Trial Innovation Network Expression of Interest:
CONCORD

Study Title	Control Coronary Disease (CONCORD) Trial
Funding I/C	Application in progress, NHLBI
Study Description	Randomized controlled trial (RCT) designed to determine whether intensive serum LDL-C lowering to <50 mg/dL or, separately, whether cardiometabolic optimization – attaining and maintaining ideal weight and optimal glycemic control (HgbA1C <5.5%), in addition to intensive LDL-C lowering to <50 mg/dL, is more effective than guideline-based usual care in preventing progression of coronary atherosclerosis when therapy is started in young adulthood (aged 30 to 40 years in men and 35 to 50 years in women). Study Medication costs not reimbursed by an Insurance Carrier will be paid for, or suppled, by the study.
Study Design (*Figure 1, Table 1)	Three arm RCT (see Figure 1 attached): Arm 1: Intensive lowering of LDL-C to <50 mg/dL Arm 2: Usual guideline-based LDL-C management Arm 3: :Intensive lowering of LDL to <50 mg/dL plus cardiometabolic intervention to achieve ideal body weight and optimal glycemic control (HgbA1C < 5.5%) Comparisons: Arm 1 versus Arm 2 (Primary Comparison); Arm 3 versus Arm 2 (Secondary Comparison); Comparison of Arm 1 to Arm 3 only as an exploratory analysis. Primary Endpoint: Desirability of Outcome Ranking (DOOR) that has high power to resolve small differences between treatment arms. **Site Activity:** (See Figure and Table) Sites identify potential subjects, likely mostly from patient chart review and invite (telephone) potential subjects to a Screening Visit at which time the trial is explained, consent is obtained, any necessary blood work is obtained and a Randomization Visit is scheduled. Prior to that visit, laboratory data are reviewed to assure eligibility for randomization. Qualified subjects present for a Randomization Visit that includes a CT coronary angiogram followed by randomization and presentation to the subject of their trial schedule, the details of which depend on the arm to which the subject is randomized. Usual care subjects have a yearly visit with a lipid panel and interview to assess for the presence of events. Individuals randomized to the other arms have visits as shown below. Additional visits are scheduled, as necessary, to re-titrate LDL-C and HgbA1C if they are found at a visit to be above 50 mg/dL or 5.5%, respectively , or if weight has increased above ideal. Note that serum LDL-C titration is by the Site PI and is expected to begin with atorvastatin and add ezetimibe if LDL-C goal is not reached with atorvastatin. If LDL-C <50 mg/dL is still not reached, then Inclisiran will be added to the regimen.
IRB	Single IRB at Johns Hopkins
Coordinating Center	DCC: George Washington; CCC University of Maryland/Johns Hopkins
Study Length	5 years
Study Enrollment #	N = 1830 (610 per arm)
Eligibility Criteria	**Inclusion Criteria** • Aged 30 - 40 years in men and 35 to 50 years in women • LDL-C >100 mg/dL • PREVENT calculator 10 year risk of incident CHD <7.5%; 30 year risk of incident CHD > 30% **Exclusion Criteria** • Prior coronary heart disease diagnosis • Prior treatment with lipid lowering agents • Pregnant at time of randomization • Coronary revascularization indicated • Drug allergy to statins or Inclisiran • Significant comorbidities limiting 5-year survival
Total # of Sites	Up to 40 sites
Site Requirements	Study sites will need to have the following at their site to be considered: • Access to CT coronary angiography • Ideal site has ready access to desired patient population via in/out of network, or rural primary care network
Site Investigator Qualifications	Site Investigators should • Be Internal Medicine or Family Practice physicians or Cardiologists • Have experience in recruiting patients for clinical trail
Key Timeline Dates:	The following dates are projections and subject to change: Site Selection Decisions: 9/30/2024 Site Selection Notifications: 9/30/2024 Enrollment begins: 3 months after site start-up: anticipate July 2025 Last Patient/Last Visit: January 2029 **Study Closure: July 2030**

Figure 1: CONCORD Trial Randomization Schema

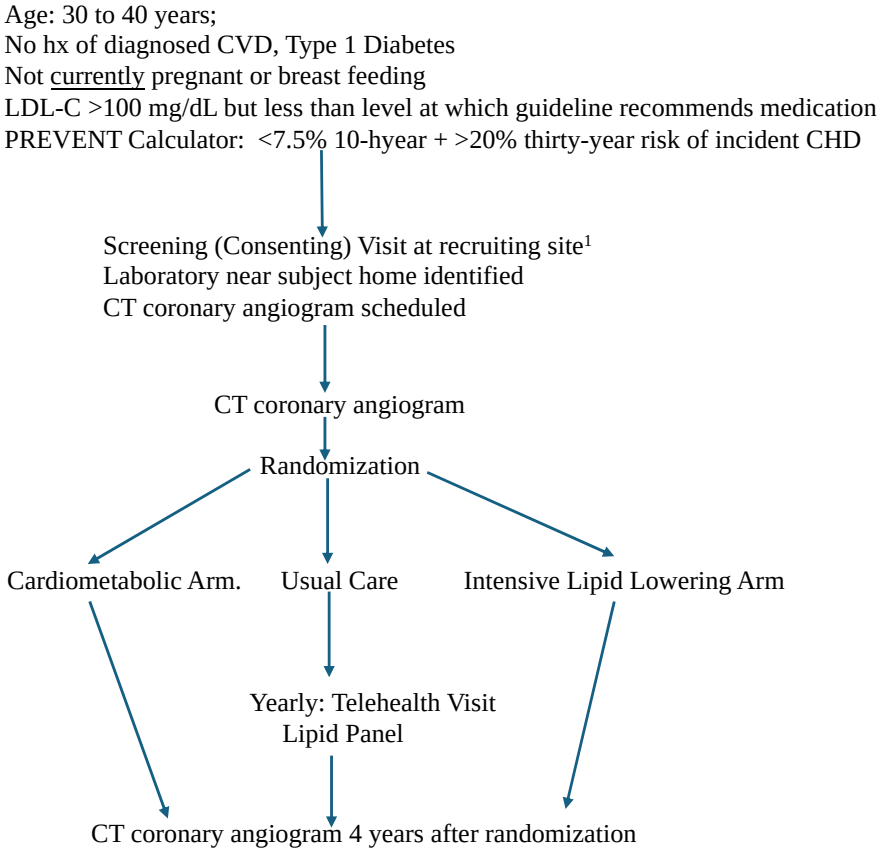

Table 1. Schedule of Events

Visits	Weeks				Months							
	0	2	4	8	7	13	19	25	31	37	43	49
Call Subject	X											
Screen Visit		X										
Randomize Visit			X									
CT Coronary Arteriogram			X									X
Usual Care Arm: Lipid Panel Telehealth/Office			X			X		X		X		X
Intensive and Cardiometabolic Arm: Lipid Panel Liver Panel Hgb A1C Telehealth/Office				X	X	X	X	X	X	X	X	X
Intensive Arm: Titrate LDL-C to <50 mg/dL.	X	X	X	X								
Intensive Arm: Retitrate as necessary if LDL-C rises above <50 mg/dL.					X	X	X	X	X	X	X	X
Cardiometabolic Arm: Titrate LDL-C to <50 mg/dL & HgA1C to <5.5%	X	X	X	X								
Cardiometabolic Arm: Retitrate as necessary if LDL-C rises above <50 mg/dL, HgA1C rises above <5.5%, or weight rises above ideal					X	X	X	X	X	X	X	X