Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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APPENDIX A. Listing of the TODAY Study Group

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APPENDIX B. Detailed Research Methods

Blood and urine were collected fasting for analysis at baseline, 6 months, and annually in TODAY and annually in TODAY2. Blood was also collected at the time of loss of glycemic control in TODAY. Samples were not collected during pregnancy, lactation or immediately postpartum. Participants who had not had an annual visit within 6 months had an additional collection at the end of thes study. Blood pressure was measured at every visit (quarterly in TODAY and the first three years of TODAY2 and then annually).

Classifications of complications and comorbidities began during the TODAY randomized trial and continued in TODAY2. Algorithms for classifications were established for each phase of TODAY, with a focus on maintaining as much consistency as possible across the phases given the changing frequency of data collection. The algorithms for each comorbidity are provided below.

Hypertension

Blood pressure was measured after a 5-minute rest with the participant in a sitting position using a CAS 740 monitor with standardized oscillometric cuff sizes at every visit. Three measurements were taken at 1-minute intervals. The average of the 2nd and 3rd systolic and diastolic measures was calculated to obtain blood pressure at that visit.

Hypertension was defined according to "Cardiovascular risk reduction in high-risk pediatric patients: a scientific statement"[1] and updated in the Summary Report of the Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents[2] as blood pressure $\geq 95^{th}$ percentile for age, sex and height or systolic blood pressure (SBP) $\geq$ 130mmHg and/or diastolic blood pressure (DBP) $\geq$ 80mmHg on three occasions with less than 2 years between the first and second and second and third, regardless of interim blood pressure. There were two definitions for hypertension for individuals on blood pressure-lowering medications: 1) 1-2 elevated blood pressures, as defined above,

less than 2 years apart with the last elevated pressure followed immediately by the start of pharmacologic treatment; 2) elevated blood pressure in an individual prescribed an anti-hypertensive medication or already on an ACE inhibitor for elevated albumin.

During the TODAY randomized trial and for the first three years of TODAY2, blood pressure was measured at each quarterly visit. During the last six years of TODAY2, participants only had annual in-person annual visit. During this period, hypertension without medications was defined as blood pressure ≥ 95th percentile for age, sex and height or systolic blood pressure ≥ 130mmHG and/or diastolic blood pressure ≥ 80mmHG on two consecutive annual visits or a single elevated blood pressure and previously prescribed anti-hypertensive medication.

LDL Dyslipidemia

Measurements of cholesterol in low density lipoprotein (LDL) from frozen plasma samples were performed at the Northwest Lipid Metabolism and Diabetes Research Laboratories by enzymatically assay on the Hitachi 917 autoanalyzer using methods standardized to the Centers for Disease Control and Prevention Reference Methods. LDL-cholesterol was calculated by the Friedewald equation. If triglycerides were >400 mg/dl, a complete lipoprotein separation by ultracentrifugation was performed using the Lipid Research Clinics Beta Quantification procedure.

LDL-C dyslipidemia and triglyceride dyslipidemia were defined according to "Cardiovascular risk reduction in high-risk pediatric patients: a scientific statement"[1] and updated in the Summary Report of the Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents.[2] A participant was classified as having LDL-C dyslipidemia if they had consecutive values of LDL-C ≥ 130 mg/dL without an intervening LDL-C value < 130 mg/dL irrespective of the time between values. There were two definitions for LDL-C dyslipidemia for individuals on cholesterol-lowering medications: 1) a single LDL-C ≥ 130 mg/dL followed immediately by the start of

pharmacologic treatment; 2) a single LDL-C ≥ 130 mg/dL and previously prescribed lipid lowering medication.

Triglyceride Dyslipidemia

A participant was classified as having triglyceride dyslipidemia if they had consecutive values of triglycerides ≥ 150 mg/dL without an intervening triglyceride value < 150 mg/dL irrespective of the time between consecutive values. There were two definitions for triglyceride dyslipidemia for individuals on cholesterol-lowering medications: 1) a single triglyceride value ≥ 150 mg/dL followed immediately by the start of pharmacologic treatment; 2) triglyceride value ≥ 150 mg/dL and previously prescribed lipid lowering medication.

Moderately and Severely Increased Albuminuria

The immunochemical measurement of albumin in urine was performed at the Northwest Lipid Metabolism and Diabetes Research Laboratories using Dade Behring reagent on a Behring Nephelometer. The target value to the assay calibrator is assigned by the reference material CRM470 prepared by the International Federation of Clinical Chemistry (IFCC). Concentrations of creatinine in urine were determined using the Creatinine Plus enzymatic Roche reagent on a Modular P analyzer (Roche Diagnostics, Inc., Indianapolis, IN); the results are traceable to the IDMS reference method. A participant was classified as having moderately increased albuminuria if they had a urine albumin/creatinine ratio (ACR) ≥ 30 mg/g on at least 2 out to 3 determinations (including a first-morning sample) within a 6-month period or 3 or more ACR values ≥ 30 mg/g with no drop in between regardless of time duration during TODAY and during the first 3 years of follow-up. Subsequently, moderately increased albuminuria was classified as ACR ≥ 30 mg/g on two consecutive annual visits or an ACR ≥ 30 mg/g and previously prescribed ACE inhibitor. Severely increased albuminuria was defined similarly using a ACR ≥300 mg/g.

Nerve Disease

Nerve disease was assessed by two methods: Michigan Neuropathy Screening Instrument (MNSI) exam and Semmes-Weinstein 5.07 10-gram monofilament. The participant was classified as having neuropathy if either of these methods were abnormal on at least 2 consecutive exams.

The MNSI exam is a validated screening tool for diabetic peripheral neuropathy consisting of 4-items administered by a health professional conducting a direct examination of each foot. Vibratory sensation is assessed using a 128-Hz tuning fork applied to the dorsal surface of the great toe. Scoring of the exam was as follows: 1) each foot with any physical abnormality received a score of 1; 2) each foot with an ulcer received a score of 1; 3) vibration sensation was considered normal (0 points) if the examiner felt vibration for less than 10 seconds after the participant stopped feeling the vibration; it was scored as impaired (0.5 points) if the examiner felt it for >10 seconds and absent (1 point) if the subject could not feel the vibration at all; and 4) reflexes at the ankle were considered normal (0 points); reduced (0.5 points) if they could only be elicited with the Jendrassic maneuver; and absent (1 point) if they could not be elicited at all. The total possible score was added across both feet to get a possible 0 to 8 points. The MNSI-exam was considered abnormal if the score (across both feet) was > 2 on at least two consecutive exams.

The monofilament examination consisted of applying a Semmes-Weinstein 5.07 10-gram monofilament to the dorsum of the great toe of each foot 10 times. Correct identification of at least 8 of the 10 applications on each foot was considered normal. Analyses were based on sustained abnormal monofilament scores (<8/10 correct responses), defined as abnormal scores at two or more consecutive visits.

Eye Disease

Eye disease was assessed by 7-field stereoscopic fundus photographs taken by certified photographers during the final year of the randomized trial and again approximately seven years later. The fundus photographs were graded according to the Early Treatment Diabetic Retinopathy Study (ETDRS) protocol. Graders at a centralized reading center at the University of Michigan, masked to treatment group assignment, assessed the photographs for severity level of diabetic retinopathy according to ETDRS scales, with a 25-step scale representing the range of diabetic retinopathy in each eye.[3] Based upon the grading in the worse eye, each participant was classified as having no retinopathy, very mild non-proliferative retinopathy (NPDR), mild NPDR, moderate NPDR, moderately severe NPDR, severe NPDR, early or stable, treated proliferative diabetic retinopathy (PDR), and high risk PDR. Additionally Ocular computed tomography was utilized to determine the presence of clinically significant macular edema.

Comorbidity Assessment

A rigorous adjudication process was established to track and document each reported comorbid event occurring outside of study visits and diagnosed by a participant's regular medical provider. During semi-annual visits, each participant underwent a structured interview by a medical provider to assess if any relevant events had occurred since the previous visit. Every affirmative answer initiated a review process that included obtaining and submitting relevant medical records to the Coordinating Center. A Comorbidity Assessment Committee (CAC), comprised of expert physicians selected from the study group, was charged with reviewing all reported comorbidities. CAC was further divided into seven sub-committees: heart, vascular, cerebrovascular, renal, nerve, eye and liver/pancreas/gallbladder. The assigned member of CAC assessed each submitted event utilizing criteria established *a priori* based on national guidelines. If questions arose, the case was discussed by the full CAC.

Definitions

<u>Heart Events</u>

Arrhythmia: Evidence of electrocardiogram (EKG), Holter monitor, or event monitor having been performed with the results reviewed and interpreted by a cardiologist and available in the medical record, or the insertion of a pacemaker or implantable cardioverter defibrillator.

Coronary Artery Disease (CAD): Medical record documentation of ≥ 50% occlusion of any coronary artery by angiography or the report of a coronary artery bypass grafting or revascularization procedure.

Congestive Heart Failure (CHF): Medical record documentation of a hospital admission with a principal diagnosis of heart failure, pulmonary edema by chest X-ray, or symptoms, signs, or physical findings consistent with CHF.

Left Ventricular Systolic Dysfunction: Mild, moderate, or severe dysfunction based upon ejection fraction from angiogram or through noninvasive testing by echocardiogram, magnetic resonance, computed tomography, or nuclear test.

Myocardial Infarction (MI): Medical record documentation of a cardiologist interpretation of a definitive MI on EKG and/or significantly elevated enzymes. The enzymes considered were troponin T and troponin I elevated to a value that indicates myocardial necrosis in the laboratory performing the test and/or CPK and CPK-MB elevated to twice the upper limit of normal for the laboratory performing the test.

Vascular Events

Peripheral Artery Disease/Vascular Insufficiency (PAD): Medical record documentation of an ankle brachial index ≤ 0.9, an imaging study (angiogram, Doppler ultrasound (US), magnetic resonance angiogram (MRA), or computed tomography (CT) scan) demonstrating > 50% stenosis in any peripheral artery (subclavian, femoral, iliac); amputation of an extremity for severe arterial vascular insufficiency; or vascular surgery for reconstruction, bypass, or percutaneous revascularization in the arteries of the lower and upper extremities.

Renal Artery Disease: Medical record documentation of an imaging study (angiogram, Doppler US, MRA, or CT scan) demonstrating > 50% stenosis in either renal artery or vascular surgery for reconstruction, bypass, or percutaneous revascularization in the renal arteries.

Deep Vein Thrombosis (DVT): Medical record documentation of a doppler US demonstrating a non-compressible vessel or an imaging study (angiogram, Doppler US, MRA, or CT scan) demonstrating the presence of a clot.

Cerebrovascular Events

Stroke: Medical record documentation of an acute episode of neurological dysfunction caused by focal or global brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction confirmed by angiogram, computed tomography, magnetic resonance imaging, neurosurgery, or autopsy.

Cerebrovascular Disease in Absence of Stroke: Medical record documentation of carotid ultrasound or angiogram demonstrating ≥ 50% narrowing of one or more carotid arteries or any major extracranial or intracranial vessels to the brain; cerebral (e.g., carotid) or cervical artery revascularization surgery; or percutaneous intervention.

Transient Ischemic Attack (TIA): Medical record documentation of a clinical diagnosis in clinic, emergency department, or hospital records or symptoms in the absence of infarct on imagining studies (angiogram, US, MRI, or CT).

Renal Events

Chronic Kidney Disease (CKD): Medical record documentation of GFR < 60 mL/min/1.73 m^2 for at least 3 months.

End Stage Renal Disease (ESRD): Medical record documentation of kidney dialysis or a kidney transplant.

Nerve Events

Peripheral Diabetic Neuropathy (PDN): Medical record documentation of a nerve conduction velocity test result consistent with PDN or diagnoses by a neurologist. If medical records indicated a diagnosis of PDN by a physician other than a neurologist the full medical record were reviewed by the assigned CAC member and diagnosis confirmed on recorded history and physical exam findings.

Autonomic Neuropathy: Medical record documentation of diagnosis of autonomic neuropathy from cardiology records (if diagnosis was by a physician other than a cardiologist, affirmation by the assigned CAC member based on full record review was required); gastroparesis diagnosed by a gastroenterologist; or gastric emptying study or test procedure (sphincter manometry, orthostatic or postural hypotension, urodynamics test, or post-void residual test).

Mononeuropathy: Medical record documentation of mononeuropathy diagnosed by a neurologist. If medical records indicated a diagnosis of mononeuropathy by a physician other than a neurologist the full medical record were reviewed by the assigned CAC member and diagnosis confirmed on recorded history and physical exam findings

Eye Events

Non-Proliferative Diabetic Retinopathy (NPDR): Medical record documentation of the diagnosis of NPDR made by an ophthalmologist or optometrist using funduscopic examination or fundus photography.

Proliferative Diabetic Retinopathy (PDR): Medical record documentation of the diagnosis of PDR by an ophthalmologist or optometrist including using funduscopic examination or fundus photography, or documentation of laser therapy, injection therapy, vitrectomy, and/or intravitreal injection for treatment of proliferative retinopathy.

Macular Edema (ME): Medical record documentation of the diagnosis of ME made by an ophthalmologist or optometrist using funduscopic examination or fundus photography or laser therapy, injection therapy, and/or intravitreal injection for treatment of macular edema.

Vitreous Hemorrhage: Medical record documentation of the diagnosis of vitreous hemorrhage made by an ophthalmologist or optometrist using funduscopic examination or fundus photography.

Blindness Due to Diabetes: Medical record documentation of the diagnosis of blindness due to diabetes made by an ophthalmologist or optometrist using a visual acuity test. Due to diabetes means directly due to or as a complication of treatment of retinopathy, macular edema, or vitreous hemorrhage.

Cataracts: Medical record documentation of the diagnosis of made by an ophthalmologist or optometrist or documented cataract surgery.

Glaucoma: Medical record documentation of the diagnosis of glaucoma made by an ophthalmologist or optometrist or documented laser surgery.

Liver, Pancreas, and Gallbladder Events

Cirrhosis: Medical record documentation of nodular liver surface contour or other markers of cirrhosis from imaging; evidence of portal hypertension (e.g., varices) from imaging or endoscopy; evidence of cirrhosis from liver biopsy; or documentation of liver transplant.

Pancreatitis: Medical record documentation of 2 of the following: (1) symptoms of abdominal pain, severe epigastric pain, or other clinical presentation; (2) characteristic findings of pancreatitis on MRI, CT scan, or transabdominal US; (3) an amylase or lipase value > 3 times the upper limit of normal.

Gallbladder Disease: Medical record documentation of gallstones detected during gallbladder imaging or endoscopic retrograde cholangio-pancreatography or gallbladder surgery.

Other Events

In addition to the comorbid event data assessed by CAC, TODAY collected information on events with a less complicated presentation. For each identified event below, medical records were obtained by each clinical site and the information necessary to confirm the event was extracted, reviewed, and recorded.

Fractures: Medical record documentation of fractures confirmed by x-ray or imagining test report with the date, location, and cause of the fracture noted.

Lower Extremity Ulcers: Medical record documentation of the date of ulcer diagnosis (not including necrobiosis alone), along with location (foot/lower leg, right/left).

Sleep Apnea: Medical record documentation of a sleep study or polysomnogram performed overnight in a sleep lab with documented apnea-hypopnea index > 5.0.

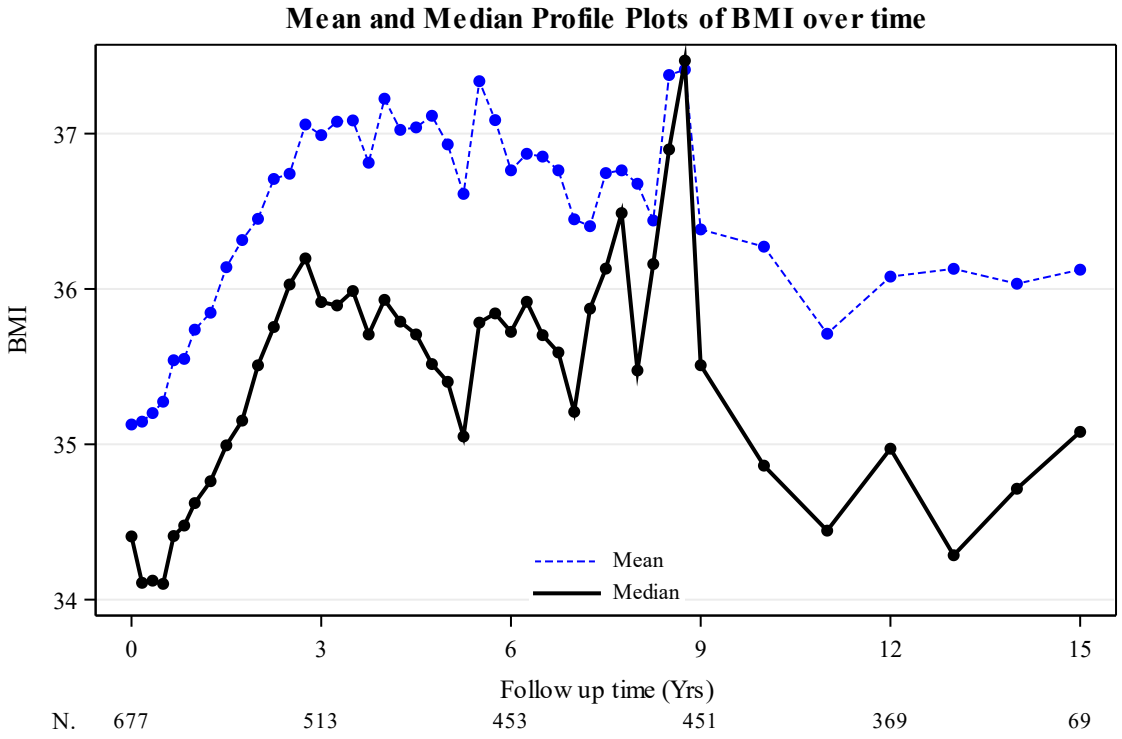
Bariatric Surgery: Medical record documentation of bariatric surgery including type of procedure, complications, length of hospital stay, and need or additional surgery.

Cancer: Medical record documentation of cancer diagnosis, including date, type, and location of cancer.

Diabetic Ketoacidosis (DKA) and Hyperosmolar Hyperglycemic Syndrome (HHS): Medical record documentation of hospitalization or emergency department diagnosis of DKA (HCO_3- < 15 mEq/L or pH < 7.3 mM and moderate or large urine ketone or serum ketone ≥ 4.0 mM) or diagnosis of HHS with glucose concentration > 600 mg/dL, serum osmolality > 330 mOsm/kg, and serum bicarbonate concentration > 15 mEq/L, and urine ketone concentration < 15 mg/dL.

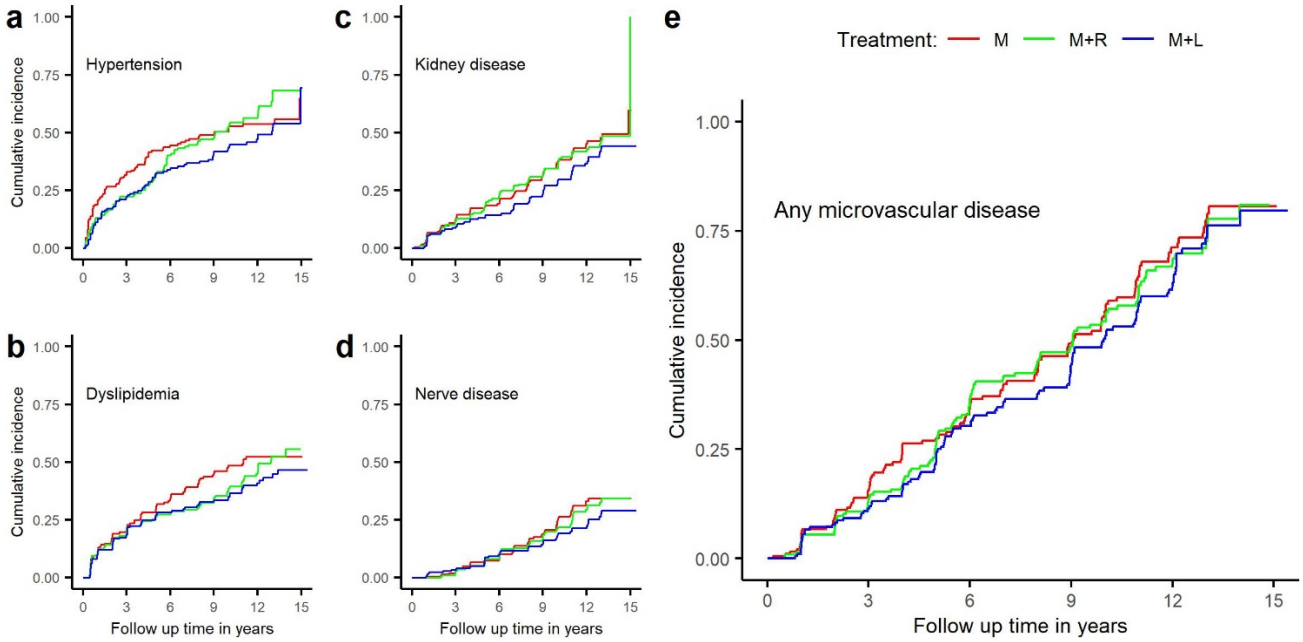
APPENDIX C. Figure S1: BMI Values Over Time

The figure shows the mean and median values of BMI in clinical trial and long term follow-up by year.



APPENDIX D. Figure S2: Comorbidities and Complications by Treatment

The figure shows comorbidities and complications during the clinical trial and long term follow-up by randomized treatment assignment: cumulative incidence plots of (a) hypertension, (b) dyslipidemia, (c) kidney disease, and (d) nerve disease, and (e) cumulative incidence plots of any microvascular complication.



APPENDIX E. Table S1: Adverse Events Reported in the Clinical Trial and Long Term Follow-up

	Clinical Trial	Long-Term Follow-up	
	2004-2011	**2011-2014**	**2014-2020***
	# participants	# participants	# participants
Serious Adverse Events			
Diabetic ketoacidosis	11	8	0
Hypoglycemia	10	5	0
Lactic acidosis	1	0	0
Pregnancy resulting in congenital anomaly	8	6	0
Targeted Adverse Events			
Swelling of ankles, feet, hands	51	40	--
Infection requiring medical attention	420	279	--
Fracture	183†	22	--
Muscle ache/pain	198	40	--
Paresthesias in hands or feet**	--	5	--
Muscle weakness, myopathy**	--	1	--
Loss of consciousness**	--	5	--
Seizure**	--	4	--
Bloating/gastroparesis**	--	7	--
Fecal incontinence**	--	0	--
Problems with sexual function**	--	2	--
Problems related to nerve damage**	--	4	--

**Only serious adverse events directly attributed to a study-related data collection procedure were considered for this fully observational phase of the study providing no treatments, intervention, management, or care. No non-serious adverse events were collected.*

†Collected as sprain or fracture requiring medical attention

***Not collected until 2012*

APPENDIX F. Table S2: Long Term Follow-up Participant Characteristics

	Long-Term Follow-up	
	2011-2014	**2014-2020**
	(n=550)	**(n=500)**
Characteristics at entry into phase		
Age in years (mean ± SD)	18.8 ± 2.4	21.7 ± 2.4
Duration of T2D in years (mean ± SD)	5.0 ± 1.4	8.1 ± 1.5
HbA1c in % (mean ± SD)	8.4 ± 2.9	9.3 ± 3.0
BMI in kg/m^2 (mean ± SD)	36.7 ± 8.4	36.6 ± 8.4
Characteristics at End of Study		
Years in study (mean ± SD)	--	12.6 ± 1.6
Age in years (mean ± SD)	--	26.4 ± 2.8
Duration of T2D in years (mean ± SD)	--	13.3 ± 1.8
HbA1c in % (mean ± SD)	--	9.4 ± 2.8
BMI in kg/m^2 (mean ± SD)	--	36.1 ± 8.4

APPENDIX G. Table S3: Diabetes Medications Prescribed at End of Study

End of Study Prescribed Diabetes Medications	%
Insulin	50.1%
Metformin	48.0%
Thiazolidinedione	0.4%
Sulfonylurea	7.5%
Glitinide	0.7%
Incretin analog	9.4%
DPP4 inhibitor	3.3%
SGLT2 inhibitor	4.6%
No diabetes medications	26.8%

APPENDIX H. Table S4: Retinopathy and Clinically Significant Macular Edema from Fundus Photography During the Clinical Trial and Long Term Follow-up

	Clinical Trial 2010-2011 (n=496)	Long Term Follow-up 2017-2018 (n=404)
Diabetic retinopathy (%)		
No definitive diabetic retinopathy	86.3	50.0
Very mild NPDR	13.7	22.8
Mild NPDR	0.0	16.3
Moderate NPDR	0.0	3.7
Moderately severe NPDR	0.0	0.7
Severe NPDR	0.0	1.2
Early or stable, treated PDR	0.0	2.2
High risk PDR	0.0	1.0
Macular edema (%)	0.0	3.5

APPENDIX I. Table S5: Unadjusted and Adjusted Models for the Development of Any Microvascular Disease in the Sensitivity Sample

Risk Factors	Sensitivity Analysis (N = 429) Hazard Ratio (95%CI)
Sex (female vs male)	0.92 (0.73, 1.16)
Race/ethnicity*	
Hispanic vs Non-Hispanic White	1.50 (1.08, 2.08)
Hispanic vs Non-Hispanic Black	1.07 (0.83, 1.37)
Non-Hispanic Black vs Non-Hispanic White	1.41 (1.01, 1.96)
Treatment	
Metformin + Rosiglitazone vs. Metformin	1.09 (0.84, 1.43)
Metformin + Lifestyle vs. Metformin	1.20 (0.84, 1.43)
Metformin + Lifestyle vs. Metformin + Rosiglitazone	0.91 (0.69, 1.19)
Age (per year)	1.03 (0.97, 1.09)
Diabetes duration (per month)	1.01 (0.99, 1.03)
Unadjusted models	
HbA1c (per 1%)	1.18 (1.14, 1.23)
BMI (per 5kg/m^2)	1.06 (0.99, 1.14)
Log insulin sensitivity (per SD)	0.83 (0.75, 0.93)
Hypertension	1.38 (1.10, 1.75)
Dyslipidemia	1.30 (1.03, 1.65)
Adjusted models**	

HbA1c (per 1%)	1.18 (1.14, 1.23)
BMI (per 5kg/m^2)	1.06 (0.98, 1.14)
Log insulin sensitivity (per SD)	0.82 (0.73, 0.92)
Hypertension	1.43 (1.12, 1.82)
Dyslipidemia	1.46 (1.14, 1.87)

** Other race/ethnicity group is excluded due to heterogeneity within the group.*

*** Adjusted for a priori selected covariates: sex, race ethnicity, and baseline age.*

Any microvascular complication defined as the first occurrence of kidney disease, nerve disease, or retinal disease.

Insulin sensitivity is calculated as 1/fasting insulin.

Sensitivity sample consists of the subset of participants who completed an end of study visit with laboratory analysis.

APPENDIX J. Table S6: Adjudicated Events and Rates of Complications

	# Events	# Patients	Event Rate (per 1000 PYr)
Heart, Vascular, and Cerebrovascular Events			
Arrhythmia	11	9	1.61
Coronary artery disease	3	3	0.42
Congestive heart failure	6	6	0.88
Left ventricular systolic dysfunction	5	5	0.71
Myocardial infarction	4	3	0.58
Deep vein thrombosis	6	6	0.88
Vascular Insufficiency	1	1	0.15
Stroke	4	3	0.58
Transient ischemic attack	1	1	0.15
Kidney Events			
Chronic kidney disease	3	3	0.44
End stage kidney disease	3	3	0.44
Neuropathy or Nerve Damage Events			
Peripheral diabetic neuropathy	7	7	1.02
Autonomic neuropathy	1	1	0.15
Diabetic mononeuropathy	9	9	1.32
Eye Disease Events			
Non-proliferative diabetic retinopathy	62	62	9.25
Proliferative diabetic retinopathy	19	19	2.78
Macular edema	17	17	2.49

Vitreous hemorrhage	7	7	1.02
Blindness due to diabetes	1	1	0.15
Cataracts	11	11	1.61
Glaucoma	5	5	0.73
Liver, Pancreas, or Gallbladder Events			
Pancreatitis	15	9	2.17
Gallbladder disease	36	28	5.28

APPENDIX K. REFERENCES

1. Kavey RE, Allada V, Daniels SR, et al. Cardiovascular risk reduction in high-risk pediatric patients: a scientific statement from the American Heart Association Expert Panel on Population and Prevention Science; the Councils on Cardiovascular Disease in the Young, Epidemiology and Prevention, Nutrition, Physical Activity and Metabolism, High Blood Pressure Research, Cardiovascular Nursing, and the Kidney in Heart Disease; and the Interdisciplinary Working Group on Quality of Care and Outcomes Research: endorsed by the American Academy of Pediatrics. Circulation. 2006 Dec 12;114(24):2710-38

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3. Fundus photographic risk factors for progression of diabetic retinopathy. ETDRS report number 12. Early Treatment Diabetic Retinopathy Study Research Group. Ophthalmology 1991;98:823-33.