Contemporary Risk Estimates of Three HbA_{1c} Variables for Myocardial Infarction in 101,799 Patients Following Diagnosis of Type 2 Diabetes

Marita Olsson,[1,2] Volker Schnecke,[1] Claudia Cabrera,[1] Stanko Skrtic,[1,3] and Marcus Lind[3,4]

Diabetes Care 2015;38:1481–1486 | DOI: 10.2337/dc14-2351

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 from diagnosis.

RESEARCH DESIGN AND METHODS

Patients with type 2 diabetes diagnosed between 1995 and 2011 were retrieved from the Clinical Practice Research Datalink in the U.K., and followed 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 HbA_{1c} metrics and MI was estimated using adjusted proportional hazards models.

RESULTS

In the overall cohort (*n* = 101,799), the risk increase for MI per 1% (10 mmol/mol) increase in HbA_{1c} was higher for updated latest and updated mean HbA_{1c} of 1.11 (95% CI 1.09–1.13) and 1.15 (1.13–1.18) than for baseline HbA_{1c} 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 HbA_{1c} <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 HbA_{1c} variables show a stronger relation with MI than baseline HbA_{1c}. The risk association between HbA_{1c} and MI has decreased over time. In recently diagnosed patients with type 2 diabetes, an increased risk of MI exists at a current HbA_{1c} 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,

[1]R&D AstraZeneca, Mölndal, Sweden
[2]Mathematical Sciences, Chalmers University of Technology, Gothenburg, Sweden
[3]Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden
[4]Department of Medicine, NU-Hospital Organization, Uddevalla Hospital, Uddevalla, Sweden

Corresponding author: Marita Olsson, marita.olsson@astrazeneca.com.

Received 6 October 2014 and accepted 7 May 2015.

This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc14-2351/-/DC1.

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_{1c} (HbA_{1c}), which reflects the mean glycemic level during the prior 2–3 months (8). Regular registration of HbA_{1c} is part of the standard of care for diabetes patients. In recent years, collection of measurements, such as HbA_{1c}, 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_{1c} have been used in studies of diabetes complications (9), most commonly, baseline HbA_{1c} and the updated mean HbA_{1c}, 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_{1c} variables and showed an association with an increased risk of MI (10).

In this study, we evaluated HbA_{1c} 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_{1c} measurements taken from diabetes diagnosis and beyond. Furthermore, we investigated changes over time in the association between HbA_{1c} 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 Datalink (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_{1c} 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_{1c} variables were constructed: baseline, updated latest, and updated mean. Baseline HbA_{1c} is the value recorded closest to date of diagnosis within 90 days before and 30 days after diagnosis. Updated latest HbA_{1c} and updated mean HbA_{1c} are time-varying variables that are recalculated each time a new HbA_{1c} measurement is recorded during the patient's follow-up. Updated latest HbA_{1c} is set to the most recent recorded value, which then represents the patient's HbA_{1c} until a new measurement is taken. Similarly, updated mean HbA_{1c} is the mean of all available HbA_{1c} 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 hazards models were constructed to assess and compare the association between each HbA_{1c} variable and MI. A basis regression model adjusted for age, sex, systolic blood pressure (SBP), and history of MI was fitted for each HbA_{1c} 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_{1c} variables were based on the estimated linear effect hazard ratios (HRs). 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_{1c} 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 $\geq$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 HbA_{1c} association over time, an interaction term between time period stratification and each of the HbA_{1c} variables was included and tested within the proportional hazards 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 HbA_{1c}

Regardless of HbA_{1c} modeling or cohort studied, there was a significant association between HbA_{1c} and MI. The estimated overall risk increase per 1% (10 mmol/mol) increase in HbA_{1c} ranged from 5% for baseline HbA_{1c} to 15% for the updated mean HbA_{1c} in the complete cohort (Table 2). Results were similar when estimated separately by sex. Tests of interaction between each of the HbA_{1c} 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 $P < 0.0001$ for the updated mean HbA_{1c}. In line with this drop of association, the HRs for the three HbA_{1c} variables were all higher in the early compared with the recent subcohort.

Comparisons of the Three HbA_{1c} Variables

According to the estimated linear effect HRs, baseline HbA_{1c} showed the weakest association with MI, followed by updated latest and updated mean HbA_{1c} (Table 2). This ranking was preserved when HRs were recalculated to reflect a 1 SD-unit increase in the HbA_{1c} 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 HbA_{1c} categories, there were discernible differences in the shape of the risk curves across HbA_{1c} levels (Fig. 2, and Supplementary Table 3). Most notable was a significantly increased risk of 19% for the updated latest variable in HbA_{1c} <6%, relative to the reference category 6–7%, where the corresponding estimates of the baseline and updated mean HbA_{1c} showed a decrease in risk of 16% and 12%, respectively. The distribution of first and last HbA_{1c} registrations of the 5,104 MI patients, as measured by updated latest variable, show that 14% of those who end up in HbA_{1c} 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 HbA_{1c} registration in category ≥10%, and 1.3% had an HbA_{1c} ≥8% at diagnosis (Supplementary Table 5).

Additional model adjustment for smoking and statin use did not substantially affect the risk estimates for the HbA_{1c} 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 HbA_{1c} 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 HbA_{1c}

Table 1—Characteristics of patients at diabetes diagnosis

	Complete cohort diagnosed in 1995–2010 *n* = 101,799	Early cohort diagnosed in 1997–2003 *n* = 32,551	Recent cohort diagnosed in 2004–2010 *n* = 67,382
Sex, *n* (%)			
Men	56,618 (56)	17,852 (55)	37,748 (56)
Women	45,181 (44)	14,699 (45)	29,634 (44)
Age, years	62.6 (13.2)	63.4 (12.8)	62.1 (13.4)
HbA_{1c} %	8.37 (2.17)	8.67 (2.15)	8.20 (2.16)
HbA_{1c}, mmol/mol	68 (24)	71 (24)	66 (24)
SBP, mmHg	141 (19)	144 (20)	139 (19)
BMI, kg/m^2*	31.3 (6.4)	30.5 (6.1)	31.7 (6.6)
LDL, mmol/L†	2.98 (1.05)	3.13 (1.01)	2.93 (1.06)
HDL, mmol/L†	1.22 (0.37)	1.24 (0.44)	1.22 (0.36)
Smoking, *n* (%)			
No	38,455 (38)	10,386 (32)	27,549 (41)
Yes	52,842 (52)	14,294 (44)	38,087 (57)
Unknown	10,502 (10)	7,871 (24)	1,746 (3)
Statins, *n* (%)			
No	40,692 (40)	19,450 (60)	19,484 (29)
Yes	61,107 (60)	13,101 (40)	47,898 (71)
MI history, *n* (%)			
No	95,464 (94)	30,363 (93)	63,369 (94)
Yes	6,335 (6)	2,188 (7)	4,013 (6)

Data are mean (SD) or as indicated. *BMI was missing in 4,556 (4.5%) of the total of 101,799 patients. †LDL and HDL were missing in 41,282 (41%) of the total of 101,799 patients.

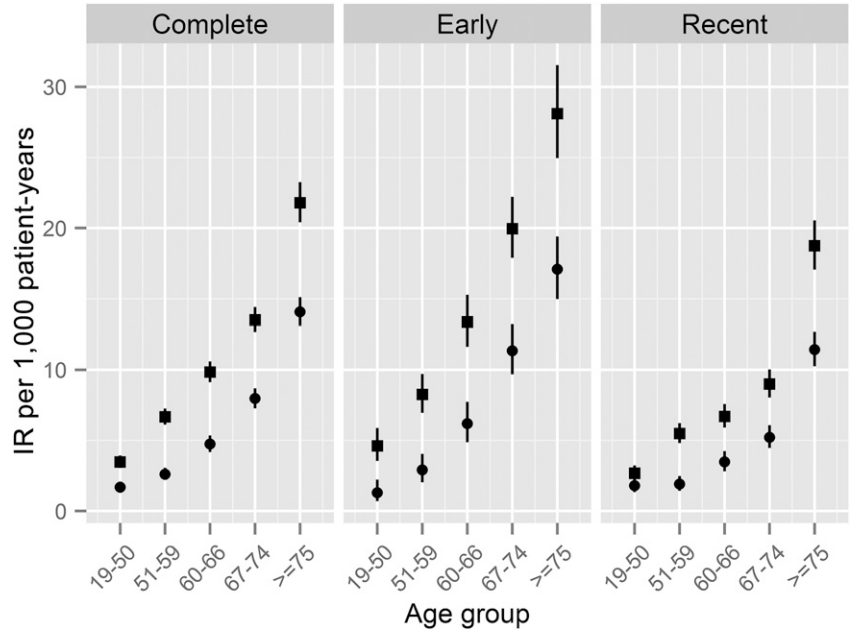

Figure 1—Incidence rates per 1,000 patient-years with 95% CIs, for men (squares) and women (circles) across age categories. Estimates are shown for the complete cohort (patients with diabetes diagnosis in 1995–2010) and for subcohorts with early diagnosis (in 1997–2003) and recent diagnosis (2004–2010).

(Supplementary Table 7). Inclusion of a diabetes treatment variable (categorized as diet, one oral antidiabetic drug, several oral antidiabetic drugs, and insulin) in the basic regression models mainly diluted the association between the HbA_{1c} and MI but had no effect on the overall risk patterns (Supplementary Table 8). A sensitivity analysis was conducted where patients with an MI event coded I25.2 were excluded (924 of 5,104 patients with a MI event). Despite the decrease in event rate, our main results persisted (data not shown).

Differences Between Early and Recent Subcohorts

There were 32,551 patients with diabetes in the early subcohort (32% of the overall cohort); 1,575 patients (31% of all MI events) 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 HbA_{1c} categories was shifted toward the lower HbA_{1c} levels in the recent compared with the early subcohort. For instance, 52% of the patients in the recent cohort had their last recorded HbA_{1c} in categories $<$6% or 6–7% compared with 44% in the early cohort (Supplementary Table 4).

The ranking of the three HbA_{1c} variables was the same in the two subcohorts, with baseline HbA_{1c} 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).

Table 2—Estimated HRs of three HbA_{1c} variables when entered as continuous linear effects

HbA_{1c} variable	Complete cohort	Early subcohort	Recent subcohort
Baseline	1.05 (1.03–1.06)	1.06 (1.04–1.09)	1.03 (1.00–1.05)
Updated latest	1.11 (1.09–1.13)	1.13 (1.10–1.17)	1.07 (1.04–1.10)
Updated mean	1.15 (1.13–1.18)	1.17 (1.13–1.21)	1.08 (1.05–1.12)

All models were adjusted for age, sex, SBP, and history of MI. The complete cohort consists of patients with type 2 diabetes who were diagnosed in 1995–2010. The early and recent subcohorts consist of patients diagnosed in 1997–2003 and in 2004–2010, respectively.

Noteworthy in the categorized variables (Fig. 2 and Supplementary Table 3) was the J-shaped appearance of the risk curve of the updated latest variable in the recent subcohort (HR for HbA_{1c} $<$6% was 1.23 [95% CI 1.08–1.40]) but not in the early subcohort (HR 1.01 [0.84–1.22]). The updated mean and the baseline variables showed no tendency of a J-shape risk curve.

CONCLUSIONS

In this population study of 101,799 patients followed from diagnosis of type 2 diabetes, we found that the updated latest and updated mean variables were stronger predictors of MI than the baseline HbA_{1c} variable. Differences found between the predictive powers of the three HbA_{1c} variables were confirmed across the two time periods studied. Furthermore, we found that for all three HbA_{1c} 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 HbA_{1c} variable and MI in the recent subcohort but not in the early subcohort.

The purpose of studying various HbA_{1c} estimates, besides comparing their predictive power, is to better understand the contribution of each on MI health outcomes. Baseline HbA_{1c} alludes to the patient's glycemic level at the time of diabetes diagnosis, whereas the updated latest HbA_{1c} reflects the most recent glycemic status available as the disease progress over time, and the updated mean HbA_{1c} 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 HbA_{1c} level $\geq$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

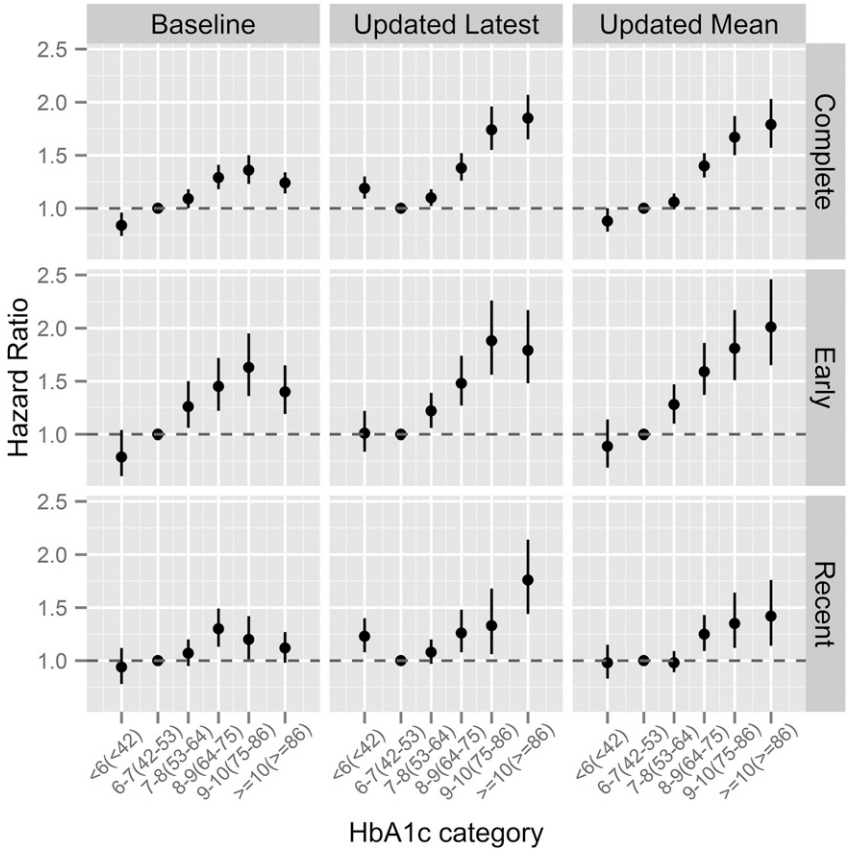

Figure 2—Estimated HRs with 95% CIs for each of the three HbA_{1c} variables, across categories of HbA_{1c} level. Reference category is 6% to <7% (42–53 mmol/mol). HR estimates are shown for the complete cohort (patients with diabetes diagnosis in 1995–2010), and separately for subcohorts with early diagnosis (in 1997–2003) and recent diagnosis (in 2004–2010). The dashed line indicates HR = 1.

to be stably below 6% to have a final mean HbA_{1c} 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 HbA_{1c} 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 HbA_{1c} showed a stronger association with MI than the baseline HbA_{1c}, 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 HbA_{1c} <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 HbA_{1c} 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 HbA_{1c} information at all time points. On top of that, the two subcohorts differ with respect to the frequency distribution of patients across the HbA_{1c} categories, where in the recent cohort, the distribution is shifted toward the lower HbA_{1c} categories. To our knowledge, however, the updated latest variable has not been used in this context before, and therefore, the elevated risk seen in HbA_{1c} <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 HbA_{1c}

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 HbA_{1c} 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 Ischemia 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 HbA_{1c} variables show stronger associations with risk of MI than baseline HbA_{1c}, and the association between HbA_{1c} 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 HbA_{1c} level of $<$6.0% (42 mmol/mol). Our results show that risk estimates of diabetes depend on both HbA_{1c} 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 Abbot 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.

References

1. Whiting DR, Guariguata L, Weil C, Shaw J. IDF diabetes atlas: global estimates of the prevalence of diabetes for 2011 and 2030. Diabetes Res Clin Pract 2011;94:311–321

2. Booth GL, Kapral MK, Fung K, Tu JV. Relation between age and cardiovascular disease in men and women with diabetes compared with non-diabetic people: a population-based retrospective cohort study. Lancet 2006;368:29–36

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;359:1577–1589

4. Seshasai SR, Kaptoge S, Thompson A, et al.; Emerging Risk Factors Collaboration. Diabetes mellitus, fasting glucose, and risk of cause-specific death. N Engl J Med 2011;364:829–841

5. Skyler JS, Bergenstal R, Bonow RO, et al.; American Diabetes Association; American College of Cardiology Foundation; American Heart Association. Intensive glycemic control and the prevention of cardiovascular events: implications of the ACCORD, ADVANCE, and VA diabetes trials: a position statement of the American Diabetes Association and a scientific statement of the American College of Cardiology Foundation and the American Heart Association. Diabetes Care 2009;32:187–192

6. Elley CR, Kenealy T, Robinson E, Drury PL. Glycated haemoglobin and cardiovascular outcomes in people with Type 2 diabetes: a large prospective cohort study. Diabet Med 2008;25:1295–1301

7. Mulnier HE, Seaman HE, Raleigh VS, et al. Risk of myocardial infarction in men and women with type 2 diabetes in the UK: a cohort study using the General Practice Research Database. Diabetologia 2008;51:1639–1645

8. Jeffcoate SL. Diabetes control and complications: the role of glycated haemoglobin, 25 years on. Diabet Med 2004;21:657–665

9. Lind M, Odén A, Fahlén M, Eliasson B. A systematic review of HbA1c variables used in the study of diabetic complications. Diabet Metabolic Syndrome: Clinical Research and Reviews 2008;2:282–293

10. Stratton IM, Adler AI, Neil HA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ 2000;321:405–412

11. The Clinical Database Research Datalink [Internet]. Available from http://www.cprd.com/intro.asp. Accessed 4 September 2014

12. Therneau TM, Grambsch PM. *Modeling Survival Data: Extending the Cox Model*. New York, Springer-Verlag, 2000, p. 107–111

13. Gerstein HC, Miller ME, Byington RP, et al.; Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med 2008;358:2545–2559

14. Patel A, MacMahon S, Chalmers J, et al.; ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med 2008;358:2560–2572

15. Duckworth W, Abraira C, Moritz T, et al.; VADT Investigators. Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med 2009;360:129–139

16. Riddle MC. Effects of intensive glucose lowering in the management of patients with type 2 diabetes mellitus in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. Circulation 2010;122:844–846

17. Grant RW, Pirraglia PA, Meigs JB, Singer DE. Trends in complexity of diabetes care in the United States from 1991 to 2000. Arch Intern Med 2004;164:1134–1139

18. Swedish National Diabetes Register. Annual Report 2012 [Internet]. Available from https://www.ndr.nu/pdf/Annual_Report_NDR_2012.pdf. Accessed 8 January 2014

19. Gaede P, Vedel P, Larsen N, Jensen GV, Parving HH, Pedersen O. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. N Engl J Med 2003;348:383–393

20. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998;352:837–853

21. Turnbull FM, Abraira C, Anderson RJ, et al.; Control Group. Intensive glucose control and macrovascular outcomes in type 2 diabetes. Diabetologia 2009;52:2288–2298

22. Zhang CY, Sun AJ, Zhang SN, et al. Effects of intensive glucose control on incidence of cardiovascular events in patients with type 2 diabetes: a meta-analysis. Ann Med 2010;42:305–315

23. Stevens RJ, Kothari V, Adler AI, Stratton IM; United Kingdom Prospective Diabetes Study (UKPDS) Group. The UKPDS risk engine: a model for the risk of coronary heart disease in Type II diabetes (UKPDS 56). Clin Sci (Lond) 2001;101:671–679

24. Zethelius B, Eliasson B, Eeg-Olofsson K, Svensson AM, Gudbjörnsdottir S, Cederholm J; NDR. A new model for 5-year risk of cardiovascular disease in type 2 diabetes, from the Swedish National Diabetes Register (NDR). Diabetes Res Clin Pract 2011;93:276–284

25. Palmer AJ, Roze S, Valentine WJ, et al. The CORE Diabetes Model: Projecting long-term clinical outcomes, costs and cost-effectiveness of interventions in diabetes mellitus (types 1 and 2) to support clinical and reimbursement decision-making. Curr Med Res Opin 2004;20(Suppl. 1):S5–S26

26. Palmer AJ, Roze S, Valentine WJ, et al. What impact would pancreatic beta-cell preservation have on life expectancy, quality-adjusted life expectancy and costs of complications in patients with type 2 diabetes? A projection using the CORE Diabetes Model. Curr Med Res Opin 2004;20(Suppl. 1):S59–S66

27. Bagust A, Hopkinson PK, Maslove L, Currie CJ. The projected health care burden of Type 2 diabetes in the UK from 2000 to 2060. Diabet Med 2002;19(Suppl. 4):1–5

28. McKinlay J, Marceau L. US public health and the 21st century: diabetes mellitus. Lancet 2000;356:757–761

29. Bagust A, Hopkinson PK, Maier W, Currie CJ. An economic model of the long-term health care burden of Type II diabetes. Diabetologia 2001;44:2140–2155

30. Herrett E, Shah AD, Boggon R, et al. Completeness and diagnostic validity of recording acute myocardial infarction events in primary care, hospital care, disease registry, and national mortality records: cohort study. BMJ 2013;346:f2350