Early Glycemic Control and Magnitude of HbA_{1c} Reduction Predict Cardiovascular Events and Mortality: Population-Based Cohort Study of 24,752 Metformin Initiators

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OBJECTIVE

We investigated the association of early achieved HbA_{1c} level and magnitude of HbA_{1c} reduction with subsequent risk of cardiovascular events or death in patients with type 2 diabetes who initiate metformin.

RESEARCH DESIGN AND METHODS

This was a population-based cohort study including all metformin initiators with HbA_{1c} tests in Northern Denmark, 2000–2012. Six months after metformin initiation, we classified patients by HbA_{1c} achieved (<6.5% or higher) and by magnitude of HbA_{1c} change from the pretreatment baseline. We used Cox regression to examine subsequent rates of acute myocardial infarction, stroke, or death, controlling for baseline HbA_{1c} and other confounding factors.

RESULTS

We included 24,752 metformin initiators (median age 62.5 years, 55% males) with a median follow-up of 2.6 years. The risk of a combined outcome event gradually increased with rising levels of HbA_{1c} achieved compared with a target HbA_{1c} of <6.5%: adjusted hazard ratio (HR) 1.18 (95% CI 1.07–1.30) for 6.5–6.99%, HR 1.23 (1.09–1.40) for 7.0–7.49%, HR 1.34 (1.14–1.57) for 7.5–7.99%, and HR 1.59 (1.37–1.84) for ≥8%. Results were consistent for individual outcome events and robust by age-group and other patient characteristics. A large absolute HbA_{1c} reduction from baseline also predicted outcome: adjusted HR 0.80 (0.65–0.97) for $\Delta = -4$, HR 0.98 (0.80–1.20) for $\Delta = -3$, HR 0.92 (0.78–1.08) for $\Delta = -2$, and HR 0.99 (0.89–1.10) for $\Delta = -1$ compared with no HbA_{1c} change ($\Delta = 0$).

CONCLUSIONS

A large initial HbA_{1c} reduction and achievement of low HbA_{1c} levels within 6 months after metformin initiation are associated with a lower risk of cardiovascular events and death in patients with type 2 diabetes.

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Lowering glycated hemoglobin (HbA_{1c}) levels to <7% (<53 mmol/mol) in most adults with type 2 diabetes has been a recommended target in treatment guidelines for more than a decade (1–4) because of the documented effect in reducing microvascular complications (5). In contrast, it remains debated whether even tighter glucose control (such as HbA_{1c} <6.5%) may be more beneficial or harmful (6) and what the true effect of tight early glucose control is on subsequent cardiovascular disease (7). Although the large clinical randomized controlled trials have failed to show a clear beneficial effect of early intensive glycemic control on cardiovascular events in type 2 diabetes (5), long-term follow-up studies from the UK Prospective Diabetes Study (UKPDS) (8) and Veterans study (9) have suggested a beneficial cardiovascular effect, termed "metabolic memory" or "legacy effect." (10) In observational research, most studies, but not all, suggest that having a low glycemic level measured at some point of time is associated with fewer cardiovascular events and mortality in type 2 diabetes (11–18). Some studies found a linear relationship between successively lower glycemic levels and fewer cardiovascular events (11,12,18), whereas others reported a J- or U-shaped curve (14–16). Comparison of these studies is hampered by inclusion of case patients with prevalent diabetes with different time of diabetes duration and by different ways of measuring glycemic control. Only two of the observational studies on cardiovascular risk began at the diagnosis of diabetes (15,18). Olsson et al. (18) found an overall increased risk of acute myocardial infarction with a time-updated HbA_{1c} <6.0% (42 mmol/mol) compared with 6–7%, whereas Östgren et al. (15) reported the lowest cardiovascular risk was seen with an early achieved HbA_{1c} level of 6.8% (51 mmol/mol). Whether the magnitude of early HbA_{1c} reduction predicts subsequent prognosis remains unknown.

Because current guidelines emphasize the importance of tight glycemic control early after diabetes diagnosis, before complications have occurred (4), further research is warranted on the association of early glycemic control with cardiovascular events, taking into account HbA_{1c} at the initiation of metformin use. Thus, using real-life data from Danish medical registries, we investigated the association of achieved HbA_{1c} level and magnitude of HbA_{1c} reduction with subsequent risk of myocardial infarction, stroke, and death in a population-based cohort of patients with incident type 2 diabetes initiating metformin.

RESEARCH DESIGN AND METHODS

Setting

We conducted this cohort study using data from existing population-based medical registries covering Northern Denmark region's 1.8 million residents (30% of Denmark's population) during 2000–2012. Linkage of all registries was made possible through the unique Civil Personal Registration number (19). In Denmark, most cases of type 2 diabetes are diagnosed by general practitioners (GPs), and an estimated 80% are also treated and monitored there. The remaining 20% are referred by their GP to diabetes outpatient specialist clinics at public hospitals (20). All prescribed medications can only be redeemed at community pharmacies (21). This study was approved by the Danish Data Protection Agency (Record number 1-16-02-1-08). Because this registry-based study did not involve patient contact, no separate permission from the Danish Scientific Ethical Committee was required according to Danish Legislation.

Study Population

Overall methods are described in more detail in previous reports (22,23). In brief, we identified all patients with type 2 diabetes aged 30 or older living in Northern Denmark who initiated first-time ever glucose-lowering drug treatment between 1 January 2000 and 31 December 2012. Patients had to have at least one available HbA_{1c} measurement within 12 months before and again ~6 months after treatment initiation (if several HbA_{1c} measurements occurred during day 60–180, the value closest to day 180 was chosen) (n = 38,418) (22). Among these individuals, we selected all patients with incident metformin monotherapy use (n = 24,752). Information on prescriptions was obtained via the Aarhus University Prescription Database, which has held complete data coverage in Northern Denmark since 1998 (21). Information on HbA_{1c} measurements was obtained via the clinical laboratory information system research database (LABKA), which has held complete data on biochemistry test results from all GPs and hospitals in the region since 2000 (24).

We also identified all metformin monotherapy initiators during 2000–2012 who did not have HbA_{1c} values measured both within 12 months before and ~6 months after metformin initiation, and these patients were the non-measurement cohort (n = 17,142).

Early Glycemic Control: Achieved HbA_{1c} and Magnitude of HbA_{1c} Change

We defined two ways to measure early glycemic control:

1. HbA_{1c} level (%) achieved 6 months after the index prescription of metformin: <6.5, 6.5–6.9, 7.0–7.4, 7.5–7.9, ≥8.
2. Magnitude of HbA_{1c} reduction, defined as the absolute change in HbA_{1c} (%) from baseline before metformin initiation to the level achieved at 6 months after prescription: Δ −4, −3, −2, −1, 0, +1, or +2 and above. In more detail, Δ −4 included reductions of −3.5% or more, Δ −3 included reductions from −2.5% to −3.4%, Δ −2 from −1.5% to −2.4%, Δ −1 from −0.5% to −1.4%, Δ 0 from −0.4% to +0.4%, Δ +1 from +0.5% to +1.4%, and Δ +2 included HbA_{1c} increases of 1.5% or more.

Cardiovascular Events and Mortality

Using the Danish National Patient Registry (DNPR) (25), we identified all patients hospitalized with myocardial infarction and stroke. Diagnoses of myocardial infarction and stroke have been previously validated with predictive values of 90% and 79%, respectively (26,27). We used the Civil Registration System to identify all deaths. We also constructed a combined outcome (death and/or myocardial infarction and/or stroke). All diagnostic codes used in the study are assembled in Supplementary Table 1. We monitored all patients from 180 days after metformin initiation until a cardiovascular event, death, emigration, or 31 December 2012.

Covariates

From the medical databases, we obtained data on patient characteristics at 180 days after metformin initiation, potentially associated with both the exposure (early glycemic control) and outcome (cardiovascular events and death). We obtained data on 19 major disease

categories included in the Charlson Comorbidity Index based on patients' entire hospital contact history within 5 years before follow-up start. We separately ascertained contacts for obesity, alcoholism-related disorders, and for any macrovascular or microvascular diabetes complication, including prior clinical biochemical indication of renal disease from the DNPR and LABKA (for definitions, see Thomsen et al. [23] and Supplementary Table 1).

From the Prescription Database, we obtained information on the redemption of any other glucose-lowering drug between 14 days after the first metformin monotherapy prescription and until follow-up start. We also obtained information on any antihypertensive treatment, statins, antiplatelet drugs, and treatment with psychiatric medications before follow-up start.

From LABKA we obtained information on the latest baseline HbA_{1c} and on the latest LDL cholesterol and total cholesterol measurement taken within 12 months before follow-up start. We assessed whether recommended cholesterol targets for persons with diabetes were met or not ($<$2.5 mmol/L for LDL cholesterol and $<$4.5 mmol/L for total cholesterol) (28).

Statistical Analyses

We used contingency tables to first describe characteristics for all patients at day 180 after metformin initiation, by achieved HbA_{1c} (%) level ($<$6.5, 6.5–6.9, 7.0–7.4, 7.5–7.9, $\geq$8), and by the magnitude of HbA_{1c} reduction in % (Δ $-$4 or more, $-$3, $-$2, $-$1, 0, +1, +2 and above). We created a stacked-bar graph figure to illustrate the distribution of achieved HbA_{1c} levels for each baseline HbA_{1c} group (Supplementary Fig. 1).

We used Cox regression analyses to compute crude and adjusted hazard ratios (HRs) with 95% CIs to examine the association between achieved HbA_{1c} level and absolute change in HbA_{1c} from baseline (%) at 6 months, respectively, and subsequent risk of cardiovascular events and death after 6 months. We adjusted all analyses for the following covariates (see Table 1 for categorization): age, sex, baseline HbA_{1c} before metformin start, year of follow-up start, micro- and macrovascular complications, obesity, alcoholism, antiplatelet drugs, statins, antihypertensive drugs, psychiatric medications, reached cholesterol target, and other glucose-lowering therapy than metformin. We repeated the adjusted analysis excluding baseline HbA_{1c}.

We repeated all analyses, stratified by age-groups and presence of comorbidity at baseline (healthy vs. comorbidity). Adjusted HRs were also stratified by baseline HbA_{1c} (%) level ($<$7.5, 7.5–8.9, and $\geq$9) (Figs. 1 and 2). As a sensitivity analyses, we repeated our analysis while censoring all end points occurring within the first 2 years (as potentially too soon for glycemic control to have had an effect) and another including only individuals with at least 5 years of full follow-up.

To adjust for the potential residual or unmeasured effect of socioeconomic status (using low education as a proxy), we also did a sensitivity analysis with external adjustment (29), where we assumed that the relative risk of cardiovascular events in those with a low educational level was 1.33 (30) and that the proportion of people with low education was 25% among patients with good glycemic control ($<$7%) and 40% in those with higher HbA_{1c} levels. We used SAS 9.2 software for all analyses.

RESULTS

Table 1 presents the 24,752 patients with first-time metformin treatment according to achieved HbA_{1c} level. Compared with those who had an HbA_{1c} of $\geq$8% at 6 months, patients who achieved HbA_{1c} $<$6.5% were to a larger extent older ($\geq$70 years: 27% vs. 17%), female (47% vs. 38%), and more likely to have initiated metformin in the most recent study years (started in 2010–2012: 60% vs. 35%). They also had slightly more macrovascular (15% vs. 12%) and microvascular (24% vs. 21%) complications at baseline, received more preventive medications, and had less medical obesity (8% vs. 11%). Patients with HbA_{1c} $<$6.5% had a much lower baseline HbA_{1c} compared with those who attained a value $\geq$8%, and more of them had received no further glucose-lowering add-on therapy within the first 180 days (Table 1). Supplementary Fig. 1 shows the distribution of HbA_{1c} achieved for each baseline HbA_{1c} group.

Table 1 also reports patient characteristics by magnitude of HbA_{1c} change. On the one hand, compared with patients with small HbA_{1c} reductions, those with a large reduction tended to be younger, had a lower prevalence of macrovascular complications, had less comorbidity, and were prescribed less preventive medication. On the other hand, patients with large reductions in HbA_{1c} had high HbA_{1c} at baseline (e.g., 93% of those with HbA_{1c} reduction of Δ $-$4% had a baseline HbA_{1c} $>$10%) and received add-on glucose-lowering therapy to a greater extent. In contrast, increasing HbA_{1c} after metformin start was unusual and indicated young age, use of psychiatric medications, and use of drugs other than metformin rather than having a specific level of baseline HbA_{1c} (Table 1).

Median follow-up for our cohort was 2.6 years (interquartile range [IQR] 1.2–4.7). We observed 439 incident myocardial infarctions, 594 strokes, and 1,845 deaths. Figure 1 shows the unadjusted cumulative incidence of a combined outcome event by achieved early glycemic level at 180 days. The incidence was consistently lower in patients who had achieved HbA_{1c} $<$6.5% and was highest in patients who had an HbA_{1c} $\geq$8% at 180 days after metformin. As a point of comparison, the outcome incidence in individuals with no available HbA_{1c} test both before and after metformin (Fig. 1, black stippled line) was similar to that in patients who achieved a low HbA_{1c}.

Figure 2 shows that after adjustment for confounders, the risk of the composite end point increased with rising levels of early achieved HbA_{1c}, compared with achievement of HbA_{1c} $<$6.5%. The adjusted HR for the combined outcome was 1.18 (95% CI 1.07–1.30) for an HbA_{1c} level of 6.5–6.99%, HR 1.23 (1.09–1.40) for 7.0–7.49%, HR 1.34 (1.14–1.57) for 7.5–7.99%, and HR 1.59 (1.37–1.84) for $\geq$8% (Fig. 2 and Supplementary Table 2). Differences between crude and adjusted HRs increased in the highest HbA_{1c} groups; that is, because patients with high HbA_{1c} were younger and had less comorbidity at baseline, their high cardiovascular risk further increased after adjustment for these differences in prognostic factors. The adjusted model not including baseline HbA_{1c} showed consistent results for myocardial infarction, stroke, and mortality but with less precise risk estimates (Supplementary Table 2). Results were also consistent within different strata of age and presence or absence of comorbidity at baseline (Supplementary Fig. 2).

Table 1—Characteristics at 6 months after metformin start among 24,752 metformin initiators, according to achieved HbA_{1c} or magnitude of absolute HbA_{1c} reduction from baseline

	Achieved HbA_{1c} level 6 months after metformin start												Magnitude of HbA_{1c} change from baseline to 6 months											
	<6.5%		6.5–6.99%		7.0–7.49%		7.5–7.99%		≥8%		Total		−4% or more		−3%		−2%		−1%		0%		+1%		+2% or more	
	n = 11,849 (48%)		*n* = 6,578 (27%)		*n* = 3,035 (12%)		*n* = 1,434 (6%)		*n* = 1,856 (8%)		*N* = 24,752 (100%)		*n* = 1,893 (8%)		*n* = 1,880 (8%)		*n* = 2,685 (11%)		*n* = 6,590 (27%)		*n* = 11,179 (45%)		*n* = 429 (2%)		*n* = 96 (0%)	
Variable	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*N*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Baseline HbA_{1c}, %																										
<6.5	3,998	34	222	3	27	1	7	1	13	1	4,267	17	0	0	0	0	3	0	415	6	3,715	38	98	23	36	30
6.5 to <6.9	3,792	32	1,950	30	251	8	47	3	24	1	6,064	25	0	0	0	0	25	1	2,150	29	3,776	39	95	23	18	15
7 to <7.4	1,096	9	1,445	22	548	18	84	6	49	3	3,222	13	0	0	1	0	87	3	1,673	23	1,383	14	64	15	14	12
7.5–7.9	696	6	940	14	569	19	201	14	134	7	2,540	10	0	0	9	1	393	15	1,537	21	504	5	79	19	18	15
8–8.9	723	6	805	12	699	23	407	28	361	20	2,995	12	10	0	256	16	1,094	43	1,246	17	307	3	55	13	27	22
9–9.9	454	4	413	6	359	12	257	18	383	21	1,866	8	185	7	636	40	659	26	310	4	56	1	14	3	6	5
≥10	1,090	9	803	12	582	19	431	30	892	48	3,798	15	2,661	93	674	43	289	11	116	2	38	0	17	4	3	3
Age-group, years																										
≤60	4,677	40	2,517	38	1,296	43	736	51	1,077	58	10,303	42	1,054	56	1,054	56	1,336	50	2,520	38	4,054	36	221	52	64	67
61–70	3,928	33	2,120	32	955	32	429	30	468	25	7,900	32	550	29	532	28	766	29	2,145	33	3,770	34	117	27	20	21
>70	3,244	27	1,941	30	784	26	269	19	311	17	6,549	27	289	15	294	16	583	22	1,925	29	3,355	30	91	21	12	13
Male sex	6,325	53	3,594	55	1,713	56	844	59	1,144	62	13,620	55	1,239	66	1,184	63	1,653	62	3,651	55	5,584	50	253	59	56	58
Calendar year																										
2000–2003	540	5	356	5	306	10	178	12	241	13	1,621	7	228	12	264	14	296	11	445	7	338	3	44	10	6	6
2004–2006	1,131	10	762	12	506	17	276	19	319	17	2,994	12	500	18	296	19	429	17	975	13	712	7	64	15	18	15
2007–2009	3,127	26	2,170	33	1,147	1	543	38	643	35	7,630	31	333	18	334	18	481	18	888	14	882	8	59	14	17	18
2010–2012	7,051	60	3,290	50	1,076	36	437	31	653	35	12,507	51	615	33	618	33	889	33	2,275	35	3,048	27	151	35	34	35
Macrovascular complications	1,774	15	1,059	16	502	17	212	15	229	12	3,776	15	154	8	213	12	382	14	1,070	16	1,866	17	76	18	15	16
Microvascular complications	2,848	24	1,661	25	781	26	326	23	386	21	6,002	24	336	18	373	20	597	22	1,754	27	2,799	25	120	28	23	24
Hospital-diagnosed obesity	885	8	474	7	232	8	129	9	200	11	1,920	8	137	7	133	7	229	9	499	8	853	8	49	11	20	21
Charlson Comorbidity Index level ≥1	2,496	21	1,486	23	688	23	318	22	359	19	5,347	22	273	14	346	18	585	22	1,496	23	2,516	23	102	24	29	30
Antiplatelet drugs	4,575	39	2,764	42	1,237	41	533	37	584	32	9,693	39	540	29	558	30	946	35	2,781	42	4,663	42	171	40	34	35
Statins	7,970	67	4,539	69	1,966	65	862	60	1,025	55	16,362	66	957	51	1,004	53	1,562	58	4,423	67	8,091	72	274	64	51	53
Antihypertensive drugs	8,763	74	4,991	76	2,238	74	982	69	1,207	65	18,181	74	1,124	60	1,190	63	1,823	68	5,057	77	8,612	77	311	73	64	67
Psychiatric medications	2,329	20	1,145	17	527	17	227	16	327	18	4,555	18	293	16	299	16	470	18	1,143	17	2,210	20	104	24	36	38
Single metformin at 6 months	11,057	93	6,076	92	2,724	90	1,215	85	1,536	83	22,608	91	1,408	74	1,497	80	2,320	86	6,109	93	10,808	97	390	91	76	79

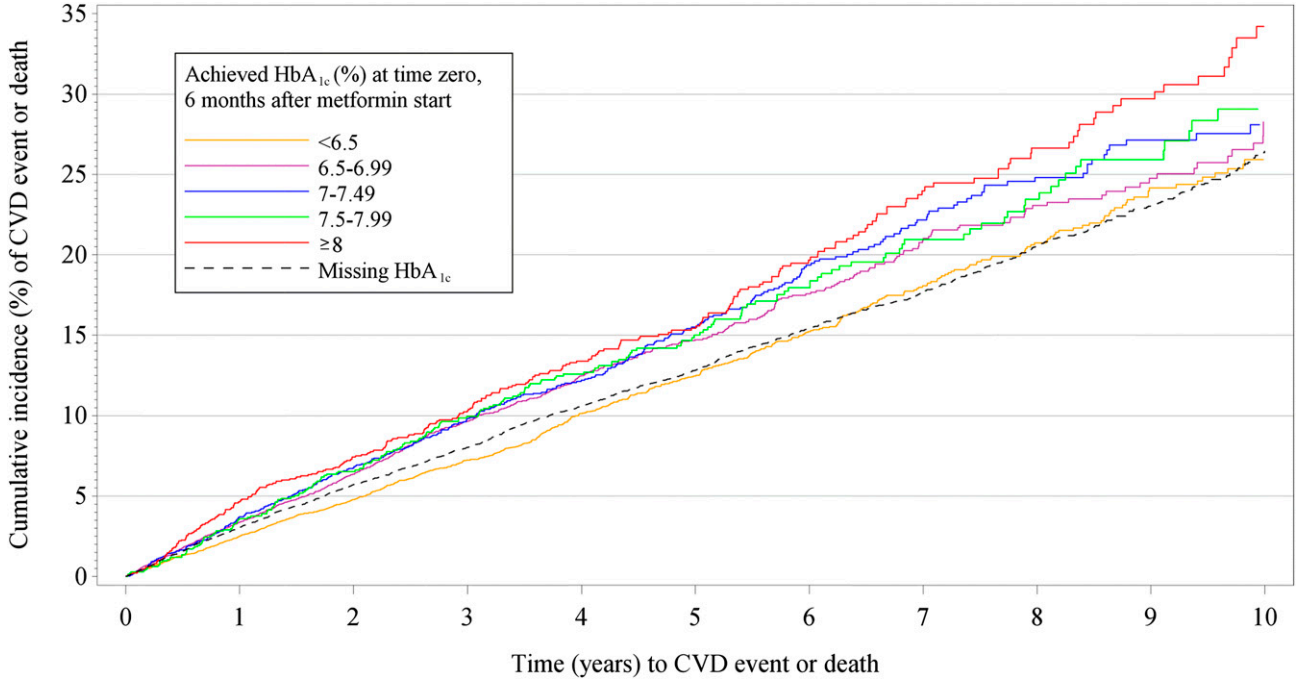

Figure 1—Combined outcome event (acute myocardial infarction, stroke, or death) by achieved early glycemic level. The cumulative incidences of a combined outcome event by achieved HbA_{1c} level 6 months after metformin start are shown among 24,752 metformin initiators in Northern Denmark during 2000–2012. As a point of comparison, the black stippled line shows the event rate among 17,134 metformin initiators in whom an HbA_{1c} measurement was missing before and after metformin initiation. Time (years) to cardiovascular disease (CVD) or death was from 6 months (180 days) after metformin initiation.

The clearest association between higher HbA_{1c} and worse outcomes was observed in patients aged 70 years or older.

Figure 3 shows that the magnitude of HbA_{1c} change predicted outcome as well. Large HbA_{1c} reductions were associated with the greatest outcome risk reductions among patients with a high baseline HbA_{1c} (i.e., >9%), although statistical precision was limited. In patients with a low baseline HbA_{1c} (i.e., <7.5%), the pattern tended to be U-shaped, with HbA_{1c} reductions corresponding to $\Delta = -2\%$ (from -1.5% to -2.4%) predicting increased outcome risk.

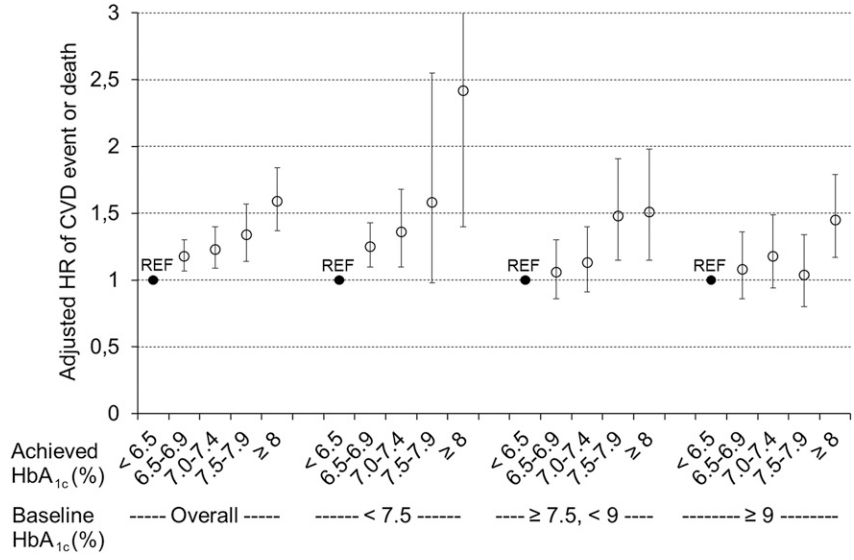

Figure 2—Adjusted HRs for combined outcome event (acute myocardial infarction, stroke, or death) by achieved HbA_{1c} 6 months after metformin initiation. HRs are stratified by baseline pretreatment HbA_{1c} levels of <7.5%, from 7.5 to <9.0%, and ≥9.0%. CVD, cardiovascular disease; REF, reference (HR associated with target <6.5%).

The overall adjusted HR for a combined outcome was 0.80 (95% CI 0.65–0.97) for $\Delta = -4$, HR 0.98 (0.80–1.20) for $\Delta = -3$, HR 0.92 (0.78–1.08) for $\Delta = -2$, and HR 0.99 (0.89–1.10) for $\Delta = -1$ compared with the reference group with no HbA_{1c} change ($\Delta = 0$) (Fig. 3 and Supplementary Table 3). An increased outcome risk was seen in patients with increasing HbA_{1c} despite metformin initiation.

A sensitivity analysis that censored all end points occurring within 2 years and was restricted to patients with at least 5 years of full follow-up (Supplementary Tables 4 and 5 and Supplementary Figs. 3 and 4) showed consistent results for both HbA_{1c} reduction and HbA_{1c} achieved, albeit statistical precision was poorer.

When we externally adjusted for unmeasured confounding resulting from socioeconomic status (proxy education) for the association between glycemic control and macrovascular events, the analyses yielded results consistent with the overall findings.

CONCLUSIONS

In this population-based study of 24,752 metformin initiators, attaining a stringent HbA_{1c} goal of <6.5% within 6 months was

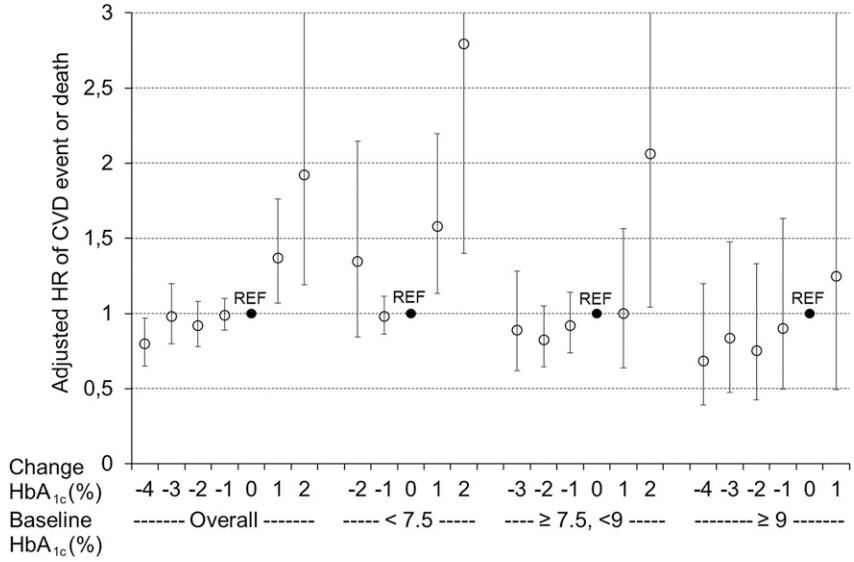

Figure 3—Adjusted HRs for combined outcome event (acute myocardial infarction, stroke, or death) by magnitude of HbA_{1c} reduction from baseline to 6 months. HRs are stratified by baseline pretreatment HbA_{1c} levels of <7.5%, from 7.5 to <9.0%, and ≥9.0%. CVD, cardiovascular disease; REF, reference (HR associated with no change in HbA_{1c}).

associated with lower risk of cardiovascular events and mortality, with the risk gradually increasing at higher HbA_{1c} levels. A large magnitude of HbA_{1c} reduction similarly was associated with a lower subsequent risk of adverse outcomes.

Our results corroborate findings from a few previous observational studies on early glycemic control showing lowered risk of macrovascular events (15,18), and also in the UKPDS trial (31), all in patients with newly diagnosed type 2 diabetes. Olsson et al. (18), monitoring 101,799 patients from the Clinical Practice Research Data Link in the U.K. between 1995 and 2011 from start of type 2 diabetes diagnoses, found an increased risk for myocardial infarction of ~60% (HR 1.6) at an HbA_{1c} of 7–8% vs. 6–7%, with a median follow-up of 5.4 years (18). Our corresponding finding was slightly lower (HR 1.5 [95% CI 1.0–2.1]) comparing HbA_{1c} of ≥8% vs. <6.5%, with a median follow-up of 2.6 years. The similar findings, despite different categorization of HbA_{1c} and use of different HbA_{1c} measure (updated means vs. early glycemic control), strengthens the validity of our results.

Our data show that achievement of stringent glycemic levels is possible in real life in at least some elderly patients with comorbidities and that reaching such levels predicts lower risk of vascular events and death. Of note, elderly patients with complications who attained stringent HbA_{1c} levels in our observational study may have been selected by caregivers through criteria that are not well described in our data, for example, by having a low risk of hypoglycemia or high patient motivation and self-care (3). In accordance, the updated statement from the American Heart Association and the American Diabetes Association suggests stringent targets for selected individual patients, including patients with a short disease duration (7).

A novel finding in our study was that the magnitude of early HbA_{1c} reduction is an independent predictor of lower cardiovascular risk and death, also after taking pretreatment HbA_{1c} level into account. Nonetheless, in the subgroup of patients who had a low baseline HbA_{1c} (<7.5%) before metformin initiation, a reduction in the order of −2% tended to be associated with worse outcomes, consistent with findings from randomized trials (5). As a result of the statistical variation and imprecision of outcome HRs associated with limited size of the change in HbA_{1c} subgroups, our findings should be interpreted with caution.

Overall, our findings suggest that rapid glycemic response may be used as a possible source of identification of a subgroup of patients with a lower risk of adverse outcomes. It is possible that rapid glycemic responders to therapy initiation (i.e., more easy-to-treat patients) may have a different pathological trajectory and a milder variant of type 2 diabetes than patients who are poor responders. It is also possible that it is the young patients with type 2 diabetes without complications that clinicians dare to treat intensively; for example , reduce HbA_{1c} >10% to <7%, supported by a recent study from Denmark (32). However, we observed a clear association between early control and improved outcomes also when restricted to people older than 70 years in our study. Moreover, we have previously observed that young patients, to a lesser extent than older patients, reach an early glycemic control <7% within 6 months, possibly related to the fact that the pretreatment HbA_{1c} with young debut of diabetes often is high (33).

The strengths of this study include a population-based design within the comprehensive Danish public health care system, and accordingly, our data reflect actual clinical practice in diabetes care. Carstensen et al. (34) showed a high sensitivity and positive predictive value (>95%) for identifying patients with type 2 diabetes using Danish registries, with GP registration as the gold standard. Positive predictive values for important comorbidities are also documented as being high in the DNPR (25). Furthermore, we have a comprehensive assessment of cardiovascular events and death, and validity of these codes are also high (26,27). We only looked at myocardial infarction, stroke, and death, yet other studies have found similar associations with glycemia for heart failure, as summed in the meta-analysis by Erqou et al. (35) Finally, we only included metformin initiators, increasing the homogeneity of the population studied and representing the clinical practice today with metformin as the preferred initial pharmacological agent for type 2 diabetes (4). Whether early glycemic control by other oral glucose-lowering drugs is associated with similar benefits remains to be proven.

Study limitations included that only approximately half of all potentially eligible patients had HbA_{1c} measurements within the right time frame around therapy start. The fact that patients with no HbA_{1c} measurement available had low outcome risks suggests that this subgroup might have been less severe at start. Over time, the frequency of HbA_{1c} measurements has increased, and because treatment guidelines have changed over time from initial lifestyle modification to

emphasizing early drug treatment, it is likely that patients had high HbA_{1c} levels in the beginning of our study period primarily as a result of late initiation of medical therapy and that HbA_{1c} measurements from recent years more reliably reflect baseline glycemic control in newly diagnosed type 2 diabetes. Nonetheless, analyses stratified by period of metformin initiation showed consistent results. Moreover, prescription redemption is only a marker of actual drug consumption. We also have to bear in mind that the guidelines have changed over time to encompass individualized therapy (3,4). Pretreatment HbA_{1c} levels have decreased substantially over time in Denmark and in other countries, and achievement of early glycemic control has improved (22).

By regression analyses and stratification, we were able to evaluate the effect of a range of possible confounders of the association between early glycemic control and cardiovascular events, and interestingly, few differences were seen comparing crude and adjusted results and in stratified analyses. Also, the analysis adjusted for potential unmeasured confounding by educational level showed consistent results. We had no data on tobacco smoking but were able to adjust for a number of smoking-related diseases. Still, imperfectly measured, unmeasured (e.g., BMI, diet, physical activity, social support, motivation, and self-care), or unknown factors may have affected our risk estimates.

In conclusion, these real-world data provide evidence that not only achievement of early glycemic control but also the magnitude of HbA_{1c} reduction predicts decreased risk of cardiovascular outcomes and mortality in metformin initiators, independent of baseline HbA_{1c} levels at treatment initiation. Whereas causality is difficult to prove in our observational study design, these results provide an early prediction tool for identification of patient subgroups with type 2 diabetes that have increased risk for cardiovascular complications and death.

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Duality of Interest. E.S.B. has been an employee of Novo Nordisk Scandinavia AB but has taken a position as a general practice physician in Søndre Land Kommune, Norway as of 1 February 2016. C.L.H. is an employee of Novo Nordisk Scandinavia AB. This study was partly supported by a research grant from Novo Nordisk A/S to Aarhus University. The Department of Clinical Epidemiology is involved in studies with funding from various companies as research grants to (and administered by) Aarhus University, including the current study. No other potential conflicts of interest relevant to this article were reported.

The Department of Clinical Epidemiology at Aarhus University had control of the data and retained final authority over design, content, and interpretation of the analyses, as well as the decision to submit the manuscript for publication.

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