of testing, holding the values of other explanatory variables fixed at their mean value.

Changes of HbA1c levels over time

The second objective was to assess the impact of frequency of testing on changes in HbA1c levels over time. A linear mixed-effects regression model with a random intercept was fitted to HbA1c levels, after screening of the sampling distribution of the data to check that the distribution was symmetric. The linear regression model included frequency of testing, sex, age (centred on the baseline mean), centre, a categorical variable for time from baseline as explanatory variables and a random intercept. A quadratic term for age was also included to assess departures from the assumption of linearity between HbA1c levels and age.

Statistical analysis

As described above, the impact of frequency of testing on the probability of achieving a target HbA1c level (≤53 mmol/mol [≤7%] or ≤48 mmol/mol [≤6.5%]) for patients with sub-optimal control at baseline was analysed using multi-state model for each target. A linear mixed-effects regression model with a random intercept was used to assess impact of testing frequency on HbA1c levels**.** All models were fitted by maximum likelihood estimation. *P*-values for the linear random effects model were calculated using Wald tests.

All analyses were performed using the statistical software R (18) with the packages “msm” (19) and “lme4” (20).

RESULTS

Descriptive statistics

The cohort of 20,690 patients (55.9% male) had a median age of 62 years (IQR=51-71 years) and a median HbA1c concentration of 65 mmol/mol (IQR=57.4-79.2 mmol/mol; 8.1%, IQR=7.4-9.4%) at baseline. Of these, 11,872 patients contributed data at baseline and 1 year, 5952 with an additional year, 2187 with 3 years and 572 with 4 consecutive years after baseline. The remaining 107 cases contributed data at baseline and other combinations of years (eg 22 cases contributed data at baseline, and years 1 and 3).

In the course of the four years, in only 20.4% (6137/30,054) of instances did the HbA1c level change from >53 mmol/mol (>7%l; above target) to ≤53 mmol/mol (≤7%; below target) between two consecutive years. Changes from HbA1c >48 mmol/mol (>6.5%) to HbA1c ≤48 mmol/mol (≤6.5%) were observed in only 10.0% (3139/31,540) of occasions.

The boxplots in Supplemental Figure S1 show the empirical distribution of HbA1c levels by frequency of testing. Although this does not account for the correlation among observations from the same individual or the effect of time, it is apparent that the overall HbA1c levels were similar across the groups.

Rates of transition and probability of achieving HbA1c target

Table 1 shows the hazard ratio estimates of a transition from HbA1c >target to HbA1c ≤target. There was no difference in rates of achieving either target between females and males. However, the hazard ratio for age was greater than one, indicating that older patients are more likely to achieve target. There were also differences between centres,

with cases from RWT more likely to achieve the 53 mmol/mol (7%) target, and those from both UHNM and RWT less likely to achieve the 48 mmol/mol (6.5%) target relative to SRFT. As expected, cases with a higher baseline HbA1c were less likely to achieve the targets compared with those with an initial HbA1c of 53-64 mmol/mol (7-8%), though those with a baseline HbA1c of >108 mmol/mol (>12%) were generally more likely to achieve target than those with values between 64 and 108 mmol/mol (8-12%).

As most guidelines on frequency of monitoring for sub-optimally controlled patients recommend 4 tests/year, this was chosen as comparator (reference category) in assessment of impact of testing frequency on achievement of target. The proportion achieving either 53 mmol/mol (7%) or 48 mmol/mol (6.5%) targets were similar for those patients who were monitored twice or three times a year, to those the reference category (4 tests/year). In contrast, compared with 4 tests/year, there was a 33% and 25% decrease in the rates of achieving the 53 mmol/mol (7%) target for monitoring frequencies of 1 and >4 times/year, respectively. Similarly, those who were monitored 1, or >4 times had a 39% and 20% reduction in the rates of achieving the 48 mmol/mol target, respectively.

Table 2 shows the estimated probability of each possible transition, holding the explanatory variables fixed at their mean value. The overall probability of achieving the 53 mmol/mol (7%) target for patients who were sub-optimally controlled the previous year was 0.20 (95% CI: 0.19, 0.21), and 0.10 (95% CI: 0.09, 0.10) for the 6.5% (48 mmol/mol) threshold. Thus, only 20% of cases were predicted to achieve the 53 mmol/mol (7%) target. Furthermore, once this target was achieved, 52% of cases were predicted to remain within target in the

subsequent year. Similarly, for the 48 mmol/mol (6.5%) target, only 10% were predicted to achieve target and 52% predicted to subsequently remain within this target.`

Figure 1 provides a graphical representation of the probability of achieving the HbA1c target in one year overall and by frequency of testing. The probability of achieving the target is comparable when 2 or 3 tests are done compared to 4 for both thresholds. However, both 1 test/ year and >4 tests/year had a lower probability of achieving either target.

Changes of HbA1c levels over time

Table 3 shows the estimated mean changes in HbA1c level over time from a linear mixed-effects model. There was no significant difference in mean HbA1c level between males and females, or between sites. However, there was a non-linear relationship between mean HbA1c values and age, as reflected by the statistical significance of both linear and quadratic terms. This relationship is illustrated in Supplemental Figure S2. It shows that HbA1c levels were higher in younger patients, but this year-on-year decrease in mean HbA1c levels becomes smaller with increasing age. Table 3 also shows the mean differences in HbA1c levels over time. This illustrates that the mean HbA1c did not change significantly during the course of the study, except in the last year where there was a statistically significant increase of 1.42 mmol/mol (0.13%) with respect to year 1. This may reflect overall disease progression over time.

There was no significant difference in mean HbA1c levels with 2 or 3 tests/year compared with 4 tests/year. However, there was a significant mean difference in HbA1c levels of 2.64 mmol/mol (95% CI: 2.00, 3.28) (0.242%, 95% CI: 0.183, 0.300) between those who have 1

and those who have 4 tests/year. Those who had >4 tests also had a slightly larger value than the reference group (those with 4 tests); mean difference was 0.52 mmol/mol (95% CI: -0.001, 1.03) (0.048%, 95% CI: 0.000, 0.095).

DISCUSSION

We demonstrated, using dynamic modelling, in a large cohort of sub-optimally controlled patients with diabetes across three UK centres, that (i) 80% of patients fail to achieve a target of ≤53 mmol/mol (≤7%) within 1 year (90% fail to achieve a target of ≤48 mmol/mol (≤6.5%)), and (ii) overall, two or three HbA1c tests/year are equivalent to four tests at achieving HbA1c target values, but one test per year was inadequate; there was no added benefit in carrying out more than four HbA1c tests/year.

Rates of transition and probability of achieving HbA1c target

Overall probability of achieving targets. The large number of patients with sub-optimal control who do not reach recommended targets, despite regular monitoring, is of major concern. Our findings that only ~20% of patients with HbA1c >53 mmol/mol (>7%) attain a target level of ≤53 mmol/mol (≤7%) one year later are similar to the 32% seen by Anichini et al (21) in a small cross-sectional sample (n=315) with a similar baseline (72.7 mmol/mol [8.8%]) and 1-year (58.5 mmol/mol [7.5%]) HbA1c values. In the study by Paul et al (10), only 18.5% of cases with a baseline HbA1c of >53 mmol/mol (>7%) had a subsequent test result below 53 mmol/mol (7%) over the 2 year follow-up period. Hence, in spite of the resources put into diabetes management, many patients remain above target HbA1c, with all the attendant adverse long-term health consequences for the individual (22-24).

Impact of monitoring frequency. Our analysis then focussed on assessment of the impact of monitoring frequency on the rate of transitions from sub-optimal to target glycaemic control. Our multistate model accommodated the adjustment to monitoring frequency that is likely to occur, for a given patient, following a high HbA1c measurement, thus providing a

dynamic assessment of glycaemic control. Our results clearly show that annual testing is inadequate, yielding a 33% reduced likelihood of achieving control compared to 4 tests/year.

Our data is consistent with the work of Fu et al (15) in 1511 patients with type 2 diabetes attending outpatient clinics, where they identified that two or more tests/year resulted in a higher proportion of patients having a HbA1c of <53mmol/mol (<7%) (26.8%) compared with those who had one test/year (24.8%). However, our analysis extends this in indicating that more than 3-4 tests/year offers limited additional benefit in this regard, while >4 tests/year resulted in a reduced probability of achieving target. This is largely in keeping with recommended monitoring frequency in most international guidance (1-3) and with our previous work (11), though our data more explicitly support the view that 2-3 times per year is equally as effective as 4 times per year in achieving commonly used targets in sub-optimally controlled diabetes patients. Importantly, our findings appeared important relative to other factors, suggesting that monitoring interval is worthy of further attention in considering opportunities to intervene in order to achieve the recommended target.

While there were no differences in the rates of transition to optimal control between male and female patients, there was a small increase in the likelihood of achieving optimal control for older patients. This may relate to the observation that HbA1c values tended to be lower for older patients (-0.27 mmol/mol per year difference in age; Supplemental Figure S2). These findings are consistent with findings in a systematic review by Mannicci et al which showed that older age was associated with a higher success rate for achieving targets in both type 1 and type 2 DM (26). The CREDIT study demonstrated that younger age was

associated with being above the 53 mmol/mol (7.0%) HbA1c target (27) after correction for a range of other covariates. This may indicate that (i) older people may be better equipped to take charge of their diabetes, (ii) prevalence of anaemia increases with age and this may result in generally lower overall HbA1c levels due to more rapid red cell turnover (28, 29), and/or (iii) with more effective screening in primary care, a proportion of less complex cases are being diagnosed with T2DM (who would have lower HbA1c value and therefore potentially attain targets more readily). As expected, individuals with lower baseline HbA1c levels were more likely to achieve target. Those with initial HbA1c value 64-75 mmol/mol (8-9%) were 51% less likely to achieve the target than those with 53-64 mmol/mol (7-8%). However, those with a baseline value (108 mmol/mol (>12%) were only 35% less likely. This may be a consequence of more active intervention within this group, including secondary care and specialist nursing/dietetic input.

Changes of HbA1c levels over time

The longitudinal analysis on the relationship between tests/year and change in HbA1c was generally consistent with findings from the dynamic moddelling analysis. This showed that one test/year results in, on average, an increase in HbA1c of 2.64 mmol/mol (0.24%) compared with 4 tests/year. Extrapolating from UKPDS data (25), this would equate to a difference in risk of 5% for diabetes-related deaths, 3% for myocardial infarction, 3% for stroke, 4% for heart failure and 9% for microvascular complications.

Strengths and limitations

While this study indicates the overall optimum testing frequency in order to achieve commonly used targets in a large cohort across three centres using dynamic modelling, we

recognise that there are limitations to the study. Laboratory records provide limited access to clinical data and we were therefore unable to explore other factors such as the differentiation between type 1 and type 2 diabetes (or gestational diabetes), or treatment/lifestyle interventions which may influence the frequency of monitoring and rates of achieving targets. Neither did we explore the reasons lack of monitoring; a topic that has been examined elsewhere (30-33) and was beyond the scope of this study. We restricted the analysis to patients with sub-optimally controlled diabetes, so results cannot be generalised to the whole population of patients with diabetes. We also recognise that guidance suggests agreeing specific treatment targets for individual patients and so our definition of the cut-off for optimal control (<53mmol/mol (<7%)) could be perceived as an over-generalisation. However, our results indicate that testing frequency is important, a finding that is of particular concern following previous work showing that many patients do not have tests at the recommended intervals (4-10).

To our knowledge, this study is the first to provide a dynamic assessment of glycaemic control. This was achieved by modelling a patient's rate of transition within a year, from sub-optimal to optimal control, as a function of frequency of HbA1c testing the previous year, patient characteristics and centre. In contrast, previous observational studies are limited in their use of a single post-baseline HbA1c measurement (or average of a few follow-up measurements) in standard logistic regression analysis to estimate the probability of achieving glycaemic control post-baseline.

As distinct from other studies, we did not stratify by baseline HbA1c. Such stratification has been attempted in previous observational cross-sectional studies by adjusting for the baseline HbA1c in linear or logistic regression analysis of a post-baseline HbA1c

measurement (e.g. 21, 34). Although it may seem sensible to adjust for the baseline value because this is likely to predict the post-baseline HbA1c measurement, it has been shown (35, 36) that adjusting for the baseline value in observational studies, may introduce bias into the estimates of the effect of an exposure (frequency of testing in the present context).

Overall conclusions

While our findings highlight the importance of HbA1c monitoring *frequency* as well as *levels* in facilitating achievement of targets, we recognise that improvements in monitoring would not, in themselves, address the fact that a very large proportion of patients are not achieving target within one year. This remains a major challenge for healthcare services and indeed the wider social environment. It also highlights the need for behavioural change in facilitating appropriate HbA1c monitoring in diabetes (1-3, 5, 7, 10) as well as in a range of other patient groups (12, 33).

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a clinical laboratory scientist perspective. A.H. and F.W.H. provided clinical advice and critique from a clinical/research diabetologist perspective. R.J.P. provided a patient perspective and ensured the team had a patient-centered focus. All authors reviewed and edited the manuscript. A.A.F. 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. All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.

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References

1. American Diabetes Association: Standards of medical care in diabetes (2018) Diabetes Care 2018;41(Suppl. 1):S1–S153.

2. National Institute for Health and Clinical Excellence. Type 2 diabetes in adults: management (NG28). (Last updated: July 2016). Available at: https://www.nice.org.uk/guidance/ng28. Accessed: 11 May 2018

3. National Institute for Health and Clinical Excellence. Type 1 diabetes in adults: diagnosis and management (NG17). (Last updated: July 2016). Available at: https://www.nice.org.uk/guidance/ng17. Accessed: 11 May 2018

4. Akan P, Cimrin D, Ormen M, Kume T, Ozkaya A, Ergor G, et al. The inappropriate use of HbA1c testing to monitor glycaemia: is there evidence in laboratory data? J Eval Clin Pract 2007;13:21-4.

5. Lyon AW, Higgins T, Wesenberg JC, Tran DV, Cembrowski GS. Variation in frequency of haemoglobin A1c (HbA1c) testing: population studies used to assess compliance with clinical practice guidelines and use of HbA1c to screen for diabetes. J Diab Sci Technol 2009; 3:411-417.

6. Laxmisan A, Vaughan-Sarrazin M, Cram P. Repeated hemoglobin A1C ordering in the VA health system. Am J Med 2011; 124:342-9.

7. Driskell OJ, Holland D, Hanna FW, Jones PW, Pemberton RJ, Tran M, et al. Inappropriate requesting of glycated hemoglobin (HbA1c) is widespread: assessment of prevalence, impact of national guidance, and practice-to-practice variability. Clin Chem 2012; 58:906-915.

8. Pivovarov R, Albers DJ, Hripcsak G, Sepulveda JL, Elhadad N. Temporal trends of hemoglobin A1c testing. J Am Med Inform Assoc 2014; 21:1038-44.

9. McCoy RG, Van Houten HK, Ross JS, Montori VM, Shah ND. HbA1c overtesting and overtreatment among US adults with controlled type 2 diabetes, 2001-13: observational population based study. Br Med J 2015; 351:h6138.

10. Paul CL, Piterman L, Shaw JE, Kirby C, Barker D, Robinson J, et al. Patterns of type 2 diabetes monitoring in rural towns: How does frequency of HbA1c and lipid testing compare with existing guidelines? Aust J Rural Health 2016; 24:371-377.

11. Driskell OJ, Holland D, Waldron JL, Ford C, Scargill JJ, Heald A, et al. Reduced testing frequency for glycated haemoglobin, HbA1c, is associated with deteriorating diabetic control. Diabetes Care 2014; 37:2731-2737.

12. Scargill JJ, Livingston M, Holland D, Duff CJ, Fryer AA, Heald AH. Monitoring thyroid function in patients on levothyroxine. Assessment of conformity to national guidance and variability in practice. Experimental and Clinical Endocrinology & Diabetes 2017; 125:625-633.

13. Parcero AF, Yaeger T, Bienkowski RS. Frequency of Monitoring Hemoglobin A1C and Achieving Diabetes Control. J Prim Care Community Health 2011; 2:205-8.

14. Phan TL, Hossain J, Lawless S, Werk LN. Quarterly visits with glycated hemoglobin monitoring: the sweet spot for glycemic control in youth with type 1 diabetes. Diabetes Care 2014; 37:341-5.

15. Fu C, Ji L, Wang W, Luan R, Chen W, Zhan S, Xu B. Frequency of HbA1c monitoring was inversely associated with glycemic control of patients with type 2 diabetes mellitus. J Endocrinol Invest 2012; 35:269-273.

16. Loh TP, Tan KM, Saw S, Sethi SK. Glycated haemoglobin: what is the diagnostic yield at shortened testing intervals? Diabetes Res Clin Pract 2011; 94:e40-2.

17. Kalbfleisch JD, Lawless JF. The Analysis of Panel Data Under a Markov Assumption. J Am Statistical Assoc 1985; 80:863-871.

18. R Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. 2016. Available at: https://www.R-project.org/. Accessed: 11 May 2018.

19. Jackson CH. Multi-state models for panel data: The msm package for R. J Statistical Software 2011; 38:1-29.

20. Bates D, Maechler M, Bolker B, Walker S. Fitting linear mixed-effects models using lme4. J Statistical Software 2015; 67:1-48.

21. Anichini R, Cosimi S, Di Carlo A, Orsini P, De Bellis A, Seghieri G, et al. Gender difference in response predictors after 1-year exenatide therapy twice daily in type 2 diabetic patients: a real world experience. Diabetes Metab Syndr Obes 2013; 6:123-9.

22. Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) Study Research Group. Intensive Diabetes Treatment and Cardiovascular Outcomes in Type 1 Diabetes: The DCCT/EDIC Study 30-Year Follow-up. Diabetes Care 2016; 39:686-93.

23. 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; 359:1577-89.

24. Gaede P, Lund-Andersen H, Parving HH, Pedersen O. Effect of a multifactorial intervention on mortality in type 2 diabetes. N Engl J Med 2008; 358:580-91.

25. Stratton IM, Adler AI, Neil HA. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. Br Med J 2000; 321:405-12.

26. Mannucci E, Monami M, Dicembrini I, Piselli A, Porta M. Achieving HbA1c targets in clinical trials and in the real world: a systematic review and meta-analysis. J Endocrinol Invest. 2014; 37:477-95.

27. Balkau B, Calvi-Gries F, Freemantle N, Vincent M, Pilorget V, Home PD. Predictors of HbA1c over 4 years in people with type 2 diabetes starting insulin therapies: The CREDIT study. Diabetes Res Clin Pract 2015; 108:432-40.

28. Virtue MA, Furne JK, Nuttall FQ, Levitt MD. Relationship between GHb concentration and erythrocyte survival determined from breath carbon monoxide concentration. Diabetes Care 2004; 27:931-5.

29. Lupescu A, Bissinger R, Goebel T. Enhanced suicidal erythrocyte death contributing to anemia in the elderly. Cell Physiol Biochem 2015; 36:773-83.

30. Sood R, Sood A, Ghosh AK. Non-evidence-based variables affecting physicians' test-ordering tendencies: a systematic review. Neth J Med. 2007; 65:167-77.

31. Smellie WS, Galloway MJ, Chinn D, Gedling P. Is clinical practice variability the major reason for differences in pathology requesting patterns in general practice? J Clin Pathol. 2002; 55:312-4.

32. Yasaitis LC, Bubolz T, Skinner JS, Chandra A. Local population characteristics and hemoglobin A1c testing rates among diabetic medicare beneficiaries. PLoS One; 2014 9:e111119.

33. Fryer AA, Smellie WS. Managing demand for laboratory tests: a laboratory toolkit. J Clin Pathol. 2013; 66:62-72.

34. Svensson E, Baggesen LM, Thomsen RW, Lyngaa T, Pedersen L, Nørrelund H, et al. Patient-level predictors of achieving early glycaemic control in Type 2 diabetes mellitus: a population-based study. Diabet Med 2016; 33:1516-1523.

35. Fitzmaurice GM, Laird NM, Ware JH. Applied longitudinal analysis. 2nd edn. Hoboken, NJ: Wiley 2011.

36. Glymour MM, Weuve J, Berkman LF, Kawachi I, Robins JM. When is baseline adjustment useful in analyses of change? An example with education and cognitive change. Am J Epidemiol 2005; 162:267–78.

Table 1 Estimated hazard rates (95% CI) for the transitions from HbA1c >target to HbA1c ≤target

Explanatory variable	Transition	
	HbA1c >53 mmol/mol to HbA1c ≤53mmol/mol (>7% to ≤7%)	**HbA1c >48 mmol/mol to HbA1c ≤48 mmol/mol (>6.5% to ≤6.5%)**
Sex		
Female	Reference	Reference
Male	0.98, (0.83, 1.16)	0.96, (0.86, 1.08)
Age	1.01, (1.00, 1.01)	1.00, (1.00, 1.01)
Frequency of tests		
4	Reference	Reference
1	0.67, (0.56, 0.80)	0.61, (0.49, 0.77)
2	0.88, (0.75, 1.03)	0.92, (0.75, 1.11)
3	0.98, (0.83, 1.16)	1.00, (0.81, 1.23)
> 4	0.75, (0.62, 0.91)	0.80, (0.63, 1.02)
Baseline HbA1c		
53-64 mmol/mol (7-8%)	Reference	Reference
64-75 mmol/mol (8-9%)	0.49, (0.40, 0.51)	0.55, (0.47, 0.64)
75-86 mmol/mol (9-10%)	0.37, (0.31, 0.43)	0.50, (0.42, 0.61)
86-108 mmol/mol (10-12%)	0.38, (0.32, 0.44)	0.53, (0.44, 0.65)
>108 mmol/mol (>12%)	0.65, (0.50, 0.83)	0.84, (0.63, 1.13)
Site		
SRFT	Reference	Reference
UHNM	1.12, (0.99, 1.27)	0.81, (0.70, 0.95)
RWT	1.23, (1.08, 1.40)	0.85, (0.72, 1.00)

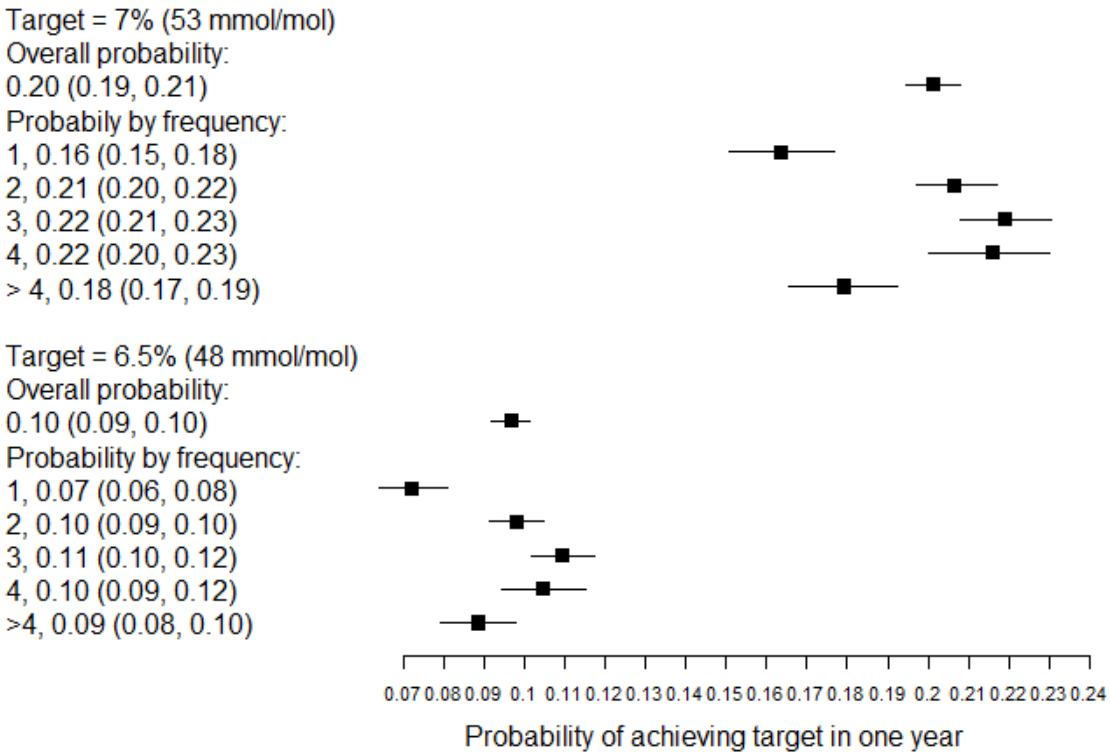
Table 2 Estimated probabilities (95%CI) of each transition in one year, holding the explanatory variables in the model (see Table 1) fixed on their mean values. For example, the probabilities of achieving targets of ≤53 mmol/mol (7%) and ≤48 mmol/mol (6.5%), with a starting point of >53mmol/mol (>7%), are presented in **bold**. Similarly, the probabilities of remaining below a target of ≤53 mmol/mol (7%), once achieved, are presented in *italics*.

	Year t	
	HbA1c ≤53 mmol/mol (≤7%)	HbA1c >53 mmol/mol (>7%)
Year t_{-1}		
HbA1c >53 mmol/mol (>7%)	**0.20 (0.19, 0.21)**	0.80 (0.79, 0.81)
HbA1c ≤53 mmol/mol (≤7%)	*0.52 (0.48, 0.55)*	0.48 (0.45, 0.52)
	Year t	
	HbA1c ≤48 mmol/mol (≤6.5%)	HbA1c >48 mmol/mol (>6.5%)
Year t_{-1}		
HbA1c >48 mmol/mol (>6.5%)	**0.10 (0.09, 0.10)**	0.90 (0.90, 0.91)
HbA1c ≤48 mmol/mol (≤6.5%)	*0.52 (0.48, 0.55)*	0.48 (0.45, 0.52)

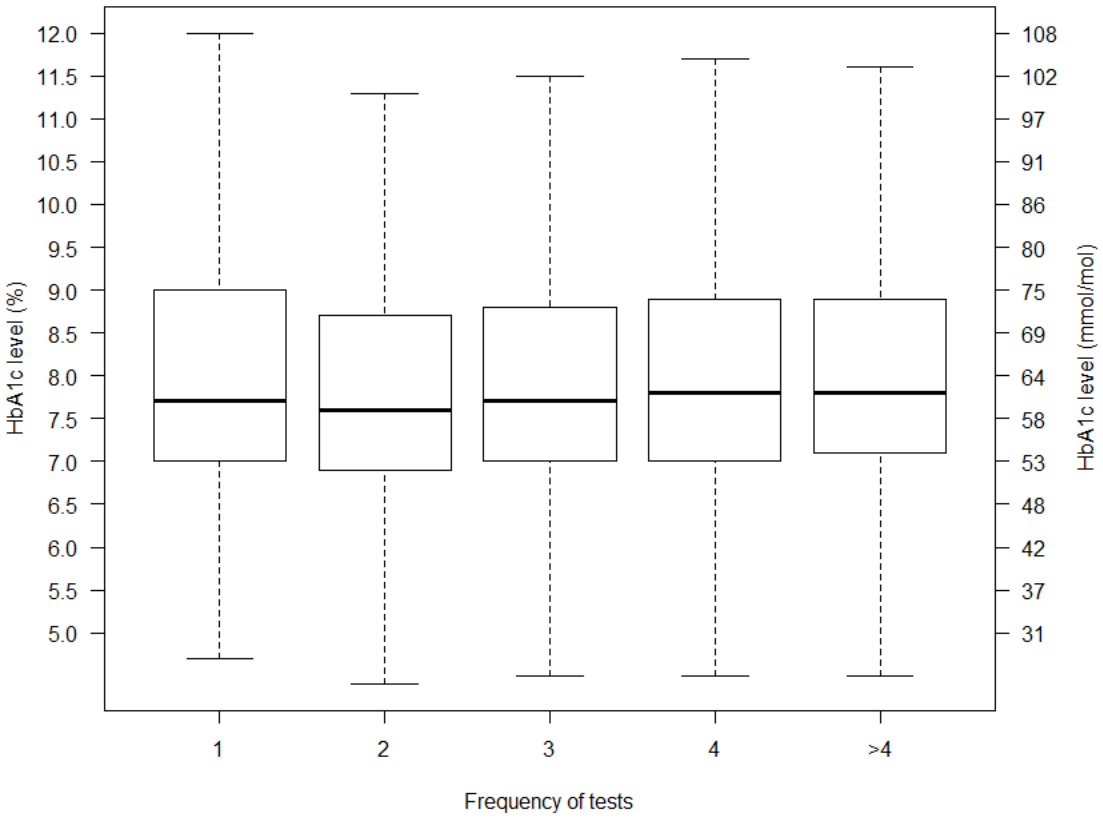
Table 3 Estimated mean differences from linear random effects model for HbA1c levels.

Explanatory variable	Mean difference in HbA1c levels (95% CI)		P-value
	(mmol/mol)	(%)	
Sex			
Female	Reference	Reference	
Male	-0.11 (-0.55, 0.34)	-0.010 (-0.050, 0.032)	0.63
Age			
Linear term	-0.27 (-0.29, -0.25)	-0.025 (-0.026, -0.023)	< 0.001
Quadratic term	0.003 (0.002, 0.004)	0.0003 (0.0002, 0.0003)	< 0.001
Frequency of tests			
4	Reference	Reference	
1	2.64 (2.00, 3.28)	0.242 (0.183, 0.300)	< 0.001
2	0.39 (-0.12, 0.90)	0.036 (-0.011, 0.083)	0.14
3	0.05 (-0.47, 0.57)	0.005 (-0.043, 0.052)	0.85
> 4	0.52 (-0.001, 1.03)	0.047 (-0.0001, 0.094)	0.05
Site			
SRFT	Reference	Reference	
UHNM	0.16 (-0.47, 0.79)	0.015 (-0.043, 0.072)	0.62
RWT	0.26 (-0.39, 0.91)	0.024 (-0.036, 0.083)	0.43
Year			
Year 1	Reference	Reference	
Year 2	-0.06 (-0.37, 0.24)	-0.006 (-0.033, 0.022)	0.69
Year 3	0.39 (-0.10, 0.88)	0.036 (-0.009, 0.081)	0.12
Year 4	1.42 (0.41, 2.43)	0.130 (0.038, 0.222)	0.01

Figure 1 Probability of transition HbA1c >target to HbA1c ≤target (95% CI); overall and by number of tests per year holding the values of other explanatory variables in the model (Table 1) fixed on their mean value.



Supplemental Figure S1 Boxplots of HbA1c levels by number of tests per year



Supplemental Figure S2 Predicted HbA1c levels by age, with 95% confidence band