Impact of Specific Glucose-Control Strategies on Microvascular and Macrovascular Outcomes in 58,000 Adults With Type 2 Diabetes

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OBJECTIVE—Comparative effectiveness research methods are used to compare the effect of four distinct glucose-control strategies on subsequent myocardial infarction and nephropathy in type 2 diabetes.

RESEARCH DESIGN AND METHODS—A total of 58,000 adults with type 2 diabetes and A1C <7% (53 mmol/mol) while taking two or more oral agents or basal insulin had subsequent A1C ≥7% (53 mmol/mol) to 8.5% (69 mmol/mol). Follow-up started on date of first A1C ≥7% and ended on date of a specific clinical event, death, disenrollment, or study end. Glucose-control strategies were defined as first intensification of glucose-lowering therapy at A1C ≥7, ≥7.5, ≥8, or ≥8.5% with subsequent control for treatment adherence. Logistic marginal structural models were fitted to assess the discrete-time hazards for each dynamic glucose-control strategy, adjusting for baseline and time-dependent confounding and selection bias through inverse probability weighting.

RESULTS—After adjustment for age, sex, race/ethnicity, comorbidities, blood pressure, lipids, BMI, and other covariates, progressively more aggressive glucose-control strategies were associated with reduced onset or progression of albuminuria but not associated with significant reduction in occurrence of myocardial infarction or preserved renal function based on estimated glomerular filtration rate over 4 years of follow-up.

CONCLUSIONS—In a large representative cohort of adults with type 2 diabetes, more aggressive glucose-control strategies have mixed short-term effects on microvascular complications and do not reduce the myocardial infarction rate over 4 years of follow-up. These findings are consistent with the results of recent clinical trials, but confirmation over longer periods of observation is needed.

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Adequate glucose control in patients with type 2 diabetes reduces the occurrence of common, devastating microvascular and macrovascular complications (1,2). However, results of recent randomized trials suggest that more aggressive treatment to achieve and maintain near-normal A1C levels may reduce microvascular complications (3–7) but not adverse cardiovascular events (3,8). The generalizability of these clinical trial results to the general population of adults with type 2 diabetes is uncertain. Enrollees in clinical trials differ from other patients with type 2 diabetes because they provide written informed consent and must meet stringent eligibility criteria related to age, comorbidity, disease severity, and other factors. Stringent criteria for trial participation increase confidence in the validity of research results while reducing the generalizability of results to "average" patients with type 2 diabetes receiving care in community-based practices.

In ACCORD (Action to Control Cardiovascular Risk in Diabetes) and ADVANCE (Action in Diabetes and Vascular disease: PreterAx and DiamicroN Controlled Evaluation), intensive treatment strategies using multiple classes of glucose-lowering agents reduced A1C to near-normal levels (3–5,8). However, neither trial significantly reduced rates of acute myocardial infarction (AMI) and, in ACCORD, those achieving near-normal glucose control (median achieved A1C 6.4% or 46 mmol/mol) had a significant 22% increase in total mortality relative to patients who achieved a median A1C of 7.5% or 58 mmol/mol (3,4,8). In the same studies, near-normal A1C control had mixed but generally positive effects on microvascular complications (6). Progression of retinopathy improved in ACCORD but not in ADVANCE. At 3.4 years of follow-up in ACCORD, intensive treatment reduced progression to microalbuminuria and macroalbuminuria but significantly increased doubling of serum creatinine and the proportion of subjects with ≥20 mL/min/1.72 m^2 decrease in estimated glomerular filtration rate (eGFR)—although these undesired effects became nonsignificant by 5 years after randomization. In ADVANCE, both eGFR and progression of albuminuria were improved at 5 years. Our objective was to assess whether the findings of ACCORD and ADVANCE apply to average patients with type 2 diabetes in community-based primary care practices.

RESEARCH DESIGN AND METHODS

We designed this cohort study to assess how different glucose-control strategies affect key microvascular and macrovascular complications of type 2 diabetes in typical patients in community-based practices. We assessed the impact of four progressively more aggressive glucose-control strategies on AMI and two measures of renal status in type 2 diabetes to ascertain whether the results of ACCORD

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and ADVANCE apply to a broader patient population and assure patients and providers that efforts to achieve near-normal glucose control are safe and do not increase risks of adverse cardiovascular outcomes.

Study sites and subjects

This study was conducted in a cohort of adults with type 2 diabetes receiving care from one of seven HMO Research Network (HMORN) sites that developed a standard set of variables in a virtual data warehouse (VDW). VDW data were used to classify diabetes status based on diagnosis codes, diabetes-specific medications, and laboratory values consistent with a diabetes diagnosis (Table 1). We searched the entire adult membership of participating HMORN health plans for enrollees who met criteria for a diabetes diagnosis and had ≥2 years of enrollment and pharmacy coverage before cohort entry (with a ≤2 month coverage gap). Eligible subjects were enrolled on the earliest date between 1 January 2001 and 30 June 2009 on which criteria for cohort entry were met.

Patients were classified as having diabetes if, in a 12-month period, they had *1*) one or more inpatient or two or more outpatient diabetes-related ICD-9 diagnostic codes (250.xx), *2*) one or more filled prescriptions for a glucose-lowering medication listed in Table 1 (except metformin or a thiazolidinedione [TZD]), or *3*) a filled prescription for metformin or a TZD plus one or more outpatient or inpatient diabetes code. Those with one or

Table 1—*Description of key outcomes and selected covariates, with data source*

Variable	Data definition	Data source(s)
Study site	Specific site: Group Health Research Institute, HealthPartners of Minnesota, Kaiser Permanente of Northern California, Southern California, Northwest, Hawaii, and Colorado	Administrative
Year of study entry	2001–2009 inclusive	Administrative
Census variable	Median neighborhood household income	Administrative
A1C values	All recorded values	Laboratory databases
Glucose-lowering medication	Specific classes: insulins, biguanides, sulfonylureas, meglitamides, TZD, α-glucosidase inhibitors, DPP-4 inhibitors, GLP-1 receptor agonists	Laboratory databases
Lipoprotein values	LDL, HDL, fasting triglycerides	Laboratory databases
Albuminuria	Microalbumin-to-creatinine ratio	Laboratory databases
eGFR	MDRD equation based on serum creatinine	Laboratory databases
Blood pressure values	SBP, DBP: all values	EMR vital signs data
BMI	Weight in kilograms divided by the square of height in meters	EMR vital signs data
Age	Years	EMR demographics
Race/ethnicity	White, black, Asian, Pacific Islander, Native American, Hispanic	EMR demographics
Sex	Male, female	EMR demographics
Coronary heart disease/MI	ICD-9-CM code 410.x	
Fatal and nonfatal AMI	ICD-9-CM code 410.x–414.x	Hospital discharges, claims, procedures
Incident CHD	ICD-9-CM code 410.x–414.x	
Cerebrovascular disease/ stroke	ICD-9-CM code 433, 434, 436	Hospital discharges or claims
Ischemic stroke	ICD-9-CM code 431, 432	
Hemorrhagic stroke	ICD-9-CM code 431–434, 436	
Peripheral arterial disease		Hospital discharges or claims
Lower-extremity amputation	ICD-9 procedure code 84.10–84.17	
Peripheral revascularization	ICD-9 procedure code 39.25, 39.29	
Congestive heart failure	ICD-9-CM code 398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 428.0, 428.1, 428.20, 428, 21, 428.22, 428.23, 428.30, 428.31, 428.32, 428.33, 428.40, 428.41, 428.42, 428.43, 428.9	Hospital discharges or claims
All CVD incidence	ICD-9-CM code 401–438	Hospital discharges, claims, linked mortality
Retinopathy	ICD-9 code, ICD-9 procedure code	Claims, EMR laboratory
Macular edema	ICD-9 code, ICD-9 procedure code	Outpatient codes or hospital discharge claims
DxCG	Based on selected ICD-9 and prescription medication code	Claims

CHD, coronary heart disease; CVD, cardiovascular disease; DBP, diastolic blood pressure; DPP-4, dipeptidyl peptidase-4; EMR, electronic medical records; GLP-1, glucagon-like peptide-1; MDRD, Modification of Diet in Renal Disease; MI, myocardial infarction; SBP, systolic blood pressure.

more codes for gestational diabetes mellitus were excluded from analysis. To be included, a person classified as having diabetes had to have one or more A1C values <7% (53 mmol/mol) while taking two or more oral agents or basal insulin followed by one or more A1C values 7–8.5% (69 mmol/mol). The requirement for oral agent or basal insulin therapy in the initial period ensured that most study subjects had type 2 diabetes because either drug alone is unsustainable therapy for type 1 diabetes. Pregnant women and those with active cancers other than nonmelanoma skin cancer, end-stage renal disease, hepatic failure, or pregnancy in the 15 months before cohort entry were excluded.

Data extraction and management

Once patients with diabetes were identified, more extensive data were extracted for each subject and consolidated in an analytic database at a single site. These data were carefully evaluated for plausibility, outlier values, and missing data by a team of programmers, statisticians, and clinicians with expertise in diabetes care. The unit of time chosen for the analysis was 90 days, and the VDW data were thus mapped into an analytic dataset in which not only the time-dependent covariates and the outcomes but also the pharmacotherapy exposures could change every 90 days during follow-up. Follow-up started on the date of the first A1C ≥7% (after one or more A1C <7% on requisite therapy) and ended on the date of a specific clinical event, death, disenrollment, or study end. Outcomes were assigned based on the date of the specific clinical event being analyzed, and separate analyses were done for AMI and the two renal outcomes.

Defining glucose treatment strategies

The principal focus of the analysis was the A1C level at which glucose-lowering therapy was intensified—not the specific medication used to intensify therapy (usually a TZD or prandial insulin). This project carefully assesses the impact of each of these strategies on subsequent occurrence of AMI and change in renal status to identify which strategy minimizes AMI or deterioration of renal status. These dynamic glucose-control strategies were each defined as follows: "Initiate an intensified treatment (a diabetes drug not used at study entry) the first time A1C reaches or drifts above X% and continue an intensified treatment (drug switching or additions were permitted) for four or more periods (~1 year), after which the intensified treatment may be interrupted." Treatment strategies were defined by substituting one of four values (7% [53 mmol/mol], 7.5% [59 mmol/mol], 8% [64 mmol/mol], or 8.5% [69 mmol/mol]) for X in the previous definition.

Macrovascular and microvascular end points

We defined three major study end points: *1)* The principal macrovascular end point was AMI, ascertained through a validated set of hospital discharge diagnoses, not including coronary revascularization (9–13). 2) The first principal microvascular end point was onset or progression of albuminuria based on urine albumin-to-creatinine ratio (UACR). Onset of albuminuria was defined as moving from a baseline UACR measurement <30 to a single follow-up UACR ≥30. Progression of albuminuria was defined as moving from a baseline UACR measurement of 30 to 300 to a single follow-up UACR measurement >300 (3). The second principal microvascular end point was defined as progressing or not progressing to a worse stage of renal function based on eGFR. For this end point, eGFR was calculated using the Modification of Diet in Renal Disease equation, which computes eGFR (in mL/min/1.72 m^2) based on measured serum creatinine value and the subject's age, sex, weight, and race at measurement. Following conventional definitions, renal function was classified as stage 1 chronic kidney disease when eGFR was ≥90 mL/min/1.72 m^2, stage 2 for 60–89 mL/min/1.72 m^2, stage 3a for 45–59 mL/min/1.72 m^2, stage 3b for 30–44 mL/min/1.72 m^2, stage 4 for 15–29 mL/min/1.72 m^2, and stage 5 for <15 mL/min/1.72 m^2. A change in stage was defined as movement from any lower-numbered stage at baseline to any higher-numbered stage based on a single follow-up eGFR measurement.

Analytic approach

Details of the motivation for and implementation of the marginal structural models (MSM) approach in this study have previously been published (14–18). In essence, MSM seeks to emulate an ideal randomized trial with perfect compliance with exposure interventions of interest and no loss to follow-up. MSM methodologies are well suited to investigate dynamic interventions such as changes in treatment made by physicians as a patient's disease stage changes over time. Unlike standard analytic methods (e.g., propensity score matching and regression models), which aim to contrast the health effects of static treatment decisions, dynamic MSM permits comparison of competing clinical strategies—a feature especially relevant to diabetes care, which typically involves changes in treatment related to the patient's evolving clinical course (19,20).

In this work, inverse probability weighting (IPW) estimation (21–23) was used to fit logistic dynamic MSM for the discrete-time hazards under the previously mentioned four dynamic therapy interventions. IPW estimates of these hazards were subsequently mapped into IPW estimates of the corresponding four survival curves. The effects of interest (i.e., comparison of the effectiveness of any two dynamic glucose-control strategies) were then based on contrasting (through risk differences and risk ratios) a cross-section of the IPW estimates of the survival curves at 4 years (i.e., based on contrasting estimates of the cumulative risks of failure within 4 years of study entry). Here, we report only risk differences. The Supplementary Data provide more detailed statistical descriptions of the specific modeling strategies (23).

RESULTS

Impact of treatment-intensification strategies on AMI

Of the 58,671 patients with type 2 diabetes in this analysis, 1,655 (2.82%) experienced an AMI during follow-up. Median follow-up was ~3.25 years, and median time to treatment intensification (TI) for the 24,127 patients (41.12%) who had ever initiated intensified treatment was ~1.5 years. Of the 859,077 observation units (patient-specific 3-month units), 64.35% were characterized by a history of TI concordant with treatment administered through one or more TI strategy of interest, and thus, 35.65% of all available person-time observations were excluded from analysis. An observation is said to be concordant with treatment administered through a TI strategy if the observation is from a patient whose TI history (before that observation) happens to match the treatment regimen he or she would have experienced had treatment decisions for this patient been made directly based on that TI strategy. The estimated cumulative risk differences at 4 years derived from the logistic MSM are given in Table 2. Table 3 shows that results

did not change significantly when treatment strategies were defined to require continuous exposure after treatment initiation. Table 4 shows that results did not change significantly when using a more aggressive right-censoring strategy to minimize missing A1C data.

The entire AMI analysis was then repeated with stratification of subjects by age <65 or ≥65 years at entry to the cohort. While <3% of all subjects experienced an AMI during the median 3.25-year follow-up, many AMIs were included in the analysis: 1,100 AMIs in 22,633 adults age ≥65 years, with another 555 AMIs in 36,038 adults <65 years in the AMI analysis. The pattern of results did not change in either of these age strata.

These results demonstrate no statistically significant differences in AMI among the four TI strategies. However, there was a trend toward fewer AMIs when intensifying treatment at A1C ≥7% compared with ≥8.5% ($P = 0.08$) or A1C ≥8% compared with ≥8.5% ($P = 0.05$). Overall, though, no strong evidence suggests an effect, whether protective or deleterious, of more or less aggressive TI strategies on AMI.

Impact of TI strategies on eGFR

Of the 58,671 subjects with type 2 diabetes, 738 with missing baseline eGFR and 6 with baseline eGFR <15 mL/min/1.72 m^2 were excluded. Of 57,927 subjects analyzed, 25,930 (44.76%) experienced decreased eGFR (based on movement to a lower stage of renal function). Median follow-up time was ~1.75 years, and median time to TI for the 16,405 patients (28.32%) who had ever initiated TI was ~1 year. Of the 556,594 observation units (patient-specific 3-month units), 71.2% had a history of TI concordant with treatment administered according to one or more TI strategy of interest, and thus, 28.8% of all available person-time observations were excluded from analysis. The estimated cumulative risk differences at 4 years derived from the logistic MSM are given in Table 2. Results did not change significantly when interventions were defined to require continuous exposure after treatment initiation (Table 3). Table 4 shows that results did not change significantly when a more aggressive right-censoring strategy was used to minimize missing eGFR and A1C data.

These results demonstrate that those who received more intensive glucose-lowering therapy when A1C was ≥7% had a significantly higher likelihood of decline in renal function than those treated when A1C was ≥8% ($P = 0.04$) or ≥8.5% ($P = 0.03$) but not compared with those treated when A1C was ≥7.5% ($P = 0.18$). These results suggest that more aggressive TI strategies may contribute to eGFR worsening over 4 years.

Impact of TI strategies on onset or progression of albuminuria

Of 58,671 subjects with type 2 diabetes, 5,884 patients with missing baseline UACR and 1,608 patients with baseline macroalbuminuria were excluded. Of 51,179 subjects with type 2 diabetes analyzed, 12,085 (23.61%) experienced onset or progression of albuminuria. The median follow-up time was ~2.5 years, and the median time to TI for the 17,581 patients (34.35%) who had ever initiated TI was ~1.25 years. Of the 623,063 observation units (patient-specific 3-month units), 67.88% had a history of TI concordant with treatment administered according to one or more of the four TI strategies of interest, and thus, 32.12% of all available person-time observations were excluded from analysis. The estimated cumulative risk differences at 4 years derived from the logistic MSM are given in Table 2. Table 3 shows that results did not change significantly when interventions were defined to require continuous

Table 2—*Estimated cumulative risk differences at 4 years comparing a TI strategy with an A1C target of Θ_1% with a TI strategy with an A1C target of Θ_2%*

Outcome	Θ_1	Θ_2	Estimation approach	Point estimate	Lower bound of 95% CI	Upper bound of 95% CI	*P*
AMI	8.5	8	IPW	0.0033	0.0000	0.0066	0.05
		7.5		0.0021	−0.0042	0.0084	0.51
		7		0.0086	−0.0009	0.0180	0.08
	8	7.5		−0.0012	−0.0071	0.0047	0.69
		7		0.0053	−0.0043	0.0148	0.28
	7.5	7		0.0065	−0.0027	0.0156	0.17
	8.5	8	Crude	0.0002	−0.0012	0.0016	0.75
		7.5		0.0009	−0.0020	0.0038	0.53
		7		0.0092	0.0012	0.0172	0.02
	8	7.5		0.0007	−0.0019	0.0033	0.6
		7		0.0009	0.0010	0.0169	0.03
	7.5	7		0.0083	0.0005	0.0160	0.04
eGFR	8.5	8	IPW	−0.0001	0.0158	0.0156	0.99
		7.5		−0.0142	−0.0371	0.0087	0.22
		7		−0.0367	−0.0706	−0.0028	0.03
	8	7.5		−0.0141	−0.0352	0.0070	0.19
		7		−0.0366	−0.0710	−0.0023	0.04
	7.5	7		−0.0225	−0.0555	0.0104	0.18
	8.5	8	Crude	−0.0048	−0.0091	−0.0006	0.03
		7.5		−0.0103	−0.0188	−0.0018	0.02
		7		−0.0211	−0.0476	0.0054	0.12
	8	7.5		−0.0055	−0.0129	0.0020	0.15
		7		−0.0163	−0.0425	0.0099	0.22
	7.5	7		−0.0109	−0.0363	0.0145	0.40
UACR	8.5	8	IPW	0.0183	0.0048	0.0318	0.01
		7.5		0.0214	0.0013	0.0415	0.04
		7		0.0357	0.0046	0.0668	0.02
	8	7.5		0.0031	−0.0147	0.0210	0.73
		7		0.0174	−0.0136	0.0484	0.27
	7.5	7		0.0143	−0.0156	0.0442	0.35
	8.5	8	Crude	0.0044	0.0003	0.0084	0.04
		7.5		0.0048	−0.0032	0.0128	0.24
		7		0.0304	0.0049	0.0559	0.02
	8	7.5		0.0004	−0.0066	0.0074	0.91
		7		0.0260	0.0008	0.0512	0.04
	7.5	7		0.0256	0.0012	0.0500	0.04

This analysis requires continuous exposure to an intensified pharmacotherapy for at least 1 year after initial TI. Crude results are not adjusted for covariates, whereas IPW results are adjusted for covariates listed in Table 1.

Table 3—*Estimated cumulative risk differences at 4 years comparing a TI strategy with an A1C target of Θ_1% with a TI strategy with an A1C target of Θ_2%*

Outcome	Θ_1	Θ_2	Estimation approach	Point estimate	Lower bound of 95% CI	Upper bound of 95% CI	*P*
AMI	8.5	8	IPW	0.0038	0.0004	0.0072	0.03
		7.5		0.0025	−0.0041	0.0091	0.46
		7		0.0037	−0.0097	0.0171	0.59
	8	7.5		−0.0013	−0.0075	0.0049	0.68
		7		−0.0001	−0.0135	0.0133	0.99
	7.5	7		0.0012	−0.0118	0.0142	0.86
	8.5	8	Crude	0.0002	−0.0012	0.0016	0.74
		7.5		0.0008	−0.0021	0.0038	0.58
		7		0.0069	−0.0023	0.0016	0.14
	8	7.5		0.0006	−0.0021	0.0033	0.66
		7		0.0066	−0.0026	0.0158	0.16
	7.5	7		0.0006	−0.0029	0.0149	0.18
eGFR	8.5	8	IPW	0.0036	−0.0128	0.0199	0.67
		7.5		−0.0163	−0.0409	0.0083	0.19
		7		−0.0348	−0.0720	0.0023	0.07
	8	7.5		−0.0199	−0.0429	0.0032	0.09
		7		−0.0384	−0.0759	−0.0009	0.04
	7.5	7		−0.0185	−0.0536	0.0165	0.30
	8.5	8	Crude	−0.0043	−0.0085	−0.0001	0.05
		7.5		−0.0106	−0.0192	−0.0020	0.02
		7		−0.0108	−0.0393	0.0176	0.46
	8	7.5		−0.0063	−0.0139	0.0013	0.11
		7		−0.0066	−0.0348	0.0217	0.65
	7.5	7		−0.0003	−0.0278	0.0272	0.98
UACR	8.5	8	IPW	0.0162	0.0013	0.0311	0.03
		7.5		0.0227	0.0002	0.0451	0.05
		7		0.0461	0.0132	0.0790	0.01
	8	7.5		0.0065	−0.0133	0.0262	0.52
		7		0.0299	−0.0026	0.0624	0.07
	7.5	7		0.0234	−0.0077	0.0546	0.14
	8.5	8	Crude	0.0038	−0.0003	0.0079	0.07
		7.5		0.0054	−0.0027	0.0135	0.19
		7		0.0361	0.0088	0.0633	0.01
	8	7.5		0.0015	−0.0056	0.0086	0.67
		7		0.0322	0.0052	0.0593	0.02
	7.5	7		0.0307	0.0043	0.0571	0.02

This analysis requires continuous exposure to an intensified pharmacotherapy after initial TI. Crude results are not adjusted for covariates, whereas IPW results are adjusted for covariates listed in Table 1.

exposure after treatment initiation. Table 4 shows that results did not change significantly when using a more aggressive right-censoring strategy to minimize missing UACR and A1C data.

These results demonstrate that those treated when A1C was ≥7% (P = 0.02), ≥7.5% (P = 0.04), or ≥8% (P = 0.01) all had significantly lower likelihood of onset or progression of albuminuria than those treated when A1C was ≥8.5%. However, there were no significant advantages related to *1*) treatment at A1C ≥7% compared with A1C ≥7.5% (P = 0.35), *2*) treating at A1C ≥7.5% vs. ≥8% (P = 0.73), or *3*) treatment at A1C ≥7% compared with ≥8% (P = 0.27). Overall, though, the results suggest a protective effect of more versus less aggressive TI strategies on onset or progression of albuminuria over 4 years.

CONCLUSIONS—Our AMI analysis showed that more intensive glucose-control strategies did not significantly reduce or increase rates of AMI. These results are quite consistent with the macrovascular results of ACCORD and ADVANCE, neither of which showed a significant decrease or increase in AMI during their 3.1- and 5.0-year respective studies (3,4,8). While <3% of all subjects in our study experienced an AMI, a stratified analysis of the 22,633 adults ≥65 years of age who had 1,100 AMIs showed the same results as the overall AMI analysis. However, studies that include larger numbers and longer follow-up periods may help answer this important clinical question.

With regard to microvascular complications, our data show that more aggressive treatment strategies were associated with reduced onset and progression of albuminuria but also with accelerated deterioration of eGFR. Substantial data from the UK Prospective Diabetes Study (UKPDS), ADVANCE, and ACCORD support the hypothesis that, in general, those with type 2 diabetes who receive treatment to lower A1C levels may have lower rates of onset and progression of albuminuria—a result that our data support (6,7,24). The negative association of more intensive glucose-control strategies with eGFR was also noted in ACCORD at 3.1 years but diminished in magnitude over a longer follow-up, which was also suggested by the survival curves in this study (data not shown) (6). This association may be due to renal hyperfiltration and may not reflect deterioration in renal function. Moreover, we included progression from stage 1 to stage 2 chronic kidney disease as deterioration, and serial eGFR measures may vary considerably in this range. Overall, the effect of more intensive glucose-control strategies on measures of renal status obtained in this comparative effectiveness research analysis is consistent with the results of ACCORD and ADVANCE, supporting the notion that the microvascular results of those studies may apply to a broad group of adults with diabetes.

An innovative aspect of this analysis is our use of dynamic MSM, an analytic approach that permits, under explicit assumptions, proper adjustment for time-dependent confounders on the causal pathway between early exposures and the outcome and enables proper adjustment for selection bias due to informative censoring. Both time-dependent confounding and selection bias raise significant concerns about the validity of traditional assessments of the effectiveness and safety of multiple treatment strategies for clinical domains such as glucose control based on standard analytic approaches with observational data (15,21–23).

Other strengths and limitations of our approach should be considered. First,

Table 4—*Estimated cumulative risk differences at 4 years comparing a TI strategy with an A1C target of Θ_1% with a TI strategy with an A1C target of Θ_2%*

Outcome	Θ_1	Θ_2	Estimation approach	Point estimate	Lower bound of 95% CI	Upper bound of 95% CI	*P*
eGFR	8.5	8	IPW	−0.0020	−0.0248	0.0208	0.86
		7.5		−0.0192	−0.0538	0.0155	0.28
		7		−0.0332	−0.0825	0.0161	0.19
	8	7.5		−0.0172	−0.0505	0.0162	0.31
		7		−0.0312	−0.0810	0.0186	0.22
	7.5	7		−0.0140	−0.0590	0.0309	0.54
	8.5	8	Crude	−0.0037	−0.0102	0.0027	0.26
		7.5		−0.0033	−0.0166	0.0100	0.63
		7		−0.0169	−0.0541	0.0202	0.37
	8	7.5		−0.0005	−0.0115	0.0124	0.94
		7		−0.0132	−0.0500	0.0236	0.48
	7.5	7		−0.0137	−0.0489	0.0216	0.45
UACR	8.5	8	IPW	0.0325	0.0128	0.0523	0.00
		7.5		0.0349	0.0056	0.0642	0.02
		7		0.0471	0.0041	0.0901	0.03
	8	7.5		0.0024	−0.0222	0.0269	0.85
		7		0.0146	−0.0280	0.0572	0.50
	7.5	7		0.0122	−0.0289	0.0534	0.56
	8.5	8	Crude	0.0099	0.0027	0.0172	0.01
		7.5		0.0089	−0.0054	0.0232	0.22
		7		0.0491	0.0095	0.0888	0.02
	8	7.5		−0.0011	−0.0135	0.0114	0.87
		7		0.0392	−0.0004	0.0788	0.05
	7.5	7		0.0403	0.0012	0.0793	0.04

This analysis requires continuous exposure to an intensified pharmacotherapy after initial TI. For each outcome analysis, each patient's follow-up was artificially right-censored the first 90-day period after the first of a gap of two 90-day periods without a new A1C or a gap of four 90-day periods without a new outcome measurement. Crude results are not adjusted for covariates, whereas IPW results are adjusted for covariates listed in Table 1.

although subjects were selected from a limited number of medical groups, they are likely more representative of the overall U.S. population of patients with type 2 diabetes than are the smaller number of very highly selected patients in ACCORD or ADVANCE. Second, although observational study designs preclude causal inference, our use of sophisticated analytic approaches to adjust for confounding and right-censoring improves confidence in the results over standard analytic methods that deal less directly with time-dependent confounding or selection bias (23,25). Third, because the effect of glucose control on diabetes complications may be related to length of follow-up, longer follow-up could change the results. Fourth, we used standard, clinically plausible methods to impute missing data but found similar results in analyses that censored patients at the time of missing data (Table 4). Finally, we could not model mortality because of the time lag in obtaining state and national mortality data.

In summary, these results confirm those of recent trials, including ACCORD and ADVANCE, and suggest that they may apply to a wider range of type 2 diabetic patients than those who met relatively narrow ACCORD or ADVANCE eligibility criteria. Moreover, the results support the potential for MSM analytic approaches to emulate (with observational data) inferences obtained through large, lengthy, and expensive randomized trials. This is an important observation because many questions that could be addressed using similar analytic methods in large databases are difficult to address in randomized trials because of cost constraints or design complexity. Additional gaps in knowledge that could be addressed using such comparative effectiveness research methods include *1*) the relative safety of various classes of diabetes-related medications, *2*) the safety of particular medications in the same class, and *3*) identification of optimal targets for A1C, blood pressure, or lipid control in subgroups of patients with diabetes.

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