

**ONLINE ONLY SUPPLEMENT (APPENDIX)**

**Appendix Table 1. Comparison of Look AHEAD, ACCORD, and ACCORDION Definitions of Complications**

<b>Outcome</b>	<b>Component</b>	<b>Look AHEAD</b>	<b>LAC (Differences from LA)</b>	<b>ACCORD</b>	<b>ACCORDION (Differences from ACCORD)</b>	<b>Note</b>
<b>MI</b>		Adjudicated through LAC for first event; collected when event occurs		Collected when event occurs		Collected in ACCORDION without adjudications; only 10% were adjudicated for quality-control purpose, but data are not available.
	Q-wave myocardial infarction	X		X		
	Aborted myocardial infarction	X		-		
	Non Q-wave myocardial infarction	X		X		
	Silent (unrecognized) myocardial infarction	X		X		
	Probable non Q-wave myocardial infarction	X		X		
	Non-fatal myocardial infarction after cardiovascular invasive interventions	X		X		Combined definitions in ACCORD protocol 5.1.b.5 and 5.1.b.6
	Non-fatal myocardial infarction after non-	X		X		

Outcome	Component	Look AHEAD	LAC (Differences from LA)	ACCORD	ACCORDION (Differences from ACCORD)	Note
	cardiovascular surgery					
<b>Stroke</b>		Adjudicated through LAC for first event; collected when event occurs		Collected when event occurs		Collected in ACCORDION without adjudications
	Definite ischemic stroke	X		X		
	Probable ischemic stroke	X		-		
	Definite primary intracerebral hemorrhage	X		X		
	Probable intracerebral hemorrhage	X		-		
	Definite subarachnoid hemorrhage	X		X		
	Probable subarachnoid hemorrhage	X		-		ACCORD just indicates subarachnoid hemorrhage
	Stroke of unknown type etiology	X		X		
	Non-fatal stroke after cardiovascular invasive interventions	X		X		

Outcome	Component	Look AHEAD	LAC (Differences from LA)	ACCORD	ACCORDION (Differences from ACCORD)	Note
	Non-fatal stroke post non-cardiovascular surgery	X		X		
<b>Angina</b>		Adjudicated through LAC for first event; collected when event occurs		Not adjudicated; collected when event occurs		
	Hospitalized angina	X				Collected every 6 months through hospitalization CRF.
	Unstable angina			X annually through hospitalization CRF (ANHX form).	X every 6 months through hospitalization CRF	
<b>Congestive heart failure (CHF)</b>		Adjudicated through LAC for first event		Not adjudicated		
	Fatal	X		X	X	
	Non-fatal	X every 6 months through hospitalization CRF		X annually through hospitalization CRF (ANHX form).	X every 6 months through hospitalization CRF	
<b>Coronary heart disease (CHD)</b>						

Outcome	Component	Look AHEAD	LAC (Differences from LA)	ACCORD	ACCORDION (Differences from ACCORD)	Note
	Nonfatal MI	X		X		
	Angina	X		X (unstable)		
	Cardiovascular death other than stroke death	X		X		
<b>Revascularization (hospitalizations)</b>		Adjudicated through LAC for first event; collected every 6 months		Not adjudicated; collected every 4 months		
	PTCA (balloon)	X		X		
	PTCA (with stent)			X		
	CABG surgery	X		X		
	Carotid angioplasty with stent	X		X		
	Carotid endarterectomy			X		
	Peripheral angioplasty, with or without stent			X		
	Peripheral vascular surgery, including aortic aneurysm			X		

Outcome	Component	Look AHEAD	LAC (Differences from LA)	ACCORD	ACCORDION (Differences from ACCORD)	Note
	Repair					
	Aortic aneurysm	X				
	Poor blood circulation or blocked or narrowed artery or arteries to the legs or feet (claudication,	X				
	peripheral arterial disease, gangrene, or Buerger's disease)					
<b>Microalbuminuria</b>	ACR – X ( $\geq 30$ mg/g)	Annually through year 4, every 2 years	Once	baseline, M24, M48, and EXIT	Twice (1st and 3rd of the clinic visits)	
<b>Macroalbuminuria</b>	ACR – X ( $\geq 300$ mg/g)	Annually through year 4, every 2 years	Once	baseline, M24, M48, and EXIT	Twice	
<b>eGFR</b>		X CKD-EPI equation; annually through year 4, every 2 years	Once	X MDRD equation; every 4 months in the Lipid Trial; every 4 months for the first year then annually thereafter in the BP trial	Twice	Wake Forest recalculated ACCORD eGFR using CKD-EPI equation
<b>Decreased eGFR</b>		<60				

Outcome	Component	Look AHEAD	LAC (Differences from LA)	ACCORD	ACCORDION (Differences from ACCORD)	Note
Severely decreased eGFR		<30				
Amputation	Hospitalization	X Amputation of a part of a leg, including toes, because of poor blood circulation, gangrene, or diabetes; collected every 6 months		Lower extremity for ischemia. (Interval and annual follow-up Misc CVD Outcomes Form triggered by hospitalization form); collected every 4 months	Every 6 months	
Foot ulcer						
	Hospitalization form	-	X Foot/leg ulcer	-		
	Outpatient procedures	-	X Foot ulcer	-		
	MNSI	X Open sore on foot; collected annually		-		
	Foot exam	-	Once	X no exam if yes to amputation/foot inspection. Collected annually	Three clinic visits	
Retinopathy	Retinal laser photocoagulation	X Every 6 month		X annually	1 <sup>st</sup> and 3 <sup>rd</sup> clinic visit	

Outcome	Component	Look AHEAD	LAC (Differences from LA)	ACCORD	ACCORDION (Differences from ACCORD)	Note
<b>Visual acuity</b>	Severe vision loss (as measured by Snellen fraction < 20/200)	-		X annually (Physical exam form)	3rd clinic visit	
<b>Neuropathy</b>	MNSI score > 2.0 ( $\geq$ 2.5)	-	Once	X annually	3 clinic visits	
<b>Hypoglycemia</b>	Symptomatic, severe hypoglycemia was defined as either a blood glucose concentration of less than 2.8 mmol/l (50 mg/dl) or symptoms that promptly resolved with oral carbohydrate, intravenous glucose, or subcutaneous or intramuscular glucagon.			X (separate questions: require any assistance, require medical assistance); collected every 4 months	X (require medical assistance); every contact (7 times in all)	
	Loss of consciousness, seizure, or a glucose < 70 mg/dL that prevented self-treatment, and required assistance of another person	X (primary outcome in LA paper); SAE	No longer collected in LAC			

\*Note: Analyses in ACCORDION were conducted on all of the cardiovascular outcomes that occurred after randomization and that were reported by the sites during the active or follow-up period, regardless of the final adjudication status.

Below are the results from the fixed effects (FE), ordinary-least-squares (OLS), and random-effects (RE) models. For both diagnostic tests (Breusch-Pagan Lagrange multiplier test and the Hausman test), the null hypothesis was rejected, indicating that an FE model is preferred over the OLS or RE models. See Appendix Table 2 for test statistics from the diagnostic tests. Results from the OLS model were adjusted for clustering by patient ID.

**Appendix Table 2. Health Utility Decrements for Complications of Diabetes: FE, OLS and RE Comparison**

Covariate	FE Coefficient	OLS Coefficient	RE Coefficient
<b>Complication Coefficients</b>			
Smoker	−0.006	−0.059*	−0.003*
BMI (one-unit increase)	−0.003*	−0.006*	−0.004*
Duration of Diabetes (time-varying)	−0.008*	−0.005*	−0.007*
Stroke Event	−0.109*	−0.154*	−0.122*
History of Stroke	−0.051*	−0.091*	−0.081*
Amputation Event	−0.092*	−0.164*	−0.098*
History of Amputation	−0.150*	−0.067*	−0.097*
Dialysis Event	−0.039*	−0.065*	−0.045*
History of Dialysis	−0.015	−0.054*	−0.024*
MI Event	−0.028*	−0.039*	−0.033*
History of MI	−0.006	−0.022*	−0.017*
CHF Event	−0.051*	−0.070*	−0.055*
History of CHF	−0.041*	−0.058*	−0.054*
Angina Event	−0.015	−0.042*	−0.023*
History of Angina	−0.028*	−0.044*	−0.036*
eGFR < 30 mL/min/1.73 m <sup>2</sup> Event	−0.043*	−0.063*	−0.048*
History of eGFR < 30 mL/min/1.73 m <sup>2</sup>	−0.025*	−0.036*	−0.030*
eGFR < 60 mL/min/1.73 m <sup>2</sup> Event	−0.014*	−0.021*	−0.015*
History of eGFR < 60 mL/min/1.73 m <sup>2</sup>	−0.015*	−0.017*	−0.016*
Revascularization Event	−0.005	−0.011	−0.008



Covariate	FE Coefficient	OLS Coefficient	RE Coefficient
History of Revascularization	0.001	−0.012*	−0.008*
Laser Photocoagulation Event	−0.011	−0.021*	−0.013*
History of Laser Photocoagulation	−0.014*	−0.023*	−0.016*
Hypoglycemia (any assistance)	0.001	−0.041*	−0.005
<b>Additional Control Variables</b>			
Age at Diagnosis	n/a	−0.002*	−0.003*
Female	n/a	−0.039*	−0.041*
Hispanic	n/a	−0.039*	−0.039*
Other Race	n/a	−0.034*	−0.016*
White Race	n/a	−0.034*	−0.031*
College Education	n/a	0.038*	0.049*
ACCORD Study Participant	n/a	−0.033*	−0.031*
Constant	0.935*	1.153*	1.155*
<b>Estimation Sample</b>			
N (total person-visit observations) <sup>†</sup>	128,873	127,096	127,096
N (total unique persons) <sup>†</sup>	15,252	15,129	15,129
RMSE	n/a	0.253	n/a
<b>Diagnostic Test Results</b>			
Breusch and Pagan Lagrange Multiplier Test Statistic for random effects	130,000, $p < 0.001$ , null is rejected		
Hausman Test Statistic	438, $p < 0.001$ , null is rejected		

Note: Results from the OLS model were adjusted for clustering by patient ID.

\*Covariates that are statistically significant at the 5% level

<sup>†</sup>The OLS and RE estimates are based on slightly fewer individuals and observations because of missing time-invariant variables for race/ethnicity and education.

Appendix Table 3 shows the fixed effects regression results for the combined sample as well as the ACCORD sample alone and the Look AHEAD sample alone. Some results differ by

sample, but most are similar. By pooling both trials in the combined sample, we have a larger number of events and a broader range of diabetes patients with which to estimate utility effects.

Therefore, the combined sample was presented as our main analysis.

**Appendix Table 3. Health Utility Decrements for Complications of Diabetes: Comparing FE results for the combined sample, ACCORD only sample, and Look AHEAD only sample.**

Covariate	Combined Sample	ACCORD Only	Look AHEAD Only
<b>Complication Coefficients</b>			
Smoker	-0.006	-0.010	0.005
BMI (one-unit increase)	-0.003*	-0.002*	-0.004*
Duration of Diabetes (time-varying)	-0.008*	-0.007*	-0.008*
Stroke Event	-0.109*	-0.108*	-0.109*
History of Stroke	-0.051*	-0.060*	-0.044
Amputation Event	-0.092*	-0.090*	-0.100
History of Amputation	-0.150*	-0.147*	-0.163*
Dialysis Event	-0.039*	-0.016	-0.105*
History of Dialysis	-0.015	-0.012	-0.034
MI Event	-0.028*	-0.018	-0.038*
History of MI	-0.006	0.004	-0.018
CHF Event	-0.051*	-0.047*	-0.050*
History of CHF	-0.041*	-0.026	-0.045*
Angina Event	-0.015	0.003	-0.026*
History of Angina	-0.028*	-0.009	-0.042*
eGFR < 30 mL/min/1.73 m <sup>2</sup> Event	-0.043*	-0.066*	0.012
History of eGFR < 30 mL/min/1.73 m <sup>2</sup>	-0.025*	-0.052*	0.027
eGFR < 60 mL/min/1.73 m <sup>2</sup> Event	-0.014*	-0.012*	-0.019*
History of eGFR < 60 mL/min/1.73 m <sup>2</sup>	-0.015*	-0.016*	-0.018*
Revascularization Event	-0.005	-0.011	0.003

<b>Covariate</b>	<b>Combined Sample</b>	<b>ACCORD Only</b>	<b>Look AHEAD Only</b>
History of Revascularization	-0.001	-0.019*	0.020
Laser Photocoagulation Event	-0.011	-0.013	-0.008
History of Laser Photocoagulation	-0.014*	-0.010	-0.015
Hypoglycemia (any assistance)	-0.001	0.001	-0.006
Constant	0.935*	0.870*	0.970*
<b>Estimation Sample</b>			
N (total person-visit observations)	128,873	53,746	75,127
N (total unique persons)	15,252	10,149	5,103

\*Covariates that are statistically significant at the 5% level

Appendix Table 4 shows the fixed effects regression results for the combined sample, The ACCORD only sample, and the ACCORD only sample with additional complications included in the fixed effects model. The additional complications available in the ACCORD dataset were neuropathy, severe vision loss, foot ulcer, and hypoglycemia requiring medical assistance. Most variables included in both models were the same or changed modestly when including the additional complications. Differences in health utility decrements for amputation are likely due to the inclusion of additional complications that are also correlated with amputation like foot ulcer events, history of foot ulcer – both of which had statistically significant health utility decrements.

**Appendix Table 4. Health Utility Decrements for Complications of Diabetes: Analyzing additional complications available in the ACCORD Study data.**

<b>Covariate</b>	<b>Combined Sample</b>	<b>ACCORD Only</b>	<b>ACCORD Only: Additional Complications</b>
<b>Complication Coefficients</b>			
Smoker	-0.006	-0.010	-0.010

<b>Covariate</b>	<b>Combined Sample</b>	<b>ACCORD Only</b>	<b>ACCORD Only: Additional Complications</b>
BMI (one-unit increase)	-0.003*	-0.002*	-0.002*
Duration of Diabetes (time-varying)	-0.008*	-0.007*	-0.006*
Stroke Event	-0.109*	-0.108*	-0.108*
History of Stroke	-0.051*	-0.060*	-0.060*
Amputation Event	-0.092*	-0.090*	-0.001
History of Amputation	-0.150*	-0.147*	-0.137*
Dialysis Event	-0.039*	-0.016	-0.016
History of Dialysis	-0.015	-0.012	-0.012
MI Event	-0.028*	-0.018	-0.018
History of MI	-0.006	0.004	0.005
CHF Event	-0.051*	-0.047*	-0.048*
History of CHF	-0.041*	-0.026	-0.026
Angina Event	-0.015	0.003	0.003
History of Angina	-0.028*	-0.009	-0.008
eGFR < 30 mL/min/1.73 m <sup>2</sup> Event	-0.043*	-0.066*	-0.066*
History of eGFR < 30 mL/min/1.73 m <sup>2</sup>	-0.025*	-0.052*	-0.052*
eGFR < 60 mL/min/1.73 m <sup>2</sup> Event	-0.014*	-0.012*	-0.012*
History of eGFR < 60 mL/min/1.73 m <sup>2</sup>	-0.015*	-0.016*	-0.015*
Revascularization Event	-0.005	-0.011	-0.010
History of Revascularization	-0.001	-0.019*	-0.019*
Laser Photocoagulation Event	-0.011	-0.013	-0.010
History of Laser Photocoagulation	-0.014*	-0.010	-0.006
Hypoglycemia (any assistance)	-0.001	0.001	0.001
Hypoglycemia (Medical assistance)			<0.001

<b>Covariate</b>	<b>Combined Sample</b>	<b>ACCORD Only</b>	<b>ACCORD Only: Additional Complications</b>
Foot Ulcer Event			-0.017*
History of Foot Ulcer			-0.022*
Severe Vision Loss Event			-0.045*
History of Severe Vision Loss			-0.023*
Neuropathy Event			-0.007*
History of Neuropathy			-0.007
Constant	0.935*	0.870*	0.870*
<b>Estimation Sample</b>			
N (total person-visit observations)	128,873	53,746	53,746
N (total unique persons)	15,252	10,149	10,149

\*Covariates that are statistically significant at the 5% level