Treatment Options for type 2 Diabetes in Adolescents and Youth

TODAY2 PHASE 2 (2014-2020) LONG-TERM POST-INTERVENTION FOLLOW-UP PROTOCOL

Sponsored by
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1 Introduction

TODAY (Treatment Options for type 2 Diabetes in Adolescents and Youth) was a multi-center clinical trial of the optimal approach to treatment of type 2 diabetes (T2D) in children and adolescents. TODAY began recruiting subjects in May 2004, completed enrollment in February 2009 with a sample size of 699, and ended in February 2011. It is followed by TODAY2, a longitudinal study to continue follow-up of the TODAY cohort beyond the end of the TODAY intervention trial. TODAY2 consists of two phases.

(1) TODAY2 Phase 1 (T2P1) was the immediate transition of TODAY participants to non-blinded, non-randomized standard diabetes care and management with monitoring and follow-up for 36 months (March 2011 to February 2014). During this period, the findings of TODAY were analyzed and interpreted by the study group.

(2) TODAY2 Phase 2 (T2P2) is a long-term longitudinal follow-up of disease progression in the TODAY cohort of participants receiving diabetes and other health care and management from self-selected sources (not provided by the study).

TODAY and TODAY2 are sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) of the National Institutes of Health (NIH). The study group is composed of investigators associated with the fifteen clinical centers (Baylor College of Medicine, Case Western Reserve University, Children's Hospital Los Angeles, Children's Hospital of Philadelphia, Children's Hospital of Pittsburgh, Columbia University, Joslin Diabetes Center, Massachusetts General Hospital, Saint Louis University, State University of New York Upstate Medical University, University of Colorado Denver, University of Oklahoma Health Sciences Center, University of Texas Health Sciences Center at San Antonio, Washington University in St Louis, and Yale University), the NIDDK project office, and the coordinating center (George Washington University Biostatistics Center).

This document is the protocol for the second phase of TODAY2. The protocol was written by the TODAY Study Group, approved by the Observational Study Monitoring Board, and approved by the Institutional Review Boards (IRB) of the participating clinical centers prior to the initiation of recruitment.

1.1 Specific Aims and Objectives

The primary objective of T2P2 is to track the progression of T2D and related comorbidities and complications in the TODAY cohort as they transition to young adulthood. We hypothesize that:

- Youth-onset T2D will progress rapidly and result in high rates of diabetes-related medical complications and comorbidities.
- The rapid rate of progression is related to increased insulin resistance characteristic of puberty, worse β-cell function, degree of glycemic control, control of non-glycemic factors, and obesity itself.

To test these hypotheses we will undertake the following primary aims:

P-1. To rigorously document the incidence and prevalence of complications and comorbidities in this cohort as they transition to young adulthood.

P-2. To identify strength of effect, singly and in aggregate, of biological and/or sociocultural factors on rates of complications and comorbidities.

Important secondary objectives are:

S-1. To compare the effect of initial TODAY treatment assignment on rates of complications and comorbidities.

S-2. To compare the effects of glycemic control and TODAY treatment assignment on β-cell

function.

S-3. To analyze the subgroup with pubertal-onset diabetes followed by apparent remission.

S-4. To examine whether complications and comorbidities differ by race-ethnicity and/or gender.

S-5. To assess relationships among psychological outcomes, health-related quality of life, participant socioeconomic characteristics, and the development of complications and comorbidities.

S-6. To describe patterns of healthcare usage in typically under-served participants as they transition from study-provided diabetes care and management to self-selected community healthcare resources.

1.2 Overall Design

Willing and consenting participants who participated in TODAY continue to be followed by TODAY clinical centers at annual outcome data collection clinic visits and interim contacts to collect recent medical and health-related history. A parent/guardian provides consent for participants who are still minors. Participants receive their clinical care and management for diabetes and other medical conditions from their own self-selected primary care physician(s) (PCP) or healthcare provider(s) (HCP).

T2P2 is expected to last 6 years, during which time treatment and comorbidities are documented, diagnoses are confirmed, and the progress of medical conditions is tracked.

1.3 Background and Significance

Type 2 diabetes (T2D) has emerged as one of the greatest global health challenges of the twenty-first century, projected to affect roughly 1 in 3 individuals born in the year 2000 at some time during their lifetime [Narayan et al., 2003]. Although T2D was formerly a disease of adulthood, youth-onset T2D now represents a substantial percentage of new cases of diabetes overall, ranging from 14% in non-Hispanic Whites to 86% in American Indians [Dabelea et al., 2007]. Like adults, youth with T2D have a high prevalence of comorbidities, such as hypertension, hyperlipidemia, non-alcoholic fatty liver disease, and metabolic syndrome, that are associated with increased cardiovascular morbidity and mortality. Cardiovascular disease (CVD) risk factors are substantially more prevalent at diagnosis in adolescents with T2D than in those with type 1 diabetes (T1D), and the progression of end-organ damage is much more rapid, including the development of micro- and macroalbuminuria and proliferative retinopathy. Since long-term microvascular and cardiovascular complications relate to duration of diabetes and to control of glycemia, the increasing number of children and youth diagnosed with T2D, if not effectively treated, could dramatically add to the economic burden of this disease over the ensuing decades. TODAY2 has identified as an important goal the study of microvascular and macrovascular complications emerging in this cohort with youth-onset T2D as they enter young adulthood.

1.4 Summary of Findings from TODAY

Launched in 2004, the TODAY clinical trial recruited 699 youth aged 10-17 within 2 years of diagnosis of T2D [TODAY Study Group, 2007; Copeland et al., 2011]. The purpose was to compare standard therapy (metformin alone) to more intensive approaches, one combining metformin plus rosiglitazone and one combining metformin plus an intensive lifestyle intervention. The primary hypothesis underlying the TODAY study was that aggressive treatment from the outset of diabetes would promote better glycemic control and preservation of

beta cell function, compared with the traditional, step-wise approach to therapy that has been used in adults.

The TODAY study demonstrated that early combination pharmacologic treatment resulted in more sustained glycemic control than standard monotherapy [TODAY Study Group, 2012], while combination therapy with intensive lifestyle did not. However, TODAY has also shown rapid deterioration of glycemic control on monotherapy, rapid loss of beta cell function, and disturbingly high rates of comorbidities. At baseline, the prevalence rates of hypertension and microalbuminuria were high (11.6 and 6.3%, respectively), and increased substantially (33.8 and 16.6%, respectively) during the course of the study. At a median 4.7 years from diagnosis, 16.2% of the participants had LV target organ injury and retinopathy was present in 13.7 % of subjects. Similarly, there were high rates of dyslipidemia (high LDLC, high TG) and chronic inflammation (elevated hsCRP, PAI-1, and homocysteine) that increased over time.

The TODAY cohort is a carefully characterized population of racially and ethnically diverse youth and adolescents with type 2 diabetes followed longitudinally who received well-resourced protocol driven management of their T2D from close to their time of diagnosis. As a resource for the study of T2D in youth it is unlikely ever to be duplicated. While the relatively short follow-up period of the clinical trial (2-6 years) was insufficient to determine the clinical course of T2D in youth, a long-term study of this large well-characterized cohort closely followed and extensively phenotyped from near onset provides an unparalleled opportunity to examine the development of complications and the potential sustained effect of early combination pharmacotherapy.

2 Outcomes and Objectives

Long-term follow-up of the TODAY cohort is likely the only systematic opportunity US researchers will have to address whether youth-onset T2D progresses similarly to adult-onset T2D or T1D, and whether early treatment to maintain glycemic control has a preventive or delaying effect on the course of the disease.

Data are collected to examine the persistence of effects of the TODAY randomized treatment assignment and early glycemic control on the progress of type 2 diabetes in this cohort, including risk and diagnosis of related comorbid medical conditions. The outcomes have been chosen because they provide insight into the mechanism by which the treatment regimens affect durable glycemic control (e.g., effects on HbA1c, insulin sensitivity, β-cell function) or because they provide information concerning the differential risks and benefits of the three treatment arms (e.g., studies of microvascular complications and cardiovascular risk). The following sections describe the various outcome measures in T2P2.

2.1 Comorbidities and Related Diagnoses

The following categories of comorbidities and diagnoses are tracked: lipid abnormalities, hypertension, liver disease, sleep apnea, renal or kidney disease, eye disease, heart disease, cerebrovascular disease, peripheral vascular or arterial disease, cancer, psychiatric event, and clinical neuropathy or nerve damage. Data are collected at annual study visits through standardized examinations, questionnaires and procedures, as well as being extracted from medical records to confirm diagnoses made by the participant's other provider(s), according to uniform study criteria. Both pace and severity of disease progression through symptoms, treatments, and procedures are tracked.

2.2 Glycemic Control and Function

Primary interest is in understanding the effect of early and sustained glycemic control and function (i.e., during TODAY) regardless of what treatment regime was used. TODAY demonstrated that metformin alone was not adequate to maintain glycemic control; TODAY2 addresses the importance of early control however it is obtained, and if the metabolic memory effect is evident in youth-onset T2D.

Data collected during T2P2 are added to the entire longitudinal dataset from TODAY and T2P1 to compare levels and patterns of glycemic control (HbA1c) and function (OGTT derivatives) between those with and without diagnoses of the microvascular outcomes described above. HbA1c has been and continues to be determined at each visit. The oral glucose tolerance test (OGTT) was performed in TODAY (baseline, month 6, month 24 and then annually, at time of primary outcome glycemic failure, and at end of study) and in T2P1 (annually). In T2P2, we continue to perform the OGTT so that all participants have data at baseline and 3, 6, and 9 years after randomization into TODAY. Since mean duration of diabetes at the start of TODAY was 7.8 months, these time points very nearly approximate the actual duration of diabetes.

The efficacy and durability of successful treatment of T2D is determined to a great extent by the ability of a specific intervention to ameliorate insulin resistance and prolong or restore effective beta cell function. Substantial information is available on the natural history of insulin resistance and secretion and the effects of various treatment regimens on these pathophysiological components of T2D in adult patients. Little is currently known about these in affected children and youth with T2D, but data suggest that both insulin resistance and the deterioration in beta cell function is more severe than in adults [Bacha et al., 2013; TODAY Study Group, 2013a]. An important component of TODAY2 is to continue to monitor insulin sensitivity and secretion in the TODAY cohort after discontinuation of randomized therapy to determine (1) the evolution of changes in insulin secretion and sensitivity as participants emerge from puberty and enter young adulthood and (2) the effect of each of the initial therapies on the progression of changes in insulin sensitivity and secretion. Measures of beta-cell preservation are calculated from the OGTT: insulin sensitivity ($1/\text{insulin}_0$), insulin secretion ($\Delta\text{C-peptide}_{30\text{-}0}/\Delta\text{glucose}_{30\text{-}0}$, $\Delta\text{insulin}_{30\text{-}0}/\Delta\text{glucose}_{30\text{-}0}$ if not on insulin), and the oral disposition index (oDI = insulin sensitivity x insulin secretion).

2.3 Microvascular Complications

Microvascular complications associated with diabetes produce significant burdens for the individual patient and are responsible for a major part of the public health care costs associated with diabetes. Microvascular complications are more common among children with T2D at the time of presentation than among those with T1D [Takahashi et al., 1990; Yokoyama et al., 2000]. There is limited evidence suggesting that progression rates of microvascular complications are also greater in youth with T2D. However, existing reports generally involve relatively few patients in a clinic setting, with the exception of the SEARCH study which, like TODAY, has demonstrated a high prevalence of microvascular complications and risk factors [SEARCH, 2006]. The TODAY cohort represents a unique population in which to study the development of microvascular complications and associated risk factors. In addition, a comparison of the effect of the treatment interventions on the prevention and slowing of rates of development of microvascular complications associated with T2D is an important secondary outcome of TODAY2 and could significantly modify the interpretation of the primary outcome results of the TODAY trial.

2.3.1 Retinopathy

Retinopathy is assessed from 7-field stereo fundus photographs graded centrally by a reading center utilizing the Early Treatment Diabetic Retinopathy Study [ETDRS, 1991] diabetic retinopathy scale. This assessment was first performed at the end of TODAY and a follow-up is performed again in T2P2. Diabetic retinopathy is defined as a reading of >20 in either eye (that is, 20/>20 or greater) on the ETDRS scale. Subjects with clinically significant macular edema (CSME) are also considered to have retinopathy.

A diagnosis of retinopathy by a non-study source that can be confirmed according to standard study criteria from acquired medical records is also included in the definition of retinopathy.

2.3.2 Nephropathy

Nephropathy is assessed by annual determinations of urinary albumin and GFR calculated using a serum creatinine and the Cockcroft-Gault equation [GFR_c = ((140-age) * (wt in kg) * (0.85 if female)) / (72 * Cr)] and by serum cystatin C measurement. Microalbuminuria is defined as confirmed urine albumin excretion 30-300 mg/day, and overt diabetic nephropathy (macroalbuminuria) as >300 mg/day and/or a GFR <70 mL/min/1.73 m^2.

Laboratory values from a non-study source that can be confirmed according to standard study criteria from acquired medical records are also included in the definition of nephropathy.

2.3.3 Neuropathy

Although definitive diagnosis of clinical neuropathy requires physical examination findings plus abnormal nerve conduction studies, formal examination of all TODAY2 subjects by a neurologist would be costly, and nerve conduction velocity studies are uncomfortable enough to impede long-term retention of this valuable cohort. The use of standardized histories and examinations such as the Michigan Neuropathy Screening Instrument (MNSI) and the Semmes-Weinstein 5.07 10-gram monofilament (SW-MF) have been shown to have good sensitivity and positive and negative predictive values compared with standard neurological examination and nerve conduction velocity determinations. Therefore, we utilize MNSI and SW-MF annually as in TODAY to assess peripheral diabetic neuropathy. Peripheral diabetic neuropathy is defined as the presence of MNSI score >2 and <8 out of 10 appropriate responses to the SW-MF in either foot.

Beginning in 2018, signs of neuropathy will be detected using quantitative measurements of vibration, light touch and sharp (pin prick) sensation, as recommended in the 2017 ADA position statement [Pop-Busui R et al., 2017]. The MNSI and the monofilament test will be continued to allow for longitudinal analysis. We will define peripheral diabetic neuropathy as an abnormal finding for pinprick testing (score≥5) [Perkins BA et al., 2001] or vibration testing (score≥5) [Perkins BA et al., 2001] in addition to continuing our previous definitions utilizing the MNSI questionnaire and SW-MF.

Neuropathic findings from a non-study source that can be confirmed according to standard study criteria from acquired medical records are also included in the definition of neuropathy.

2.4 Macrovascular (Cardiovascular) Risk Indicators

Studies suggest that obese adolescent patients with T2D may have unfavorable patterns of both traditional and non-traditional risk factors associated with cardiovascular morbidity and mortality. Individuals who develop T2D at an early age may also develop CVD at an early age. Information on overt cardiovascular complications in adolescents with T2D is limited but previous reports have shown increased nighttime systolic and diastolic blood pressure and diminished nocturnal decline in blood pressure, increased posterior and septal wall thickness, left ventricular (LV) hypertrophy, and increased aortic pulse wave velocity, a measure of vascular stiffness [Gungor et al., 2005; Pinhas-Hamiel and Zeitler, 2007]. More recent reports have confirmed and extended these findings. Girls with T2D have larger LV dimensions and LV mass along with impaired diastolic filling and systolic longitudinal function compared to lean and overweight non-diabetic subjects [Whalley et al., 2009]. Approximately 50% meet published criteria for LVH and LV dilatation and 25% have evidence of elevated LV filling pressure in association with structural abnormalities In TODAY, 16.2% of participants had evidence for LV damage at a median duration of diabetes of just over 4 years [TODAY Study Group, 2013b].

In T2P2 the primary macrovascular risk measurements consist of an echocardiogram to assess cardiac function and pulse wave velocity (PWV) to assess arterial stiffness. These are follow-up procedures of an initial echocardiogram performed in the last year of TODAY and an initial PWV in the last year of T2P1. EKG is performed with the echocardiography to determine the R-R interval both lying and standing, as a measure of cardiac autonomic neuropathy. PWV is highly reproducible and strongly associated with cardiovascular events [Urbina et al., 2010; Urbina et al., 2011]. We also continue to obtain a cardiovascular risk factor and lipid profile.

Diagnoses of macrovascular events by a non-study source that can be confirmed according to standard study criteria from acquired medical records are reported, although anticipated to be rare.

2.5 Sleep Disorders and Quality

Over the past decade, both laboratory and epidemiologic studies have identified poor sleep quality and obstructive sleep apnea (OSA) as putative novel risk factors for type 2 diabetes [Cappuccio et al., 2010; Tasali, Leproult, et al, 2008; Marshall et al., 2009]. Evidence indicates that OSA is both a risk factor for type 2 diabetes and an exceptionally frequent co-morbidity with an adverse impact on glycemic control [Tasali, Mokhlesi, Van Cauter, 2008]. Several studies have established a robust association – independent of adiposity and other known confounders – between the presence and severity of OSA and insulin resistance and glucose intolerance in non-diabetic adults [Punjabi and Beamer, 2009; Punjabi et al., 2004; Punjabi et al., 2002; Seicean et al, 2008].

Data collected include measures of circadian rhythm, social jet lag, fragmentation, and arousal determined by (1) self-administered standard questionnaires linked to the annual visit and (2) in-lab polysomnograms.

2.6 Psychological and Health-Related Quality of Life

We collect life events data (e.g., educational and employment status) and administer self-report standardized inventories for depression, eating disorders, and health-related quality of life as in TODAY. The specific instruments to assess psychological problems include the following participant self-report standard surveys: (a) the Beck Depression Inventory II (BDI-II) [Beck et al., 1961; Beck et al., 1996], (b) the Patient Health Questionnaire (PHQ) scales for somatic symptoms, anxiety, and alcohol use [Spitzer et al., 1999], (c) the Eating Disorder Diagnostic

Scale (EDDS) [Stice et al., 2000; Stice et al., 2004], and (d) life event exposure based on the Yeaworth Adolescent Life Change Event Scale [Yeaworth et al., 1980; Yeaworth et al., 1992]. Participant are also interviewed about emotional or mental health problems involving referral, treatment, or hospitalization, and psychiatric diagnoses made by a non-study source that can be confirmed according to standard study criteria from acquired medical records are also recorded.

Health-related quality of life is collected by participant self-report using the Pediatric Quality of Life Inventory version 4.0 [Varni et al., 2008; Varni et al., 2009] with age-specific versions for teen (13-18), young adult (19-25), and adult (≥26).

2.7 Body Composition and Physical Examination

We continue to collect physical measurements (height, weight, blood pressure) and perform a physical examination to review systems. Although other measurements of body composition were collected in TODAY (e.g. DEXA), only the physical measurements listed are currently collected.

2.8 Cause of Death for Participants

The National Death Index (NDI) will be used to search for T2P2 participants who have not been seen at their local center and have not been contacted for at least 1 year as well as for participants known to be deceased. The NDI is a central computerized index of death record information from state vital statistics offices nationwide. Each center will submit their cases to the NDI. Coding that includes cause of death will be obtained. Records will be searched for all years for which vital status cannot be confirmed. If permitted by the local IRB, follow-back investigations will be undertaken to obtain medical records as required. Central review of cause of death will be adjudicated by an internal T2P2 committee.

2.9 Safety

We have collected extensive safety data during TODAY and T2P1. In the former we administered experimental treatments as part of a clinical trial, and during the latter we were responsible for patient care and management and administering study provided standard care treatments. We are especially cognizant of our responsibility to monitor specifically the long-term safety effects and possibility of lingering or persistent risk of early exposure to rosiglitazone. Rosiglitazone has been associated with increased risk for low bone density, fractures, congestive heart failure, and macular edema in adults. In T2P2, we continue to record occurrence of fractures as a targeted adverse event. We perform follow-up cardiac function by echocardiography and we identify the presence of macular edema through follow-up retinal studies.

3 Recruitment and Enrollment

All subjects randomized into the TODAY study are eligible to participate in T2P2, whether they participated in T2P1 or not. There are no additional inclusion or exclusions criteria for participation in T2P2. We attempt to reconnect with participants who have not had contact with the study team for some time. We do not pursue participants who formally withdrew informed consent during TODAY or T2P1.

Informed consent is obtained from participants 18 or older; parental consent and youth assent are obtained for participants still considered minors. The informed consent/assent process

includes provision of information in verbal and written form and the opportunity for discussion and questions. The T2P2 informed consent process (1) maximizes potential participant and family understanding of the study and how it differs from the previous protocols and (2) allows an informed decision regarding continued participation, including personal risks and benefits. This process is designed to meet the ethical obligations to the participant and improve retention by fostering a progressively increasing understanding of TODAY2 by the participant and family, as well as the development of a positive relationship with the clinic staff. It is an interactive, conversational process, with the ultimate goal of maximum understanding of TODAY2 including both the responsibility of the participant to TODAY2 and the responsibility of the study investigators and staff to the participant. It is anticipated that one result of this process is maximized retention of participants in TODAY2.

4 Participant Care and Management

The start of T2P2 represents the end of study-provided care and management of the participant's diabetes and other medical conditions. The participant makes his/her own medical decisions including selection of healthcare provider (HCP) and primary care physician (PCP). The clinical center institutions that have been involved in TODAY and TODAY2 may become the participant's chosen HCP – and, in fact, this is encouraged – but clinical procedures and activities are separate from the T2P2 research procedures and activities. Treatments, education, etc. are delivered according to good clinical practice and not paid for by TODAY2.

A summary of data and findings from the annual visit is sent to the HCP/PCP designated by participant. Occurrence of an established 'alert' level is communicated promptly.

5 Research Procedures and Approach

The table shows that data collection has been designed to ensure continuity of longitudinal data acquisition in the cohort through TODAY, T2P1, and T2P2.

Table of Data Collection Showing Continuity Across the 3 Study Phases		**TODAY**	**T2P1**	**T2P2**
baseline demographics	• age, sex, race-ethnicity, family history	x		
health history	• events, diagnoses, treatments, procedures, tests	x	x	x
	• healthcare usage, diabetes care and management	x		x
socio-economic history	• environment (school, work, housing), smoking, life stressors	x		x
physical examination and measurements	• height, weight, blood pressure, systems review, female reproductive status	x	x	x
	• pubertal status, fitness, nutrition, physical activity	x		
	• pancreatic autoimmunity	x	x	
	• LFT	x	x	x
glycemic control and β-cell function	• HbA1c, OGTT	x	x	x
DXA		x		
microvascular complications	• retinopathy (fundus photography and OCT)	x		x
	• nephropathy (serum creatinine and cystatin C, ACR)	x	x	x
	• neuropathy (MNSI, SW-MF, tuning fork, pin prick)	x	x	x
macrovascular risk indicators	• pulse wave velocity		x	x
	• echocardiography	x		x
	• cardiovascular risk laboratory values and lipid panel	x	x	x

sleep studies	• questionnaires and in-lab polysomnogram			x
psychology and behavior	• depression inventory, alcohol use, eating disorders • somatic symptoms and anxiety	x		x x
health-related quality of life		x		x
safety (serious adverse events)		x	x	x
blood and urine for storage		x	x	x

5.1 Data Collection

The table lists the schedule of data collection, measurements, and assessments. Participants attend a clinic visit once a year, continuing the annual visit schedule from TODAY and T2P1. In addition to standard annual outcomes data collection, special follow-up procedures are also performed at annual visits according to a schedule that does not burden or overwhelm activities and procedures at a single visit. In addition, participants are contacted on an interim basis to maintain up-to-date contact information and to identify recent diagnoses and other medical history that generate acquisition of medical records to track the progress of the disease or condition.

Measurements and Assessments	standard annual visit	special follow-up procedures	interim contact
health history, events, diagnoses, treatments, procedures	x		x
socio-economic history • life events (e.g., education, employment, housing, pregnancy) • risk factors (e.g., smoking, alcohol) • family health history	 x x x		
glycemic control and function • HbA1c • OGTT (glucose, insulin, c-peptide, proinsulin)	 x 	 (a)	
microvascular complications • fundus photography • microalbumin (urine) • MNSI • SW-MF • Pinprick (beginning year 5) • Graduated tuning fork (beginning year 5)	 x x x x x	 once (year 4)	
macrovascular risk indicators • PWV • echocardiography • cardiovascular risk lab values (lipid panel)	 x	 once (year 5) once (year 2)	
sleep • questionnaires • polysomnogram	 	 once (years 2-3) once (years 2-3)	
psychological • BDI-II • PHQ • EDDS	 x x x	 	

health-related quality of life • PedsQL	x		
physical examination • height, weight, BP • systems review • lab values LFT, serum creatinine, serum cystatin C	x x x		
blood and urine for storage (b)	x		
safety	x		x

(a) OGTT is performed on visits at 72 months (6 years) and 108 months (9 years) from baseline TODAY.

(b) Stored blood is used to derive cardiovascular risk markers of timely interest; specific uses are to be determined, but consideration is given to longitudinal follow-up of measures made during TODAY such as free fatty acids, lipoprotein subclass levels, LDL particle size, density and subfractions, fibrinogen, hsCRP, PAI-1, IL-6, leptin, and adiponectin.

5.2 Participant Retention

Retention refers to efforts to prevent participant dropout or withdrawal from the study. It is critically important to successfully engage and retain participation over the course of the study.

As an incentive, participants receive:

- $200 for a complete annual study visit including collection and performance of all outcomes
- $50 for a partial annual study visit including completion of forms and questionnaires only
- $25 for completing a 6-month interim contact
- $50 for completing each special procedure (retinal examination, pulse wave velocity, and echocardiogram)
- $25 for completing the sleep questionnaires
- $100 for completing the polysomnogram (overnight sleep study)

Participants are also reimbursed for travel and other expenses incurred in attending the annual visits.

In the last year of T2P1 we started using retention and contact methods to test what worked best for each participant so that we could continue successful individual-specific approaches into T2P2. It is anticipated that methods of contact appropriate for our cohort are less likely to be mailed hard copy documents and more likely to include phone (especially mobile or 'smart' phone) and forms of e-communication such as e-mail, text, chat, etc. Social media and networking venues such as Facebook also provide ways to keep connected and include options for keeping messages and communications private.

Communications methods and strategies are used both to maintain interest and connection, as well as to maintain more direct contact. For example:

- providing information and updates such as
  - announcement and synopsis of publications and presentations made from TODAY data
  - new links and resources about young people managing and living with T2D
- celebratory greetings on holidays, birthdays, graduations, and anniversaries
- announcements of updates made to the clinic Facebook page and invitations to visit
- reminders of upcoming TODAY visits and procedures

Attrition is monitored regularly by the Procedures Oversight Committee. An attempt is made to collect data on the reason for leaving the study in the case of a participant who withdraws. Assistance is offered to any site with a higher than average attrition rate. Sites are also encouraged to share their ideas and experiences via regular communication and conference calls for study staff.

5.3 Confidentiality

The study complies with HIPAA guidelines regarding confidentiality of patient data.

Patients who participated in the TODAY study were assigned a study identification number:

- the first three digits indicate the clinical center and
- the next three digits are individually assigned to a participant by each clinical center (001-999).

In addition, each patient randomized is associated with an acrostic or 'nickname' of up to 6 alpha-numeric characters that was selected by the clinical center coordinator with input from the participant according to the following guidelines:

- neutral, i.e., not offensive, and
- unrelated to personal characteristics or identifiers, e.g., no initials or identifiable nicknames.

The purposes of the acrostic are (1) to act as a check and back-up of the study ID number in case of transcription or entry error, (2) to facilitate coordinator recall of a specific patient, and (3) to 'personalize' incentive items and other study materials provided to the participant.

All data, including forms and specimens, are labeled with the study ID, including forms and specimens. All data transferred to the coordinating center, reading centers, and central cores identify the participant only with the study ID and acrostic. The coordinating center does not receive any personal identifiers.

Each clinical center maintains a file on each participant that includes personal identifiers, linking name and contact information to the study ID. These data are not entered into the study data management system or into any file intended to be sent to the coordinating center. Participant files are kept in secure locations and the clinical center is responsible for taking every other reasonable measure (those set by the state, the site, and the study) to ensure and maintain record confidentiality and patient privacy.

Training sessions cover confidentiality principles and procedures.

6 Safety Monitoring and Reporting and Risk Management

The T2P2 study design is observational and involves data collection only – i.e., no treatments, interventions, or management are included. T2P2 data collection procedures represent known clinical tests and procedures that may be used for youth with T2D. They are performed according to standard instructions by appropriately trained individuals. Anticipated risks and threats to safety are minimal to non-existent.

An Observational Study Monitoring Board (OSMB) consisting of appropriately qualified independent experts provides review of data on study progress and participant safety. The purpose of the board is to assure independent review as to whether study participants are exposed to unreasonable risk because of study participation, and to monitor study progress and

integrity. Board members are chosen by NIDDK in consultation with the study investigators, and typically convene twice a year (every 6 months) unless a need arises. The coordinating center produces a report according to pre-determined format, contents, and reporting frequency. The reports present information regarding (1) adverse events and safety violations experienced by study patients as a result of undergoing the study procedures and (2) conduct of the study, including withdrawals and visit attendance. Following each OSMB deliberation, minutes are provided for the clinical centers to submit to the IRB.

The Committee for Oversight of Procedures (COP) also reviews safety violations and study progress in regular conference calls. Members represent all levels of the study group – both staff and investigators. COP looks at possible trends over time and by clinical center to identify potential problems, and takes action to resolve any problems.

6.1 Definitions of Events

An adverse event in T2P2 is any dangerous or unsafe occurrence as a consequence of performing a study-related data collection procedure. An adverse event is considered serious if it meets any of the following criteria:

a. The event results in an inpatient hospitalization (any overnight stay associated with an admission).
b. The event results in the prolongation of a hospital stay.
c. The event results in permanent or severe disability.
d. The event results in death.
e. A pregnancy results in a congenital anomaly.
f. The event is life-threatening.
g. Treatment is required to prevent a serious event.

These criteria are established by the FDA and are not all applicable to non-treatment observational studies like T2P2.

6.2 Adverse Event and Serious Adverse Event Reporting

The timely and complete reporting of adverse events is a critical requirement of study conduct.

Clinical centers report events to the coordinating center in a timely fashion via the web-based data management system. Serious adverse events (SAE) must be reported to the coordinating center within 24 hours. This notification should occur even if data are incomplete. Additional data and follow-up information are sent subsequently as an update to the original report. The coordinating center immediately forwards SAE reports to the study group chair, the NIDDK project office, and the OSMB chair. SAEs are also reported to the local IRB and any other institutional monitoring committee, as per local requirements

For T2P2, events related to study procedures are expected to occur during the conduct of the procedure, at the study clinic visit, or soon after. The participant is instructed to contact the clinical center with any serious adverse event meeting the above criteria.

6.3 Potential Risks and Procedures to Minimize Risks

Risks from participating in the study are related to study procedures:

- Risks of blood draw are pain when the needle is inserted and possible bruising at the site.
- Risks associated with the OGTT are the same as those for having blood drawn and possible stomach discomfort after drinking the glucola.
- Risk associated with measuring the stiffness of arteries (PWV) is brief pressure when the SphygmoCor pulse wave velocity test instrument is placed on the skin.
- Risk associated with polysomnogram sleep study is possible discomfort due to the electrodes or sleeping in the laboratory.

We also recognized that there may be risks associated with the examinations and blood tests administered in TODAY2. Some people are upset, embarrassed, or uncomfortable during a physical examination or answering certain questions.

Procedures to minimize risks include administration of all data collection by study staff with the required training and certification. Study staff are instructed to explain what they are going to do prior to the procedure and then explain what they are doing as they go through each step of the procedure. Such communication and giving the participant a chance to ask questions and set the pace can ameliorate any problems. Participants are able to stop or refuse a procedure or question at any time.

Females have a pregnancy test performed before the PWV and the echocardiogram.

7 Data Processing and Management

The coordinating center develops and maintains a central database integrating all of the study data.

7.1 Data Management System

Data are entered at the clinical centers into the MIDAS web-based data entry application. The database application guides the study staff member through the data entry process. If an invalid response is entered, the computer signals and provides a message about the error and how to solve it. At any point during entry, the staff member can make an electronic note concerning a particular response. The system includes programmed skip patterns as required by the case report forms, and also includes quality control checks such as lists of valid values for multiple choice items. The system provides automated consistency checking so the study staff can resolve inconsistencies quickly without a lengthy communication with the coordinating center. The same checking is also run on the central database at the coordinating center to verify that centers are resolving consistency checks.

7.2 Quality Control Procedures

7.2.1 Edits and Audits

Range checks, inter-item checks, cross-table checks, and double data entry verification are used where appropriate to ensure accurate data entry. Specific quality control procedures are run to check for missing, incorrect, and questionable values immediately after they are entered. Reports with the necessary patient identifying information and the problem values are produced and sent to the clinical centers for correction. When returned, corrected values are checked again for consistency with other items. The goals are to make quality control a continuous

process, to make the turnaround time between error detection and correction as short as possible, and to document any changes made to the database.

7.2.2 Training and Certification

The coordinating center arranges for study-wide, small group, site, and individual training and re-training. Study-wide training sessions are at least annual, and held in conjunction with the annual study group meeting. Investigators and outside experts may be assigned to lead sessions. The purpose of training is to assure that the study is conducted in a standardized manner across all locations (clinical centers) and time (years of follow-up). Training is based on the study manual of procedures. Throughout the study, new staff are trained by the existing clinical center study staff, which hopefully includes overlap with the previous position holder, with assistance from the coordinating center.

In order to remain certified to engage in study procedures, study staff must attend training session or make up sessions and must pass any tests or criteria established.

The clinical center must also pass certification criteria, including supplying the coordinating center with the current IRB approval letter and stamped informed consent forms.

7.2.3 Site Visits

The two types of site visits are (1) scheduled monitoring and (2) as needed to address specific concerns.

The coordinating center organizes site visits to audit and monitor study procedures and records, engages in local problem solving, and provides training/retraining as needed. The site visit team includes representatives from the coordinating center and, as needed, investigator(s) or coordinator(s) from other clinical centers and a representative of the NIDDK program office. Each visit follows a predetermined format and site visitors complete a checklist to record findings. The site visit team reviews study procedures and compares data collection records to listings from the central database.

Site visits conducted to address specific problems at the clinical center are attended by investigators representing study leadership, the NIDDK project office, the coordinating center, and others as needed.

7.3 Backup, Data Security, and Confidentiality

The coordinating enter applies the Biostatistics Center's data backup and security policies to ensure the safety and confidentiality of the data. Backup procedures include: twice-weekly system backup, daily incremental backup, and off-site fire proof storage. Security procedures include: logon and link password protection, remote password logon and dial-back modems, and for internet access, separate Web servers which use SSL and encryption algorithms. Regularly updated virus scanning software is used routinely to check personal computers for computer viruses. University computing facilities provide support in the event of a disaster.

The coordinating center maintains confidentiality of patient data and emerging results per a confidentiality policy, which every staff member is required to sign annually.

7.4 Archival and Study Close-out

At the end of the study, after all data have been received and edited, the database is archived in computer readable format, including: readme documentation files, text files of study documents (forms annotated with variable names, protocols, and manuals of procedures), data files in the form of SAS transport files and input statements, data dictionaries, and program code documenting primary derived variables.

After the results have been published, a de-identified version of the central database is transferred to the NIDDK Central Repository to be made available to other investigators.

8 Statistical Considerations

8.1 Power

Power calculations are based on the second primary objective (P-2) to test the effect of early glycemic control during TODAY (defined as the overall mean HbA1c [DCCT/EDIC, 2000] during TODAY, regardless of treatment) on the prevalence of various microvascular and macrovascular outcomes. Computations are based on applying a logistic regression model for a single continuous normal covariate.

The overall mean of HbA1c per participant during TODAY was 7.1% (SD 1.7%) and was approximately normally distributed. Expected prevalence rates for microvascular and macrovascular outcomes were based on data from the Royal Prince Alfred Hospital (Sydney, Australia) diabetes clinical database [Constantino et al., 2013], restricted to a similar maximum duration of 15 years since T2D diagnosis. RPAH average HbA1c was 8.0% (SD 1.6%) and rates were 17.4% for retinopathy, 32.7% for nephropathy, 13.7% for neuropathy, 46.9% for any microvascular disease, and 3.1% for any macrovascular disease. This database is the best current source of rates of comorbidities.

Based upon odds ratios reported by DCCT/EDIC [DCCT/EDIC, 2000], the table gives power for a two-sided test with a significance level of 0.05 under various conditions: (1) sample size of 500 (close to the 506 projected) and 450 (representing ~10% lost-to-follow-up) and (2) a range of odds ratios.

Outcome	OR=1.4		OR=1.5		OR=1.6	
	N=450	N=500	N=450	N=500	N=450	N=500
Retinopathy	71%	76%	86%	89%	94%	96%
Nephropathy	87%	90%	96%	97%	99%	99%
Neuropathy	63%	68%	80%	83%	89%	92%
Any microvascular	92%	95%	98%	99%	99%	99%

Rates of macrovascular disease are expected to be too low at this point in follow-up to test with adequate power.

8.2 Methods of Analysis

P-1: Compute both crude rates of incidence and prevalence for complications and comorbidities, as well as rates adjusted for person years since the start of TODAY, along with 95% confidence intervals. Graphical methods such as forest plots, commonly portrayed

in meta-analysis reviews, will be utilized to visually summarize the TODAY2 results together with reported data from other studies[60,61].

P-2, S-1, S-2, and S-5: Logistic regression, Poisson regression, or generalized linear mixed model (GLMM) methodology appropriate for longitudinal analysis of the effect of glycemic control and original TODAY treatment assignment on occurrence of complications and comorbidities (P-2 and S-1) or β-cell function outcomes (S-2) during TODAY2. Outcomes can be modeled separately as well as combined, and may be modeled as continuous, scales, scores, or presence/absence of event. Tests for trends and comparisons between levels of the factors or between treatment groups will be evaluated at single or multiple points in time. Longitudinal relationships between other factors (β-cell function markers, insulin resistance, obesity, psychological and quality of life measures, socioeconomic characteristics) and the development of complications and comorbidities (S-5) will also be assessed using GLMM.

S-3: Analyses above repeated in the subgroup with pubertal-onset diabetes followed by apparent remission.

S-4: Pre-planned subgroup analysis by gender and by race-ethnicity using methods described above.

S-6: Patterns of healthcare evaluated descriptively.

8.3 Other Statistical Considerations

- We apply the intent-to-treat principle that participants are analyzed according to their original TODAY treatment group assignment.
- Covariates are included in the analysis as appropriate. Selection may be based upon descriptive analysis, investigator expertise, and reports in the literature (e.g., the inclusion of duration of diabetes in DCCT/EDIC analyses).
- Data imputation is performed if amount missing is >5% using multiple imputation techniques based on non-missing data and covariates. One reason for missing data is dropout and withdrawal. Comparisons are made between participants and those who withdraw (either by formally removing informed consent or by chronic 'no-show' and lost contact). Such comparisons convey whether the data that are missing are missing completely at random (MCAR), missing at random (MAR), or missing not at random (MNAR). Imputation schemes and interpretation of results depend on the characterization [Rubin, 1987; Little and Rubin, 2002; Schafer, 2000].

9 Study Administration

9.1 Organization

The major organizational components and their responsibilities are described:

- The *TODAY2 Steering Committee*, composed of the principal investigators of the 15 clinical centers, the coordinating center, and the NIDDK project office, is the primary decision making body for the study with overall responsibility for the design and conduct of study protocols.
- The *NIDDK project office* participates in all decision-making activities and selects and oversees the activities of the Observational Study Monitoring Board.
- The *clinical centers* are located at Baylor College of Medicine, Case Western Reserve University, Children's Hospital of Los Angeles, Children's Hospital of Philadelphia, Children's Hospital of Pittsburgh, Columbia University College of Physicians and Surgeons, Joslin

Diabetes Center, Massachusetts General Hospital, Saint Louis University, State University of New York Upstate Medical University, University of Colorado Denver, University of Oklahoma Health Sciences Center, University of Texas Health Sciences Center at San Antonio, Washington University at St Louis, and Yale University. They are responsible for recruiting and retaining patients and implementing the protocol.

- The *coordinating center* is located at the George Washington University Biostatistics Center with responsibility for coordinating all aspects of the study, including production and distribution of materials and documents, set-up and administration of the data management system, maintenance of the central database, analysis of results, and report of results in collaboration with the other investigators.
- *Central resources, reading centers, and cores* operate under subcontract to the coordinating center and include: Central Biospecimen Laboratory (CBL), Fundus Photography Reading Center, Echocardiography Reading Center, Pulse Wave Velocity Reading Center, Sleep Central Core. In collaboration with the coordinating center and study investigators, central laboratories and reading centers perform the following tasks:
    1. Establish procedures and standards for training staff involved in the measurement, collection, preparation, handling, transfer, and all other procedures and processes.
    2. Conduct training sessions and contribute training materials to the study manuals of procedures.
    3. Provide or facilitate the acquisition of equipment and materials, including specifying brands, sizes, and suppliers as applicable.
    4. Establish procedures for data entry and transfer of data to the coordinating center.
    5. Develop procedures for the internal as well as external quality control, and provide periodic reports on the quality control surveillance.
    6. Provide long-term storage of reserve specimens or materials as directed by the Steering Committee for use in ancillary or future studies.

  Each director represents the laboratory or center on Steering Committee conference calls and on other conference calls where the director's participation is deemed necessary.
- *Working committees* include Operations, Procedures Oversight, ComorbidityAssessment, Laboratory and Procedure Monitoring, Publications & Presentations, Ancillary Studies.

9.2 Study Website

The coordinating center maintains the study website, which is a secure site requiring a user ID and password combination for access. The web server utilizes the Secure Socket Layer (SSL) protocol that encrypts all traffic to and from the server. Investigators, coordinators, consultants, and other study staff who would benefit from access to the information on the website are each given a unique user ID and password, which identifies the user to the web server and can be used to restrict access to particular web pages if desired.

The website contains study documents such as the protocol, manual of procedures, and forms, study calendar, directory, meeting and conference call information, links to other sites, tracking reports, minutes, and agendas.

9.3 Study Group Policies

The study group has adopted 3 policies similar to those used by other NIDDK collaborative groups.

- Conflict of Interest Policy. TODAY2 collaborators are required to disclose any financial or related interest that could present an actual conflict of interest or be perceived to present a conflict of interest. Disclosure is required to protect each individual's reputation and career from potentially embarrassing or harmful allegations of inappropriate behavior, and to protect the integrity of TODAY2 study research. Forms are kept on file at the coordinating center.
  The TODAY2 Operations Committee determines (1) if the disclosed interests could directly and significantly affect the performance of study responsibilities and (2) the management, reduction, or elimination of the conflict. In addition to complying with the TODAY2 conflict of interest policies, collaborators must certify that they have complied with all of their local and institutional requirements regarding conflict of interest and disclosure. This is accomplished by supplying the coordinating center with copies of the local IRB letter of approval and stamped informed consent form(s).

- Publications & Presentations Policy. The policy is administered by the TODAY2 Publications & Presentations Committee with approval from the TODAY2 Steering Committee. The policy includes guidelines for authorship, submission and review of proposed publications and presentations, ownership of the data, and setting priorities for coordinating center statisticians.

- Ancillary Studies Policy. The policy is administered by the TODAY2 Ancillary Studies Committee with approval from the TODAY2 Steering Committee. Proposals from external investigators to have access to data from the central database are reviewed according to established criteria.

9.4 Protocol Amendments

Adoption of protocol amendments requires two-thirds majority approval by voting members of the TODAY2 Steering Committee. The amended protocol is approved by the OSMB and is resubmitted to the IRB along with revised informed consent forms, if applicable.

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