Glycemic Control, Complications, and Death in Older Diabetic Patients

The Diabetes and Aging Study

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OBJECTIVE—To identify the range of glycemic levels associated with the lowest rates of complications and mortality in older diabetic patients.

RESEARCH DESIGN AND METHODS—We conducted a retrospective cohort study (2004–2008) of 71,092 patients with type 2 diabetes, aged ≥60 years, enrolled in Kaiser Permanente Northern California. We specified Cox proportional hazards models to evaluate the relationships between baseline glycated hemoglobin (A1C) and subsequent outcomes (nonfatal complications [acute metabolic, microvascular, and cardiovascular events] and mortality).

RESULTS—The cohort (aged 71.0 ± 7.4 years [means ± SD]) had a mean A1C of 7.0 ± 1.2%. The risk of any nonfatal complication rose monotonically for levels of A1C >6.0% (e.g., adjusted hazard ratio 1.09 [95% CI 1.02–1.16] for A1C 6.0–6.9% and 1.86 [1.63–2.13] for A1C ≥11.0%). Mortality had a U-shaped relationship with A1C. Compared with the risk with A1C <6.0%, mortality risk was lower for A1C levels between 6.0 and 9.0% (e.g., 0.83 [0.76–0.90] for A1C 7.0–7.9%) and higher at A1C ≥11.0% (1.31 [1.09–1.57]). Risk of any end point (complication or death) became significantly higher at A1C ≥8.0%. Patterns generally were consistent across age-groups (60–69, 70–79, and ≥80 years).

CONCLUSIONS—Observed relationships between A1C and combined end points support setting a target of A1C <8.0% for older patients, with the caution that A1Cs <6.0% were associated with increased mortality risk. Additional research is needed to evaluate the low A1C–mortality relationship, as well as protocols for individualizing diabetes care.

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People aged >60 years comprise >40% of the type 2 diabetic population in the U.S., yet identifying the optimal glucose control level for older patients with diabetes remains a significant challenge. The widely accepted recommendation that all patients pursue a glycated hemoglobin (A1C) <7.0% is based largely on the results of the UK Prospective Diabetes Study (1), which actively excluded people aged >65 years (2,3).

More recent trials have generated controversy regarding the effects of pursuing very low glucose levels (A1C <6.5%) in older diabetic patients. In 2008, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Trial (4), the Action in Diabetes and Vascular Disease Trial (5), and the Veterans Affairs Diabetes Trial (6) provided some of the first data describing the impact of pursuing very intensive glucose lowering in the elderly. Two of the trials (5,6) found that intensive glucose lowering prevented the progression of nephropathy; however, none of the trials demonstrated a clear cardiovascular benefit. Further complicating this picture, the ACCORD trial found a higher rate of mortality in the intensive glucose-lowering arm (4).

As with clinical trials, observational studies in diabetes also have provided conflicting insights into the potential impacts of different levels of glycemic control. Numerous epidemiological studies have found a continuous relationship between A1C levels and microvascular and cardiovascular complications with no clear threshold (7). However, a recent observational study (8) of the relationship between A1C levels and mortality has reported an elevated risk of mortality at both the lower and upper ends of long-term glucose levels.

Although the pursuit of very low glucose levels may not always be appropriate, failing to address very high glucose levels may significantly increase the risk of acute metabolic events, chronic complications, and mortality. Medical organizations have confused matters by recommending different glycemic targets. Recommended glycemic targets range from an A1C <6.5% from the American Association of Clinical Endocrinologists (9), to an A1C <7.0% from the American Diabetes Association, to an A1C <8.0% from geriatric diabetes care guidelines for older patients with limited life expectancy (10). Unfortunately, there has been limited evidence for any of these targets of glycemic control for older patients, especially for the oldest older patients. We sought to identify the range of glycemic levels associated with the lowest rates of complications and mortality in a large, contemporary, multiethnic cohort of older diabetic patients.

RESEARCH DESIGN AND METHODS

—The Kaiser Permanente Northern California Diabetes Registry (also referred to here as the Registry) is a well-characterized population, maintained continuously since 1993, that has been the basis for extensive epidemiological research (11–13). Registry eligibility is based on multiple sources of data, including pharmacy records, laboratory

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Table 1—*Population description by baseline A1C categories*

		Baseline A1C							
	Overall	<6.0	6.0–6.9	7.0–7.9	8.0–8.9	9.0–9.9	10–10.9	≥11	*P*
n	71,092	10,921	32,125	17,454	5,962	2,372	1,125	1,133	
Demographics									
Age categories (years)									
60–69	33,374 (46.9)	4,665 (42.7)	13,863 (43.2)	8,592 (49.2)	3,323 (55.7)	1,460 (61.6)	722 (64.2)	749 (66.1)	<0.001
70–79	27,323 (38.4)	4,349 (39.8)	13,051 (40.6)	6,573 (37.7)	2,028 (34.0)	701 (29.6)	313 (27.8)	308 (27.2)	
≥80	10,395 (14.6)	1,907 (17.5)	5,211 (16.2)	2,289 (13.1)	611 (10.3)	211 (8.9)	90 (8.0)	76 (6.7)	
Female	33,708 (47.4)	4,567 (41.8)	15,588 (48.5)	8,516 (48.8)	2,862 (48.0)	1,082 (45.6)	544 (48.4)	549 (48.5)	<0.001
Race/ethnicity									
Non-Hispanic white	38,465 (54.1)	6,992 (64.0)	17,957 (55.9)	8,748 (50.1)	2,758 (46.3)	1,070 (45.1)	506 (45.0)	434 (38.3)	<0.001
Black	6,851 (9.6)	785 (7.2)	2,865 (8.9)	1,857 (10.6)	691 (11.6)	290 (12.2)	159 (14.1)	204 (18.0)	
Hispanic	7,657 (10.8)	1,014 (9.3)	3,269 (10.2)	1,975 (11.3)	767 (12.9)	304 (12.8)	152 (13.5)	176 (15.5)	
Asian/Pacific Islander	8,423 (11.9)	826 (7.6)	3,782 (11.8)	2,396 (13.7)	818 (13.7)	320 (13.5)	146 (13.0)	135 (11.9)	
Other/mixed	8,107 (11.4)	1,077 (9.9)	3,538 (11.0)	2,126 (12.2)	781 (13.1)	318 (13.4)	132 (11.7)	135 (11.9)	
Missing	1,589 (2.2)	227 (2.1)	714 (2.2)	352 (2.0)	147 (2.5)	70 (3.0)	30 (2.7)	49 (4.3)	
Clinical characteristics									
Duration of diabetes (years)									
0–4	30,589 (43.0)	7,084 (64.9)	15,810 (49.2)	5,054 (29.0)	1,373 (23.0)	573 (24.2)	301 (26.8)	394 (34.8)	<0.001
5–9	17,116 (24.1)	2,034 (18.6)	7,520 (23.4)	4,666 (26.7)	1,593 (26.7)	684 (28.8)	322 (28.6)	297 (26.2)	
10–14	11,503 (16.2)	959 (8.8)	4,412 (13.7)	3,625 (20.8)	1,435 (24.1)	558 (23.5)	267 (23.7)	247 (21.8)	
15–19	4,985 (7.0)	348 (3.2)	1,835 (5.7)	1,722 (9.9)	645 (10.8)	234 (9.9)	98 (8.7)	103 (9.1)	
≥20	6,891 (9.7)	496 (4.5)	2,548 (7.9)	2,387 (13.7)	916 (15.4)	323 (13.6)	127 (11.3)	92 (8.1)	
Systolic blood pressure									
≥130 mmHg	41,127 (57.9)	5,967 (54.6)	18,381 (57.2)	10,428 (59.8)	3,548 (60.1)	1,434 (60.5)	686 (61.0)	647 (57.1)	<0.001
<130 mmHg	25,737 (36.2)	4,262 (39.0)	11,924 (37.1)	6,008 (34.4)	1,986 (33.3)	775 (32.7)	366 (32.5)	416 (36.7)	
Missing	4,228 (5.9)	692 (6.3)	1,820 (5.7)	1,018 (5.8)	392 (6.6)	163 (6.9)	73 (6.5)	70 (6.2)	
LDL cholesterol									
≥100 mg/dL	34,517 (48.6)	5,300 (48.5)	15,210 (47.3)	8,258 (47.3)	3,065 (51.4)	1,316 (55.5)	648 (57.6)	720 (63.5)	<0.001
<100 mg/dL	32,608 (45.9)	4,901 (44.9)	15,223 (47.4)	8,311 (47.6)	2,568 (43.1)	904 (38.1)	393 (34.9)	308 (27.2)	
Missing	3,967 (5.6)	720 (6.6)	1,692 (5.3)	885 (5.1)	329 (5.5)	152 (6.4)	84 (7.5)	105 (9.3)	
Triglycerides									
≥200 mg/dL	19,947 (28.1)	2,279 (20.9)	8,570 (26.7)	5,395 (30.9)	1,967 (33.0)	852 (35.9)	441 (39.2)	443 (39.1)	<0.01
<200 mg/dL	45,589 (64.1)	7,669 (70.2)	21,229 (66.1)	10,804 (61.9)	3,512 (58.9)	1,292 (54.5)	556 (49.4)	527 (46.5)	
Missing	5,556 (7.8)	973 (8.9)	2,326 (7.2)	1,255 (7.2)	483 (8.1)	228 (9.6)	128 (11.4)	163 (14.4)	
Estimated GFR									
≥90	6,444 (9.1)	918 (8.4)	2,554 (8.0)	1,650 (9.5)	667 (11.2)	298 (12.6)	164 (14.6)	193 (17.0)	<0.001
60–89	32,674 (46.0)	4,941 (45.2)	14,736 (45.9)	8,112 (46.5)	2,754 (46.2)	1,095 (46.2)	509 (45.2)	527 (46.5)	
30–59	22,754 (32.0)	3,474 (31.8)	10,703 (33.3)	5,491 (31.5)	1,810 (30.4)	687 (29.0)	309 (27.5)	280 (24.7)	
15–29	1,770 (2.5)	304 (2.8)	795 (2.5)	426 (2.4)	142 (2.4)	53 (2.2)	25 (2.2)	25 (2.2)	
<15	194 (0.3)	47 (0.4)	94 (0.3)	38 (0.2)	10 (0.2)	1 (<0.1)	1 (<0.1)	3 (0.3)	
Missing	7,256 (10.2)	1,237 (11.3)	3,243 (10.1)	1,737 (10.0)	579 (5.3)	238 (0.02)	117 (1.1)	105 (1.0)	

Table 1—*Continued*

	Overall	Baseline A1C							*P*
		<6.0	6.0–6.9	7.0–7.9	8.0–8.9	9.0–9.9	10–10.9	≥11	
Albuminuria/proteinuria*									
Normal	43,734 (61.5)	7,235 (66.2)	20,580 (64.1)	10,325 (59.2)	3,242 (54.4)	1,209 (51.0)	583 (51.8)	559 (49.3)	<0.001
Microalbuminuria	11,126 (15.7)	1,362 (12.5)	4,654 (14.5)	2,974 (17.0)	1,140 (19.1)	515 (21.7)	228 (20.3)	253 (22.3)	
Overt proteinuria	452 (5.9)	452 (4.1)	1,524 (4.7)	1,172 (6.7)	538 (9.0)	247 (10.4)	125 (11.1)	115 (10.2)	
Missing	12,059 (17.0)	1,872 (17.1)	5,367 (16.7)	2,982 (17.1)	1,042 (17.5)	401 (16.9)	189 (16.8)	206 (18.2)	
Lower-extremity amputation	877 (1.2)	109 (1.0)	339 (1.1)	232 (1.3)	106 (1.8)	44 (1.9)	24 (2.1)	23 (2.0)	<0.001
Laser photocoagulation	5,335 (7.5)	351 (3.2)	1,779 (5.5)	1,748 (10.0)	799 (13.4)	354 (14.9)	147 (13.1)	157 (13.9)	<0.001
Acute metabolic complication	351 (0.5)	39 (0.4)	93 (0.3)	82 (0.5)	49 (0.8)	37 (1.6)	19 (1.7)	32 (2.8)	<0.001
Acute infection	3,528 (5.0)	631 (5.8)	1,537 (4.8)	822 (4.7)	268 (4.5)	136 (5.7)	65 (5.8)	69 (6.1)	0.63
Myocardial infarction	6, 656 (9.4)	1,018 (9.3)	2,894 (9.0)	1,654 (9.5)	616 (10.3)	253 (10.7)	116 (10.3)	105 (9.3)	0.004
Stroke	3,155 (4.4)	551 (5.1)	1,430 (4.5)	748 (4.3)	267 (4.5)	84 (3.5)	43 (3.8)	32 (2.8)	<0.001
Congestive heart failure	6,632 (9.3)	1,068 (9.8)	2,862 (8.9)	1,625 (9.3)	582 (9.8)	266 (11.2)	100 (8.9)	129 (11.4)	0.01
Cancer	1,209 (1.7)	222 (2.0)	552 (1.7)	275 (1.6)	92 (1.5)	35 (1.5)	12 (1.1)	21 (1.9)	0.01
Chronic obstructive pulmonary disease	7,493 (10.5)	1,355 (12.4)	3,410 (10.6)	1,727 (9.9)	590 (9.9)	214 (9.0)	98 (8.7)	99 (8.7)	<0.001
Depression	17,015 (23.9)	2,743 (25.1)	7,593 (23.6)	4,111 (23.6)	1,451 (24.3)	552 (23.3)	294 (26.1)	271 (23.9)	0.48
Glucose-lowering drugs									
Insulin	12,470 (17.5)	724 (6.6)	3,951 (12.3)	4,318 (24.7)	1,948 (32.7)	818 (34.5)	369 (32.8)	342 (30.2)	<0.001
Sulfonylurea	35,953 (50.6)	3,435 (31.5)	14,417 (44.9)	10,806 (61.9)	4,068 (68.2)	1,646 (69.4)	798 (70.9)	783 (69.1)	<0.001
Thiazolidinedione	6,565 (9.3)	407 (3.7)	2,453 (7.6)	2,141 (12.3)	872 (14.6)	371 (15.6)	174 (15.5)	147 (13.0)	<0.001
Metformin	26,819 (37.7)	1,881 (17.2)	10,585 (33.0)	8,525 (48.8)	3,288 (55.2)	1,306 (55.1)	622 (55.3)	612 (54.0)	<0.001
Acarbose	483 (0.7)	24 (0.2)	142 (0.4)	168 (1.0)	87 (1.5)	38 (1.6)	14 (1.2)	10 (0.9)	<0.001
Repaglinide	90 (0.1)	5 (0.1)	42 (0.1)	22 (0.1)	10 (0.2)	3 (0.1)	3 (0.3)	5 (0.4)	<0.001

Data are *n* (%). *All complications or conditions were prevalent at baseline.

data, and outpatient, emergency room, and hospitalization diagnoses of diabetes. Data from clinical information systems are downloaded annually. Kaiser clinicians are encouraged to provide diabetes care according to internal care guidelines that mirror national clinical practice guidelines (general treatment goals: A1C <7.0%; LDL cholesterol <100 mg/dL; and blood pressure ≤130/80 mmHg).

We included type 2 diabetic subjects from the Registry who were aged ≥60 years at baseline (1 January 2004) and who had continuous Kaiser membership and pharmacy benefits for at least 12 months before baseline. From the initial eligible population of 228,740 patients, we excluded 62,347 for noncontinuous Kaiser membership or pharmacy benefits, 22,427 for type 1 diabetes or unknown diabetes (14), and 63,790 for being aged <60 years. We additionally excluded individuals with evidence of end-stage renal disease before baseline (n = 1,127) and no A1C test result during the year prior to baseline (n = 7,957). The remaining 71,092 subjects were used for these analyses.

Time frame for analysis

Person-time follow-up started on 1 January 2004 and ended with the first occurrence of any of the defined nonfatal end points, death, discontinuation of Kaiser membership or pharmacy benefits (discontinuation defined as a gap of at least 3 months in coverage), or the end of our 4-year observation window (31 December 2007).

Outcomes

Nonfatal outcomes and the date of first occurrence were identified via hospitalization records, based on established coding algorithms using primary diagnostic (ICD-9) or current procedural terminology (CPT) codes (see the Supplementary Materials) (12). Acute metabolic events were defined as hospitalizations for diabetes with other coma, diabetes with hyperosmolarity, diabetes with ketoacidosis, and uncontrolled diabetes. Chronic microvascular events were defined as end-stage renal disease, amputation, or severe diabetic eye disease. Chronic cardiovascular events were categorized as coronary artery disease (myocardial infarction, coronary artery bypass surgery, or angioplasty), congestive heart failure, cerebrovascular disease (ischemic or hemorrhagic stroke or carotid endarterectomy), or peripheral vascular disease.

Mortality and dates of death were captured from the California State Mortality File and Social Security Death Records. We also created two combined outcomes: "Any complication" was defined as the presence of any of the three nonfatal outcomes described above. "Any complication or death" was defined by the occurrence of any of the three nonfatal outcomes or death.

A1C

The main exposure of interest was the most recent A1C within 1 year prior to baseline. Northern California Kaiser medical facilities send all their A1C samples to be analyzed by a single, regional laboratory. This laboratory is licensed by the state's Department of Health Services, inspected and accredited by the College of American Pathologists, and uses the standardization of A1C implemented by the National Glycohemoglobin Standardization Group. We categorized A1C as <6.0, 6.0–6.9, 7.0–7.9, 8.0–8.9, 9.0–9.9, 10.0–10.9, and ≥11.0%. For stratified analyses, we collapsed A1C categories ≥9.0% because of the small numbers of patients at that upper distribution of A1C.

Assessment of covariates

Baseline covariates evaluated in this analysis were demographics (age, sex, and race/ethnicity); duration of diabetes; systolic blood pressure; laboratory findings within 1 year prior to baseline, including estimated glomerular filtration rate (GFR) and urinary albumin excretion (microalbuminuria or proteinuria); BMI; prevalent complications and comorbidities (history of lower-extremity amputation, photocoagulation, hospitalization for acute metabolic event, myocardial infarction, stroke, congestive heart failure, cancer, chronic lung disease, and depression); smoking; number of inpatient admissions in the previous year; and baseline use of glucose-lowering medications.

Statistical analysis

All analyses were performed using SAS version 9.1 (SAS Institute, Cary, NC), and associations were considered statistically significant at the 0.05 level. We first calculated crude incidence densities for each outcome (number of events per 1,000 person-years). We then specified Cox proportional hazards models for each outcome, generating hazard ratios (HRs) for baseline glycemic control (A1C <6.0% as reference group). Bivariate analyses were first performed followed by multivariate analyses, accounting for potential confounders, including age, sex, race/ethnicity, duration of diabetes, systolic blood pressure, use of glucose-lowering medications, smoking status, glucose-monitoring adherence, GFR (chronic kidney disease stages 1–5), microalbuminuria, and proteinuria.

To address the issue of missing data, we used multiple imputations with our adjusted models (15). We found no substantive differences between results from models with complete data and models using multiple imputations. All results presented are from models with complete data. To address the dynamic nature of A1C over time, we also conducted sensitivity analyses using extended Cox models (time-dependent effects).

RESULTS—The mean age of the population was 71.0 years; 14.6% were over the age of 80 years (Table 1). The population was ethnically diverse, with 45.9% of subjects composed of nonwhite racial/ethnic groups.

The mean A1C was 7.0%. A total of 15% of the population had an A1C <6.0%, 60% had an A1C <7.0%, and 6.5% had an A1C ≥9.0%. The most frequently prescribed medications for glucose control were sulfonylureas (50.6%), followed by metformin (37.7%), and any form of insulin (17.5%). The mean duration of diabetes was 8.3 years. Across A1C categories, patients with lower baseline A1C values tended to be older and more likely to be non-Hispanic white. Patients with lower A1C values also were more likely to have a shorter duration of diabetes, better cholesterol control, and lower GFR, but less evidence of other microvascular complications (e.g., microalbuminuria, laser photocoagulation). Patients with lower A1C levels also were much less likely to be treated with insulin.

The mean follow-up time was 3.1 years. Chronic cardiovascular events had the highest incidence (47.2 per 1,000 person-years), followed by mortality (40.4 per 1,000 person-years), chronic microvascular events (26.7 per 1,000 person-years), and acute metabolic events (1.2 per 1,000 person-years) (Table 2).

The risk of acute metabolic events, based on point estimates, increased steeply with each unit change in A1C above 6.0%; this increased risk became statistically significant above the A1C of 7.0%. The adjusted HR for an A1C of 7.0–7.9% was 2.35 (95% CI 1.31–4.23) and increased to 11.52 (5.166–23.47) at an A1C ≥11.0% (reference: A1C <6.0%). Adjusted HRs were somewhat attenuated compared with unadjusted HRs, but the steep, monotonic pattern persisted.

There was a similar, stepwise relationship between baseline A1C and chronic microvascular events. In the unadjusted model, the increased risk associated with higher glucose levels was significantly different than the reference (A1C <6.0%), starting at A1C 6.0–6.9% (HR 1.56 [95% CI 1.41–1.72]). The A1C–microvascular event relationship was attenuated in the adjusted model but still suggested an increased risk beginning at A1C ≥6.0% (1.11 [0.99–1.25]). The risk became significantly higher than the reference for A1C levels ≥7.0% (1.25 [1.11–1.41]) for A1C 7.0–7.9%.

For chronic cardiovascular events, A1C levels ≥6.0% also were associated with a significantly increased risk in both unadjusted and adjusted models. The risk increased continuously without a clear threshold level, although the risk increase was less steep than that observed for acute metabolic or chronic microvascular events.

Unlike the nonfatal complications, mortality had a U-shaped relationship with baseline A1C. In unadjusted models, the risk of mortality was significantly lower for A1C levels between 6.0 and 8.9% relative to A1C levels <6.0%. After adjustment, this general pattern of lower risk in the midrange of A1C still was observed, although the lower risk for A1C levels between 8.0 and 8.9% was no longer statistically significant. The mortality risk did not differ statistically between reference group (A1C <6.0%) and A1C ≥9.0% in the unadjusted model, although the point estimates for A1C ≥10.0% indicated a somewhat higher risk. In adjusted models only, mortality risk became significantly higher once A1C levels exceeded 10.0% (HR 1.21 [95% CI 1.01–1.45]).

When evaluating "any complication," we found that the risk rose steadily with each incremental rise in baseline A1C without a clear threshold, although the steepness of the relationship was attenuated in adjusted models. After adding death to this combined end point (i.e., "any complication or death"), the risk increased significantly at A1C ≥6.0% in the unadjusted model. However, after adjustment, the risk increase was not significant until A1C was ≥8.0%.

The epidemiologic patterns observed in the overall population were similar across the three age-groups (60–69, 70–79, and ≥80 years), with some notable exceptions (Table 3). All three age-groups had U-shaped mortality curves with the highest risk of death among patients with A1C levels at the extremes (A1C <6.0 and ≥9.0%). For patients aged 60–69 years, the lowest point estimate for mortality risk was observed with A1C levels between 7.0 and 7.9%. For patients aged ≥70 years, the mortality risk was statistically lower across a broader range of A1C categories (e.g., A1C 6.0–7.9% for the aged ≥80 years group) compared with the reference group. For the "any complication" outcome, patients aged 60–69 years had a continuous, positive relationship between A1C and complications with no clear threshold. For older patients, the increased risk (relative to the reference) of any complications was significantly higher at the threshold of A1C ≥7.0%. For the "any complication or death" outcome, there was an increased risk in the outcome for all age-groups when A1C exceeded 8.0%, although for patients aged >80 years, this was statistically significant only for A1C ≥9.0%.

In analyses of effect modification, the relationships between A1C and mortality or the combined outcomes were not significantly different for those with differing durations of diabetes (data not shown). In a sensitivity analysis using extended Cox models that accounted for the time-varying nature of A1C, the overall forms of the relationships between A1C and complications did not change from the baseline analyses, although the strengths of the associations weakened, particularly for chronic complication events (data not shown). For extended Cox models of the "any complication" outcome, A1C was significantly associated with a higher risk of events at A1C ≥8.0%, instead of A1C ≥6.0%, whereas for the "any complication or death" outcome, A1C became significantly associated with higher risk at A1C ≥10%, instead of A1C ≥8.0%.

CONCLUSIONS

—The clinical uncertainty surrounding the care of older diabetic patients can be lessened with more in-depth study of this important subpopulation (16). With our large, contemporary, geriatric cohort, we found a U-shaped relationship between A1C and mortality for the overall cohort and for each age category. This U-shaped

Table 2—*Baseline A1C, complications, and mortality: overall population results**

Outcome	Incidence density (events per 1,000 person-years)	Model	Baseline A1C						
			<6.0	6.0–6.9	7.0–7.9	8.0–8.9	9.0–9.9	10–10.9	≥11
Acute metabolic events	1.23	Unadjusted HR (95% CI)	1	1.59 (0.97–2.60)	2.86 (1.74–4.69)	4.53 (2.66–7.73)	6.34 (3.51–11.46)	8.43 (4.34–16.40)	12.36 (6.73–22.70)
		Adjusted HR (95% CI)	1	1.44 (0.82–2.53)	2.35 (1.31–4.23)	3.82 (2.03–7.18)	4.95 (2.45–10.02)	6.60 (2.99–14.56)	11.52 (5.66–23.47)
Chronic microvascular events	26.68	Unadjusted HR (95% CI)	1	1.56 (1.41–1.72)	2.78 (2.51–3.08)	4.17 (3.73–4.66)	4.34 (3.79–4.97)	4.94 (4.19–5.81)	5.05 (4.29–5.94)
		Adjusted HR (95% CI)	1	1.11 (0.99–1.25)	1.25 (1.11–1.41)	1.53 (1.34–1.75)	1.52 (1.29–1.79)	1.72 (1.41–2.10)	2.04 (1.68–2.47)
Chronic cardiovascular events	47.15	Unadjusted HR (95% CI)	1	1.12 (1.05–1.19)	1.28 (1.20–1.37)	1.46 (1.35–1.59)	1.48 (1.33–1.65)	1.55 (1.34–1.79)	1.80 (1.57–2.07)
		Adjusted HR (95% CI)	1	1.09 (1.01–1.17)	1.14 (1.06–1.24)	1.26 (1.14–1.39)	1.28 (1.12–1.46)	1.39 (1.17–1.66)	1.77 (1.51–2.09)
Mortality	40.42	Unadjusted HR (95% CI)	1	0.83 (0.79–0.88)	0.82 (0.77–0.88)	0.84 (0.78–0.92)	0.92 (0.82–1.04)	1.07 (0.92–1.25)	1.12 (0.96–1.30)
		Adjusted HR (95% CI)	1	0.84 (0.79–0.90)	0.83 (0.76–0.90)	0.90 (0.81–1.00)	1.02 (0.88–1.17)	1.21 (1.01–1.45)	1.31 (1.09–1.57)
Any complication	69.90	Unadjusted HR (95% CI)	1	1.22 (1.16–1.29)	1.66 (1.57–1.76)	2.12 (1.98–2.26)	2.22 (2.04–2.42)	2.36 (2.11–2.65)	2.51 (2.25–2.81)
		Adjusted HR (95% CI)	1	1.09 (1.02–1.16)	1.18 (1.10–1.27)	1.38 (1.27–1.50)	1.42 (1.27–1.58)	1.52 (1.32–1.74)	1.86 (1.63–2.13)
Any complication or death	97.97	Unadjusted HR (95% CI)	1	1.05 (1.01–1.10)	1.30 (1.24–1.36)	1.59 (1.51–1.69)	1.68 (1.56–1.82)	1.82 (1.65–2.01)	1.92 (1.74–2.11)
		Adjusted HR (95% CI)	1	0.98 (0.93–1.03)	1.03 (0.97–1.09)	1.20 (1.12–1.29)	1.25 (1.14–1.37)	1.35 (1.20–1.52)	1.63 (1.46–1.84)

*Cox proportional hazards models adjusted for age; sex; race/ethnicity; duration of diabetes; systolic blood pressure; use of insulin, sulfonylurea, or thiazolidinedione; smoking status; glucose-monitoring adherence; GFR (chronic kidney disease stages 1–5); microalbuminuria; and proteinuria.

Table 3—*Age-stratified results: adjusted analyses

Outcome	Baseline A1C				
	<6.0	6.0–6.9	7.0–7.9	8.0–8.9	≥9
Mortality					
Age-group					
60–69	1	0.92 (0.79–1.07)	0.83 (0.70–0.99)	0.91 (0.74–1.11)	1.17 (0.96–1.43)
70–79	1	0.83 (0.75–0.92)	0.85 (0.75–0.96)	0.86 (0.73–1.01)	1.11 (0.93–1.32)
≥80	1	0.83 (0.74–0.93)	0.83 (0.72–0.95)	1.05 (0.86–1.27)	1.20 (0.96–1.50)
Any complication					
Age-group					
60–69	1	1.12 (1.00–1.25)	1.20 (1.07–1.35)	1.44 (1.26–1.64)	1.58 (1.38–1.81)
70–79	1	1.08 (0.98–1.19)	1.21 (1.09–1.35)	1.35 (1.19–1.53)	1.50 (1.30–1.73)
≥80	1	1.11 (0.97–1.27)	1.18 (1.02–1.38)	1.28 (1.03–1.58)	1.43 (1.12–1.83)
Any complication or death					
Age-group					
60–69	1	1.04 (0.94–1.14)	1.08 (0.98–1.20)	1.28 (1.14–1.44)	1.43 (1.27–1.60)
70–79	1	0.98 (0.91–1.06)	1.07 (0.98–1.17)	1.18 (1.06–1.31)	1.36 (1.20–1.53)
≥80	1	0.94 (0.86–1.04)	0.96 (0.85–1.07)	1.13 (0.96–1.33)	1.25 (1.04–1.51)

*Models adjusted for sex; race/ethnicity; duration of diabetes; systolic blood pressure; use of insulin, sulfonylurea, or thiazolidinedione; smoking status; glucose-monitoring adherence; GFR (chronic kidney disease stages 1–5); microalbuminuria; and proteinuria.

relationship was not commonly reported in older epidemiological studies but has been found in more recent studies. Using datasets from the 1990s, Blaum et al. (17) found a linear relationship between A1C and mortality, whereas Nelson et al. (18) found that an A1C ≥8.0% was significantly associated with an increased risk of mortality. In contrast, Currie et al. (8) recently evaluated a large U.K. general population of diabetic patients and found a U-shaped association, with the risk of mortality elevated at low glucose levels (A1C 6.1–6.6%) and at high glucose levels (A1C 10.1–11.2%). Likewise, post hoc analyses of the ACCORD trial results have revealed a U-shaped A1C-mortality relationship in the control arm (19). In contrast, analyses of the intensive arm have revealed a linear A1C-mortality association. The ACCORD findings suggest that glucose-lowering treatments may alter the relationship between glucose levels and mortality. Considering all of these studies in total, the differences between the older and more recent studies are likely attributed to secular changes in glycemic control levels, greater use of combination therapies, and the arrival of newer therapeutic classes. In our cohort, patients with A1C <6.0% used less insulin in comparison with other patients. Sulfonylureas were the most frequently used oral agents, with heavy use of tolazamide and glyburide.

It remains to be seen whether observations of an elevated risk of mortality at low A1C levels represent an actual effect of glucose control or are a result of other factors associated with low A1C levels. Older patients with lower A1C levels may suffer from poor nutritional status, frailty, or sarcopenia, each of which may contribute to an elevated mortality risk (20). The possibility that factors other than glucose control may explain the A1C-mortality relationship is reinforced by the observation of a U-shaped mortality curve in a nondiabetic population (21). The relationship between low A1C and mortality clearly deserves additional study, especially in the elderly.

Our findings regarding A1C and the incidence of chronic complications are consistent with previous literature, primarily conducted in younger patients, demonstrating a continuous relationship between glycemic control and microvascular and cardiovascular complications (7,22). Importantly, our analyses of these outcomes indicate that these continuous relationships also exist among the oldest patients, conditioned on survival. For the overall study population, no glycemic control threshold was evident for the "any complication" outcome. For patients aged >70 years, a statistically significant higher risk was evident above a 7.0% threshold.

The most important results from our study concern the distinctions between the risk of "any complication" versus the most inclusive outcome, "any complication or death." Unlike the risk of "any complication," the risk of "any complication or death" significantly increased relative to the reference group after A1C levels exceeded 8.0%. This outcome integrates the U-shaped curve associated with mortality and the continuous curve associated with complications. Findings for this outcome identify glycemic thresholds that minimize mortality while enhancing quality of life through the prevention of complications.

The relationship between baseline A1C and the "any complication or mortality" outcome differed modestly by age-group, suggesting the impact of competing mortality. Within each A1C strata above the reference level, the HR attenuated with increasing age. Thus, although the general pattern was similar, the slopes became less steep and less statistically significant with advancing age. The A1C 8.0% threshold appeared to demarcate a risk increase for patients aged 60–79 years. For patients aged >80 years, the point estimate for A1C 8.0–8.9% indicated an increased risk, but this result was not statistically different from the reference; instead, there was a 9.0% threshold for these oldest patients. The differences in results for those aged ≥80 years versus those aged 60–79 years may be attributed to mortality becoming an increasingly random event (with respect to diabetes) as age increases (23).

This study has several limitations worth noting. Given the limitations of observational research and our short follow-up time, we cannot assume that our findings have a purely causal basis, and, thus, relationships described in this

article should be subjected to additional research. Residual confounding or reverse causality might explain an apparent short-term increase of complications or increased mortality. We also based our primary conclusions on the relationship between baseline A1C and time to event, consistent with the approach used in most previous studies. We find that when we account for the time-varying nature of A1C, the relationship between A1C and chronic complications actually weakens, whereas the relationship with acute metabolic events actually strengthens. These differences were anticipated, given that a time-dependent exposure analyzed with the extended Cox model is more sensitive to short-term effects, whereas a fixed baseline risk factor analyzed with the standard Cox model is more sensitive to long-term effects (24). In addition, our conclusions regarding A1C thresholds might have differed with the use of even more granular increments of A1C (e.g., half-point increments). Our conclusions also might have changed if we had greater statistical power. Numerous results revealed point estimates that indicated a positive association but with CIs bracketing unity. Although we evaluated multiple outcomes, we did not evaluate the risk of hypoglycemia, which is another important clinical consideration. Our cohort was limited to patients enrolled in an integrated, managed-care system, where diabetes care may differ somewhat from that provided in other settings. Previous comparisons of diabetes care in Kaiser with that of other managed-care settings have found that the quality of Kaiser's care is representative of typical care across the U.S. This cohort had relatively good glycemic control on average but did include sufficient numbers of individuals with very high A1C levels to evaluate outcomes across the spectrum of A1C levels.

With respect to prevention of complications, our results indicate that older people have a graded relationship between A1C and complications. On the other hand, we observed a distinct U-shaped relationship between A1C and mortality. Our results suggest that A1C in older patients should be maintained below 8.0% to prevent both complications and mortality, with the caution that A1C levels <6% were associated with an increased mortality risk. Additional research is needed to identify the mechanisms that underlie the increased mortality among those with very low A1C. In addition, ongoing research on care individualization in the elderly suggests that life expectancy (2), comorbid conditions (3), and patient preferences (25) may be important considerations in setting glycemic goals below 8.0%. Although we await the findings from this important research, the observational data presented here provide additional guidance for caring for the rapidly growing population of older diabetic patients.

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E.S.H. developed the study design, analyzed and interpreted data, drafted the manuscript, critically revised the manuscript, and obtained funding. J.Y.L. acquired data, carried out the statistical analysis, analyzed and interpreted data, and critically revised the manuscript. H.H.M. acquired data, analyzed and interpreted data, critically revised the manuscript, and provided administrative support. P.M.J. analyzed and interpreted data, critically revised the manuscript, and provided administrative support. A.J.K. developed the study design, analyzed and interpreted data, critically revised the manuscript, and obtained funding.

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