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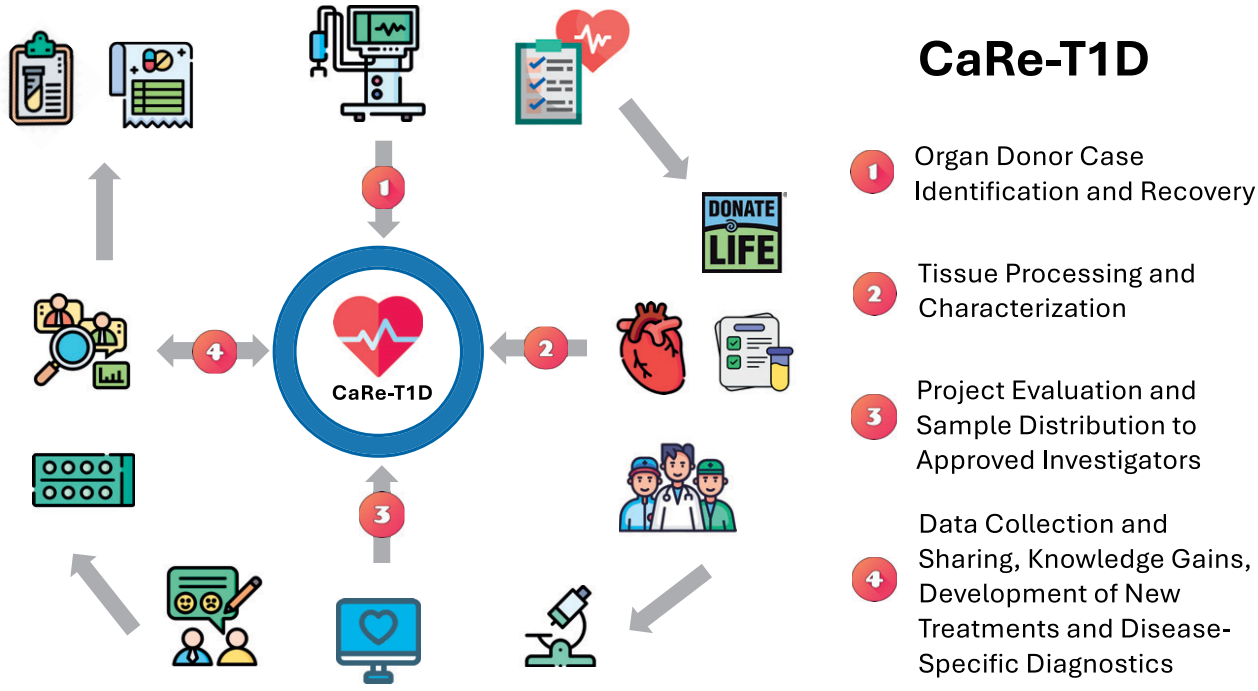
Diabetes 2025;74(7):1078–1088 | https://doi.org/10.2337/db25-0017



The Cardiovascular Repository for Type 1 Diabetes (CaRe-T1D): An NIDDK Initiative to Advance Understanding of Mechanisms Underlying Cardiovascular Disease in Type 1 Versus Type 2 Diabetes

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Cardiovascular disease (CVD) is a leading cause of morbidity and mortality in individuals with diabetes. Individuals with type 1 diabetes have a two- to fourfold higher risk of CVD in comparison with the general population, driven by an earlier onset and increased lifetime incidence of CVD events and mortality. Similarly, type 2 diabetes confers two- to threefold increased CVD risk, usually alongside metabolic syndrome, obesity, and hypertension. Despite advancements in methods for achieving glycemic control, the CVD burden remains disproportionately high in diabetes. The mechanisms driving elevated risk are complex and variably multifactorial, involving hyperglycemia, insulin resistance, dyslipidemia, inflammation, and a hypercoagulable state. Unfortunately, critical gaps in understanding persist on how these factors interact to promote CVD in type 1 versus type 2 diabetes, particularly across disease stages and age. Addressing these knowledge gaps is essential to developing targeted therapies that can effectively mitigate CVD risk. To meet this need, the National Institute of Diabetes and Digestive and Kidney Diseases, in partnership with the National Heart, Lung, and Blood Institute, recently formed the Cardiovascular Repository for Type 1 Diabetes (CaRe-T1D) program. Its mission is to elucidate the molecular and cellular pathways linking diabetes with CVD through the provision of high-quality human tissues for investigator-led analyses using cutting-edge technologies and collaborative data sharing to advance precision medicine and reduce the global burden of diabetes-associated cardiovascular complications.

ARTICLE HIGHLIGHTS

- CaRe-T1D established a biorepository and scientific consortium to advance research on cardiovascular complications in diabetes.
- The goal is to determine how cardiovascular disease differs in type 1 versus type 2 diabetes.
- Heart, kidney, carotid and peripheral arteries, and blood from organ donors with type 1 diabetes, with type 2 diabetes, or without diabetes will be distributed to approved investigators to address the pathogenesis of diabetic cardiovascular disease.
- CaRe-T1D is a resource of human cardiovascular tissue and a database with the results from tissue analysis.

Cardiovascular disease (CVD) is a leading cause of morbidity and mortality in individuals with diabetes (1). Risk of CVD, including myocardial infarctions, heart failure, stroke,

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Received 7 January 2025 and accepted 5 March 2025

This article is part of a special article collection available at https://diabetesjournals.org/collection/2745/NIDDK-75th-Anniversary-Collection.

The views expressed in this article are those of the authors and do not necessarily represent the views of the National Institutes of Health or the U.S. Department of Health and Human Services.

and peripheral vascular disease, is two- to fourfold higher for individuals with either type 1 diabetes or type 2 diabetes than for individuals without diabetes (2). As such, the severity and frequency of CVD render it a key concern for people living with diabetes and a major focus with respect to their disease management (3). There, are, however, distinct patterns of prevalence of CVD based on diabetes type due to the earlier age of onset and a reduced association with obesity-driven risk factors in type 1 diabetes, although for both types of diabetes, chronic hyperglycemia, insulin resistance, and associated comorbidities, including hypertension and dyslipidemia, contribute to the overall development of CVD (3–5). The aim of this article is to review the similarities and differences in CVD between type 1 and type 2 diabetes, identify knowledge gaps in this field, and introduce a new National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) resource—the Cardiovascular Repository for Type 1 Diabetes (CaRe-T1D)—established as a biorepository of human cardiovascular tissue to help address these gaps.

The prevention and treatment of diabetes complications have been a central mission of NIDDK throughout its 75 years of supporting diabetes research. Diabetes Research Strategic Plans in 2000 and 2011 have guided NIDDK-supported research efforts in highlighting advances, key questions, and future directions in diabetes complications research. Indeed, the NIDDK, alone and in collaboration with the National Heart, Lung, and Blood Institute (NHLBI) and other National Institutes of Health (NIH) institutes, has supported numerous studies performed in seeking to improve understanding of diabetes-associated CVD, including the identification of risk factors, elucidating its pathophysiology, and testing of therapeutic interventions. A selection of such studies is shown in Table 1.

PATHOGENIC MECHANISMS OF DIABETIC MACROVASCULAR DISEASE

Clinical and preclinical studies of diabetic coronary artery disease, peripheral artery disease, and cerebrovascular disease suggest that the accelerated atherosclerotic CVD (myocardial infarction, stroke, peripheral vascular disease) involves a multifactorial interplay between metabolic and vascular dysregulation. More specifically, chronic hyperglycemia contributes to endothelial dysfunction through mechanisms involving oxidative stress, inflammation, and advanced glycation end products (6). These processes result in impaired nitric oxide production and promote vasoconstriction and vascular stiffness, as well as enhance atherogenesis (7). In type 2 diabetes and often in type 1 diabetes, insulin resistance is associated with increased adipose tissue lipolysis and hepatic lipid synthesis, leading to dyslipidemia characterized by high triglycerides, low HDL cholesterol, and small, dense, low-density lipoprotein particles, which are more prone to oxidation (8). Additionally, insulin resistance is associated with an inflammatory state that amplifies atherogenesis (9). Emerging studies have also highlighted the role of novel risk factors, including gut microbiota dysbiosis and endothelial progenitor cell dysfunction, further complicating the CVD landscape in diabetes (10).

Notably, most clinical studies on cardiovascular complications of diabetes have been focused on type 2 diabetes, given the significantly higher prevalence (10- to 20-fold) in comparison with type 1 diabetes (11,12,13). Consequently, this emphasis has limited our understanding of the distinct and overlapping pathogenic mechanisms underlying these complications in type 1 versus type 2 disease. Addressing this gap is a primary motivation for the CaRe-T1D program as it would appear essential for improving outcomes and guiding preventive strategies for CVD care.

UNDERSTANDING CVD IN TYPE 1 VERSUS TYPE 2 DIABETES

As far back as 2014, the American Heart Association and American Diabetes Association recognized that knowledge gaps exist for type 1 diabetes–related cardiovascular pathophysiology (2,14). Those reports highlighted the need for an improved understanding of disease-specific differences in atherosclerosis, as well as acute myocardial infarction outcomes, myocarditis prevalence, coronary microangiopathy, and heart failure patterns, among individuals with type 1 diabetes, those with type 2 diabetes, and those without diabetes. Multiple challenges stand in the way of appropriately addressing this knowledge gap, most notably the lack of access to relevant tissues, limitations of preclinical models, and the much higher prevalence of type 2 versus type 1 diabetes.

Mortality

Macrovascular disease, including atherosclerotic CVD and heart failure, clearly represents an important contributor to complications of type 2 diabetes and, in turn, accelerated mortality; yet, CVD complications are also increasingly recognized for their impact on people living with type 1 diabetes (15). For example, data for >27,000 patients with type 1 diabetes over many decades in a Swedish registry demonstrated that 10–15 life-years were lost due to CVD, representing the major contributor to mortality and early death (16). Again, highlighting the shortcomings of studies in this area, in the report of the only substantial investigation comparing people with type 1 diabetes versus type 2 diabetes at similar ages of diagnosis (i.e., before age 30 years and followed for 25 years [17]) the predominant primary causes of death were CVD in both cohorts. However, CVD risk was higher with a notable excess of CVD deaths seen in the type 2 diabetes cohort in comparison with those with type 1 diabetes (50.0% vs. 30.3%).

Risk Factors

The risk factors for CVD appear largely similar between type 1 and type 2 diabetes, the most important similarities

Table 1—NIDDK support of diabetic CVD

Studies	NIH collaboration	Years	Research type	Description	CV findings	Reference no.
Pathobiology ofMacrovascular Disease in Diabetes	NHLBI	1976–2021	Program project grant	Synergistic research projects and scientific cores for the study of the fundamental and clinical aspects of diabetic CVD.	Seminal findings on the role of dyslipidemia in the CVD of type 1 and type 2 diabetes.	
DCCT/EDIC		1983–present	Clinical trial	Comparison of the effects of intensive blood glucose control versus conventional therapy on the development of complications in individuals with type 1 diabetes.	Intensive therapy significantly reduced the incidence of major CV events (nonfatal myocardial infarction, stroke, or CV death).	20
Pittsburgh Epidemiology of Diabetes Complications (EDC) study		1986–present	Prospective cohort study	Follow-up of a cohort of individuals diagnosed with type 1 diabetes at Children's Hospital of Pittsburgh between 1950 and 1980 and study of the prevalence and risk factors of complications associated with childhood-onset type 1 diabetes.	Higher risk of developing certain diabetes complications, particularly autonomic neuropathy and coronary artery disease, among individuals with lower socioeconomic status.	56
Action to Control Cardiovascular Risk in Diabetes (ACCORD)	NHLBI*	1999–2009	Clinical trial	Investigation of whether aggressively managing blood glucose, cholesterol levels, and blood pressure in people with type 2 diabetes through intensive therapy could significantly reduce the risk of CV events in comparison with standard therapy.	Intensive glucose lowering aimed at achieving significantly lower blood glucose levels, in comparison with standard therapy, resulted in a significantly higher risk of death and did not provide a benefit in reducing CV events. Intensive blood pressure and cholesterol level control did not reduce CV events.	57–59
SEARCH for Diabetes in Youth (SEARCH) study	CDC	2000–2013	Multicenter cohort study	Study of the natural history of and risk factors for CVD in children and young adults with type 1 and type 2 diabetes.	Youth with both types of diabetes show signs of CVD risk early in the course of the disease (e.g., reduced heart rate variability and increased intima-media thickness) in comparison with youth without diabetes.	60–62
Bypass Angioplasty Revascularization Investigation in 2 Diabetes (BARI-2D)	NHLBI*	2001–2009	Clinical trial	Study of the best treatment approach for people with type 2 diabetes and coronary artery disease, with comparison of strategies: prompt revascularization (either surgery or angioplasty) vs. intensive medical therapy alone, and insulin sensitization therapy vs. insulin provision therapy.	No significant difference in overall survival or major CV events between revascularization and medical therapy alone, with potential benefit from revascularization in certain subgroups; similar outcomes between insulin sensitization and insulin provision strategies.	63

Continued on p. 1081

Table 1—Continued

Studies	NIH collaboration	Years	Research type	Description	CV findings	Reference no.
Look AHEAD (Action for Health in Diabetes)	NHLBI, NINR, and NCMHHD	2001–2012	Clinical trial	Study of the impact of an intensive lifestyle intervention on CV outcomes in individuals with overweight or obesity with type 2 diabetes.	The group receiving the intensive lifestyle intervention achieved significant weight loss and improvements in various health markers but without resultant reduction in CV events, in comparison with a diabetes support and education group.	64
RFA-HL-04-013, Progression of Cardiovascular Disease in Type 1 Diabetes	NHLBI*	2004–2009	Individual R01 grants	Supported basic and clinical studies to enhance the understanding of the onset and progression of CVD in people with type 1 diabetes.		
Trial to Assess Chelation Therapy 2 (TACT2)	NCCIH,* NHLBI, and NIEHS	2016–2024	Clinical trial	Investigation of whether EDTA-based chelation therapy, combined with high-dose oral multivitamins, could reduce the risk of CV events in people with diabetes and a history of a myocardial infarction.	Neither chelation therapy nor high-dose vitamins alone or together significantly reduced the risk of major CV events like myocardial infarction, stroke, or all-cause mortality in comparison with placebo.	65–66
RFA-HL-21-014, Understanding and Reducing Cardiovascular Disease in Type 1 Diabetes Mellitus	NHLBI*	2021–present	Individual R01 grants	Supports research that enhances the understanding of the pathophysiology and epidemiology of CVD among individuals with type 1 diabetes and advances the development of interventions to reduce CVD risk among these individuals.		
RFA-DK-21-010, CARE-T1D, biorepository	NHLBI	2021–present	Consortium	Supports a data coordinating center that first establishes a biorepository of human CV tissue and then serves as a coordinating center resource for discovery and mechanistic research to increase our knowledge of the CV complications of type 1 diabetes.		
RFA-DK-23-021, CARE-T1D, consortium	NHLBI	2024–present	Consortium	Consortium of investigative teams for individual and collaborative studies using CaRe-T1D resources to advance our knowledge of the pathogenesis of CVD in type 1 diabetes.		

CDC, Centers for Disease Control and Prevention; CV, cardiovascular; NCMHHD, National Institute on Minority Health and Health Disparities; NIEHS, National Institute of Environmental Health Sciences; NINR, National Institute of Nursing Research. *Lead institute.

being age, duration of diabetes, macroalbuminuria > microalbuminuria, chronic renal disease, and smoking (2). A major problem exists, however, in terms of evaluating CVD risk in people with type 1 versus type 2 diabetes, specifically regarding the need to correct for age and duration of disease. The hyperglycemia of type 1 diabetes commonly presents acutely, whereas the typical person with type 2 diabetes, at the time of diagnosis, has already experienced years of cardiovascular damage from obesity, insulin resistance, hypertension, and dyslipidemia (8). Based, in part, on knowledge gains afforded by outcomes of randomized controlled trials (RCTs), lipid and lipoprotein disorders and hypertension are also thought to play a more important role in type 1 than type 2 diabetes (5,13,18). Although most people with type 2 diabetes have obesity and are insulin resistant, body weight in individuals with type 1 diabetes is increasingly more like that of the general population with overweight and sometimes with obesity (15), with estimates of insulin resistance in type 1 disease associated with increased CVD events (19). Most importantly, the findings of the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study, the only RCT focused on type 1 diabetes (20) and one where meta-analysis in type 2 diabetes was compared with substantial observational data (21), indicated that hyperglycemia is a much greater predictor of CVD in type 1 than in type 2 disease (22).

Coronary Atherosclerosis

These observations form the basis for an obvious question: is the atherosclerotic process identical in type 1 versus type 2 diabetes? In terms of what is known, results from studies of inflammation in coronary arteries obtained postmortem in people with type 1 and type 2 diabetes with similar age (mean 50.4, SD 12.3 years) and glycohemoglobin (mean 11.4%, SD 2.5%) were somewhat overlapping; however, only limited consideration was given with respect to interpretation in regard to disease duration (23). In addition, there were two times fewer acute coronary thrombi in type 1 diabetes than in type 2 diabetes and a healed infarct was present in 33% and 73% of cases, respectively (24). Coronary calcification, assessed with either computed tomography (CT) or electron beam tomography, informs the management of coronary artery disease (25,26). Among asymptomatic patients with type 1 diabetes or type 2 diabetes of similar age, coronary artery disease is more extensive in type 2 diabetes, with increases in total and obstructive lesions and more noncalcified plaques in comparison with type 1 diabetes (27). The Coronary Artery Calcification in Type 1 Diabetes (CACTI) study showed a significant increase in coronary artery calcium volume for women with type 1 diabetes in comparison with women without diabetes over the menopause transition (28) and may contribute to the high risk of CVD among women with type 1 diabetes. a greater relative risk than for women with type 2 diabetes, in comparison with women without diabetes (5). Finally, in a recent report, most of the differentially expressed genes for coronary heart disease progression in patients with type 1 diabetes with acute myocardial infarction were related to immune and inflammatory responses (29). Overall, based on these data, a key hypothesis remaining and subject to testing is that the atherosclerotic process in type 1 diabetes differs from that of type 2 diabetes, with more extensive early inflammation followed by progressive stabilization, fibrosis, and calcification. A key challenge is how to best address this process in humans.

Other Cardiovascular Differences Between Type 1 and Type 2 Diabetes

Roles of autoimmunity (30,31) and autonomic neuropathy (32) represent facets that may negatively influence cardiovascular outcomes in type 1 diabetes, even with less severe myocardial hypertrophy and coronary atherosclerosis. Indeed, a balanced autonomic function is essential for cardiovascular stability and arrhythmia prevention (33). One meta-analysis reported a relative risk for cardiovascular events of 5.54 in type 1 diabetes vs. 2.45 in type 2 diabetes for those with and without autonomic neuropathy (34). Investigation of autoimmunity and autonomic neuropathy using human myocardial tissue could elucidate their roles in type 1 and type 2 diabetes CVD.

Very few studies have included examination of heart size in these two forms of diabetes despite its role as a predictor of heart failure and sudden death. The results of one such effort in comparing heart weights in individuals with type 1 diabetes (mean 425, SD 119 g) and type 2 diabetes (524, SD 140 g) and individuals without diabetes (434 ± 121 g) suggest type 2 diabetes–associated elevations in heart weight, whereas type 1 diabetes weights align with those of the control group (24). Other areas for study on vascular and myocardial pathology include epicardial adipose tissue (EAT), perivascular adipose tissue, and arterial adventitia that are metabolically active (35). Increased EAT has been linked to higher incidence of interstitial fibrosis in individuals without diabetes (36). While EAT has been studied in type 1 diabetes (37) and type 2 diabetes (38), direct comparisons between these populations are lacking, highlighting an unmet research need.

CVD Treatment in Type 1 Versus Type 2 Diabetes

Aside from DCCT/EDIC results, RCTs on modifying CVD risk in people living with type 1 diabetes are lacking. Moreover, guidelines and recommendations from the American Diabetes Association (39), American College of Cardiology/American Heart Association (40), European Society of Cardiology/European Association for the Study of Diabetes (41), and Endocrine Society (42) are variable and largely based on expert opinion rather than results from RCTs (e.g., for use of statins, blood pressure goals, and aspirin for primary prevention). Important questions in need of address are whether RCTs for basic prevention measures are ethical and whether there are sufficient observational data for consolidation of recommendations on when to

start statin therapy in type 1 diabetes based on LDL cholesterol levels, other CVD risk factors, and disease duration (14).

There has been a major advance in the prevention of CVD complications in type 2 diabetes with the results of multiple RCTs showing significant cardioprotective effects of two new drug classes, glucagon-like peptide 1 receptor agonists and sodium–glucose cotransporter 2 (SGLT2) inhibitors (43–45), the development of which was based on basic research discoveries supported by the NIDDK (https://www.niddk.nih.gov/news/archive/2016/story-discovery-sglt2-inhibitors-harnessing-kidneys-help-treat-diabetes and https://www.niddk.nih.gov/news/archive/2021/story-discovery-medications-diabetes-obesity-emerged-research-pancreatic-hormone). These drugs were developed to lower glucose levels but were subsequently found to decrease risk of myocardial infarction, stroke, and hospitalization for heart failure for people with type 2 diabetes and even for those without diabetes. These drugs have not been tested in large trials for CVD protection in type 1 diabetes and are not approved for use in this population. Because SGLT2 inhibitors increase the risk of diabetic ketoacidosis in people with type 1 diabetes (46), the NIDDK is currently supporting studies to test whether continuous ketone monitoring, as part of a risk mitigation strategy, can improve the safety of SGLT2 inhibitors in type 1 diabetes.

THE EVOLVING ROLE AND LIMITATIONS OF PRECLINICAL MODELS FOR UNDERSTANDING DIABETES-RELATED CVD

As early as the 1950s, at the time of the creation of NIDDK, coronary atherosclerosis was a known complication of diabetes (47), with investigators studying rabbits rendered diabetic by the pancreatic β-cell toxin alloxan. They faced the first of many conundrums in using animal models to decipher the role of glucose and lipids in the development of diabetic macrovascular disease. Diabetic rabbits fed a high-cholesterol diet developed hypercholesterolemia to the same degree as the nondiabetic rabbits on the same diet, but, paradoxically, the diabetic rabbits showed much less or no atherosclerosis of the aorta (48). We now understand that these diabetic rabbits develop severe hypertriglyceridemia and "are protected against atherogenesis because the major part of plasma cholesterol is carried in large lipoproteins to which the artery is not very permeable" (49). Severe hypertriglyceridemia and hypercholesterolemia also occur in mice after induction of diabetes and, therefore, present a challenge to their use as a model of diabetes-accelerated atherosclerosis because of the difficulty of separating the effects of diabetes, per se, from the strong effect of hyperlipidemia on promoting atherosclerosis (50). In the 1990s, the first murine model susceptible to both atherosclerosis and diabetes (i.e., BALB/c mice administered multiple-low-dose streptozotocin and fed a high-fat diet) showed that diabetes promotes atherosclerosis even in the absence of significant changes in plasma lipid levels and without hyperinsulinemia (51).

In 2001, NIDDK established the Animal Models of Diabetic Complications Consortium (AMDCC), which became the Diabetes Complications Consortium (DiaComp), to generate and phenotype new models of diabetes complications. Complementary to this effort and in the same year, NIDDK started the Mouse Metabolic Phenotyping Centers (MMPC) and, now, the MMPC-*Live* program, as a resource for state-of-the-art metabolic and physiologic phenotyping for mouse models of diabetes and its complications (52). Animal models developed and tested in these programs and at other laboratories have provided valuable information regarding disease mechanisms and therapeutic testing despite their limitations of not fully replicating human pathology. Differences in anatomy, physiology, genetics, and disease progression between species contribute to these limitations. For instance, rodents have higher heart rates, distinct lipid metabolism, and natural resistance to atherosclerosis compared with humans (53). Moreover, the macrovascular complications of diabetes are influenced by complex factors such as aging, extended disease duration, and nephropathy, which are challenging to model precisely in animal models.

The limitations of animal models have led to a change over time in their use to study diabetic cardiovascular complications. Today, studies on disease pathogenesis often involve a human-first approach, taking advantage of the availability of resources from clinical studies and advances in molecular and cellular tools. For example, when predictors of CVD risk, such as genetic markers, circulating proteins, or histologic features, are discovered in cohorts with diabetes in clinical studies, the identified target is then tested in murine models for a possible role in a causal pathway of diabetes-accelerated atherosclerosis (54). Preclinical models then do not need to meet the unattainable goal of fully reproducing human disease but can be deployed successfully to dissect specific questions raised by the study of human tissue (50).

THE ROLE FOR CARE-T1D TO ADDRESS RESEARCH GAPS IN CVD IN TYPE 1 DIABETES

NIDDK, in collaboration with NHLBI, established CaRe-T1D in 2022 with the goal of better understanding the pathogenesis of cardiovascular complications in type 1 diabetes and type 2 diabetes, especially the differences between these diabetes types. The long-term goal is to translate the discoveries using CaRe-T1D resources into development of new therapies to prevent and treat the cardiovascular complications of type 1 diabetes and type 2 diabetes. CaRe-T1D is the newest addition to a series of successful NIDDK consortia involving the provision of a unique biologic resource, a coordinating center with cutting-edge bioinformatics capabilities, and outstanding investigators working together using innovative approaches. The CaRe-T1D initiative has been implemented in a stepwise fashion, with the first

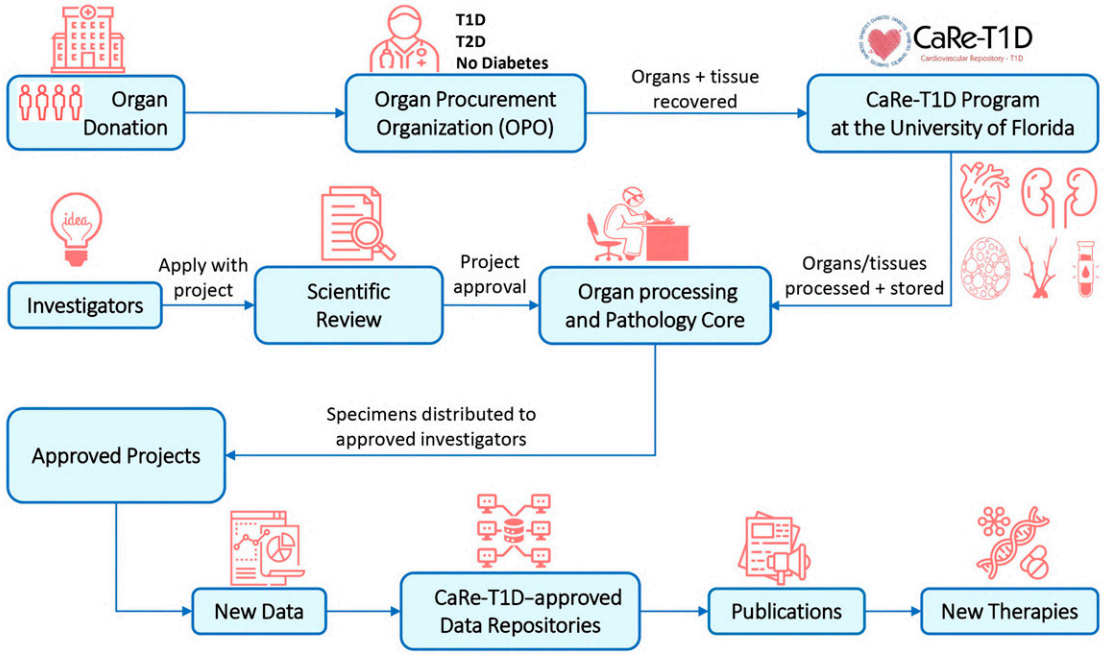

Figure 1—Workflow diagram of the CaRe-T1D consortium operations. The diagram highlights the existing approach for recruiting organ donors and facilitating approved research projects, which are externally funded by the NIDDK and NHLBI.

phase involving the creation of a biorepository of human cardiovascular tissue, followed by peer-reviewed selection of a network of investigators proposing hypothesis-driven research. Each investigative team will use the biorepository samples for multimodal data acquisition as part of mechanistic studies to advance our understanding of CVD in settings of type 1 versus type 2 diabetes (Fig. 1). Since its inception, CaRe-T1D has benefited from the guidance of a dedicated scientific advisory board whose expertise spans the consortium's diverse activities. The scientific advisory board provides strategic input on key factors, including adherence to FAIR principles (Findability, Accessibility, Interoperability, and Reuse), defining innovation in the field, aligning research with clinical needs, tissue appropriation, case selection criteria, and identifying knowledge gaps. Their critical recommendations have been—and will remain—instrumental in ensuring that CaRe-T1D leverages the latest scientific advancements.

CaRe-T1D: Biorepository

The purpose of CaRe-T1D is to collect, assess, and store high-quality organ donor tissues, for which there is careful annotation of clinical data, that are readily accessible to investigators. Specifically, CaRe-T1D will include: *1*) the collection and storage of human cadaveric tissues from organ donors with type 1 diabetes, with type 2 diabetes, and without diabetes; *2*) the performance of quality control (QC) and basic histopathologic examination; *3*) the development of a data portal with easily accessible sample annotation information; and *4*) the creation of a process for distribution of the biosamples and data to qualified investigators. The rapid initiation of the CaRe-T1D program was achieved due to the productive relationships between the University of Florida Diabetes Institute and all 56 U.S. organ procurement organizations (OPOs) along with a centralized 24/7/365 call center and the Organ Processing and Pathology Core (OPPC), developed to procure, swiftly process, and bank a complete CVD-related tissue panel. CaRe-T1D has and will continue to include collection of hearts, kidneys, carotid arteries, EAT, and blood from organ donors whose legal representatives provide consent for tissue research. These tissues were selected based on their relevance to the study of CVD in diabetes and their availability due to routine inclusion in the workflow of a given OPO. Specifically, tissues in this program are collected by organ transplant surgeons and affiliated teams, whereas other tissues are typically recovered through tissue recovery programs or eye banks, which follow different recovery protocols and timelines. Over time, an aim of CaRe-T1D is expansion of collection efforts to include additional tissues susceptible to diabetes-related complications (e.g., brain, nerve, eye) through collaborations with other agencies, when feasible.

The OPOs evaluate the entire U.S. organ donor pool for inclusion in CaRe-T1D based on established program inclusion and exclusion criteria and the goal of an even distribution of age- and sex-matched tissues across the three groups. In the case of acceptance, the organ recovery is then performed according to protocols established for organ transplantation (https://www.asts.org/docs/default-source/public-comments/procedural-standards-for-deceased-donor-organ-recovery—approved-jan.-2022.pdf?sfvrsn=11804cd3_5). Whenever possible, a complete tissue panel

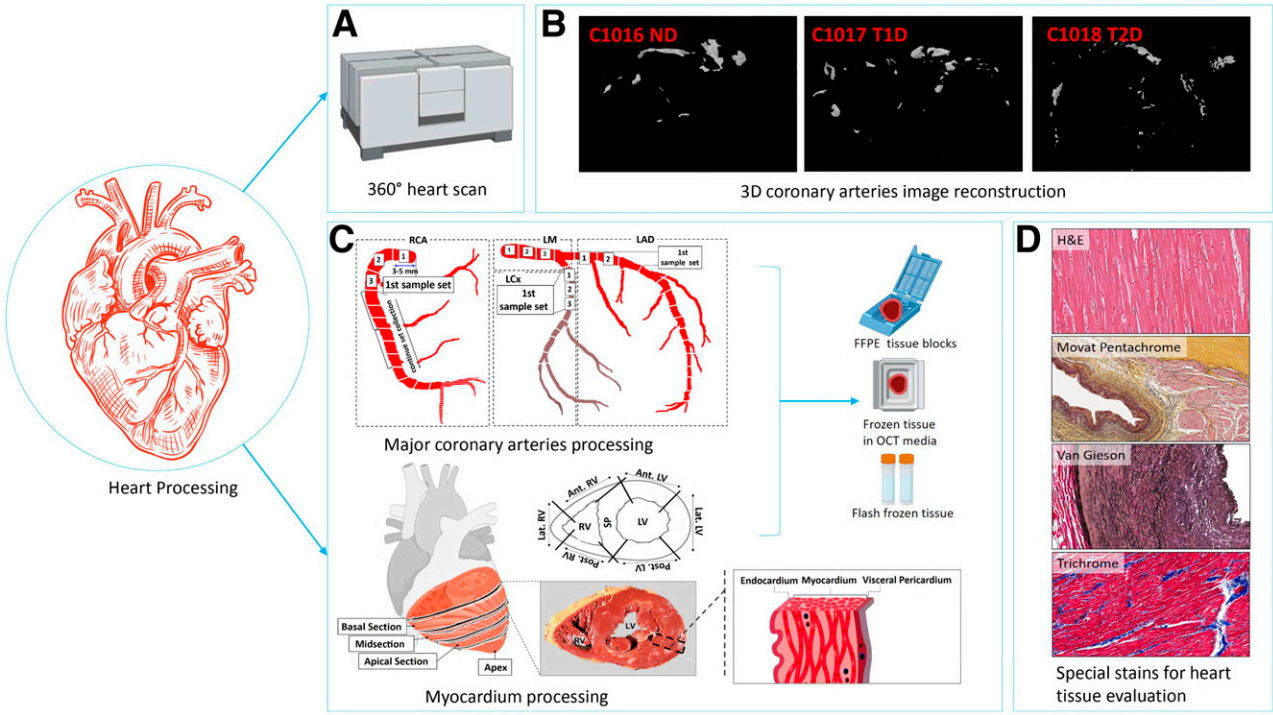

Figure 2—Scheme of the heart processing. *A*: A whole heart scan is performed using a microCT before organ dissection. *B*: Three-dimensional (3D) visualization of coronary arteries calcification. *C*: A schematic representation of coronary arteries and myocardium tissue collection and sample preparation. Major coronary arteries are serially sectioned transversely at 3- to 5-mm intervals through the entire length of the artery and divided to be fixed in formalin and processed in FFPE tissue blocks, flash frozen tissue vials, or fresh tissue blocks frozen in OCT media. The heart is transversely sectioned from the apex to the atria level into three equal segments representing basal, middle, and apical portions of the heart ventricles. Myocardium transmural tissue blocks are taken from the anterior (Ant.), lateral (Lat.), and posterior (Post.) surfaces of the left ventricles (LV) and anterior and posterior surfaces of the right ventricle (RV), ventricular septum (SP), and apex, which are processed in FFPE tissue blocks, flash frozen tissue vials, or fresh tissue blocks frozen in OCT media. H&E, hematoxylin-eosin; LAD, left anterior descending coronary artery; LCx, left circumflex coronary artery; LM, left main coronary artery; ND, no diabetes; RCA, right coronary artery; T1D, type 1 diabetes; T2D, type 2 diabetes. *D*: Panel of special stains for histopathological evaluation of the heart.

that includes heart (myocardium, coronary arteries, and epicardial fat), kidney, aorta, common carotid arteries, and blood (serum, plasma, and cellular components) is obtained from each donor for the biorepository, and a small amount of pancreatic tissue is obtained as part of the CaRe-T1D assessment of diabetes type. Comprehensive clinical data are obtained from the last, terminal hospital admission records and the United Network for Organ Sharing (UNOS) questionnaire for donation.

The recovered organs/tissue are shipped and processed at the centralized facility at the University of Florida. The whole heart undergoes microCT imaging that detects vessel calcification (Fig. 2). Then, anatomical dissection is systematically performed by highly experienced staff to prepare biospecimens in a variety of formats (e.g., formalin-fixed paraffin-embedded [FFPE] blocks, optimal cutting temperature [OCT] compound blocks, and flash frozen) for each tissue type with protocols evolving as needed to support emerging requirements for research applications. Processed samples are stored in appropriate conditions for long-term preservation. Each donor can generate up to 220 aliquots of tissue from the heart including coronary arteries and epicardial fat, 80 aliquots from the kidney, and 200 histology slides with tissue-specific staining (Fig. 2).

Integral to the tissue processing and, ultimately, the quality of the biorepository are extensive QC procedures. CaRe-T1D only accepts donors with brief hospital stays and when there has been a short time from cessation of perfusion. Ongoing evaluation is performed for these criteria based on the results of the QC procedures performed at CaRe-T1D. The tissue undergoes histopathologic examination by board-certified pathologists and QC analysis that includes a panel of four stains for heart tissue and three stains for kidney tissue. Kidney samples are also collected for electron microscopy assessment. The results of the histopathologic examinations are available to investigators. As an additional assessment of tissue quality, bulk RNA is assessed, yielding an average RNA integrity number (RIN) score of 7.8 for myocardium and aorta tissue. The clinical data also undergo careful assessment for confirmation of CVD and diabetes type. The latter is evaluated according to the clinical history, including medications; high-resolution HLA typing; measurement of type 1 diabetes–associated islet autoantibodies (55); and pancreatic histology (Fig. 3). For the first 60 donors, two cases

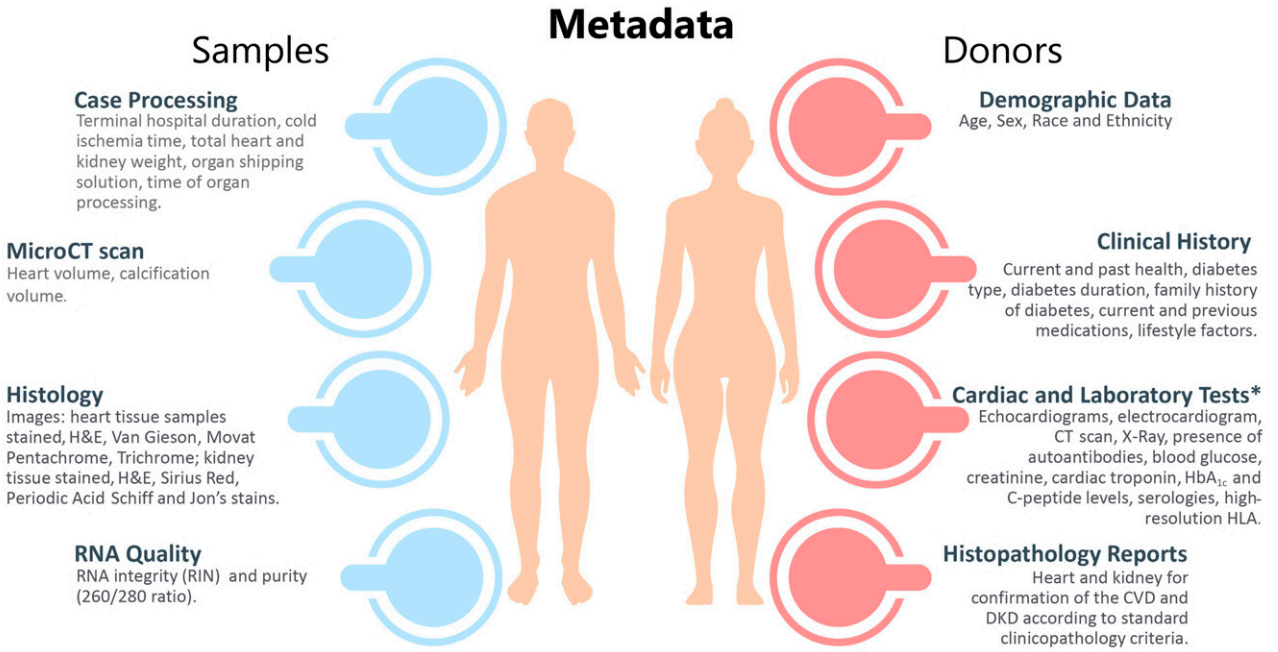

Figure 3—Types of metadata collected in CaRe-T1D. DKD, diabetic ketoacidosis; H&E, hematoxylin-eosin. *If available.

could not be classified as type 1 diabetes or type 2 diabetes and are listed separately as Other-Diabetes.

The goal of CaRe-T1D is for all of its resources to be readily accessible to investigators. The public CaRe-T1D website (www.care-T1D.org) includes summary data on the donors, tissue processing procedures, and an application for investigators to access the full searchable data portal for CaRe-T1D that includes de-identified donor information and data from the consortium. This resource is designed to assist investigators in selecting and ordering sample sets for their research and to support the visualization and sharing of all externally generated data types. Investigators can request tissue samples through an application process outlined on the CaRe-T1D website. In addition, CaRe-T1D will issue letters of support for grant applications, confirming the availability of tissue and data for proposed projects. Beyond letters of support, tissue samples will be provided to researchers pending approval by an expert ad hoc committee that evaluates proposals based on scientific merit and feasibility. CaRe-T1D is compliant with the NIH data sharing policies and is working with the NHLBI Biologic Specimen and Data Repository Information Coordinating Center (BioLINCC) repository (www.biolincc.nhlbi.nih.gov/home) for long-term data storage.

CaRe-T1D Consortium

In addition to the biorepository, CaRe-T1D is building a consortium of investigative teams to advance our understanding of the mechanisms of CVD in type 1 diabetes and how they are similar or different from mechanisms of CVD in type 2 diabetes and without diabetes. Recently, through a funding opportunity from NIDDK and NHLBI (RFA-DK-23-021), six research teams were selected and started the CaRe-T1D consortium. These investigations will include application of multimodal approaches for deep phenotyping of CaRe-T1D specimens on the anatomical, cellular, and molecular levels to study CVD progression in type 1 versus type 2 diabetes. Generated data will be shared among consortium members and the broader research community. Quarterly and annual meetings will bring together the investigative community to share results and foster collaborations. In recognition that these six studies will not address all critical scientific questions, an aim of the CaRe-T1D program is to expand the research effort by attracting new investigators with innovative ideas to the consortium.

VISION FOR FUTURE DIAGNOSIS AND TREATMENT OF CVD IN DIABETES

The CaRe-T1D consortium represents a pioneering initiative in NIDDK's 75-year history of advancing research and translational science to improve outcomes for individuals with type 1 and type 2 diabetes. In integrating a biorepository of well-characterized human cardiovascular tissue, leading experts in diabetes and CVD research, and innovative methodologies that were inconceivable when NIDDK was founded in 1950, CaRe-T1D has the potential to drive paradigm-shifting advancements in disease management. This consortium marks the beginning of a new era in diabetes complications research. We encourage the diabetes research community to engage in this initiative to maximize CaRe-T1D's potential in driving groundbreaking discoveries and fostering the development of novel,

targeted therapies for cardiovascular and renal diseases in type 1 and type 2 diabetes.

Acknowledgments. The graphical abstract was made with icons from Freepik (www.freepik.com), with multiple uses of Freepik images from Rakib Hassan Rahlm.

Funding. The CaRe-T1D program is supported by grant funding from the NIH (grant U24 DK133700) through the Special Diabetes Program for Type 1 Diabetes. Organ collection and processing were performed with additional support from the Network for Pancreatic Organ donors with Diabetes (nPOD) (Research Resource Identifier RRID:SCR_014641), a collaborative type 1 diabetes research project supported by Breakthrough T1D and The Leona M. and Harry B. Helmsley Charitable Trust (grant 3-SRA-2023-1417-S-B). OPOs partnering with nPOD to provide research resources are listed at https://npod.org/for-partners/npod-partners/. Approved research projects using tissues from CaRe-T1D are supported by funding from the NIDDK and NHLBI (RFA-DK-23-021).

The content and views expressed are the responsibility of the authors and do not necessarily reflect the official view of nPOD.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

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