



# Dual versus monotherapy with SGLT2 inhibitor and GLP-1 receptor agonist: PRECIDENTD pragmatic randomized trial

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## ABSTRACT

**Background** Dual therapy with sodium-glucose co-transporter 2 inhibitors (SGLT2i) and glucagon-like peptide-1 receptor agonists (GLP-1RA) is frequently recommended. We compared rates of medication initiation and discontinuation between participants assigned to treatment with a single medication class or dual therapy in the feasibility phase of the PREvention of Cardiovascular and DiabEtic kidney disease in Type 2 Diabetes (PRECIDENTD) pragmatic trial.

**Methods** PRECIDENTD randomly assigned participants with type 2 diabetes (T2D) and ASCVD or high ASCVD risk to fill prescriptions for SGLT2i, GLP-1RA, or dual therapy (1:1:1) using their own insurance. Analyses compared medication fill and discontinuation rates of assigned medication(s), Patient-Reported Outcomes Measurement Information System (PROMIS) Physical and Mental Health Scores, and Modified Kansas City Cardiomyopathy Questionnaire (mKCCQ)-12 between the combined monotherapy (SGLT2i or GLP-1RA) and dual therapy (SGLT2i and GLP-1RA) groups.

**Results** This report includes 173 insured participants [median age 67 years (IQR 62, 72), 46% female, 35% non-White, 67% with ASCVD]; 113 assigned to monotherapy and 60 to dual therapy. Monotherapy vs dual therapy fill rates were 84% vs 53% ( $P < .001$ ) 4 months after randomization and 87% vs 68% overall ( $P = .004$ ) during 10-month median follow-up. Of those who filled medication, 22% in monotherapy and 49% in dual therapy discontinued a study medication ( $P = .002$ ), mostly due to side effects. PROMIS and mKCCQ-12 scores showed no change.

**Conclusions** Despite efforts to facilitate medication uptake in the feasibility phase of the PRECIDENTD pragmatic trial, barriers to initiation and ongoing use challenge the use of combination SGLT2i and GLP-1RA in T2D.

**Trial registration** [ClinicalTrials.gov](https://clinicaltrials.gov), NCT05390892, <https://clinicaltrials.gov/study/NCT05390892>. (Am Heart J 2026;294:107332.)

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## Background

Professional guidelines recommend the use of sodium-glucose cotransporter-2 inhibitors (SGLT2i) or glucagon-like peptide-1 receptor agonists (GLP-1RA) to reduce adverse cardiovascular, kidney, and mortality outcomes in patients with type 2 diabetes (T2D) and increased cardiovascular or renal risk.<sup>1,2</sup> In placebo-controlled trials, SGLT2i reduce atherosclerotic cardiovascular disease (ASCVD), heart failure, and chronic kidney disease (CKD) outcomes,<sup>3</sup> while higher potency GLP-1RA have shown benefit in ASCVD, heart failure with preserved

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ejection fraction (HFpEF), and CKD.<sup>4,6</sup> However, no direct randomized comparison of SGLT2i and GLP-1RA for cardiovascular and kidney outcomes has been performed. Additionally, given the putative complementary benefits of these medication classes, guidelines have increasingly recommended dual therapy with both classes for those not meeting glycemic targets despite a dearth of evidence weighing the benefits, risks, and feasibility of combination therapy.<sup>1,7,8</sup>

We designed the PREvention of Cardiovascular and Diabetic kidney disease in Type 2 Diabetes (PRECIDENTD) trial to evaluate the comparative effectiveness of SGLT2i, GLP-1RA, or both classes (dual therapy) on cardiac, kidney, mortality, and patient-reported outcomes. Funded by the Patient-Centered Outcomes Research Institute (PCORI) in 2021, the funding mechanism required completion of a feasibility phase before a decision to proceed with the trial, with the potential for the final trial design to be modified by feasibility findings. In collaboration with professional and patient partners and participants, PRECIDENTD implemented an innovative pragmatic trial design in which eligible participants with T2D and ASCVD or high ASCVD risk consented to random assignment to 1 of 3 treatment groups: prescription of SGLT2i, GLP-1RA, or dual therapy. To be generalizable to real-world patient experience where free medications are not provided, participants used their own health insurance coverage to obtain their assigned medication(s).

Herein, we describe the results of the feasibility phase which evaluated whether sites could execute the protocol and whether participants would enroll and could initiate and continue study medications at sufficiently high rates for valid evaluation of the study hypotheses in the full study phase. The trial's data and safety monitoring board (DSMB) reviewed unblinded data on rates of medication initiation and continuation. The feasibility phase demonstrated that monotherapy initiation was feasible and the trial components comparing SGLT2 to GLP-1RA monotherapy were approved to continue with certain modifications. However, despite support from central and local site staff, uptake of and adherence to dual therapy was judged to be insufficient to continue this group in the trial. Here, we report the findings from the feasibility phase that supported these decisions, comparing rates of medication initiation and continuation in the pooled monotherapy to the dual therapy group over a median 10-month treatment period. Data from both monotherapy groups are pooled because a masked, randomized comparison between those groups is ongoing.

## Methods

**Trial design.** PRECIDENTD was designed as a pragmatic, parallel, 3-arm randomized controlled trial with 1:1:1 allocation of eligible participants to an SGLT2i, GLP-1RA, or dual therapy with combined SGLT2i and GLP-

1RA. The specific medication within each class was selected by the site investigator from a preferred list based on evidence of cardiovascular benefit and the participant's pharmacy benefit plan coverage. To enroll a sufficiently high-risk population, the protocol aimed to enroll 70% of participants with established ASCVD (secondary prevention cohort) and 30% with indicators of high ASCVD risk (primary prevention cohort), determined by clinical criteria. Patient and professional research partners have participated in trial design since its inception and continue to advise on trial conduct. The initial protocol was approved by the Mass General Brigham (MGB) Institutional Review Board (IRB) and conducted at 8 sites across the U.S. (seven sites affiliated with the National Patient-Centered Clinical Research Network [PCORnet]) during the feasibility phase. This report on the feasibility phase of the trial includes all randomized participants from the first on September 26, 2022, through the last randomization into the 3-arm trial on January 25, 2024, with randomized patients followed until July 1, 2024.

**Participants.** All participants had T2D based on clinical diagnosis, with hemoglobin A1c (HbA1c)  $\geq 6\%$  (42 mmol/mol). Inclusion criteria for the secondary prevention cohort were age 40-80 years and established ASCVD in any vascular bed based on clinical diagnosis or credible participant self-report. Inclusion criteria for the primary prevention cohort were age 60-80 years with at least one of the following additional high-risk features: active smoking, HbA1c  $\geq 8\%$  (64 mmol/mol), or Stage 3a CKD (estimated glomerular filtration rate 45-59 ml/min/1.73m<sup>2</sup>) with urinary albumin-to-creatinine ratio of  $< 200$  mg/g. Exclusion criteria included a history of diabetic ketoacidosis, active foot ulcer, history of pancreatitis, hospitalization for heart failure within the prior year, known left ventricular ejection fraction  $< 40\%$ , active or recently active cancer, and known inability to afford study medication. Full criteria for the feasibility phase are available in Protocol Version 1.5 (Supplement). Patients currently taking SGLT2i or GLP-1RA (or both) were eligible to enroll if they were willing to accept the randomly assigned treatment allocation. Participants provided written informed consent, including agreement to obtain study medication through their own health insurance. Sites attempted to ascertain whether study medication was accessible to participants by asking probing questions about pharmacy benefits or sending a test prescription.

PRECIDENTD trial leadership was based at 4 study sites: the Clinical Coordinating Center (Mass General Brigham [MGB]), the Data Coordinating Center (MGB), the Engagement Core (Vanderbilt University Medical Center), and the PCORnet Core (Duke Clinical Research Institute [DCRI]). Eight enrolling sites identified potential participants through study-specific electronic health record (EHR) queries developed in partnership with DCRI. The Clinical and Data Coordinating Centers

worked closely with the Engagement Core to train sites in outreach and recruitment methods. Recruitment and randomization occurred through both in-person or virtual visits. Study sites partnered with participants' own usual diabetes care provider and used EHR data to assess medical history and prescribe medication. Data collection and management used Research Electronic Data Capture (REDCap) tools hosted by the MGB Research Applications team. REDCap is a secure, web-based application designed to support data capture for research studies.<sup>9</sup> Study coordinators and investigators completed site data forms using EHR data and participant self-report to confirm diagnoses. Participants used the same web-based system to complete patient-reported outcome measures (PROMs).

**Interventions.** The study intervention was random assignment to SGLT2i, GLP-1RA, or dual therapy (SGLT2i plus GLP-1RA). For SGLT2i, the protocol specified empagliflozin 10 mg, dapagliflozin 10 mg, or canagliflozin 100 mg. Use of SGLT2i medications that lacked evidence of cardiovascular benefit was discouraged. Preferred GLP-1RA were dulaglutide goal dose 1.5 mg weekly, liraglutide goal dose to 1.8 mg daily, or semaglutide goal dose 0.5 mg weekly. During the feasibility phase, tirzepatide and oral semaglutide were allowed but not preferred given the lack of available cardiovascular outcome data at that time. Study investigators and usual care providers had discretion to further increase medication doses as clinically indicated. Participants assigned to dual therapy who were not already taking 1 class prior to randomization initiated the GLP-1RA first to allow titration, followed by the SGLT2i. In addition to prescribing the medication, sites supported medication initiation through usual care processes such as support for obtaining prior authorization through templates to promote approval, outlining team-based processes and best practices, identifying patient assistance programs, etc. The coordinating center, supported by an interactive text messaging system, reached out to participants to help troubleshoot problems with obtaining assigned medication. Finally, the manual of operations and training webinars promoted knowledge sharing to help sites support medication initiation and adherence. The coordinating center supplied study-specific instructions and materials to educate all participants in the use and adverse effects of their assigned medication (Figure S1). Patient partners reviewed the informed consent form to improve clarity and the consent process, identified early barriers to medication adherence, suggested strategies for troubleshooting these, and contributed to education materials. All participants had a visit 2 months after randomization to promote retention and adherence and to initiate the SGLT2i in the dual therapy arm. Sites followed participants until medication(s) were initiated and reported confirmed initial medication pickup on a REDCap form. Thereafter, participants were transitioned back to

usual diabetes care providers, who were asked to try to maintain the participant on the randomly assigned medication(s) while adjusting other diabetes medications as needed. Outcome and adverse event assessments, including current self-reported medication use, occurred at 2, 6 and every subsequent 6 months after randomization. Participant compensation was \$100 at randomization and annually in the feasibility phase.

**Outcomes.** For this report on the feasibility phase of PRECIDENTD, the main outcomes are medication initial fill rates in the pooled monotherapy groups compared to the dual therapy group. We also report medication discontinuation rates among those who started medication, reasons for medication noninitiation and discontinuation; secondary outcomes included adverse events (AEs), global health measured using the Patient-Reported Outcomes Measurement Information System (PROMIS) Scale V1.2<sup>10</sup>, and a modified version of the Kansas City Cardiomyopathy Questionnaire, 12-item version (mKCCQ).<sup>11</sup>

Medication initiation and adherence were ascertained through several sources. One week after a visit when a protocol-specified treatment was prescribed, the Clinical Coordinating Center contacted the participant to ascertain medication initiation or its barriers, and to assist with access challenges. At scheduled study visits (2, 6, and every subsequent 6 months after randomization), participants provided additional information on timing of initiation, and any treatment interruptions or discontinuations with reasons. Specifically, participants completed the 1-item Summary of Diabetes Self-Care Activities Measure Medication Subscale and Adherence to Refills and Medications Scale for Diabetes.<sup>12</sup>

The feasibility process measure of overall initial medication fill rates was defined as the number of participants who reported ever obtaining the assigned medication(s) during the feasibility phase divided by the total number of participants; we also report this rate by 10 weeks (allowing a 2 week grace period for the 2-month follow up visit) and 4 months after randomization (when all participants should have had time to initiate both medications, allowing for a wide assessment window) after randomization. For the dual therapy group, participants had to start both treatments to qualify as filling initial randomly assigned therapy and were considered to have discontinued dual therapy if they stopped at least one of these 2 treatments (restricted to those who started both treatments).

For the ongoing PRECIDENTD trial, the primary outcome is the total (first and recurrent) number of episodes of myocardial infarction, stroke, arterial revascularization, hospitalization for heart failure, development of end-stage kidney disease, kidney transplantation, and mortality, counting all events from randomization until end of study. The overall trial sample size was based on a power calculation to detect this primary outcome.

This outcome will not be reported until the trial is complete.

Secondary endpoints included in this report are: the change in PROMIS V1.2 Physical and Mental Health scores from baseline to 12 months; the slope in mKCCQ-12 Overall Summary Score from baseline to 6 and 12 months; and serious AEs, including targeted AEs (severe hypoglycemic episodes, diabetic ketoacidosis, genital fungal infections, amputation, fractures, worsening diabetic retinopathy, pancreatitis, and gallbladder disease), obtained at 6- and 12-month study visits. The PROMIS Scale V1.2 was administered at baseline and 12 months, and the mKCCQ at baseline, 6, and 12 months. PROMIS is a validated global measure of physical and mental health with scores ranging from 0 to 100 normalized to the US population such that a score of 50 with standard deviation of 10 represents the mean population-level response to a given construct; scores above and below the mean represent greater or lesser degrees of the construct.<sup>10,13</sup> The KCCQ-12 is a disease-specific measure scaled from 0 to 100, initially designed to capture symptoms of heart failure. However, the instrument broadly assesses quality of life and cardiovascular symptoms common in people with cardiometabolic conditions and has been adapted for use in other cardiometabolic disease conditions, including type 2 diabetes without clinical heart failure.<sup>14,15</sup> In keeping with this approach, our adaptation for this population replaced 6 instances of the words “heart failure” in the instrument with “your health” or “health.” For example, we changed “Please indicate how much you have been limited by *heart failure* ... over the past 2 weeks” to “Please indicate how much you have been limited by *your health* ... over the past 2 weeks.” In addition, we deleted a prompt in item 1 that describes heart failure. KCCQ score changes of 5, 10, and 20 points represent small, moderate-to-large, and large-to-very-large clinical changes.<sup>16</sup>

**Sample size.** There was no power calculation for the feasibility phase, as feasibility is determined based on metrics of trial conduct.<sup>17</sup> The recruitment target for the feasibility phase was 400 participants.

**Randomization.** Eligible and willing participants were randomly assigned in a 1:1:1 ratio using blocks of size 6 to treatment with SGLT2i, GLP-1RA, or dual therapy based on an algorithm programmed into and implemented by the REDCap system. Randomization was stratified by site, primary or secondary prevention, and age <65 or ≥65 years. As a pragmatic trial, neither participants nor local investigators were blinded, though the principal investigators (BME and DJW) and the staff at the MGB Clinical Coordinating Center do not have access to trial data stratified by randomized treatment group.

**Statistical methods.** Primary analyses used Chi-squared tests to compare rates of treatment uptake, overall and by 10 weeks and 4 months after randomization between the pooled monotherapy groups and the dual therapy group,

as well as rates of discontinuation among initiators. Since some participants entered the study on 1 or both study medications, we performed sensitivity analyses examining the following subgroups: not on either medication class at baseline (de novo monotherapy or dual therapy), assigned to the same single medication class (concordant monotherapy), assigned to switch to the alternate medication class (discordant monotherapy), or on 1 class at baseline and assigned to dual therapy (adding another class dual therapy), to determine whether rates of medication initiation and continuation differed meaningfully among these groups. P values are not reported for these subgroups given small sample sizes. Comparisons between monotherapy groups are not shown to maintain blinding of the ongoing study. Comparisons of time trends between monotherapy and dual therapy groups in PROMIS and mKCCQ scores at baseline, 6 months (for mKCCQ only) and 12 months after randomization used all available measures, assuming missing values were missing at random. Linear mixed effects models included a random participant effect and fixed effects of time, treatment, and a treatment by time interaction. Analyses used the R version 4.4.2, and the R package for the mixed models was nlme version 3.1-166.<sup>18,19</sup>

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## Results

Between September 1, 2022 and January 23, 2024, 602 people were formally screened for PRECIDENTD. Of those, 28% ( $n = 166$ ) were ineligible and 44% ( $n = 262$ ) declined. Among screened patients providing reasons, the most common reasons for declining were unwillingness to be randomly assigned to a medication (21%) or concern that the study would be too burdensome (11%). Median (IQR) time from screening to randomization was 4 (1, 11) days. The last feasibility phase randomization occurred on January 25, 2024. Of the 173 enrolled in the feasibility phase, 113 (65%) were randomly assigned to monotherapy and 60 (35%) to dual therapy (Figure 1: CONSORT).

Median (IQR) duration of follow up was 305 (197, 374 [min-max 1-603]) days, or 10 months. Median (IQR) age was 67 (62, 72), 46% were female, 65% reported White and 25% reported Black race, and 67% had established ASCVD at baseline (Table 1). Twenty-five percent had history of myocardial infarction and 14% had history of heart failure hospitalization >12 months prior to enrollment. HbA1c and body mass index medians (IQR) were 7.3% (6.7, 8.3) and 32 kg/m<sup>2</sup> (28, 37), respectively. Thirty-one percent were treated with GLP-1RA and 20%

**Table 1.** Baseline characteristics of the study population in pooled monotherapy and dual therapy groups

|   | Monotherapy<br>(N = 113) | Dual therapy<br>(N = 60) | Total (N = 173)   |
|---|--------------------------|--------------------------|-------------------|
| <i>Demographics</i>                           |                          |                          |                   |
| <i>Cohort</i>                                 |                          |                          |                   |
| Primary                                       | 37 (32.7%)               | 21 (35.0%)               | 58 (33.5%)        |
| Secondary                                     | 76 (67.3%)               | 39 (65.0%)               | 115 (66.5%)       |
| <i>Age group</i>                              |                          |                          |                   |
| <65 years                                     | 46 (40.7%)               | 23 (38.3%)               | 69 (39.9%)        |
| ≥65 years                                     | 67 (59.3%)               | 37 (61.7%)               | 104 (60.1%)       |
| Age at screening (years)                      | 66 (62, 72)              | 68 (62, 74.2)            | 67 (62, 72)       |
| Weight (lbs)                                  | 205 (179, 236)           | 200.5 (173.2, 240)       | 204 (175, 237)    |
| BMI (kg/m <sup>2</sup> )                      | 32.1 (27.6, 36.5)        | 32.4 (27.9, 38.1)        | 32.3 (27.7, 36.8) |
| Male  | 64 (56.6%)               | 29 (48.3%)               | 93 (53.8%)        |
| <i>Race (self-reported)</i>                   |                          |                          |                   |
| White/Caucasian                               | 70 (61.9%)               | 43 (71.7%)               | 113 (65.3%)       |
| Black/African-American                        | 32 (28.3%)               | 12 (20.0%)               | 44 (25.4%)        |
| Asian   | 6 (5.3%)                 | 3 (5.0%)                 | 9 (5.2%)          |
| Other or multiple*                            | 5 (4.4%)                 | 2 (3.3%)                 | 7 (4.0%)          |
| Hispanic (self-reported)                      | 3 (2.7%)                 | 0                        | 3 (1.7%)          |
| <i>Health insurance</i>                       |                          |                          |                   |
| Health insurance                              | 112 (99.1%)              | 60 (100.0%)              | 172 (99.4%)       |
| <i>Insurance plan</i>                         |                          |                          |                   |
| Medicare                                      | 67 (42.4%)               | 35 (43.8%)               | 102 (42.9%)       |
| Medicaid                                      | 15 (9.5%)                | 8 (10.0%)                | 23 (9.7%)         |
| Employer/Union                                | 34 (21.5%)               | 19 (23.8%)               | 53 (22.3%)        |
| Other†  | 42 (26.6%)               | 18 (22.5%)               | 60 (25.2%)        |
| <i>Insurance deductible</i>                   |                          |                          |                   |
| \$0-\$500                                     | 23 (20.4%)               | 11 (18.3%)               | 34 (19.7%)        |
| \$501-\$1,000                                 | 5 (4.4%)                 | 0                        | 5 (2.9%)          |
| \$1,001-\$1,500                               | 2 (1.8%)                 | 0                        | 2 (1.2%)          |
| \$1,501-\$2,000                               | 0                        | 1 (1.7%)                 | 1 (0.6%)          |
| \$2,001 or more                               | 2 (1.8%)                 | 4 (6.7%)                 | 6 (3.5%)          |
| I don't know.                                 | 62 (54.9%)               | 32 (53.3%)               | 94 (54.3%)        |
| Missing                                       | 19 (16.8%)               | 12 (20.0%)               | 31 (17.9%)        |
| <i>Education n(%)</i>                         |                          |                          |                   |
| < High school diploma                         | 4 (3.5%)                 | 5 (8.3%)                 | 9 (5.2%)          |
| High school diploma/GED                       | 24 (21.2%)               | 11 (18.3%)               | 35 (20.2%)        |
| College credit/associate degree               | 33 (29.2%)               | 13 (21.7%)               | 46 (26.6%)        |
| College completion or higher                  | 52 (46.0%)               | 31 (51.7%)               | 83 (48.0%)        |
| <i>Medical history</i>                        |                          |                          |                   |
| Established ASCVD‡                            | 76 (67.3%)               | 39 (65.0%)               | 115 (66.5%)       |
| History of heart attack                       | 27 (23.9%)               | 16 (26.7%)               | 43 (24.9%)        |
| History of stroke                             | 16 (14.2%)               | 8 (13.3%)                | 24 (13.9%)        |
| CABG  | 18 (15.9%)               | 9 (15.0%)                | 27 (15.6%)        |
| Hospitalized for heart failure >12 months ago | 14 (12.4%)               | 10 (16.7%)               | 24 (13.9%)        |
| Diabetic neuropathy                           | 41 (36.3%)               | 20 (33.3%)               | 61 (35.3%)        |
| High blood pressure                           | 96 (85.0%)               | 51 (85.0%)               | 147 (85.0%)       |
| Atrial fibrillation                           | 18 (15.9%)               | 10 (16.7%)               | 28 (16.2%)        |
| <i>Baseline medications</i>                   |                          |                          |                   |
| Concordant therapy                            | 26 (23.0%)               | 1 (1.7%)                 | 27 (15.6%)        |
| Metformin                                     | 77 (68.1%)               | 45 (75.0%)               | 122 (70.5%)       |
| Sulfonylurea or glinide                       | 21 (18.6%)               | 11 (18.3%)               | 32 (18.5%)        |
| SGLT2 inhibitors                              | 25 (22.1%)               | 10 (16.7%)               | 35 (20.2%)        |
| GLP-1 receptor agonists                       | 33 (29.2%)               | 21 (35.0%)               | 54 (31.2%)        |
| Insulin use                                   | 28 (24.8%)               | 16 (26.7%)               | 44 (25.4%)        |
| DPP-4 inhibitor                               | 8 (7.1%)                 | 5 (8.3%)                 | 13 (7.5%)         |
| Other glucose lowering medication             | 11 (9.7%)                | 7 (11.7%)                | 18 (10.4%)        |
| Statins                                       | 95 (84.1%)               | 49 (81.7%)               | 144 (83.2%)       |
| ACE inhibitor                                 | 39 (34.5%)               | 20 (33.3%)               | 59 (34.1%)        |
| Angiotensin receptor blocker                  | 34 (30.1%)               | 23 (38.3%)               | 57 (32.9%)        |
| <i>Laboratory values§</i>                     |                          |                          |                   |
| HbA1c (%)                                     | 7.2 (6.7, 8.3)           | 7.4 (6.7, 8.2)           | 7.3 (6.7, 8.3)    |

(continued on next page)

**Table 1.** (continued)

|                                | Monotherapy<br>(N = 113) | Dual therapy<br>(N = 60) | Total (N = 173)    |
|--------------------------------|--------------------------|--------------------------|--------------------|
| HbA1c category                 |                          |                          |                    |
| <6                             | 2 (1.8%)                 | 0                        | 2 (1.2%)           |
| ≥6-<6.5                        | 20 (17.7%)               | 10 (16.7%)               | 30 (17.3%)         |
| ≥6.5-<8                        | 49 (43.4%)               | 29 (48.3%)               | 78 (45.1%)         |
| ≥8                             | 42 (37.2%)               | 21 (35.0%)               | 63 (36.4%)         |
| Total cholesterol (mg/dL)      | 143.5 (118, 172)         | 149 (126, 188.8)         | 146.5 (119, 177.2) |
| HDL cholesterol (mg/dL)        | 40.5 (34.2, 48)          | 42.5 (37, 51.8)          | 41 (35, 48)        |
| Triglycerides (mg/dL)          | 123.5 (95, 207.8)        | 144 (99, 227)            | 133 (97.5, 219.5)  |
| LDL cholesterol (mg/dL)        | 72 (48, 99)              | 72.5 (59, 100.5)         | 72 (52, 99)        |
| eGFR ml/min/1.73m <sup>2</sup> |                          |                          |                    |
| <45 mL                         | 0                        | 0                        | 0                  |
| 45-59mL                        | 29 (25.7%)               | 19 (31.7%)               | 48 (27.7%)         |
| ≥60mL                          | 84 (74.3%)               | 41 (68.3%)               | 125 (72.3%)        |
| UACR (mg/g)                    | 6 (0.7, 19)              | 10 (4.6, 20.7)           | 7 (1, 20.1)        |

Continuous variables are presented as median (IQR) and categorical variables as number (percent).

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; DPP-4, dipeptidyl peptidase-4 inhibitor; eGFR, estimated glomerular filtration rate; GLP, glucagon-like peptide-1; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein cholesterol LDL, low-density lipoprotein cholesterol; SGLT2 sodium-glucose co-transporter 2; UACR, urinary albumin to creatinine ratio.

\*Other or multiple includes American Indian/Alaska Native, Native Hawaiian/ Pacific Islander, Multiracial, prefer not to answer, unknown, other, or missing.

†Other includes personally purchased, TRICARE or Other Military Health Care, VA, Indian Health Service, State-Specific, no insurance, unknown or other plans.

‡Established ASCVD includes history of heart attack or stroke, coronary artery disease or a history of coronary revascularization, carotid or cerebrovascular disease, or peripheral artery disease.

§N for laboratory results are HbA1c n = 173; total cholesterol and HDL cholesterol n = 156; triglycerides n = 155; LDL cholesterol n = 153; eGFR n = 173; UACR n = 96.

were treated with SGLT2i prior to enrollment (Table 1). All but 1 participant had health insurance: 59% Medicare, 31% employer-based, 14% personally purchased, and 13% Medicaid.

Overall medication fill rates were 87% in the monotherapy and 68% in the dual therapy group ( $P = .004$ ); rates were 80% and 48% at 10 weeks and 84% and 53% at 4 months, respectively ( $P$ -values < .001 (Figure 2, Table S1). Among those not on either medication class at baseline (Table S2), overall medication fill rates were 81% for de novo monotherapy and 40% for de novo dual therapy, with a 97% fill rate in those already on 1 medication who were randomly assigned to add a second medication (Table S3). Discordant monotherapy (switching) fill rates were similar (89%,  $n = 18$ ). Reasons for not starting medication, when reported (reporting was optional, and participants could provide more than 1 reason), most commonly included difficulty affording the medication (7% [ $n = 8$ ] in monotherapy, 7% [ $n = 4$ ] in dual therapy), getting the medication (3% [ $n = 3$ ] in monotherapy, 7% [ $n = 4$ ] in dual therapy), and with insurance coverage of the medication (2% [ $n = 2$ ] in monotherapy and 3% [ $n = 2$ ] in dual therapy). Seven participants in the dual therapy group (12%) compared to 3 in the monotherapy group (3%) reported not wanting “to get the medication for another reason” (Table S4).

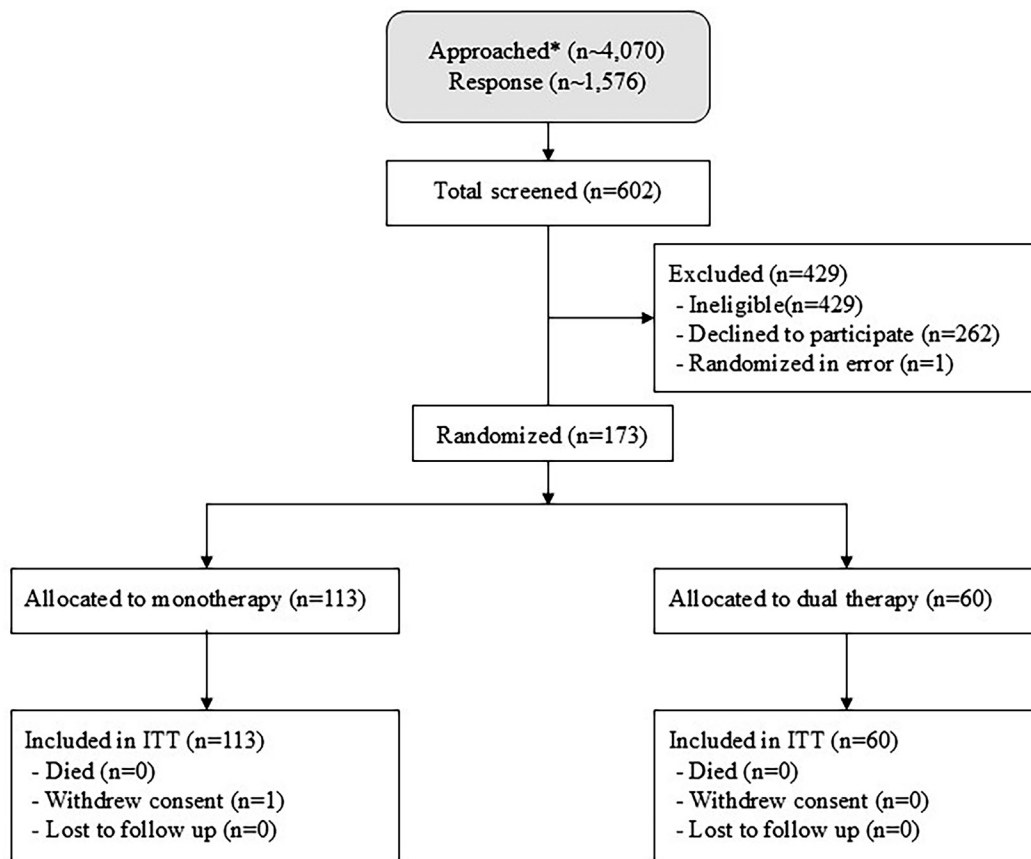
Of participants who obtained the study medication, 22% of monotherapy and 49% of dual therapy discontinued study medication (which could include stopping

1 medication in the dual therapy group;  $P = .002$ ; Figure 3). The most common reason for stopping study medication was “side effects or other problems caused by the medication” (Table S5). At each of 3 benchmark times (2, 6, and 12 months after randomization), the proportion of all participants on drug was significantly higher in the monotherapy group compared to the dual therapy group (Table S6). This pattern was consistent, with even greater differences between monotherapy and dual therapy groups, when those not taking either medication class at baseline were considered (Table S7).

Global health, measured by PROMIS V1.2 Mental and Physical Health T-scores, were slightly below the US population mean, similar between groups at baseline, and did not significantly change over time, with no difference between groups (Figure S1). The median mKCCQ Overall Summary Score was 82 (IQR 60, 94), similar between groups at baseline, and showed a numerically modest but nonsignificant increase in the mean mKCCQ Score during follow up ( $P = .055$ , Figure S2). There was no difference between monotherapy and dual therapy groups in mKCCQ Overall Summary Scores over follow up ( $P = .13$ ). Between baseline and 6 months, the median change (IQR) in the mKCCQ Overall Summary score was 4.2 (IQR -3.1, 11.8) in the monotherapy groups and 6.8 (IQR -1.8, 15) in the dual therapy group.

Adverse events in monotherapy and dual therapy arms are reported in Table S8. While comparable percent-

**Figure 1.** CONSORT diagram for the feasibility phase of the trial. Patients were randomized in the 3-arm feasibility phase of PRECIDENTD between September 1, 2022 and January 23, 2024. \*Approached patients were broadly defined as those identified through electronic health record queries or common data model queries as potentially eligible for the study and sent electronic or paper invitation messages.



ages of subjects in both groups reported at least 1 adverse event during the feasibility phase (24.8% in the monotherapy vs 20% in the dual therapy group) and slightly more total first adverse events were reported in the monotherapy group (26.5 vs 21.7 first events per person in monotherapy vs dual therapy groups, respectively), among subjects reporting at least 1 adverse event, those in the monotherapy group reported 1.5 events per reporter vs 3.8 events per reporter in the dual therapy group.

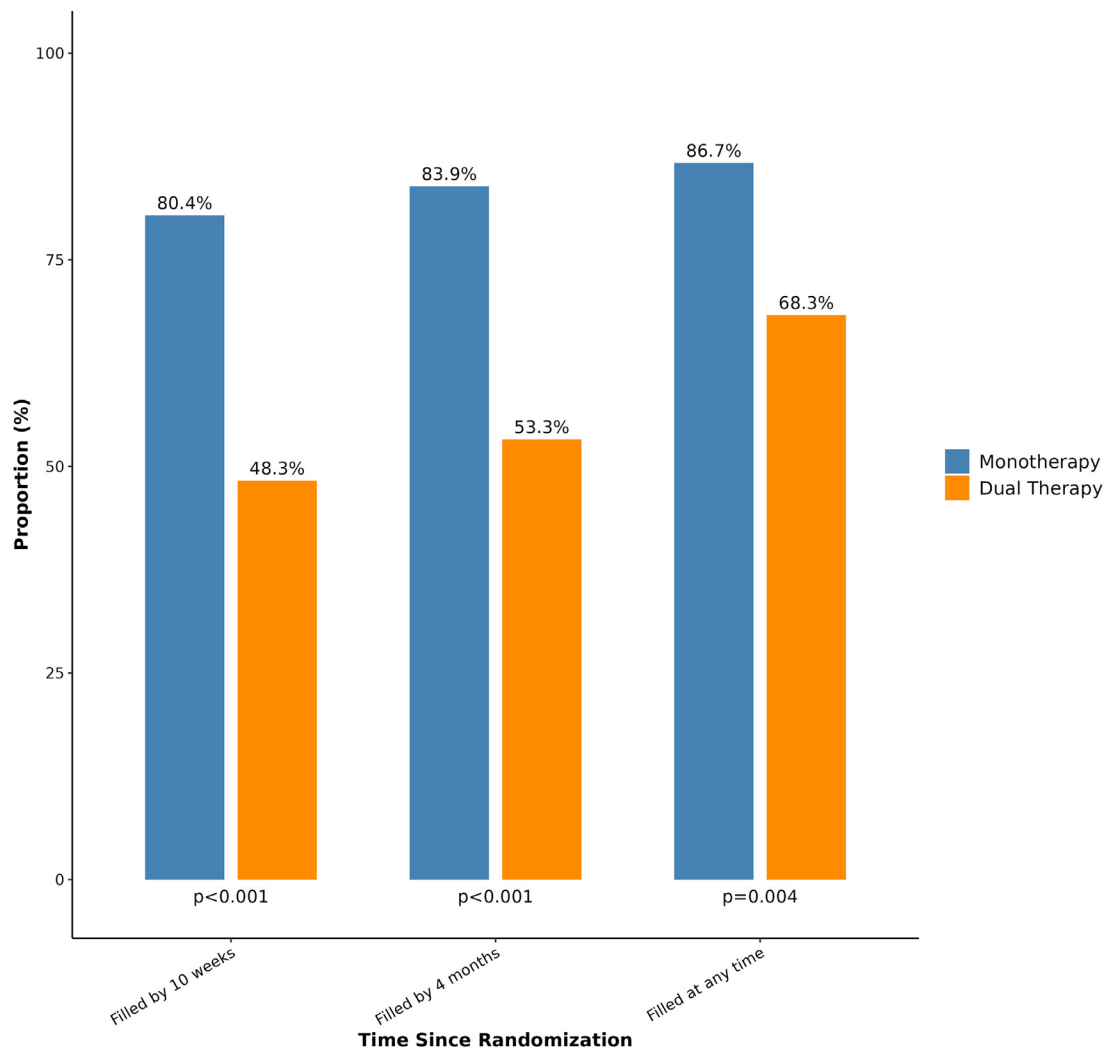
## Discussion

PRECIDENTD is a pragmatic, randomized controlled trial that originally aimed to compare the effectiveness of SGLT2i, GLP-1RA, or dual therapy for improving cardiovascular, kidney, mortality, and patient-reported outcomes among participants with type 2 diabetes and ASCVD or high ASCVD risk. In the feasibility phase, 173 participants were enrolled and randomly assigned to one

of the 2 monotherapy groups (SGLT2i or GLP-1RA) or to dual therapy (SGLT2i and GLP-1RA). In the evaluation of the feasibility phase, we compared initiation and continuation of the assigned treatments, patient-reported health measures, and adverse events among participants assigned to the pooled monotherapy groups to those assigned to the dual therapy group. We observed lower medication fill rates and higher discontinuation rates in the dual therapy group compared to the pooled monotherapy groups overall. These differences were more pronounced in sensitivity analyses restricted to those not taking either medication class at baseline. There were no significant differences in the PROMIS V1.2 Physical Health score or the mKCCQ Overall Summary Scores by randomized treatment assignment, although power for these comparisons was limited. Adverse event rates were low and did not differ by treatment group.

Given the markedly lower medication fill rate and higher discontinuation rate in the dual therapy group,

**Figure 2.** Proportion of study participants who filled their prescription for study medication for monotherapy (either SGLT2i or GLP-1RA) vs dual therapy (both SGLT2i and GLP-1RA) in the PRECIDENTD feasibility phase. The number of participants who could fill their prescription was 113 in the monotherapy group and 60 in the dual therapy group.

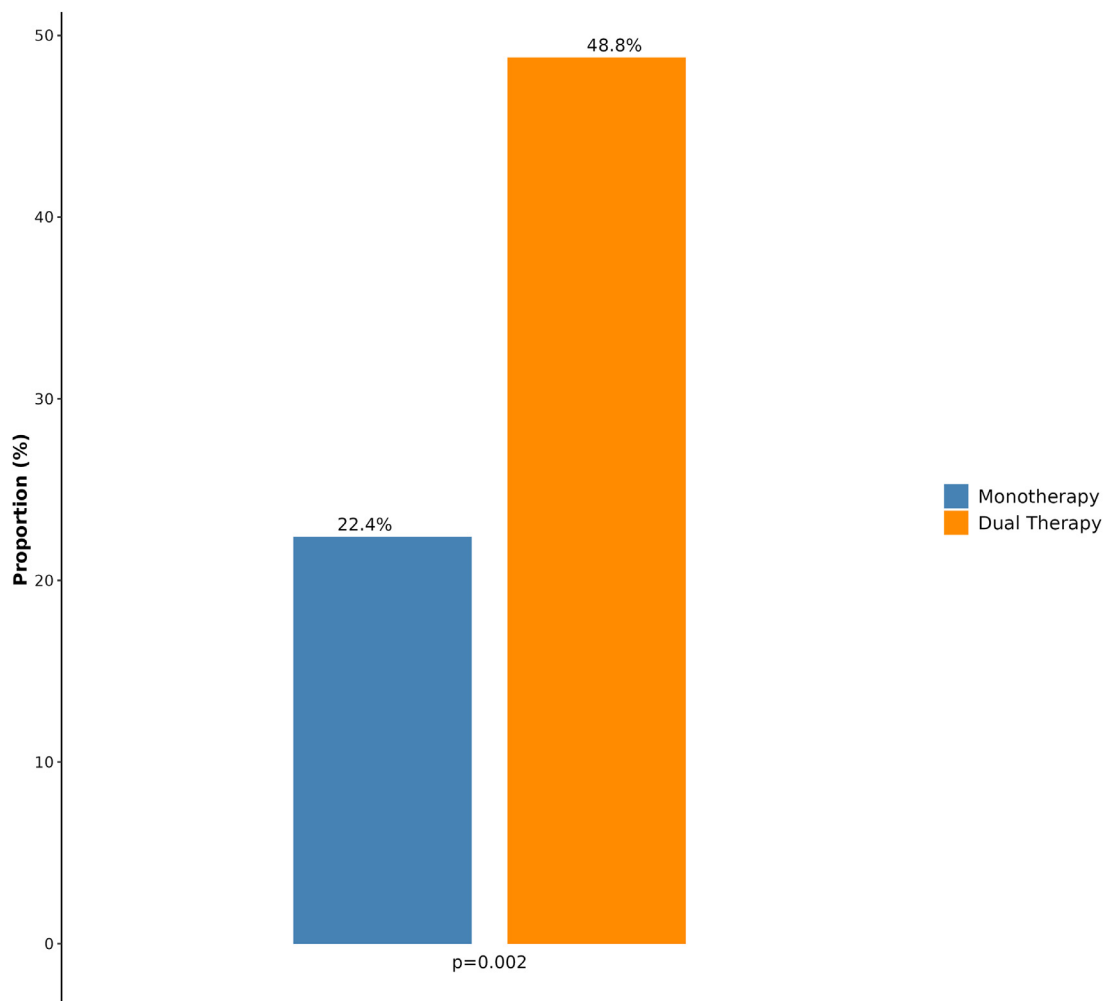


the feasibility phase of PRECIDENTD demonstrated that valid comparison of the effect of dual therapy compared with either SGLT2i or GLP-1RA monotherapy on major cardiovascular, renal, and mortality events in PRECIDENTD would not be possible. The DSMB determined that the patterns described herein were evident. Also, asking participants to pay for their own expensive medications combined with limited participant reimbursement was considered a remediable barrier to low overall recruitment in the feasibility phase, in which the original recruitment target was 400 patients. Therefore, in consultation with our patient and professional research partners and the funder, we closed the dual therapy arm after the feasibility phase and continue the trial with a 1:1 randomization to monotherapy with either SGLT2i or

GLP-1RA. Upon close of the feasibility phase, monotherapy participants continued in the trial, and dual therapy participants had the option to be re-randomized to single therapy or to conclude their participation. To enhance recruitment, participant compensation was increased to \$500 at randomization and annually in the ongoing full trial phase to offset the cost of participation. After implementing these changes, we observed a 3- to 5-fold increase in monthly enrollment in the full study phase, even prior to launching new study sites.

Dual therapy with SGLT2i and GLP-1RA is currently recommended by the American Diabetes Association and European Society of Cardiology guidelines,<sup>1,8</sup> among others. The lower rate of medication initiation we observed in the dual therapy group has implications for the prac-

**Figure 3.** Proportion of study participants who discontinued their prescription for study medication for monotherapy (either SGLT2i or GLP-1RA) vs dual therapy (both SGLT2i and GLP1-RA) in the PRECIDENTD feasibility phase. Only participants who filled their study medication at least once were included in this analysis ( $n = 98$  for monotherapy and  $n = 41$  for dual therapy).



tical implementation of this recommendation. All participants in this study had health insurance and anticipated being able to obtain the medication prior to enrollment, but this was not achievable for many participants. Interestingly, participants taking 1 medication class at baseline had high rates of initiation of the second medication class. This group represented less than half of the patients assigned to dual therapy, in a cohort in which nearly everyone had insurance. The high rate of uptake in this group may be a sign that current use of an expensive medication is a marker of adequate insurance coverage and motivation; additionally, these participants were offered an additional treatment rather than being asked to stop a current treatment. While subgroup analyses of participants taking dual therapy in clinical trials that provide study medication suggest patients already taking 1

class (eg, SGLT2i) still derive benefit from the addition of the alternative class (eg, GLP-1RA),<sup>7,20</sup> the results presented here suggest that those achieving high uptake of dual SGLT2i and GLP-1RA are a selected population and dual therapy may be infeasible in the majority of patients in usual care in the U.S., at least in its current insurance milieu.

Participants who did not start medications reported difficulty with affordability and access as the most common barriers. It is also possible that the delayed start of the second medication or not wanting to add another medication contributed to decreased uptake in the dual therapy group, which had a higher rate not wanting to start the medication “for another reason.” Other barriers may include changing insurance coverage over time and GLP-1RA shortages during the study period. Among partic-

ipants who initiated study medications, those assigned to dual therapy had a 2-fold higher discontinuation rate (49%) than those assigned to pooled monotherapy (22%). Medications were most commonly stopped due to side effects, which raises concern for the tolerability and sustainability of dual therapy in real-world populations. In general, discontinuation rates of these medication classes are high. Overall prevalence of GLP-1RA discontinuation was 37% at 1 year in a recent national US sample,<sup>21</sup> and 26% of veterans discontinued SGLT2i at 1 year, despite lower patient costs for these drugs within the VA Health-care system.<sup>22</sup>

Given the paucity of randomized trial data directly comparing dual therapy with SGLT2i and GLP-1RA to monotherapy, the patient-reported outcome measures are of interest. Similar to other studies, PRECIDENTD used a modified KCCQ-12, with item stems changed to query “general health” rather than “heart failure” for application in a population without heart failure at baseline.<sup>14,15</sup> Modified KCCQ scores in PRECIDENTD were higher at baseline (in the low 80s, with higher scores indicating better health) compared to a population with T2D and heart failure with preserved ejection fraction (60 assessed by KCCQ-23)<sup>4</sup> but comparable to a routine care heart failure population (82 assessed by KCCQ-12).<sup>23</sup> In PRECIDENTD, mKCCQ scores showed a modest numerical but statistically nonsignificant improvement over time in both groups, corresponding to a small effect size. Thus, the mKCCQ-12 may be responsive to change in a cardiometabolic population without active or recognized heart failure and may suffice to detect a meaningful clinical difference in a larger study population, if present. These observations are limited by relatively small sample size, sparse data, and differential adherence by randomized treatment groups. These results might differ in a population better able to adhere to randomly allocated therapy.

**Limitations.** There are several limitations to this analysis. As a report of the feasibility phase of PRECIDENTD, this study was not powered to detect clinical outcomes or differences in patient-reported outcome measures. The comparison between pooled monotherapy groups and the dual therapy group was not prespecified. Because they had enrolled in a trial, participants likely had more support than might exist for starting and adhering to medications in usual care; thus, rates of medication uptake and persistence might be lower in usual care.

## Conclusions

In its feasibility phase, the PRECIDENTD pragmatic trial attempted an ambitious 3-group randomization to evaluate pressing comparative effectiveness questions in cardiometabolic medicine. Because our pragmatic approach required participants to pay for their own study medication, we observed real-world barriers to medica-

tion initiation not present in traditional trials that provide medication to participants. Despite nearly all participants having health insurance, anticipating being able to afford study medication, and committing to participate in a randomized controlled trial, those randomly assigned to dual therapy had lower medication fill rates and higher medication discontinuation rates than those assigned to monotherapy, especially among those not on either medication class at baseline. Patient-reported outcome measures were similar in monotherapy and dual therapy groups on both global and disease-specific health measures but power for this comparison was limited. The PRECIDENTD feasibility phase results call into question the viability of dual therapy at a population level in the current United States health care context. The full phase of PRECIDENTD is ongoing, focused on the monotherapy comparison of SGLT2i and GLP-1RA medication classes.

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## Disclaimer

All statements in this report, including its findings and conclusions, are solely those of the authors and do not necessarily represent the view of the Patient-Centered Outcomes Research Institute (PCORI), its Board of Governors, or Methodology Committee.

## Prior presentation

Aspects of this work were presented in abstract form at ACC March 29-31, 2025, Chicago, IL and the American Diabetes Association Scientific Sessions June 23, 2025, Chicago IL.

## Declaration of competing interests

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## CRedit authorship contribution statement

**Deborah J. Wexler:** Writing - review & editing, Writing - original draft, Investigation, Funding acquisition, Conceptualization. **Lindsay S. Mayberry:** Writing - review & editing, Funding acquisition, Conceptualization. **Lyndsay A. Nelson:** Writing - review & editing, Investigation, Funding acquisition. **Jeremy Lema-Driscoll:** Writing - review & editing, Project administration, Formal analysis, Data curation. **Ligia C. Flores:** Writing - review & editing, Formal analysis, Data curation. **Maureen Malloy:** Writing - review & editing, Project administration. **Jean G. MacFadyen:** Writing - review & editing, Project administration, Formal analysis, Data curation. **Joseph Shen:** Writing - review & editing, Formal analysis, Data curation. **Elaine Zaharris:** Writing - review & editing, Project administration. **Harsha Karanchi:** Writing - review & editing, Project administration, Investigation. **Ranee Chatterjee:** Writing - review & editing, Investigation. **Catherine P. Benziger:** Writing - review & editing, Investigation. **Jake E. Decker:** Writing - review & editing, Investigation. **Rita Kalyani:** Writing - review & editing, Investigation. **Camila Manrique-Acevedo:** Writing - review & editing, Investigation. **Jacqueline Lonier:** Writing - review & editing, Investigation. **Edward Simeone:** Writing - review & editing, Investigation. **Kathleen Mieras:** Writing - review & editing, Investigation. **Amanda R.O. Siqueira:** Writing - review & editing, Investigation. **Russell L. Rothman:** Writing - review & editing, Investigation, Conceptualization. **W. Schuyler Jones:** Writing - review & editing, Funding acquisition, Conceptualization. **Robert J. Glynn:** Writing - review & editing, Writing - original draft, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Brendan M. Everett:** Writing - review & editing, Writing - original draft, Project administration, Investigation, Funding acquisition, Conceptualization.

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## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.ahj.2025.107332](https://doi.org/10.1016/j.ahj.2025.107332).

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