Historical HbA_{1c} Values May Explain the Type 2 Diabetes Legacy Effect: UKPDS 88

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OBJECTIVE

Type 2 diabetes all-cause mortality (ACM) and myocardial infarction (MI) glycemic legacy effects have not been explained. We examined their relationships with prior individual HbA_{1c} values and explored the potential impact of instituting earlier, compared with delayed, glucose-lowering therapy.

RESEARCH DESIGN AND METHODS

Twenty-year ACM and MI hazard functions were estimated from diagnosis of type 2 diabetes in 3,802 UK Prospective Diabetes Study participants. Impact of HbA_{1c} values over time was analyzed by weighting them according to their influence on downstream ACM and MI risks.

RESULTS

Hazard ratios for a one percentage unit higher HbA_{1c} for ACM were 1.08 (95% CI 1.07–1.09), 1.18 (1.15–1.21), and 1.36 (1.30–1.42) at 5, 10, and 20 years, respectively, and for MI was 1.13 (1.11–1.15) at 5 years, increasing to 1.31 (1.25–1.36) at 20 years. Imposing a one percentage unit lower HbA_{1c} from diagnosis generated an 18.8% (95% CI 21.1–16.0) ACM risk reduction 10–15 years later, whereas delaying this reduction until 10 years after diagnosis showed a sevenfold lower 2.7% (3.1–2.3) risk reduction. Corresponding MI risk reductions were 19.7% (22.4–16.5) when lowering HbA_{1c} at diagnosis, and threefold lower 6.5% (7.4–5.3%) when imposed 10 years later.

CONCLUSIONS

The glycemic legacy effects seen in type 2 diabetes are explained largely by historical HbA_{1c} values having a greater impact than recent values on clinical outcomes. Early detection of diabetes and intensive glucose control from the time of diagnosis is essential to maximize reduction of the long-term risk of glycemic complications.

The UK Prospective Diabetes Study (UKPDS) demonstrated that intensive glycemic control, which achieved 0.9% lower HbA_{1c} levels on average compared with conventional glycemic control, lowered the risk of microvascular complications in patients with type 2 diabetes (T2D) (1). The risks for all-cause mortality (ACM) and myocardial infarction (MI) were not reduced, although the 16% numerical MI risk reduction was borderline statistically significant ($P = 0.052$). A subsequent patient-level meta-analysis of Action to Control Cardiovascular Risk in Diabetes (ACCORD), Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled

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Evaluation (ADVANCE), UKPDS, and Veterans Affairs Diabetes Trial (VADT), however, confirmed a 15% MI risk reduction for a 0.88% lower HbA_{1c} (2).

Ten-year posttrial monitoring of surviving UKPDS participants, with virtually no glycemic differences between those randomized previously to intensive or conventional glycemic strategies, revealed relative risk reductions of 16% for ACM ($P = 0.007$) and 15% for MI ($P = 0.01$) (3). These findings, suggesting there is a "legacy" effect conferred by earlier improved glycemic control with increasingly beneficial effects on ACM and MI risks over time (3), have helped influence guidelines to advocate early more intensive postdiagnosis glucose-lowering therapy. Many patients, however, still do not reach their glycemic targets (4–6). Because significant resources are required to promote early diabetes detection (e.g., screening large populations) and to optimize glycemic control after diagnosis, it is essential for care givers, patients, and decision makers to know to what extent early intensive glycemic control can reduce the risk of long-term complications.

In this UKPDS analysis, we examine the degree to which relationships between individual historical HbA_{1c} values over time and downstream risks of ACM and MI may explain the T2D glycemic legacy effect.

RESEARCH DESIGN AND METHODS

Population

The UKPDS design and results have been described previously (1,3,7,8). Briefly, participants were stratified by ideal body weight ($<$120% vs. $\geq$120%) (8), with nonoverweight participants assigned randomly to an intensive (insulin or sulfonylurea) or conventional (diet) glycemic management strategy. Overweight participants assigned to the intensive glycemic strategy could also be allocated to metformin (8). The aim for all participants was a fasting plasma glucose $<$6.0 mmol/L, with second-line glucose-lowering therapy permitted only if fasting plasma glucose values became $>$15 mmol/L or unacceptable signs of hyperglycemia developed.

After UKPDS closeout, all surviving participants entered a 10-year posttrial monitoring period and were returned to routine care, with no attempt made to maintain trial-allocated treatment regimens (3). They were seen annually at UKPDS centers for the first 5 years with collection of standardized data, including HbA_{1c}. Thereafter, participants were monitored remotely by means of annual participant- and general practitioner-completed questionnaires.

In this analysis, only those assigned originally to an intensive glycemic strategy with a sulfonylurea or insulin, or to a conventional glycemic strategy with diet, were evaluated. HbA_{1c} values were measured annually in the UKPDS. Participants were excluded if they had a missing baseline HbA_{1c} value or did not have at least one follow-up HbA_{1c} value recorded during the 2 years preceding ACM or MI. HbA_{1c} values, measured as % (7), have been converted to mmol/mol according to guidelines (9).

Relationship of Historical HbA_{1c} Values to Downstream ACM and MI Risks

Time-to-event analysis of diabetes complications and HbA_{1c} is commonly performed using baseline or updated mean HbA_{1c} values (10–13). However, none of these HbA_{1c} metrics consider how HbA_{1c} values, measured at different historical time points, may vary in their individual contribution to the downstream risk of diabetes-related complications. Accordingly, we used a model in which historical HbA_{1c} values were weighted unequally to allow for different risk contributions at each time point. This was done using a multivariable regression model where optimal weights for historical HbA_{1c} values were estimated simultaneously with the effect of the influence weighted HbA_{1c} variable and coefficients for other covariates (14,15). The overall temporal relationship of HbA_{1c} with ACM and MI was investigated by estimating the degree to which the instantaneous risk (hazard) of ACM and MI at 15 and 20 years after diagnosis could be ascribed to HbA_{1c} values measured at previous time points.

ACM and MI Hazard Ratios in Relation to HbA_{1c}

The impact of HbA_{1c} values on diabetes-related complications has commonly been estimated by calculating hazard ratios (HRs) in relation to a one percentage unit (11 mmol/mol) difference in HbA_{1c} (10,13–15). We estimated ACM and MI HRs at 5, 10, 15, and 20 years after diagnosis of diabetes, assuming a one percentage unit (11 mmol/mol) higher HbA_{1c} from diagnosis onward. To further understand the impact of historical HbA_{1c} levels on downstream ACM and MI risks (legacy effects), we also estimated ACM and MI HRs at 10–20 years after diagnosis in relation to a one percentage unit (11 mmol/mol) lower HbA_{1c}, imposed at diagnosis of diabetes or delayed until 5 or 10 years later. These estimations were repeated for HbA_{1c} decrements of 0.5% (5.5 mmol/mol) and 2.0% (22 mmol/mol).

ACM and MI Relative Risks Relating to Historical HbA_{1c} Values

To study how prior HbA_{1c} values might influence the incidence of downstream ACM and MI over a longer time period, we estimated ACM and MI relative risks at 0–10, 10–15, and 10–20 years after diagnosis when a lower HbA_{1c} was imposed immediately compared with delaying this until 5 or 10 years later.

Impact of UKPDS Randomized Glycemic Strategies

To evaluate whether factors other than glycemic control might explain differences in outcomes, we investigated the extent to which assignment to an intensive or conventional glycemic control strategy, irrespective of achieved HbA_{1c} values, affected the incidence of ACM and MI.

Statistical Analyses

We used a multivariable Poisson regression model that included HbA_{1c}, age, sex, and diabetes duration with the total follow-up period for each patient subdivided into small intervals of 0.2 years, for each of which a constant hazard was assumed. HbA_{1c} was included in the model as a time-dependent weighted integral of all prior HbA_{1c} values, with values weighted unequally to allow for a potential different risk contribution at each time point. The influence-weighted HbA_{1c} variable was computed by first creating a continuous HbA_{1c} curve using linear interpolation between observed HbA_{1c} values, which was then weighted by a piecewise exponential weight function with one knot. The optimal HbA_{1c} weight function parameters were estimated simultaneously with the coefficients of the

covariates in the model using maximum likelihood estimation.

Likelihood ratio tests were used to assess the significance of individual model parameters, with corresponding CIs computed by test inversion (16). Estimates and CIs for influence-weighted HbA_{1c} HRs at various follow-up times and for relative risks associated with imposed immediate or delayed HbA_{1c} reductions were computed from the corresponding regression coefficient, fixing the HbA_{1c} weight function parameters at their estimated values. Model fit was assessed by comparing observed and expected event numbers for various age categories and follow-up times. Additional model and statistical methodology details can be found here (14,15) and in the Supplementary Material (additional statistical analysis details).

Data and Resource Availability

Data may be accessed after a written research proposal and support from investigators and upon request and an appropriate data transfer agreement is in place.

RESULTS

Patient Characteristics

Requisite UKPDS data were available for 3,802 participants with 775 ACM events and for 3,219 participants with 662 MI events. Their mean age at diagnosis of diabetes was 53.3 (SD 8.6) years, and 38.8% were women. For ACM and MI analyses, there were 3,321 (87%) and 3,219 (85%) participants, respectively, monitored for >5 years. The number of participants included in the analyses with follow-up of >10 and 15 years for ACM were 2,742 (72%) and 1,299 (34%), respectively, and for MI were 2,544 (67%) and 1,156 (30%), respectively.

ACM and MI HRs in Relation to HbA_{1c}

Higher HbA_{1c} values were associated significantly with both higher ACM and MI risks (both $P < 0.0001$). HRs for ACM and MI in relation to imposed 0.5% (5 mmol/mol), 1% (11 mmol/mol), and 2% (22 mmol/mol) higher HbA_{1c} values during the first 5, 10, 15, or 20 years after the diagnosis of diabetes are presented in Table 1. Each 1% (11 mmol/mol) higher HbA_{1c} was related to steadily higher HRs over time for ACM and MI, suggesting increasingly harmful effects of earlier hyperglycemia. HRs for ACM per 1% (11 mmol/mol) higher HbA_{1c} value were 1.08 (95% CI 1.07–1.09), 1.18 (1.15–1.21), and 1.36 (1.30–1.42) at 5, 10, and 20 years of follow-up, respectively, while MI HRs increased from 1.13 (1.11–1.15) at 5 years to 1.31 (1.25–1.36) at 20 years.

Imposing a one percentage unit (11 mmol/mol) lower HbA_{1c} from the diagnosis of diabetes significantly lowered the instantaneous risk (hazard) of ACM or MI events 15 and 20 years later, compared with reducing HbA_{1c} by the same amount from 10 years after diagnosis (Fig. 1). ACM HRs (95% CI) at 15 and 20 years after diagnosis when reducing HbA_{1c} from diagnosis, compared with from 10 years after diagnosis, were, respectively, 0.78 (0.76–0.81) vs. 0.93 (0.92–0.94) and 0.73 (0.70–0.77) vs. 0.84 (0.82–0.87). Corresponding MI HRs were, respectively, 0.79 (0.76–0.82) vs. 0.88 (0.87–0.90) and 0.76 (0.73–0.80) vs. 0.82 (0.80–0.85). HRs calculated when HbA_{1c} lowering was delayed approached those of immediate HbA_{1c} lowering somewhat more rapidly for MI than for ACM (Fig. 1). Similar relationships over time were found for ACM and MI when HbA_{1c} was lowered by one-half or two percentage units (Supplementary Figs. 2 and 3).

Relative Risks of ACM and MI 10–20 Years After Diagnosis in Relation to Early or Delayed Imposed Lowering of HbA_{1c}

To study glucose-lowering legacy effects over longer time periods, we estimated the effect of imposing immediate or delayed HbA_{1c} reductions on ACM and MI risks between 0–10, 10–15, and 10–20 years after diagnosis. The estimated ACM relative risk reduction was 18.8% (95% CI 21.1–16.0) at 10–15 years per one percentage unit lower HbA_{1c} when imposed from diagnosis, but sevenfold smaller at 2.7% (3.1–2.3) when imposed 10 years after diagnosis. The corresponding MI estimates showed a threefold smaller relative risk reduction comparing delayed with immediate imposition of a lower HbA_{1c} (Table 2). For the period 10–20 years after diagnosis, delayed compared with immediate imposition HbA_{1c} lowering by one percentage unit (11 mmol/mol) resulted in an approximately threefold smaller ACM relative risk reduction and a twofold smaller MI relative risk reduction (Table 2). Similar legacy effects for ACM and MI risks were seen with imposed

Table 1—HRs for ACM and MI per one-half, one, and two percentage unit (5.5, 11, and 22 mmol/mol) higher HbA_{1c} (%) values over the first 5, 10, 15, and 20 years after the diagnosis of T2D

Years after diagnosis	HR (95% CI) per 0.5 percentage units higher	HR (95% CI) per 1 percentage units higher	HR (95% CI) per 2 percentage units higher
ACM			
5	1.04 (1.03–1.04)	1.08 (1.07–1.09)	1.16 (1.14–1.19)
10	1.09 (1.07–1.10)	1.18 (1.15–1.21)	1.40 (1.33–1.47)
15	1.13 (1.11–1.15)	1.28 (1.23–1.32)	1.64 (1.51–1.75)
20	1.17 (1.14–1.19)	1.36 (1.30–1.42)	1.86 (1.68–2.03)
MI			
5	1.06 (1.05–1.07)	1.13 (1.11–1.15)	1.28 (1.22–1.33)
10	1.10 (1.08–1.12)	1.22 (1.17–1.25)	1.48 (1.38–1.57)
15	1.13 (1.10–1.15)	1.27 (1.22–1.32)	1.62 (1.49–1.75)
20	1.14 (1.12–1.17)	1.31 (1.25–1.36)	1.71 (1.55–1.86)

All HRs are statistically significant with $P < 0.0001$. The hazard ratio per z-units increase in HbA_{1c} during t years after diagnosis is given by Eq. 5 in the Supplementary Material. The model coefficients of the HbA_{1c} weight function and covariates included in the model are presented in Supplementary Table 1.

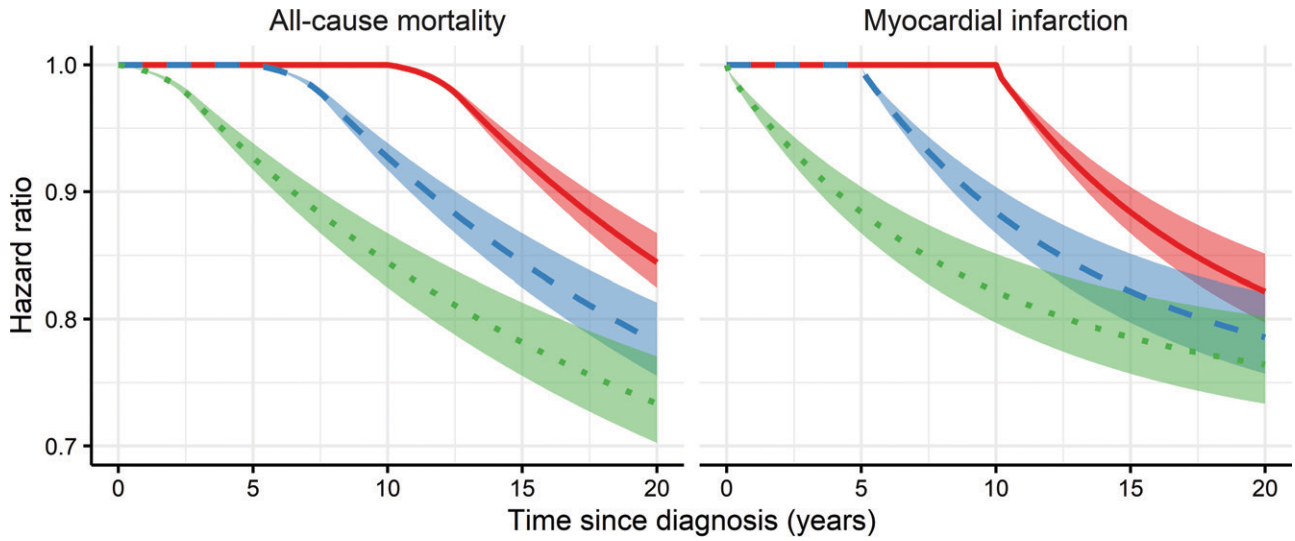

Figure 1—Time-dependent HRs for all cause-mortality (left) and myocardial infarction (right) from 0 to 20 years after diagnosis of type 2 diabetes, assuming a one percentage unit lower HbA_{1c} from diagnosis (green dotted lines), and when the same degree of HbA_{1c} lowering was imposed from 5 years (blue dashed lines), and from 10 years (red solid lines) after diagnosis. The shaded regions represent 95% confidence limits. HRs were calculated according to Eq. 6 in the Supplementary Material.

0.5% and 2.0% lower HbA_{1c} values (Supplementary Table 2).

Relationship of Historical HbA_{1c} Values to Downstream ACM and MI Risks

The overall temporal relationships of HbA_{1c} with ACM and MI are shown in Fig. 2. HbA_{1c} values measured during the first 10 years after diagnosis contributed to 69% (95% CI 60–75) of the HbA_{1c} total effect on ACM risk 15 years after diagnosis and to 45% (33–54) at 20 years (Fig. 2). The corresponding MI estimates were 49% (95% CI 37–56) and 27% (16–35).

Impact of Age, Sex, and Assigned Glycemic Control Strategy

Older age and male sex were associated significantly (both $P < 0.0001$) with increased ACM and MI risks (Supplementary Table 1). When HbA_{1c} was included in the model, the glycemic control strategy assignment (intensive versus conventional) effect was attenuated and not associated with ACM ($P = 0.15$) or MI ($P = 0.07$).

Model Checks

Details of the final model estimated parameters, including coefficients of the HbA_{1c} weight function, are provided in Supplementary Table 1. Several model checks were performed, with no lack-of-fit detected. The model-predicted cumulative number of UKPDS participants experiencing an ACM or MI event was similar to that observed (Supplementary Fig. 4). A sensitivity analysis to assess the impact of baseline HbA_{1c}, which excluded HbA_{1c} values and deaths during the first 4 years after diagnosis, showed similar time associations between HbA_{1c} and ACM. Similar patterns were also seen when an interaction term for time and HbA_{1c} was included in the model.

CONCLUSIONS

Principal Findings

In this analysis of the UKPDS and its posttrial monitoring period, we found that historical HbA_{1c} values were associated with strong legacy effects for the downstream incidence of ACM and MI. Analyses exploring the impact of delaying the imposition of a 1% lower HbA_{1c} until 10 years after diagnosis of diabetes, compared with doing this immediately, showed a sevenfold lower risk reduction for ACM at 10–15 years. At 10–20 years after diagnosis, the risk of death was reduced by threefold when HbA_{1c} was lowered from diagnosis. Similar time-dependent effects were observed for MI, but HbA_{1c} legacy effects were numerically greater for ACM than MI. The impact on ACM and MI risks of delaying imposition of improved glycemic control after the diagnosis of diabetes increased steadily with time. Thus, a one percentage unit (11 mmol/mol) higher HbA_{1c} level was associated with an 8% greater ACM risk at 5 years, increasing to 36% at 20 years. The risks for ACM and MI were captured by HbA_{1c}, whereas the assigned glycemic strategy group was not significant when HbA_{1c} was included in the model. This finding strongly supports the fact that the long-term ACM and MI risk reductions seen in the UKPDS intensive glycemic strategy group are driven by the early introduction of improved glycemic control (1,3). The somewhat stronger legacy effect we see for ACM, compared with MI, reflects the increased ACM risk reduction from 6% to 13% during UKPDS posttrial monitoring, while the degree of MI risk reduction was essentially unchanged (16% vs. 15%) (3).

Other Studies

The existence of a strong legacy effect of earlier glycemic control on cardiovascular disease is supported by findings from studies of patients with type 1 diabetes. In the Epidemiology of Diabetes Interventions and Complications (EDIC) follow-up of the Diabetes Control and Complications Trial (DCCT) study, participants previously assigned to intensive glycemic therapy had fewer cardiovascular disease events, even though the glycemic difference between the intensive and conventional groups was not maintained (17,18). ACM and MI reductions were not seen with intensive glycemic therapy in any of the three large-scale glucose-lowering

Table 2—Estimated relative risks of ACM and MI between 0–10, 10–15, and 10–20 years after diagnosis assuming a one percentage unit (11 mmol/mol) lower HbA_{1c} from diagnosis, and when the same HbA_{1c} lowering was imposed from 5 and from 10 years after diagnosis

Years after diagnosis	HbA_{1c} lowered at diagnosis	HbA_{1c} lowered 5 years after diagnosis	HbA_{1c} lowered 10 years after diagnosis
ACM			
0–10	0.928 (0.919–0.939)	0.987 (0.985–0.989)	1.00
10–15	0.812 (0.789–0.840)	0.885 (0.870–0.902)	0.973 (0.969–0.977)
10–20	0.785 (0.758–0.815)	0.848 (0.829–0.871)	0.928 (0.919–0.939)
MI			
0–10	0.893 (0.877–0.911)	0.968 (0.963–0.973)	1.00
10–15	0.803 (0.776–0.835)	0.851 (0.830–0.876)	0.935 (0.926–0.947)
10–20	0.788 (0.760–0.823)	0.826 (0.803–0.855)	0.893 (0.877–0.911)

Data are presented as relative risk (95% CI) per one percentage unit lower HbA_{1c}. The relative risk of an event in a time interval 0–10, 10–15, or 10–20 years after diagnosis was calculated according to Eq. 11 in the Supplementary Material.

studies performed over 3–5 years in patients with generally long-standing T2D (19–21). This may reflect the initially smaller risk reductions with improved HbA_{1c} or the late introduction of improved glycemic control in patients with diabetes of long duration. Minimizing hyperglycemia plays a major role in reducing the risk of diabetic complications, particularly microvascular complications (1,3,8), while other glucose-lowering drugs, such as metformin, glucagon-like peptide 1 (GLP-1) receptor analogs, and sodium–glucose cotransporter 2 inhibitors, likely also act via additional nonglucose-lowering mechanisms to reduce ACM and MI risks (8,22,23). Nonetheless, while the risks of MI and death have reduced over time, these remain substantially higher for people with T2D (24,25).

Explanations and Interpretations

The legacy effect of earlier hyperglycemia on diabetic complications appears to explain the increasing impact of historical HbA_{1c} values on ACM and MI risks over time. Legacy effects in T2D and "metabolic memory" in type 1 diabetes have been the subject of much debate (3,17,26–29). Certain pathways associated with diabetes complications may be active later but initiated from earlier increases in glucose, where reactive oxygen species have been proposed to play an essential role (26,30). The reason legacy effects are somewhat greater for ACM than MI is speculative. It is possible that to some extent, death may occur in a time-delayed fashion from several diabetes-related complications (including MI), a fact that may explain how HbA_{1c} affects death and MI with time. Early hyperglycemia leading to nephropathy, initiating processes increasing future risks of ACM and MI, including hypertension, altered lipid metabolism, and inflammatory processes, may also be a major contributor (31,32). In multiple studies, renal complications have been major risk factors for future cardiovascular disease and mortality (13,31–33).

Implications

Although early more intensive glycemic control in UKPDS participants with newly diagnosed T2D has shown ACM

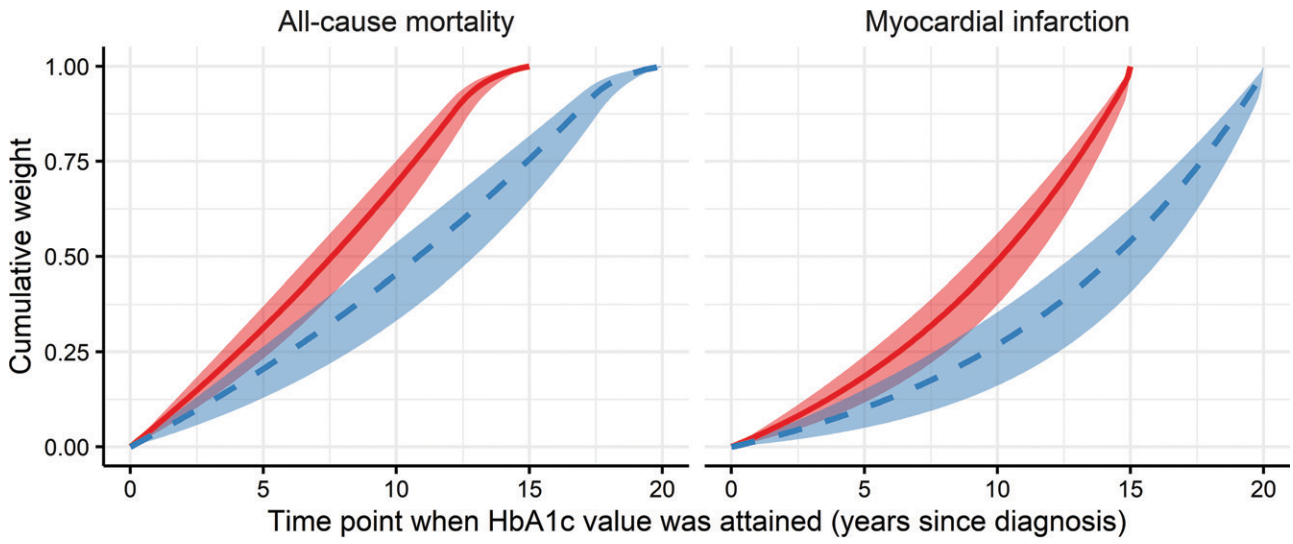

Figure 2—Contribution of historical HbA_{1c} values to their impact on the instantaneous risk (hazard) of all-cause mortality (left) and myocardial infarction (right) at 15 years (red solid lines) and 20 years (blue dashed lines) after diagnosis. The legacy effect of historical HbA_{1c} values on diabetes complications was more pronounced for ACM than for MI. The shaded regions represent 95% confidence limits. Details on the calculations may be found in Eq. 7 in the Supplementary Material.

and MI risk reductions in the longer-term, associations with individual historical HbA_{1c} values and their long-term effects have not been studied. Here we show that imposing a lower HbA_{1c} immediately after the diagnosis of T2D is associated with severalfold greater risk reductions in ACM and MI 10–20 years later compared with delayed HbA_{1c} lowering. T2D is a worldwide epidemic affecting >463 million individuals and causing a large proportion of severe renal, visual, and cardiovascular disease events as well as amputations and shorter life expectancy (34). In addition, many people have undetected diabetes (34). Our results imply that societies should focus even more on early T2D detection and glucose optimization. Moreover, programs in both children and adults without diabetes could prevent or delay diabetes onset and thereby minimize glycemic exposure at an even earlier time period.

Guidelines today recommend screening high risk groups (e.g., obese individuals and first-degree relatives of individuals with T2D) (4,5), but few structural programs exist in many countries. If T2D remains undetected, glucose levels can increase over many years without symptoms but with elevated HbA_{1c} values that are associated with greatly increased risk, as we have shown here; for example, a 2% (22 mmol/mol) higher HbA_{1c} increases ACM risk by 40% after 10 years and by 86% after 20 years.

Another implication is that glycemic control contributes more to risk of ACM and MI than previously thought. Our study found an ACM risk increase of >30% at 20 years per unit HbA_{1c} increase compared with 10–20% in previous studies (10–13). The difference is due to the increasing effects over time, which likely will increase even more for many patients over a lifetime horizon. Besides the need for early detection of diabetes and glycemic optimization, our findings support the need for strict glycemic control when treating people with T2D in clinical practice. Effects of glucose-lowering treatments in cardiovascular outcome trials have likely underestimated the effects of glycemic control because the beneficial effects, according to the current results, increase over at least 15–20 years and thus far beyond the duration of most studies, which have generally been 3–5 years (19–23,28,29). The increasing and larger risk reductions seen here over time need to be considered when making treatment decisions in clinical practice, writing guidelines, and performing health care economic analyses.

These results are also of interest in light of the current coronavirus disease 2019 pandemic. Individuals with T2D with a high mortality risk after coronavirus disease 2019 infection are generally those with advanced diabetes complications (35,36). To help minimize such risks in future viral epidemics, our findings highlight the crucial need for early implementation of intensive glycemic control in people with newly diagnosed T2D to reduce end-organ damage.

Strengths and Limitations

Strengths of our study include the UKPDS long-term follow-up with detailed HbA_{1c} and adjudicated complication data. Also, participants were monitored from the diagnosis of T2D, which is essential to capture as much information as possible on early hyperglycemic effects. The model we used has previously shown a better fit than traditional models and variables used for describing HbA_{1c} in relation to diabetic complications (10,14,15). Although it shows a good fit here, we cannot exclude residual confounding due to the study's observational nature. In particular, partial confounding may exist between the studied HbA_{1c} variable, which varies nonlinearly with time since diagnosis, and nonlinear effects of diabetes duration. None of the conducted sensitivity analyses, however, revealed any such patterns. Because the current analyses focused on the relative impact of historical HbA_{1c} values, we did not evaluate risk factors other than age, sex, and treatment group. Moreover, it should be noted that healthy living habits, which may be associated with improved glycemic control and were not controlled for in the current analysis, can also influence the risk of MI and mortality. For future estimations of the probability of ACM or MI for individuals, it will be essential to include other risk factors and covariates. However, HbA_{1c} is already known to be an independent risk factor for MI and ACM, as shown in multiple studies, including the UKPDS (11–13). In the current study, intraindividual HbA_{1c} values (i.e., for each participant) were evaluated to determine their relative contributions over time to MI and ACM. While it would be of interest to determine and also adjust for time-dependent effects of other risk factors (smoking, weight, blood pressure, and lipid profiles), they did not vary greatly over time in UKPDS, and such analyses would be complex to perform.

The use of statins and renin-angiotensin-aldosterone system inhibitors in UKPDS were confined primarily to the posttrial monitoring period. It is possible that by reducing overall cardiovascular risk, they might to some extent influence the effect ascribed to historical HbA_{1c} values but not fundamentally change the relationship between HbA_{1c} and complications.

In conclusion, the adverse effects of HbA_{1c} on ACM and MI increase over time. Strong HbA_{1c} legacy effects exist for both of these outcomes but appear greater for ACM. Given these large legacy effects, early detection of T2D (screening) and glycemic optimization needs greater emphasis in guidelines, by health care providers, and in clinical practice to more effectively prevent long-term complications and achieve a more normal life-expectancy for people with T2D.

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