Contemporary Risk Estimates of Three HbA1c Variables for Myocardial Infarction in 101,799 Patients Following Diagnosis of Type 2 Diabetes

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OBJECTIVE
This study evaluated the risk of myocardial infarction (MI) by impaired glycemic control in a contemporary large cohort of patients with type 2 diabetes followed up from diagnosis.

RESEARCH DESIGN AND METHODS
Patients with type 2 diabetes diagnosed between 1995 and 2011 were retrieved from the Clinical Practice Research Data Link in the U.K., and followed up from diagnosis until event of MI or end of study in 2013. Two subcohorts were defined: an early cohort with those diagnosed from 1997 to 2004 and a recent cohort with those diagnosed from 2004 to 2011. Association between each of three HbA1c metrics and MI was estimated using adjusted proportional hazard models.

RESULTS
In the overall cohort (n = 101,799), the risk increase for MI per 1% (10 mmol/mol) increase in HbA1c was higher for updated latest and updated mean HbA1c of 1.11 (95% CI 1.09–1.13) and 1.15 (1.13–1.18) than for baseline HbA1c of 1.05 (1.03–1.06). In the early subcohort, the corresponding risk estimates were greater than those in the recent subcohort. When categorized, the updated latest variable showed an increased risk for HbA1c <6% (42 mmol/mol), relative category 6–7%, in the recent but not in the early subcohort, with hazard ratios of 1.23 (1.08–1.40) and 1.01 (0.84–1.22), respectively.

CONCLUSIONS
The two time-updated HbA1c variables show a stronger relation with MI than baseline HbA1c. The risk association between HbA1c and MI has decreased over time. In recently diagnosed patients with type 2 diabetes, an increased risk of MI exists at a current HbA1c of <6.0% (42 mmol/mol).

The global burden of diabetes has risen dramatically during the last two decades and is expected to affect more than 500 million adults worldwide by 2030, with the majority having type 2 diabetes (1). Patients with type 2 diabetes have a shorter life-expectancy, and myocardial infarction (MI) is the most common cause of the excess risk of death in these patients (2–4). Studies of glycemia as a risk factor for cardiovascular events have shown somewhat different results. Three large clinical trials,
conducted over 3–5 years, failed to demonstrate clearly beneficial effects of intensive glycemic control on cardiovascular outcomes (5); however, follow-up from the UK Prospective Diabetes Study (UKPDS) showed an association between intensive glucose control and a reduced risk of MI over 20 years (3). Observational studies have generally shown a lesser risk of MI at lower glycemic levels (6,7). However, no population-based real-world studies have evaluated the importance of glycemic control on the development of MI beginning at the diagnosis of diabetes and onward.

The most commonly used measure of glycemia is hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>), which reflects the mean glycemic level during the prior 2–3 months (8). Regular registration of HbA<sub>1c</sub> is part of the standard of care for diabetes patients. In recent years, collection of measurements, such as HbA<sub>1c</sub>, from primary care for use in research databases has been greatly simplified by automated electronic data transfer. Improved information on biomarkers specific to the development of cardiovascular disease (CVD) may also significantly contribute to the understanding of the progression of diabetes. However, the most appropriate method to account for repeated measurements is not obvious when factors for CVD events are evaluated in a statistical model. Various metrics of HbA<sub>1c</sub> have been used in studies of diabetes complications (9), most commonly, baseline HbA<sub>1c</sub> and the updated mean HbA<sub>1c</sub>, which at the time point for each new registration is the mean of all measurements taken so far. The landmark UKPDS trial evaluated both of these HbA<sub>1c</sub> variables and showed an association with an increased risk of MI (10).

In this study, we evaluated HbA<sub>1c</sub> in relation to MI in a large contemporary population of patients with type 2 diabetes in the U.K. and compared three distinct methods using HbA<sub>1c</sub> measurements taken from diabetes diagnosis and beyond. Furthermore, we investigated changes over time in the association between HbA<sub>1c</sub> and MI in a subcohort of patients with diabetes diagnoses from 1997 to 2003 compared with patients diagnosed from 2004 to 2010.

**RESEARCH DESIGN AND METHODS**

Data were obtained from the Clinical Practice Research Data Link (CPRD), where primary health care practitioners in the U.K. record daily patient information. The CPRD uses data sets linked from the U.K. health system to provide researchers with access to high-quality anonymous health care data that includes demographic, laboratory, prescribed drug, and diagnosis (11). Ethical approval was granted by the CPRD Scientific Committee and the National Information Governance Board of Ethics and Confidentiality Committee.

We identified 362,713 patients with type 2 diabetes in the CPRD diagnosed between 1 January 1995 and 31 December 2010. Date of diagnosis was defined as the first recorded diagnosis or use of type 2 diabetes medication. Patients aged 18 years or older were included if they had a record in the CPRD at least 1 year before diagnosis, no MI events within 1 year before diagnosis, and information on sex, age, blood pressure, and at least one recorded HbA<sub>1c</sub> measurement near the time of diagnosis. Patients younger than age 40 using insulin at diagnosis and continuing with insulin as the only glucose-lowering medication were excluded due to potential misclassification as type 1 diabetes. Follow-up time was defined as the time from diagnosis until the date of MI, death, or dropout from the register for any other reason, or the end of the study on 31 July 2013, whichever came first. MI was identified using the earliest record from the CPRD or Hospital Episode Statistics (HES) system. The MEDCODE and ICD-10 codes used to define MI events are listed in Supplementary Table 1.

Three different HbA<sub>1c</sub> variables were constructed: baseline, updated latest, and updated mean. Baseline HbA<sub>1c</sub> is the value recorded closest to date of diagnosis within 90 days before and 30 days after diagnosis. Updated latest HbA<sub>1c</sub> and updated mean HbA<sub>1c</sub> are time-varying variables that are recalculated each time a new HbA<sub>1c</sub> measurement is recorded during the patient’s follow-up. Updated latest HbA<sub>1c</sub> is set to the most recent recorded value, which then represents the patient’s HbA<sub>1c</sub> until a new measurement is taken. Similarly, updated mean HbA<sub>1c</sub> is the mean of all available HbA<sub>1c</sub> measurements.

Baseline values for other risk factors were determined by taking the value closest to diagnosis date, within a 2-year interval consisting of 1 year before and 1 year after diagnosis. Smoking status was assigned “yes” if the patient had at least once been recorded as a smoker or former smoker, “no” if all records indicated nonsmoker, and “unknown” if no information was available. Use of statins was defined as an indicator of any drug prescriptions of statins during the 2-year baseline time interval.

Two subcohorts were defined according to the time of diagnosis: an early subcohort consisted of patients diagnosed from 1 January 1997 to 31 December 2003 and a recent subcohort consisting of patients diagnosed from 1 January 2004 to 31 December 2010. Follow-up lasted until 31 July 2006 in the early subcohort and until 31 July 2013 in the recent subcohort to permit equal maximum follow-up in both groups.

**Statistical Analysis**

Proportional hazard models were constructed to assess and compare the association between each HbA<sub>1c</sub> variable and MI. A basis regression model adjusted for age, sex, systolic blood pressure (SBP), and history of MI was fitted for each HbA<sub>1c</sub> variable. History of MI is an indicator for having had an MI event more than 1 year before diagnosis of diabetes (patients who had an MI less than 1 year before diagnosis were excluded). Because the U.K. Quality Outcomes Framework introduced legal measures in 2003 to improve health care recording, which led to increased recording of variables related to both type 2 diabetes and CVD in the CPRD, models were stratified into two time periods to allow for different baseline hazard functions before and after the end of 2003.

Overall comparisons of the HbA<sub>1c</sub> variables were based on the estimated linear effect hazard ratios (HR). In addition, gradients of risk (i.e., the HR per SD unit increase) were calculated to provide a scale-free comparison (9). To further investigate the shape of the risk curves associated with MI, models were fitted with each HbA<sub>1c</sub> variable categorized as follows: ≤6% (42 mmol/mol), 6 to <7% (42–53) used as reference category, 7 to <8% (53–64), 8 to <9% (64–75), 9 to <10% (75–86), and ≥10% (86). Because of a strong interaction between sex and age, separate analyses for men and women were performed. Additional adjustment for smoking and statin use was...
examined to assess a possible effect on the HR estimates. Subgroup analyses of patients with baseline information on BMI and LDL and HDL cholesterol were performed for the entire cohort and separately for the early and recent subcohorts. Potential deviations from model assumptions were evaluated based on the scaled Schoenfeld residuals, and penalized spline functions were used to check the functional form of continuous covariates (12). To investigate change in HbA1c association over time, an interaction term between time period stratification and each of the HbA1c variables was included and tested within the proportional hazard regression models.

**RESULTS**

Median follow-up of the 101,799 patients was 5.4 years, men comprised 56% of the cohort, mean age was 63 years at diabetes diagnosis, mean SBP was 141 mmHg, 60% were taking statins, and 52% were smokers or former smokers at diagnosis (Table 1). Patients in the early subcohort were an average of 1 year older at diagnosis and had higher SBP and lower BMI than patients in the recent subcohort. Smoking was more common, but the use of statins was less common in the early compared with the recent subcohort.

The incidence rate of MI was significantly higher in the early subcohort, (Supplementary Table 2). Figure 1 shows the estimated incidence rates per age quintile for men and women separately, estimated in the complete cohort and in the two subcohorts.

**Relationship Between MI and HbA1c**

Regardless of HbA1c modeling or cohort studied, there was a significant association between HbA1c and MI. The estimated overall risk increase per 1% (10 mmol/mol) increase in HbA1c ranged from 5% for baseline HbA1c to 15% for the updated mean HbA1c in the complete cohort (Table 2). Results were similar when estimated separately by sex. Tests of interaction between each of the HbA1c variables and time period (before and after 1 January 2004) showed a significant decrease in association in the later period, with \( P = 0.02 \) for the linear effect baseline, \( P = 0.004 \) for the updated latest, and \( P < 0.001 \) for the updated mean HbA1c. In line with this drop of association, the HRs for the three HbA1c variables were all higher in the early compared with the recent subcohort.

**Comparisons of the Three HbA1c Variables**

According to the estimated linear effect HRs, baseline HbA1c showed the weakest association with MI, followed by updated latest and updated mean HbA1c (Table 2). This ranking was preserved when HRs were recalculated to reflect a 1 SD-unit increase in the HbA1c variable, although the difference between updated latest and updated mean diminished. The estimated HRs (95% CI) per 1-unit higher SD of the baseline, the updated latest, and the updated mean were 1.10 (1.07–1.13), 1.17 (1.14–1.21), and 1.21 (1.18–1.24), respectively. By HbA1c categories, there were discernible differences in the shape of the risk curves across HbA1c levels (Fig. 2, and Supplementary Table 3). Most notable was a significantly increased risk of 19% for the updated latest variable in HbA1c <6%, relative to the reference category 6–7%, where the corresponding estimates of the baseline and updated mean HbA1c showed a decrease in risk of 16% and 12%, respectively. The distribution of first and last HbA1c registrations of the 5,104 MI patients, as measured by updated latest variable, show that 14% of those who end up in HbA1c category <6% started in category ≥10% and that ~29% had their first registration in the categories ≥8%. In contrast, among those who end up in category <6% when measured by the updated mean variable, none had a first HbA1c registration in category ≥10%, and 1.3% had an HbA1c ≥8% at diagnosis (Supplementary Table 5).

Additional model adjustment for smoking and statin use did not substantially affect the risk estimates for the HbA1c variables (Supplementary Table 6). In subgroup analyses of the 59% of all patients with baseline information on BMI and LDL and HDL cholesterol, HRs for all three HbA1c variables were lower than the HRs in the main analyses. The characteristics and ranking of the variables did not deviate from the main analyses. Separate subgroup analyses of the early and recent subcohorts, comprising 38% and 71% of patients respectively, resulted in a similar degree of risk attenuation associated with HbA1c.
evaluation of HbA1c metrics in relation to MI results persisted (data not shown). Despite the decrease in event rate, our main finding was that patients with an MI event had an MI during follow-up. In the recent subcohort, 67,382 patients had 2,120 MI events, which comprised a larger proportion (66%) of patients in the overall cohort but a smaller proportion of all MI events (42%). The frequency distribution of patients across the HbA1c categories was shifted toward the lower HbA1c levels in the recent compared with the early subcohort. For instance, 52% of the patients in the recent cohort had their last recorded HbA1c in categories <6% or 6–7% compared with 44% in the early cohort (Supplementary Table 4).

The ranking of the three HbA1c variables was the same in the two subcohorts, with baseline HbA1c having the lowest HR and the updated mean the highest HR, but with less conspicuous differences among the three variables in the recent compared with the early cohort (Table 2). In the recent subcohort, 67,382 patients had 2,120 MI events, which comprised a larger proportion (66%) of patients in the overall cohort but a smaller proportion of all MI events (42%). The frequency distribution of patients across the HbA1c categories was shifted toward the lower HbA1c levels in the recent compared with the early subcohort. For instance, 52% of the patients in the recent cohort had their last recorded HbA1c in categories <6% or 6–7% compared with 44% in the early cohort (Supplementary Table 4).

CONCLUSIONS

In this population study of 101,799 patients followed up from diagnosis of type 2 diabetes, we found that the updated latest and updated mean variables were stronger predictors of MI than the baseline HbA1c variable. Differences found between the predictive powers of the three HbA1c variables were confirmed across the two time periods studied. Furthermore, we found that for all three HbA1c variables, the relation with MI was less strong for patients diagnosed during the recent period (2004–2010) compared with the earlier period (1997–2003). Hence, the importance of hyperglycemia as a risk factor for MI has decreased over time. In the recent subcohort, more diabetes patients received statin medications, and the mean blood pressure level was lower. Contributing to the complexity was the finding of a distinct J-shaped association between the updated latest HbA1c variable and MI in the recent subcohort but not in the early subcohort.

The purpose of studying various HbA1c estimates, besides comparing their predictive power, is to better understand the contribution of each on MI health outcomes. Baseline HbA1c alludes to the patient’s glycemic level at the time of diabetes diagnosis, whereas the updated latest HbA1c reflects the most recent glycemic status available as the disease progress over time, and the updated mean HbA1c carries a smoothed version of the patient’s glycemic history from diagnosis onward. As an illustration of the different characteristics of the updated latest and updated mean variables, it was noted that among those MI patients who had a HbA1c level ≥8% at their first registration, the updated latest variable places a strikingly higher percentage in the <6% category at their last registration than the updated mean does (29% vs. 1.3%). This makes sense because a patient needs...
to be stably below 6% to have a final
mean \( \text{HbA1c} \) in this category.

The importance of good glycemic control in patients with type 2 diabetes has been broadly debated (5), especially since three clinical trials found no beneficial effects on CVD or mortality (13–15). Several explanations have been discussed regarding the absence of an effect of intensive therapy in reducing CVD and mortality. One plausible explanation is the lack of follow-up time, supported by the fact that beneficial effects on MI and mortality only first emerged after the 10-year follow-up of the UKPDS (3). Other possibilities are the counter effects of hypoglycemia and weight gain while glycemic control improves, as well as improving glycemic control at an early or late stage of the disease (5,16).

In the current study, it was surprising that the risk estimates for all three \( \text{HbA1c} \) variables were lower during the recent compared with earlier follow-up period, which indicates that glucose-lowering effects may differ among contemporary patients. The findings indicate that the relative effect of hyperglycemia for the development of MI is less, which is essential for prognosis in clinical practice. These findings may also partly explain the absence of preventive effects by intensive glycemic control in the three contemporary trials discussed above. Although an explanation is speculative, patients with diabetes today are treated more rigorously with statins and antihypertensive medications (17,18) that may interact with benefits of improved glycemic control (19). Another unexpected finding was that the updated latest \( \text{HbA1c} \) showed a stronger association with MI than the baseline \( \text{HbA1c} \), which indicates that recent glycemia is of importance. Although this result is seemingly contradicted by the UKPDS (3), where beneficial effects of intensive glycemic control emerged only after relatively lengthy follow-up of 10–20 years, at the end of the original UKPDS (20), intensive glycemic control showed a borderline preventive effect on MI. In addition, meta-analyses of randomized trials of intensive glycemic control have shown a preventive effect on MI after ~5 years of follow-up (21,22). The present results, in combination with previous findings, indicate that glycemic control is important to the prevention of MI and, more importantly, perhaps within a shorter time perspective than 10–20 years.

The significantly increased risk for \( \text{HbA1c} <6\% \) shown by the updated latest variable in the recent cohort likely reflects differences in the composition of the two subcohorts as well as in the characteristics of the \( \text{HbA1c} \) variables. The absence of an increased risk when estimated by the baseline or the updated mean variables could be due to a greater temporal sensitivity of the updated latest variable in emphasizing the most recent \( \text{HbA1c} \) information at all time points. On top of that, the two subcohorts differ with respect to the frequency distribution of patients across the \( \text{HbA1c} \) categories, where in the recent cohort, the distribution is shifted toward the lower \( \text{HbA1c} \) categories. To our knowledge, however, the updated latest variable has not been used in this context before, and therefore, the elevated risk seen in \( \text{HbA1c} <6\% \) needs to be confirmed in other studies.

Risk engines used to guide clinicians in daily practice and health-economic analyses are generally based on observational analyses of the relation between glycemic control and complications (23,24). Cost-effectiveness studies of novel glucose-lowering drugs similarly rely on such relations (25,26), which is also the case for other health-economic analyses, such as those estimating diabetes-related costs to society (27–29). The present finding showing a reduced association between glycemic control and MI over time emphasizes the need to regularly update risk estimates using contemporary data.

A strength of the current study is the large population studied, which we believe is the largest observational study of glycemic control and MI in patients with type 2 diabetes. The size is essential to obtain adequately precise risk estimates for comparing different \( \text{HbA1c} \)
variables and cohorts. Although information on statin use was available in all studied patients, a weakness includes the large number of patients with missing information on cholesterol levels. However, analyses were repeated in subgroups of patients with cholesterol information, which yielded similar risk patterns in the three HbA1c variables but overall weaker risk estimates. Another limitation is that only MI events from the CPRD and HES were available to us at time of the analysis, Myocardial Ischamia National Audit Project data were not included. That all three repositories are needed to cover all recorded MI events has recently been reported (30).

In conclusion, the two time-updated HbA1c variables show stronger associations with risk of MI than baseline HbA1c, and the association between HbA1c and risk of MI has decreased over time. In recently diagnosed patients with type 2 diabetes, an increased risk of MI exists at a current HbA1c level of <6.0% (42 mmol/mol). Our results show that risk estimates of diabetes depend on both HbA1c metric type and temporal aspects of the cohort. This is important to consider when clinical trials are designed as well as in the development of health-economic models, risk engines, and clinical guidelines.

Duality of Interest. M.O., V.S., C.C., and S.S. are employed by AstraZeneca. M.L. has been a consultant or received honoraria from AstraZeneca, Medtronic, Novo Nordisk, and Pfizer, received research grants from Abbott Scandinavia, AstraZeneca, DexCom, Novo Nordisk, and Pfizer, and participated in advisory boards for Novo Nordisk. AstraZeneca funded access to the CPRD database. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. All authors took part in the design of the study and interpretation of the results. M.O. conducted the statistical analysis. M.O. and M.L. wrote the manuscript. V.S. retrieved the data from CPRD and reviewed and contributed to writing the manuscript. C.C. and S.S. reviewed and contributed to writing the manuscript. M.O. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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