Effect of Intensive Compared With Standard Glycemia Treatment Strategies on Mortality by Baseline Subgroup Characteristics

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial

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OBJECTIVE — To determine if baseline subgroups in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial can be identified for whom intensive compared with standard glycemia treatment had different effects on all-cause mortality.

RESEARCH DESIGN AND METHODS — Exploratory post hoc intention-to-treat comparisons were made between intensive and standard glycemia groups on all-cause mortality by subgroups defined by baseline characteristics.

RESULTS — There were few significant interactions between baseline characteristics and effects of intensive versus standard glycemia treatment on mortality: self-reported history of neuropathy (hazard ratio [HR] 1.95, 95% CI 1.41–2.69) versus no history of neuropathy (0.99, 0.79–1.26; P value for interaction 0.0008), higher A1C (A1C >8.5%: HR 1.64, 95% CI 1.22–2.22; A1C 7.5–8.4%: 1.00, 0.75–1.34; A1C <7.5%: 1.00, 0.67–1.50; P value for interaction 0.04), and aspirin use (HR 1.45, 95% CI 1.13–1.85, compared with 0.96, 0.72–1.27, in non-users; P value for interaction 0.03).

CONCLUSIONS — We found a remarkable similarity of effect from intensive compared with standard glycemia treatment on mortality across most baseline subgroups. No differential effect was found in subgroups defined by variables anticipated to have an interaction: age, duration of diabetes, and previous history of cardiovascular disease. The three baseline characteristics that defined subgroups for which there was a differential effect on mortality may help identify patients with type 2 diabetes at higher risk of mortality from intensive regimens for glycemic control. Further research is warranted.

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Numerous epidemiological studies have demonstrated a relationship between elevated A1C and a greater risk of cardiovascular (CVD) events and mortality in type 2 diabetes (1–3). Therefore, it has been hypothesized that a reduction to near-normal levels of A1C in patients with type 2 diabetes would reduce the risk of these adverse outcomes. Three large randomized controlled clinical trials testing this hypothesis in individuals with longstanding type 2 diabetes reported their main results in the past 2 years (4–6).

The Data Safety Monitoring Board of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial discontinued the intensive glycemia arm because of an increase in all-cause mortality in the intensive glycemia arm compared with the standard glycemia arm. The finding of excess mortality in the intensive arm of the ACCORD trial has led to controversy about implementation of intensive glucose control in patients with type 2 diabetes (7,8). Adding to the controversy were results of the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) and Veterans Affairs Diabetes Trial (VADT), demonstrating that although there was no significant reduction in the primary end point of CVD events, there was no increase in mortality with the intensive glycemia arm compared with the standard glycemia arm (4,6), which has raised questions about reasons for these discrepancies (9–12).

A critical question relates to the applicability and generalizability of the conclusions of the ACCORD trial to the broader population or to specific subgroups of patients with type 2 diabetes. Indeed, pre-specified subgroup analyses in ACCORD did suggest a significant benefit of intensive glycemic control on CVD events in those participants with lower A1C at entry or absence of CVD event by history, but there was no suggestion of a differen-

Table 1—Baseline variables

Demographics	Medical history	Medications	Lab tests
Age, race/ethnicity, sex, lives alone, clinical network, BMI, waist circumference, education, year randomization	Prior CVD event, prior coronary heart failure, diabetes duration, history of neuropathy, peripheral neuropathy, retinal laser/surgery, visual acuity, smoking, depression, blood pressure, electrocardiogram	Sulfonylureas, metformin, thiazolidinediones, any insulin HCTZ, ACE inhibitors, β-blockers, calcium-channel blockers, fibrates, statins, aspirin, antidepressants	A1C, LDL, HDL, triglyceride, serum creatinine, glomerular filtration rate (modified diet renal disease), urinary albumin-to-creatinine ratio

Demographics: age (<65, $65–69$, $70–74$, ≥75 years), race/ethnicity (Hispanic, white, black, or other), lives alone (vs. with others), clinical center network (7 CCNs), BMI (<30, $30–34$, ≥35 kg/m^2), waist circumference (<96.7, $96.7–106.6$, $106.7–116.1$ cm), education ($<$high school, high-school graduate, attended some college or technical school, college graduate), year of randomization into ACCORD ($2001–2005$). Medical history: diabetes duration ($0–5$, $6–10$, $11–15$, ≥16 years), history of neuropathy/nerve problems ("Has the participant ever been told by a physician that he or she has neuropathy/nerve problems": yes/no), peripheral neuropathy (pedal amputation or a score >2 on the clinical examination portion of the MNSI), visual acuity ($<20/40$, $20/20–20/40$, $\geq20/20$), smoking status (current, former, never), blood pressure (<135, ≥135), electrocardiogram selected variables (any gross abnormalities, evidence of prior infarction, Q-T interval on electrocardiogram corrected for heart rate [QTc]). Medication use: yes/no at baseline. Laboratory variables: A1C (<7.5, $7.5–8.4$, $\geq8.5\%$), LDL cholesterol (<100, $100–119$, ≥120 mg/dl), HDL cholesterol (quartiles, mg/dl), triglycerides (<300, ≥300 mg/dl), serum creatinine ($0.1–1.0$, >1 mg/dl), glomerular filtration rate (modified diet renal disease) (quartiles ml/min), urinary albumin-to-creatinine ratio (<30, $30–300$, ≥300 mg/g). HCTZ, hydrochlorotiazide.

tial effect on mortality (5). However, these observations are based on only a few subgroup analyses at the time of the primary publication. The effect on mortality of intensive compared with standard glycemia treatment may have been modified by other possible characteristics of patients at entry. We have therefore carried out exploratory post hoc analyses of the effects of intensive compared with standard glycemia treatment in ACCORD participants categorized by various baseline characteristics on all-cause mortality at the time of discontinuation of the intensive glycemia treatment of ACCORD, with the goal to determine if particular subgroups at higher or lower risk from the intensive intervention can be identified.

RESEARCH DESIGN AND
METHODS — ACCORD is a multi-
center randomized clinical trial testing the effect of very tight control of blood glucose in patients with type 2 diabetes compared with standard therapy on a composite outcome of CVD death, nonfatal MI, and nonfatal stroke. The factorally designed trial is also testing effects of intensive blood pressure control compared with standard (the Blood Pressure trial) and use of fenofibrate plus statin compared with placebo plus statin (the Lipid trial).

The treatment goal for the intensive arm was an A1C of $<6\%$, whereas the treatment goal for the standard arm was A1C of $7–7.9\%$, with the expectation that the mean A1C for the standard arm would be $\sim7.5\%$. The mean duration of the trial was expected to be 5 years, but the intensive glycemia arm of the study was dis-

continued on 5 February 2008 because of excess mortality in the intensive group, and all participants were transitioned to the standard glycemia treatment protocol. Complete details of the study design and conduct have been previously published (13,14).

The dataset for the current analyses is the same as that for the 2008 main results paper, which includes all randomized participants from enrollment until 10 December 2007, an average trial follow-up of 3.5 years (5). Subgroup definitions are indicated in Table 1; baseline characteristics to define the subgroups were divided into four categories: *1*) demographic and anthropometric characteristics, *2*) medical history characteristics, *3*) medication use, and *4*) laboratory variables. Analyses were conducted using intention-to-treat comparisons between the intensive glycemia and standard groups on the mortality rate within each subgroup as defined in Table 1 above (15). Analyses were conducted at the ACCORD coordinating center using SAS 9.2 (SAS Institute, Cary, NC). Cox proportional-hazards regression analysis was used to examine the risk of all-cause mortality by glycemia arm within each subgroup. A test of the interaction between the baseline variable and treatment arm was done to assess homogeneity of the treatment effect across levels of subgroups, i.e., to determine if effects on mortality of intensive versus standard glycemia treatments differed between the subgroup categories. All analyses were adjusted for the study stratification factors: *1*) history of CVD (except for the analysis of CVD variables), *2*) assignment to the Lipid or Blood Pres-

sure trial (each trial had different eligibility criteria), *3*) assignment to the Lipid trial and randomized to fenofibrate, and *4*) assignment to the Blood Pressure trial and randomized to the intensive blood pressure intervention. Where possible, categorical variables were also assessed as continuous variables to determine if the results differed from the categorical analysis. Multiple Cox regression analyses were performed to determine if any observed trends persist after adjusting for multiple baseline characteristics. Because these were exploratory analyses, no *P* value adjustment was made for multiple comparisons.

RESULTS — Overall, 257 participants experienced the end point of all-cause mortality in the intensive glycemia arm and 203 participants experienced the end point of all-cause mortality in the standard glycemia arm, as previously reported (5.0 vs. 4.0%; hazard ratio (HR) 1.22; 95% CI 1.01–1.46; $P = 0.04$) (10).

Tables of all the subgroup analyses with all the variables examined are in the online appendix (available at http://care.diabetesjournals.org/cgi/content/full/dc09-1471/DC1). Here we specifically note those of significance and borderline significance.

None of the baseline demographic and anthropometric characteristics had a statistically significant interaction with glycemia group assignment on mortality (Fig. 1). The highest BMI category (≥35 kg/m^2) showed the highest HR for intensive versus standard glycemia (HR 1.70, 95% CI 1.20–2.41) compared with BMI $<30–34$ kg/m^2 (1.05, 0.76–1.44) and

	Standard Glycemia % Deaths (N)	Intensive Glycemia % Deaths (N)	Intensive to Standard Hazard Ratio	Interaction P-Value
Demographic Characteristics				
Age < 65 years	2.57% (3382)	3.68% (3397)		0.4049
65-69	4.86% (947)	6.08% (938)		
70-74	7.08% (537)	7.75% (516)		
75+	12.45% (257)	12.64% (277)		
BMI < 30 kg/m2	4.26% (1901)	4.80% (1918)		0.0778
30-34	4.26% (1690)	4.60% (1675)		
35+	3.20% (1529)	5.68% (1532)		
Waist Circ < 96.7 cm	3.70% (1271)	4.08% (1275)		0.1003
96.7-106.6	4.15% (1253)	3.76% (1225)		
106.7-116.0	3.97% (1286)	5.01% (1277)		
116.1+	3.87% (1267)	6.78% (1297)		
Randomized 2001	9.88% (577)	10.39% (597)		0.1698
2003	4.78% (1591)	6.10% (1573)		
2004	2.45% (1591)	4.31% (1601)		
2005	2.27% (1364)	2.21% (1357)		
Caucasian	4.41% (3199)	5.57% (3194)		0.2139
Hispanic	4.21% (380)	2.79% (358)		
Afr-American	3.03% (956)	5.22% (996)		
Asian/Other	2.89% (588)	2.93% (580)		
Medical History Characteristics				
Prior CVD	5.66% (1783)	7.62% (1825)		0.5327
No Prior CVD	3.05% (3340)	3.57% (3303)		
Prior CHF	10.20% (245)	14.06% (249)		0.7061
No Prior CHF	3.50% (4835)	4.53% (4836)		
Prior MI on ECG	6.80% (250)	5.31% (226)		0.1251
No Prior MI on ECG	3.92% (4392)	5.00% (4396)		
Diab Dur 0-5 years	4.26% (1455)	4.34% (1474)		0.4461
6-10	3.15% (1459)	4.62% (1472)		
11-15	3.34% (987)	4.33% (971)		
16+	5.18% (1178)	6.88% (1163)		
History of Neuropathy	4.11% (1410)	7.84% (1327)		0.0008
No Neuropathy	3.84% (3646)	4.10% (3708)		
Prior Amputation	10.64% (94)	12.09% (91)		0.9253
No Prior Amputation	3.84% (5029)	4.88% (5037)		

0   1   2   3   4

Intensive Therapy Better   Standard Therapy Better

Figure 1—*Demographic characteristics and medical history. HRs are shown for all-cause mortality in intensive versus standard glycemia groups within demographic and medical history subgroups, adjusted for the study stratification factors: 1) history of CVD (except for the analysis of CVD variables), 2) assignment to the Lipid or Blood Pressure trial (each trial had different eligibility criteria), 3) assignment to Lipid trial and randomized to fenofibrate, and 4) assignment to the Blood Pressure trial and randomized to the intensive blood pressure intervention.*

BMI $<30\,kg/m^2$ (1.01, 0.81–1.48; *P* value for interaction = 0.078). Similarly, the two highest quartiles for waist circumference also showed the highest HR for intensive versus standard glycemia (*P* value for interaction = 0.10). We did not find significant interactions for age, sex, race, living alone, clinical network, and education level or randomization year.

Among the baseline medical history subgroups (Fig. 1), participants with a self-reported history of neuropathy/nerve problems had a greater risk of mortality in the intensive glycemia arm compared with the standard glycemia arm (*P* value for interaction = 0.0008). Moreover, the interaction between self-reported history of neuropathy/nerve problems and glycemia arm continued to remain highly significant (*P* = 0.006) after adjusting for age, sex, waist circumference, smoking, diabetes duration, hypoglycemic agents used, history of retinopathy, history of amputation, and systolic blood pressure.

However, the presence of peripheral neuropathy at baseline, as documented by pedal amputation or a score >2 on the clinical examination portion of the Michigan Neuropathy Screening Instrument (MNSI) was not associated with increased mortality in the intensive arm over the standard arm (Fig. 1). We did not find a predictive association for excess mortality in the intensive group for prior CVD disease, duration of diabetes, history of retinal surgery, smoking, depression, systolic blood pressure, electrocardiogram variables, or prior amputation.

The analysis of medications reported at baseline (Fig. 2) found that use of aspirin was associated with excess mortality in the intensive group (HR 1.45, 95% CI 1.13–1.85) compared with nonusers (0.96, 0.72–1.27; *P* value for interaction = 0.03). A similar but not statistically significant differential effect occurred for use of antidepressant medications at baseline (HR 1.87, 95% CI 1.10–3.20, for us-

ers compared with 1.15, 0.94–1.40, for nonusers; *P* value for interaction = 0.08). We did not find any diabetes medication or combination of diabetes medications at baseline to be predictive of higher mortality in the intensive group versus the standard group. Furthermore, no hypolipidemic agent or antihypertensive medication had an interaction with group assignment in predicting mortality.

Laboratory test results at baseline (Fig. 2) found that participants with baseline blood levels of A1C >8.5% in the intensive glycemia arm had a higher risk of death than the participants with the same baseline levels in the standard arm (HR 1.64, 95% CI 1.22–2.22), whereas this increased risk was not apparent if baseline A1C was <7.5% (1.00, 0.67–1.50) or between 7.8 and 8.4% (1.00, 0.75–1.34) (*P* value for interaction = 0.04). None of the other lab values examined showed a statistically significant interaction with the glycemia trial arm,

	Standard Glycemia % Deaths (N)	Intensive Glycemia % Deaths (N)	Intensive to Standard Hazard Ratio	Interaction P-Value
Medications				
On Insulin	4.81% (1829)	6.23% (1750)		0.6740
Not On Insulin	3.49% (3291)	4.38% (3376)		
On BP Meds	4.21% (4252)	5.14% (4225)		0.3421
Not On BP Meds	2.76% (871)	4.43% (903)		
On Statins	3.69% (3197)	4.64% (3166)		0.9225
Not On Statins	4.41% (1926)	5.61% (1962)		
On Antidepressants	3.03% (693)	5.79% (656)		0.0848
Not On Antidepressants	4.11% (4430)	4.90% (4472)		
On Aspirin	3.83% (2771)	5.73% (2808)		0.0309
Not On Aspirin	4.12% (2352)	4.14% (2320)		
Lab Values				
A1c < 7.5	4.40% (1022)	4.83% (1036)		0.0444
7.5 to 8.4	4.09% (2200)	4.18% (2226)		
8.5+	3.60% (1887)	6.14% (1857)		
LDL-c < 100	4.04% (2498)	4.94% (2447)		0.7930
100 to 119	3.19% (1067)	4.71% (1146)		
120+	4.26% (1525)	5.44% (1508)		
HDL-c < 34	4.98% (1164)	6.85% (1182)		0.8964
34-39	3.49% (1291)	4.48% (1318)		
40-47	3.86% (1322)	5.13% (1307)		
48+	3.50% (1313)	3.86% (1294)		
GFR < 75.4	5.39% (1242)	6.76% (1301)		0.3014
75.4-89.5	4.11% (1288)	4.06% (1256)		
89.6-105.1	3.33% (1293)	4.73% (1268)		
105.2+	2.92% (1266)	4.55% (1276)		
Alb:Creat Ratio < 30	3.26% (3494)	3.71% (3504)		0.5480
30-300	4.75% (1241)	7.06% (1260)		
> 300	8.45% (343)	10.91% (330)		

Intensive Therapy Better ← → Standard Therapy Better

Figure 2—*Medication and laboratory tests. HRs are shown for all-cause mortality in intensive versus standard glycemia groups within the medication and laboratory tests subgroups adjusted for the study stratification factors: 1) history of CVD (except for the analysis of CVD variables), 2) assignment to the Lipid or Blood Pressure trial (each trial had different eligibility criteria), 3) assignment to Lipid trial and randomized to fenofibrate, and 4) assignment to the Blood Pressure trial and randomized to the intensive blood pressure intervention.*

including LDL or HDL cholesterol, triglycerides, serum creatinine, estimated glomerular filtration rate, or albumin-to-creatinine ratio. Figure 3 shows the log of the HR (compared with the standard arm at baseline A1C of 7.0) for all-cause mortality by treatment group. A visual review indicates that after ~8.2, the higher the A1C at baseline in the intensive glycemia group, the higher the participant's risk. No such relationship is seen in the standard glycemia group.

Multiple Cox regression analysis including the three variables (self-reported history of neuropathy, A1C, and aspirin use) found to have statistically significant interactions with the glycemia arm at the 0.05 level lend support to the univariate finding (A1C >8.5%, HR 1.64, 95% CI 1.22–2.22, P value for interaction = 0.0012), self-reported history of neuropathy/nerve problems at baseline (1.95, 1.41–2.7, P value for interaction

<0.0001), and use of aspirin (1.45, 1.13–1.85, P value for interaction = 0.0032).

CONCLUSIONS — In these analyses from ACCORD, we found a remarkable similarity of effect on mortality of intensive compared with standard glycemia arm assignment across numerous post hoc baseline subgroups. Importantly, no differential effect of intensive versus standard treatment on mortality was found in subgroups defined by variables anticipated to have such an interaction: age, duration of diabetes, previous history of CVD disease (Figs. 1–2). Nevertheless, we did find that the intensive treatment had a higher effect on mortality in subgroups defined by three baseline clinical variables: A1C ≥8.5% (interaction P = 0.044), aspirin use (interaction P = 0.03), and self-reported history of neuropathy/ nerve problems (interaction P = 0.0008). However, because of the multiple com-

parisons and the post hoc nature of these analyses, the interaction P values for A1C and aspirin use should only be considered suggestive. A marginal differential effect also was found in subgroups with higher BMI and higher waist circumference at baseline.

Consistent with the prevailing epidemiologic evidence of the relationship between glycemic control and mortality (1–3,16,17), the increase in mortality in the intensive arm was observed among those participants with higher (≥8.5%) compared with lower (<8.5%) A1C at baseline. This effect was evident when A1C was examined as a categorical variable but was seen to a lesser extent when we examined A1C as a continuous variable. The spline plot of HRs across levels of baseline A1C imply an increasingly higher risk with higher baseline A1C in the intensive arm, but not in the standard arm. Individuals with higher A1C at baseline may rep-

Mortality By Baseline A1c
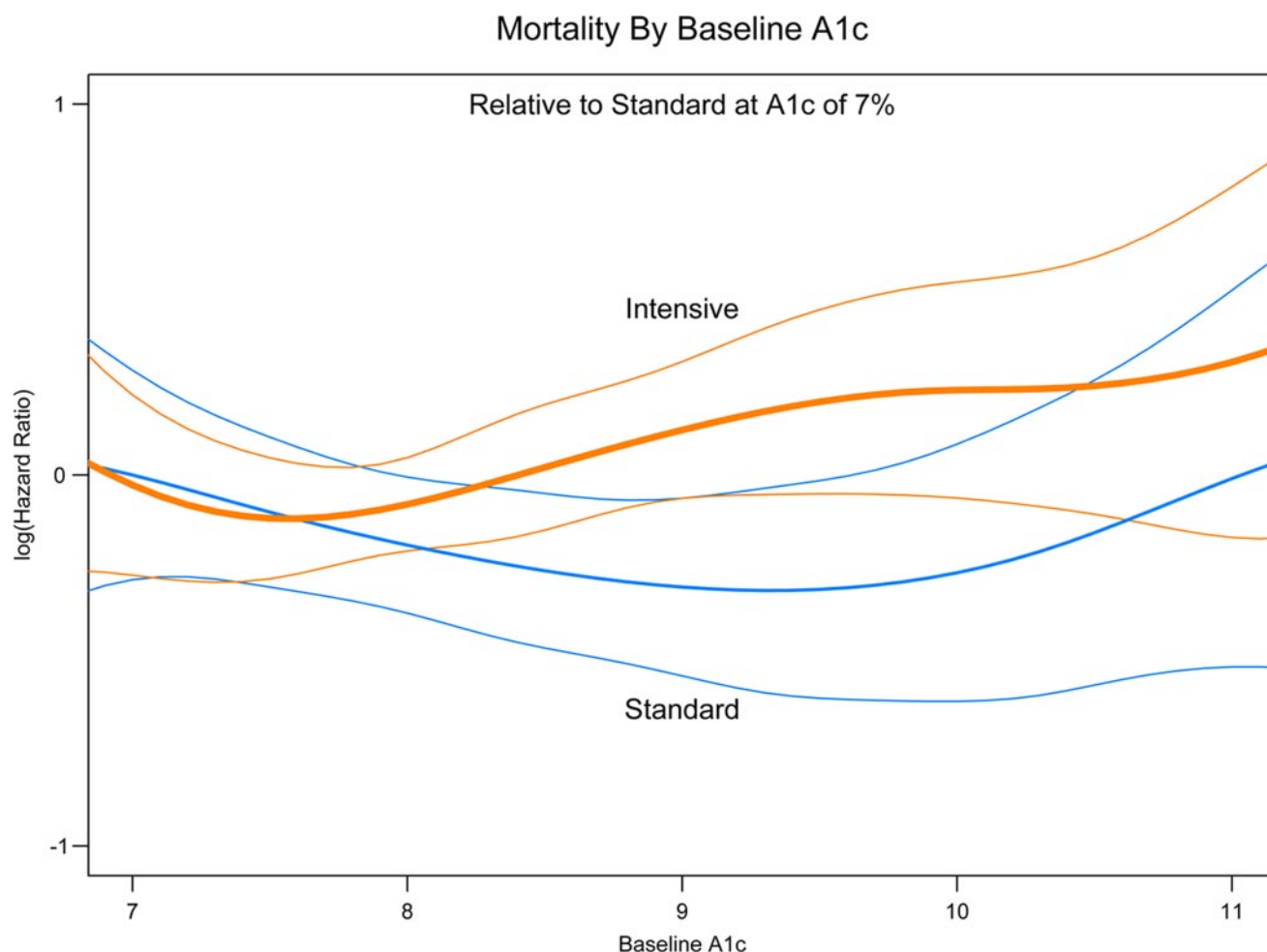
Figure 3—*A1C and all-cause mortality. Spline curves displaying the log of the HR for all-cause mortality by treatment and baseline A1C are shown. All HRs are with respect to standard glycemia with baseline A1C of 7.0. The bold line represents the intensive treatment group, the finer line the standard group, and the colored lines the 95% CIs.*

resent individuals with more difficult disease to manage and/or individuals who may adhere less to therapy. Whether individuals at highest risk ultimately achieved or failed to achieve more intensive treatment targets will require additional analysis.

Baseline participant report of neuropathy/nerve problems defined a subgroup in which the intensive approach for glycemia treatment had a differential effect on mortality, with a highly significant *P* value of 0.0008. Peripheral neuropathy is a common complication of diabetes, and excess mortality has been related to diminished peripheral sensation (16,18), foot ulceration, and history of lower-extremity amputation (19). Yet in our cohort, neither MNSI-documented peripheral neuropathy nor history of amputation was associated with a differential effect on mortality from intensive compared with standard glycemia treatment

(although very few participants with an amputation entered the study). The discrepancy suggests the two methods of detecting neuropathy may identify different populations. Indeed, the MNSI detected peripheral neuropathy in 4,357 participants in contrast to 2,737 participants who reported a history of neuropathy, of whom 61% had also an MNSI score indicative of neuropathy. The discordance among various indexes of neuropathy in their strength for predicting outcomes (symptoms versus physical findings) was also apparent in the DIAD study (20), where a significant relation to CVD outcomes was found with one symptom (numbness) and one sign ("absent sensation"), but it was borderline for a different symptom (pain) and had no relation to yet another symptom (tingling) and two physical signs (absent vibration, absent reflex). The discrepancy does not diminish the possible importance of neuropa-

thy as a predictor for worse outcomes from intensive glycemia treatment, or even as an etiologic agent of CVD outcomes or mortality; this issue deserves further study.

Lastly, there was a differential effect on mortality of intensive compared with standard treatment by use of aspirin at baseline. Although aspirin use is recommended for patients with type 2 diabetes (21), the evidence supporting its benefit is now being reconsidered (22). Recent clinical trials including or limited to those with type 2 diabetes (23–25) have not shown a significant reduction in either CVD mortality or overall mortality in patients with type 2 diabetes, although these studies often included populations considered to be at lower risk of CVD disease than the population recruited for the ACCORD trial. A possible explanation could be that aspirin use is merely a proxy for those at higher risk of CVD disease,

although we did not see an increased risk among those with a history of CVD disease at baseline.

There are a number of important limitations to the analyses conducted for this article. First, we cannot exclude the possibility that the findings of significant interactions are due to chance alone. For a set of 38 independent variables, we would expect to find $P < 0.05$ for at least 1.9 variables by chance alone, suggesting the results for A1C and aspirin use should be interpreted with caution, since P values were very close to the 0.05 level. Nonetheless, self-report of neuropathy had a very strong statistical significance. Data from other sources will be required for confirmation of the findings presented. Many of the baseline characteristics were self-reported by participants; although a certain amount of misclassification may be expected, we would not expect this to differ by study arm. Finally, these analyses should be considered exploratory and hypothesis generating, since the subgroups were not defined a priori and ACCORD was not powered to look at specific subgroups—nor was the study powered for an analysis of mortality, since the pre-specified primary outcome was the rate of major CVD events.

In summary, we have identified three baseline characteristics that defined subgroups in which there was a differential effect on mortality of the intensive compared with standard glycemia treatment in ACCORD: A1C ≥8.5%, self-reported history of neuropathy, and aspirin use at study entry. The interactions in the A1C and aspirin use were of marginal significance and can only be considered suggestive and will require additional study. Of note is that the most significant association found was with self-report of neuropathy. Importantly, other baseline characteristics that were hypothesized to identify subgroups with differential effects on mortality by treatment arm did not have such interaction, including increasing age, duration of diabetes, and history of CVD disease. Further analysis of the role of neuropathy on mortality in type 2 diabetes is warranted. The ACCORD study group is currently performing additional analyses to define the possible role of autonomic neuropathy—as well as other factors—in the outcomes observed.

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