National Institutes of Health
National Institute of Diabetes and Digestive and Kidney Diseases

Diabetes Mellitus Interagency Coordinating Committee
Type 1 Diabetes and Cardiorenal Outcomes: Informing a Practice Changing Trial

Hybrid Meeting
September 18, 2026

EXECUTIVE SUMMARY

The National Institutes of Health (NIH) National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), in collaboration with the National Heart, Lung, and Blood Institute (NHLBI), sponsored a meeting on September 18, 2026, titled "Diabetes Mellitus Interagency Coordinating Committee (DMICC) Type 1 Diabetes (T1D) and Cardiorenal Outcomes: Informing a Practice Changing Trial." This meeting highlighted the need for a future clinical trial that can identify and test effective interventions to manage and potentially prevent cardiorenal outcomes in T1D. Prior to the meeting, NIDDK and NHLBI organized a DMICC working group composed of diabetes, cardiovascular, and renal experts. The DMICC working group's charge was to present existing gaps and opportunities in T1D cardiorenal research and to suggest options regarding prospective study designs, interventions, and cohorts at the DMICC T1D and Cardiorenal Outcomes meeting for NHLBI and NIDDK to review when considering a proposed study. This working group was co-chaired by Dr. Paul M. Ridker, Harvard University, Brigham and Women's Hospital, and Dr. Robert Eckel, University of Colorado Anschutz Medical Campus. Working group members met regularly for approximately 9 months prior to the DMICC T1D and Cardiorenal Outcomes meeting, and during these meetings, the working group met with professional societies, academic investigators, and patient advocacy groups to obtain their perspectives that would be incorporated into the working group's planning efforts.

Speakers and attendees provided key suggestions and options to be considered by NIDDK and NHLBI when developing a T1D cardiorenal outcomes clinical trial, including discussing inclusion and exclusion criteria, maximizing collaborations for effective participant recruitment, engaging patients and patient advocacy groups to ensure materials are understandable, and maximizing data collection and harmonization. Partnerships among federal agencies, nonprofit organizations, global organizations, researchers, and patient advocacy groups were emphasized. In addition, the meeting provided a platform for attendees to provide their input about the DMICC working group's recommended options. The meeting also featured patients with T1D who provided firsthand testimonies regarding clinical trial participation and the necessity for a cardiorenal outcomes study to improve standards of care.

The objectives of the meeting were to—

- Obtain input and perspectives from scientific experts and patients with T1D regarding possible study options, interventions, and cohorts to be considered for a future clinical trial for cardiovascular and renal outcomes in T1D.

- Receive suggestions from scientific experts, panelists, and individuals with T1D, which can inform future NIDDK and NHLBI programmatic decisions.

Attendees heard opening remarks from Dr. William T. Cefalu, Director, Division of Diabetes, Endocrinology, and Metabolic Diseases, NIDDK; Dr. David C. Goff, Acting Director, NHLBI; Dr. Griffin P. Rodgers, Director, NIDDK; and Dr. Gina Wei, Acting Deputy Director, Clinical Research and Strategic Initiatives, NHLBI. Following that, DMICC working group members presented their perspectives on design options to be considered for a T1D cardiorenal outcomes clinical trial. Subsequent discussions encompassed numerous topics—including confounding factors, comorbidities, and risk mitigation—that must be carefully considered when designing a T1D cardiorenal outcomes clinical trial. Panelists and attendees identified potential challenges and limitations that should be addressed to maximize findings and shift standards of care.

Welcome and Introduction to the DMICC

Dr. Cefalu delivered an overview of the Special Diabetes Program (SDP)—a federal, congressionally mandated initiative that supports large-scale consortia and high-risk, high-impact T1D research that aims to prevent, treat, or cure T1D and T1D-mediated complications. SDP funding is administered to multiple NIH institutes and centers and the Centers for Disease Control and Prevention. The current appropriation for fiscal year 2026 is $200 million. SDP has six goals: (1) identify the genetic and environmental causes of T1D, (2) prevent or reverse T1D, (3) develop cell replacement therapy, (4) improve T1D management and care, (5) attract new talent and apply new technologies to T1D research, and (6) prevent or reduce T1D-mediated complications. Dr. Cefalu provided examples of research funded for each goal of the SDP, including The Environmental Determinants of Diabetes in the Young (or TEDDY), Type 1 Diabetes TrialNet, Collaborative Islet Transplant Registry (or CITR), Human Islet Research Network (or HIRN), and Closed Loop and Education for hypoglycemia Awareness Restoration (or CLEAR), among others. He emphasized that SDP has resulted in landmark progress that has improved the health and quality of life for patients with T1D. He continued that SDP has invested heavily in T1D complications-based research as one of its goals, including the Cardiovascular Repository for Type 1 Diabetes (or CaRe-T1D). Dr. Cefalu highlighted that preventing or decreasing complications, particularly cardiorenal complications caused by T1D, was a major reason for organizing this meeting.

Dr. Wei briefly outlined the collaboration between NIDDK and NHLBI. She emphasized that this collaboration is critical to address gaps to improve cardiorenal outcomes in patients with T1D, noting that neither institute can overcome this challenge alone. Dr. Wei explained that this collaborative effort began when program staff discussed the scientific need for a cardiorenal outcomes trial for T1D, which led to the creation of a working group and external panel. She discussed the DMICC meeting's agenda, highlighting that a central theme for the sessions would focus on important study design considerations for a potential prospective cardiorenal clinical trial.

Opening Comments

Dr. Rodgers highlighted that the DMICC serves as a critical platform for diabetes-centered collaborations across federal agencies. NIDDK has played an important role in guiding the

committee, fostering collaborations, and promoting communication that is imperative for addressing T1D. He reiterated that SDP has resulted in groundbreaking U.S. Food and Drug Administration (FDA)–approved therapies and technologies—including an advanced glucose monitor and artificial pancreas—that have improved quality of life for patients with T1D. SDP also has resulted in the first approved prevention therapy for T1D. Dr. Rodgers emphasized that T1D-mediated long-term complications are an urgent, unmet need for patients. He stressed that attendee input will inform and guide NIDDK's future directions in T1D research.

Dr. Goff expressed his appreciation for the opportunity to partner with NIDDK on this effort. He noted that past collaborations with NIDDK, including the Action to Control Cardiovascular Risk in Diabetes (or ACCORD) trial, resulted in key data and findings that advanced type 2 diabetes (T2D) research. Dr. Goff explained that previous collaborations have established observational studies and biorepositories; a T1D cardiorenal outcomes clinical trial deserves prioritization. He emphasized that the input received today on important topics related to developing a clinical trial—including design options, feasibility, and endpoints—would be important for informing potential funding opportunities.

Objectives, Goals, and Perspectives: DMICC Co-Chairs

Dr. Eckel provided an overview of cardiorenal outcomes clinical trials for T2D, highlighting that more than 15 major trials have been completed since 2016. He provided data on physiological parameters (e.g., A1C, systolic blood pressure, low-density lipoprotein cholesterol [LDL-C], coronary artery calcium [CAC]) of patients with T1D and emphasized that clinical trials for cardiorenal outcomes and interventions for these patients are lacking. Dr. Eckel provided firsthand testimony of living with T1D, noting that technological advancements have been critical for managing the disease. Dr. Ridker discussed the guiding principles for developing a cardiorenal outcomes clinical trial for patients with T1D. He reviewed key considerations for a clinical trial, including patient population, potential interventions, outcomes, trial design, statistical analyses, operational efficiency, risk management, and enrollment. Dr. Ridker briefly reviewed several clinical trial options (i.e., two-by-two factorial trial design, 3-arm parallel trial design, and two 2-arm parallel trials with an umbrella design) that could be considered.

Highlights

- Cardiorenal pathophysiology and outcome data from T2D clinical trials should not be extrapolated to patients with T1D. These diseases demonstrate key differences, including disease duration, pathology, autoantibodies, and prevalence of cardiorenal risk factors.

- The FDA no longer requires two clinical trials to establish the efficacy of drugs submitted for approval. Drug marketing authorizations can be based on one clinical trial and confirmatory evidence.

- In patients with T1D, the underlying mechanisms and early processes involved in atherosclerosis development remain poorly understood. Research is needed to determine pathophysiological differences in atherosclerosis for T1D and T2D.

- T1D is associated with an increased risk of cardiorenal disease-related events and mortality. Monitoring specific physiological parameters—including albuminuria and estimated glomerular filtration rate (eGFR)—becomes more important as disease duration and age increase.

- There is a gap in knowledge for cardiorenal disease prevention in patients with T1D because there have been few randomized controlled trials (RCTs). The primary RCT for this topic is the Diabetes Control and Complications Trial (DCCT), which occurred between 1982 and 1993. DCCT observational data demonstrate that improved glycemic control reduces cardiorenal events and mortality.

Perspectives

Dr. Maria Mori Brooks, University of Pittsburgh School of Public Health, presented on trial design options and statistical analysis plans for a T1D cardiorenal outcomes clinical trial. She provided a brief overview of the three suggested trial design options (i.e., two-by-two factorial trial design, 3-arm parallel trial design, and two 2-arm parallel trials with an umbrella design), highlighting the benefits and limitations of each approach. Dr. Brooks outlined key design elements for glucagon-like peptide-1 receptor agonists (GLP-1RA) and sodium-glucose co-transporter 2 inhibitors (SGLT2i). Dr. Brendan Everett, Brigham and Women's Hospital, discussed the guiding approach and underlying philosophy—including broad applicability and patient relevance—for the proposed design options. He spoke about the advantages and disadvantages of clinical outcomes, surrogate outcomes, and secondary and tertiary outcomes. Dr. Everett provided the rationale for a combined composite cardiorenal outcome, noting that chronic kidney disease (CKD) and cardiovascular disease (CVD) share risk factors (e.g., smoking, dyslipidemia, albuminuria, low eGFR) and have similar pathophysiological features. He presented data demonstrating the benefits of GLP-1RA and SGLT2i for patients with T2D and discussed anticipated results.

Highlights

- Time-to-event for composite major adverse cardiac events (MACE) over 5 years would be an important primary endpoint to analyze. MACE endpoints include all-cause death, myocardial infarction (MI), stroke, hospitalization for heart failure (HHF), revascularization, and end-stage kidney disease (ESKD). Secondary endpoints (e.g., individual time-to-event endpoints, macroalbuminuria) could be considered.

- Previously collected T1D data were used to calculate statistical power and sample size. A power of 90 percent and an alpha value of 0.05 were proposed. To detect a 20 percent risk reduction with a 15 percent event rate, approximately 7,000 participants would be needed. This sample size assumes that 10 percent of participants will not complete follow-up visits and 5 percent of participants will drop in or drop out. Patient eligibility criteria and endpoints will influence power and sample size calculations.

- DMICC working group members provided the two 2-arm parallel trials with an umbrella design as an option. This approach was deemed feasible and would address key research questions for GLP-1RA and SGLT2i interventions.

- Clinical outcomes—including MI, HHF, and ESKD—are a primary concern for patients, caretakers, and health care providers. These endpoints require larger sample sizes and longer follow-up durations and may be limited to high-risk patients.

- Surrogate outcomes include eGFR slope, albuminuria reduction, and Kansas City Cardiomyopathy Questionnaire (or KCCQ) score. Surrogate outcomes allow for a smaller sample size and shorter follow-up duration, but these endpoints hinder extrapolation, do not provide enough evidence to alter clinical care practices, and are applicable only to high-risk patients.

- A secondary hierarchical composite endpoint would be beneficial to incorporate into the clinical trial. Including secondary and tertiary outcomes in a clinical trial allows researchers to determine additional benefits (e.g., weight, blood pressure, eGFR slope), monitor potential risks (e.g., severe hypoglycemia, diabetic ketoacidosis [DKA]), and identify mediators of disease.

Discussion

- Patients with T1D experience higher event rates if they are over 60 years old or have had the disease for more than 15 years. Age and disease duration should be considered when outlining inclusion and exclusion criteria to ensure that adult-onset T1D is studied. Inclusion criteria (e.g., CAC score) should be considered carefully. Younger individuals may benefit more from receiving interventions, which could reduce recurrent events.

- The proposed risk event rate was based on previous data obtained from registries.

- Detecting a smaller risk reduction will require a larger sample size. Time to first event may provide appropriate statistical power. In addition, gathering data on recurrent events is a possible approach for increasing power using the same sample size.

- A joint cardiovascular and renal endpoint was highlighted as a crucial suggestion for any proposed trial, especially in severe disease settings. Collecting these data would address gaps in knowledge about T1D-related ESKD and CVD.

- NIH funding for a clinical trial is very desirable because pharmaceutical companies have not shown interest in pursuing T1D cardiorenal outcomes research. The budget would remain the same regardless of the selected clinical trial design.

Perspectives (*continued*)

In this session, Dr. Sarah de Ferranti, Boston Children's Hospital, provided an overview about background discussions and evaluations that resulted in DMICC members considering GLP-1RA and SGLT2i interventions as the most feasible options. She briefly discussed other interventions—including finerenone use, blood pressure optimization, LDL-C reduction, and early prevention strategies—that were considered but not pursued further in their deliberations because of implementation challenges. Dr. de Ferranti presented data demonstrating the benefits of SGLT2i and GLP-1RA use in different patient populations—including patients with T2D,

heart failure (HF), and CKD. She also explained that several clinical trials using SGLT2i and GLP-1RA interventions in patient populations with T1D are ongoing, but these studies do not evaluate important cardiorenal outcomes. Dr. Jennifer Green, Duke University School of Medicine, presented key considerations when selecting patient populations for a clinical trial. She noted the importance of accurately defining the disease phenotype, and she provided examples of disease criteria (e.g., clinical diagnosis, autoantibodies) that were used in previous clinical trials. Dr. Green outlined the proposed inclusion and exclusion criteria, noting previous discussions and data that were the rationale for these suggestions. She reviewed criteria that were specific to the GLP-1RA or SGLT2i interventions and briefly outlined a potential enrollment algorithm.

Highlights

- Clinical trials using SGLT2i for patient populations with T1D—including the Dapagliflozin Evaluation in Patients With Inadequately Controlled Type 1 Diabetes (or DEPICT 1)—demonstrate a modest improvement in glycemia and weight but an increased risk of DKA. Safety and feasibility concerns (e.g., patient monitoring to minimize DKA risk) may pose a challenge for the standardized implementation of SGLT2i in patient populations with T1D. DMICC working group members suggested including this intervention to (1) evaluate efficacy, (2) assess safety, and (3) identify effective risk mitigation strategies for patients with T1D.

- Sotagliflozin to Slow Kidney Function Decline in Persons with Type 1 Diabetes and Diabetic Kidney Disease (or SUGARNSALT) is an ongoing clinical trial that is studying the potential benefits of sotagliflozin to prevent or delay the progression of ESKD in patients with both T1D and HF.

- Clinical trials using GLP-1RA interventions in patient populations with T1D demonstrate a reduction in body weight and insulin dose without causing excessive hypoglycemia, demonstrating a reasonable safety profile in this patient population. DMICC working group members developed key considerations for a potential GLP-1RA intervention—including population eligibility. Carefully selecting the drug and dosage is critical for maximizing cardiorenal outcomes and clinical trial credibility.

- Primary outcomes that align with a drug's mechanism of action should be considered for selection.

- DMICC working group members suggested that for a future clinical trial, a clinical diagnosis of T1D and continuous treatment of T1D with insulin within 1 year of diagnosis should be considered as inclusion criteria. Potential exclusion criteria were proposed, including suspected T2D, monogenic forms of diabetes, and development of diabetes after pancreatic disease. Additional data—such as autoantibodies, C-peptide, glucose, and polygenic risk score—could be collected but not required for eligibility determination.

- DMICC working group members suggested that a high-risk patient population be selected for the clinical trial. These patients would be at risk for events at a rate that

supports study feasibility—previous NHLBI trials demonstrated that event rates often occur less frequently than predicted by observational data.

- A clinical trial that has independent intervention study arms allows for expanded eligibility criteria and recruitment of a larger patient population, whereas a clinical trial that simultaneously tests multiple interventions would be more restrictive for patient enrollment.

- DMICC working group members discussed that inclusion and exclusion criteria could be similar for GLP-1RA and SGLT2i interventions. However, several criteria—including HF diagnosis, hemoglobin A1C levels, eGFR, and body mass index—could differ. Also, an enrollment algorithm could assign patients into a study arm based on the presence or absence of HF. If a patient has HF, they could be eligible for the SGLT2i study arm. If a patient does not have HF, they could be randomly assigned to either the SGLT2i or GLP-1RA study arm.

Discussion

- Weight reduction as a confounding factor for the GLP-1RA intervention was discussed as a concern. To minimize this concern, a lower dose of the drug intervention was suggested. Previous data demonstrate that a lower dose produces favorable CVD outcomes without modifying weight.

- Researchers must carefully consider the dosage for interventions. Too low of a dose may prevent risk reduction benefits from being observed.

- A risk-benefit analysis is important for any intervention in a clinical trial. Advanced technology—including continuous ketone monitors—and increased awareness have the potential to mitigate risks. A combinatorial therapy may increase certain risks (e.g., DKA) and would need to be carefully assessed throughout a clinical trial.

- If a patient is already taking a GLP-1RA or an SGLT2i, it would be questionable to ask them to stop the medication to be eligible for the trial. Researchers could instead consider whether these patients may be eligible for a combinatorial therapy study arm. However, if a patient was previously prescribed GLP-1RA or SGLT2i medication and is no longer taking it, they could be eligible for the proposed clinical trial as long as they did not stop taking the medication because of adverse events.

- Additional inclusion and exclusion criteria (e.g., autoantibodies) and measurements (e.g., continuous glucose monitoring [CGM]) should be carefully considered when designing the clinical trial.

- The increasing off-label use of these interventions highlights the urgency of conducting this type of clinical trial.

- Researchers must collaborate with partners and organizations to enroll enough patients to make the clinical trial feasible. Researchers should consider recruiting patients from outside of the United States if the required sample size cannot be obtained domestically.

- Researchers also should ensure that a statistically significant percentage of patients in each study arm are women to determine the efficacy of different interventions in this population.

Open Discussion

During this discussion session, attendees had the opportunity to raise questions about and provide feedback on the presentations from the morning session. The discussion spanned several key topics of options to consider regarding the design and development of a T1D cardiorenal outcomes clinical trial, including CGM, placebo and intervention selection, and exclusion criteria. Several key themes—such as ensuring patient retention and treatment adherence, minimizing confounding factors, and maximizing data collection and clinical trial impact—were highlighted during the session.

Discussion Highlights

- One option is to have a study arm randomize patients to GLP-1RA if underlying CVD is present or SGLT2i if renal complications are present. Clinicians may be unaware if a patient is taking a GLP-1RA medication. Trust and transparency between clinical trial coordinators and patients are vital to ensure an accurate medication list is obtained during study recruitment.

- Medications (e.g., statins) can have long-lasting benefits and lower disease risk several years after discontinuation. This could impact clinical trial results and hinder the opportunity to generate knowledge about T1D-related cardiorenal outcomes. Because of this, researchers need to carefully examine which medications to consider as exclusion criteria.

- Data show an increased prevalence of GLP-1RA use, which could impact clinical trial feasibility. To prevent confounding factors, it is important to consider real-world data before finalizing the study design.

- CGM to track glycemic variability is suggested. These data would help elucidate differences in the pathophysiology of T1D and T2D and complications in high-risk populations (e.g., people with uncontrolled diabetes). NIH is encouraged to work with the FDA to incorporate a CGM tool in the clinical trial, if the trial moves forward.

- Patients with T1D can develop complications quickly. Exclusion criteria related to complications, comorbidities, and disease duration should be considered carefully. Additional screening measures may be needed during patient recruitment.

- It is important for the clinical trial to represent the broad range of populations within the United States so that results are applicable to the entire patient population with T1D.

- NIH is encouraged to review funding mechanisms to identify an option that would accelerate the timeline and limit delays in conducting the clinical trial.

- The data collected from a T1D cardiorenal outcomes clinical trial must be useful for secondary studies. The clinical trial data should be relevant and made available to address research questions that arise from new T1D topic areas.

- Calculated sample sizes are an estimation. Drop-in and dropout rates should be accounted for when completing sample size calculations. Patient retention is critical to minimize complications resulting from dropouts.

- Interim monitoring during clinical trials is important to ensure treatment adherence. Noncompliance will negatively impact the clinical trial.

- NIH should consider whether a common placebo is ideal. Subcutaneous and oral placebos have different benefits and challenges. It was suggested that NIH connect with the FDA and pharmaceutical companies once a clinical trial consideration has moved forward to determine a useful placebo option for the clinical trial.

- Additional medications, such as amylin receptor agonists, are available or are being developed for T1D treatment. Researchers must carefully select the clinical trial interventions. Innovative medications may become the standard of care and could cause the clinical trial to become obsolete.

- DKA mitigation strategies are being developed. Continuous monitoring will allow clinicians to screen for adverse reactions—including DKA—in patients when selecting the appropriate drug dosage. A mitigation strategy should be implemented in the clinical trial to minimize DKA episodes.

- Fasting and eating can cause fluctuations in ketones and glycemic levels. Correlations between symptom severity and glycemic levels could be explored with CGM.

Panel Perspectives and Discussion

External partners, collaborators, and patients play a crucial role in the design and development of a clinical trial. A panel of subject-matter experts and patient advocates with different backgrounds and from a broad range of organizations were selected to provide key insights. Panel members highlighted that standards of care recommendations require hard clinical endpoints (HCEs), surrogate markers foster additional studies, and risk mitigation strategies reduce hesitancies. Key themes identified during the discussion included meaningful exclusion criteria, recruitment challenges, collaborations, and patient education.

Highlights

- Dr. Courtney Ackeifi is a staff scientist at Breakthrough T1D studying cardiometabolic therapies to treat and cure T1D. Cardiorenal disease is a strategic priority at Breakthrough T1D. She explained that she advocates for the SDP and participates on advisory boards to

guide the implementation of SDP-developed interventions. Dr. Ackeifi emphasized that patients with T1D are undertreated, although this population has an increased risk of cardiorenal complications. She indicated that insurance companies require clinical data for treatment coverage, highlighting an unmet need for patients with T1D. Dr. Ackeifi provided the following suggestions: (1) include biomarkers and surrogate endpoints to promote clinical trial feasibility and clinical practice utility, (2) allow stakeholders to review clinical trial materials—such as eligibility criteria and protocols—to ensure the data translate to implementation and clinical adoption, and (3) minimize factors that hinder participant recruitment.

- Dr. Joshua Neumiller is a volunteer for the American Diabetes Association (ADA). He expressed his excitement for the prioritization of T1D research and explained that the ADA emphasizes standards of care for patients, noting that clinical trials for T2D-related cardiorenal outcomes have caused major shifts in T2D patient care. Dr. Neumiller provided several suggestions for NIH to consider, including (1) partnering with patient groups to leverage their communication channels and networks, (2) identifying ideal targets for pharmacotherapies, (3) prioritizing HCEs (e.g., MACE) over surrogate endpoints to support changes in evidence-rated recommendations for patient care, (4) determining how vital signs (e.g., blood pressure) and screening tests (e.g., lipid levels) will be managed, (5) confirming whether other therapies (e.g., angiotensin II receptor blockers) should be included, and (6) stratifying participant recruitment based on presumed benefits and possible comorbidities. He continued that the stratification of patients allows researchers to simultaneously address several scientific queries.

- Dr. Amy K. Mottl serves on the Saving Kidneys, Hearts, and Lives Steering Committee of the American Society of Nephrology. She commented that the size of the patient population hinders incentives and funding from industry for T1D research, highlighting the need for an NIH-supported clinical trial. Dr. Mottl noted that this is an important opportunity to collaborate with the FDA to innovate clinical trial design. The selection of HCEs and surrogate endpoints (e.g., albuminuria) is critical to translate findings from future clinical trials into standard-of-care recommendations as new T1D therapies become available. Dr. Mottl suggested that NIH (1) use a patient-centered hierarchical approach for clinical endpoints, (2) identify factors (e.g., DKA) that cause clinician hesitancy in administering new therapies, (3) consider the severity of comorbidities (e.g., CKD) when choosing inclusion and exclusion criteria, and (4) incorporate both a primary kidney and cardiovascular HCE.

- Dr. Julio Rosenstock is the Director of the Dallas Diabetes Research Center and a clinical professor at The University of Texas Southwestern Medical Center. He represented a group of academic investigators who provided options for a proposed trial. He explained that extrapolating data from patients with T2D to patients with T1D should not continue. Dr. Rosenstock emphasized that HCEs and composite outcomes must be prioritized to ensure that findings are translated into changes in standards of care. He continued that the findings must be generalizable to the broad range of patient populations with T1D. Dr. Rosenstock noted that clinical equipoise is critical and discussed a two-by-two factorial design option for a trial that was proposed by the academic team that he represented. He discussed that the two-by-two factorial design allows researchers to

understand several key scientific questions. He advised NIH to (1) study combinatorial treatment, (2) determine whether the two drugs enhance effects, (3) prevent confounding factors and control physiological factors (e.g., blood pressure, glucose levels) that may influence findings, and (4) review inclusion and exclusion criteria.

- Dr. Gordon Tomaselli is a Professor Emeritus at Albert Einstein College of Medicine and serves as the National Executive Vice President, Research and Grants Administration, for the American Heart Association (AHA). AHA emphasizes partnerships to amplify impact. Dr. Tomaselli explained that numerous factors have caused CVD to be metabolically driven, and AHA's research portfolio reflects this. He suggested (1) incorporating a holistic approach for outcome measures to maximize the understanding of other prevalent T1D-mediated complications, including cognitive dysfunction and vascular disease; (2) selecting a registry and ensuring data harmonization; (3) ensuring findings result in pragmatic recommendations for T1D treatment; and (4) partnering with the Global Cardiovascular Research Funders' Forum.

- Ms. Eugenia Araiza is a nutritionist at Healthy Diabetes and a patient with T1D. She briefly reviewed her personal experience living with T1D and explained that a T1D diagnosis impacts the entire family. Ms. Araiza emphasized that T1D advancements have been minimal over the past 30 years. She suggested that clinicians consider (1) increasing education efforts, particularly for screening and preventing complications; (2) modifying information (e.g., pamphlets) into easily understandable material for the public; (3) maximizing connections between diabetes educators and patients; and (4) ensuring that the clinical trial accurately represents patients with T1D from different backgrounds. Ms. Araiza encouraged NIH to support studies that investigate how menopause impacts T1D because clinicians cannot effectively navigate this issue.

- Ms. Phyllis Kaplan is a patient with T1D. She provided an overview of her previous experiences participating in clinical trials. Ms. Kaplan has volunteered for 12 clinical trials and two research studies, highlighting that involvement in these opportunities has increased her knowledge about her health. In a study she participated in, she was informed that her CAC score was in the highest range among people in her age group. Ms. Kaplan continued that this incident highlights an underlying problem in health care—primary care physicians only review basic physiological measurements, which does not provide an accurate assessment of developing complications or comorbidities. She explained that many patients are interested in prevention and mitigation strategies, so standards of care must be modified to mirror this patient priority.

Discussion

- The design and development of a T1D cardiorenal outcomes clinical trial is a highly collaborative effort, and the primary goal of clinical trials is to guide evidence-based recommendations for standards of care. Such a clinical trial also provides an opportunity to include the collection of specific data types (e.g., biomarkers) and endpoints that could inform secondary studies. Some attendees suggested that modifying label indications would not be a focus for this clinical trial.

- Patients are concerned about T1D-related complications and believe that certain technologies (e.g., insulin pumps) may not prevent complications from occurring.

- Language in clinical trial materials (e.g., consent forms) should be designed so that patients can easily understand the information. Scientific jargon hinders patient recruitment efforts. Researchers must partner with patient groups when designing recruitment materials.

- If a clinical trial to address cardiorenal outcomes includes certain interventions, such as SGLT2i, ketone monitoring data and risk mitigation strategies from previous studies can be incorporated. State-of-the-art ketone monitoring devices would be an incentive for patient participation. However, clinical trial coordinators (CTCs) must be able to effectively communicate the benefits of health care tools (e.g., CGM device) to patients, emphasizing the importance of CTC-driven education.

- Patients with T1D have an increased risk of developing other diseases (e.g., hyperthyroidism, autoimmune diseases). NIH and researchers are encouraged to determine whether the prognoses with specific diseases will be considered as exclusion criteria because the underlying pathophysiology of other diseases may impact results. Patients who are motivated to participate in clinical trials have been disqualified previously from studies because they have had additional autoimmune diseases.

- NIH and researchers should consider how to maximize patient participation in the clinical trial. Exclusion criteria must be balanced with patient enrollment. Attendees agreed that age would be a criterion—pediatric patients were not considered as options during the meeting. Patients with other conditions, including hypertension and dyslipidemia, should be considered. If these participants enroll in the study, there could be an opportunity to get these other physiological parameters (e.g., blood pressure) under control, as well.

- An attendee noted that recruiting more than 10 patients with T1D per site is difficult, highlighting that an ongoing T1D clinical trial took 18 months to recruit fewer than 300 patients across 80 sites in nine countries. The attendee continued that a number of sites will be needed to fulfill the estimated sample size and this will be a logistical challenge. An international study may be justified to obtain the required enrollment numbers to conduct the trial, and collaborations with global organizations would be beneficial.

- Patient advisory committees can provide guidance on cardiorenal outcomes and endpoints that are a priority to patients.

- Several attendees underscored the urgency of conducting a clinical trial to address cardiorenal outcomes because GLP-1RA use for weight management is becoming more prevalent.

- NIH is encouraged to select a pragmatic clinical trial design. Some attendees emphasized that a combinatorial therapy study arm (i.e., double intervention) is of interest to the community. Previous studies, such as the ACCORD trial, did not demonstrate positive

results for the double intervention compared with the placebo. Some attendees also noted that simultaneously titrating two drugs was a concern and suggested considering an oral small-molecule GLP-1RA. In addition, smaller effect sizes could be a challenge, but findings would be more generalizable.

- Data collection across sites must be harmonized, and the resulting dataset should be made accessible to researchers outside of the study.

- The proposed interventions have well-characterized side effects and adverse event profiles, which reduce potential risks for clinical trial participants. Potential risks should be monitored and mitigated.

Summary of Today's Discussion

Dr. Ridker thanked attendees for their comments and for discussing the benefits and weaknesses of the proposed suggestions. NIDDK and NHLBI will review the options discussed and determine how to proceed with the potential development of a T1D cardiorenal outcomes clinical trial. Dr. Ridker emphasized that a pragmatic approach is required to navigate institutional requirements that would hinder the progression of this effort. Dr. Ridker commented that based on his previous experiences, pharmaceutical companies—unlike NIH—do not ensure that the Nation's broad range of socioeconomic backgrounds are represented in clinical trials. He continued that this is important because the data should be generalizable to all patients with T1D.

Dr. Eckel expressed his appreciation for the opportunity to co-chair the workshop. He thanked the working group members and professional societies for their contributions. Dr. Eckel reiterated that, despite living with T1D, his own research has not focused specifically on the disease; instead, he has prioritized the metabolic underpinnings of CVD prevention. He summarized the importance of a clinical trial design that comprehensively gathers the necessary data. Exclusion criteria and thresholds must be identified. Dr. Eckel emphasized that T1D onset and early disease progression remain poorly understood. An international study may be warranted, highlighting that patient recruitment at diabetes-centric centers may not be enough to fulfill participant recruitment.

Final Comments

Dr. Wei thanked the DMICC co-chairs and working group members for volunteering their time to provide guidance and expertise about research opportunities that would improve outcomes for patients with T1D. She noted that NHLBI looks forward to advancing T1D research and that she appreciates the thorough suggestions and ideas from attendees. Dr. Cefalu concurred with Dr. Wei's remarks. He noted that moving this initiative forward will be a collaborative, intersectoral effort. Dr. Cefalu reiterated that NIDDK and NHLBI support the development of a T1D cardiorenal outcomes clinical trial, highlighting that other institutes, centers, and offices are interested in participating in this effort based on today's discussions. He concluded that NIH is committed to supporting research that benefits people with chronic diseases and that NIH staff may follow up with attendees to seek their continued input and expertise in advancing these critical efforts.

Conclusion

Designing and developing a rigorous T1D cardiorenal outcomes clinical trial will require input from the entire diabetes community. It calls for a collaborative approach—such as relying on feedback from patient groups—to improve trust and transparency, maximize education, and enhance meaningful scientific discoveries. The clinical trial would likely require researchers to collaborate with nonprofit organizations and global partners to successfully fulfill study enrollment requirements. The success of any proposed clinical trial may also mean that researchers should connect with pharmaceutical companies and the FDA to identify interventions and placebos that optimize clinical trial efficiency. Overall, a potential T1D cardiorenal outcomes clinical trial should include (1) patient engagement throughout the design process; (2) sufficient patient enrollment to ensure statistical power for primary and secondary analyses; (3) advanced technologies and mitigation strategies to minimize risk; and (4) the collection of surrogate, primary, secondary, and possibly tertiary outcomes to support future T1D studies.

Planning Committee

- Beena Akolkar, Ph.D., NIDDK, NIH
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Panelists

- Courtney Ackeifi, Ph.D., Breakthrough T1D
- Eugenia Araiza, DN, DCES, Patient Perspective
- Phyllis Kaplan, Patient Perspective
- Amy K. Mottl, M.D., M.P.H., American Society of Nephrology
- Joshua Neumiller, Pharm.D., American Diabetes Association
- Julio Rosenstock, M.D., The University of Texas Southwestern Medical Center
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