Pragmatic Trials of Branded Pharmaceuticals: Challenges and Opportunities

NIH Collaboratory Grand Rounds
July 19, 2024

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PRECIDENTD
Prevention of Cardiovascular and Diabetic Kidney Disease in Type 2 Diabetes

Dualities of Interest

- Dr. Everett has received investigator-initiated support from the Patient Centered Outcomes Research Institute (PCORI), NHLBI, American Heart Association, Novartis, and Novo Nordisk and has served as consultant to the American Heart Association (Circulation), Eli Lilly and Company, Ipsen Pharma, Janssen Pharmaceuticals, Kowa Pharmaceuticals, Novo Nordisk, Roche Diagnostics, and has royalty income from UpToDate

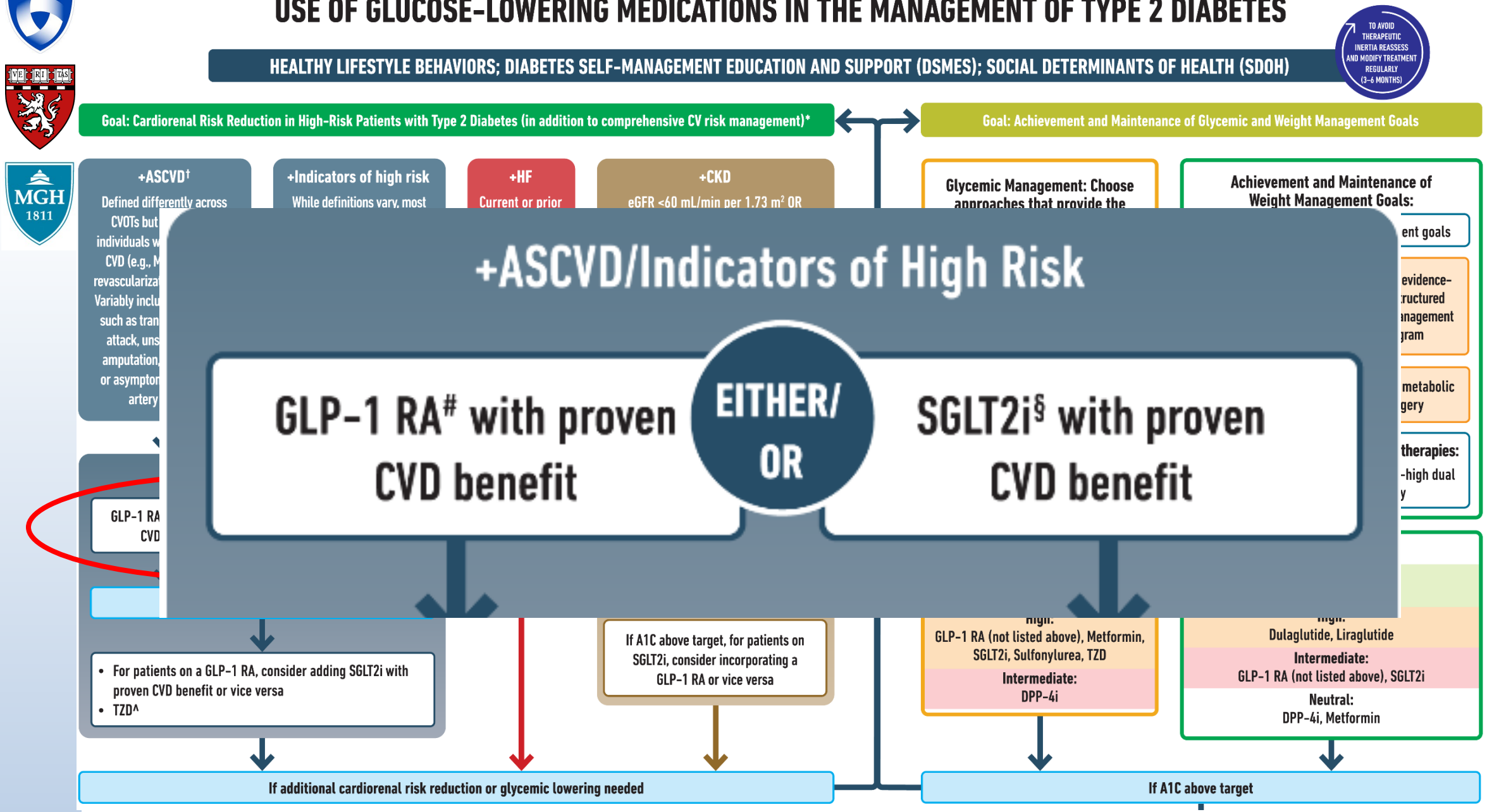
- Dr. Wexler has received investigator-initiated support from the Patient Centered Outcomes Research Institute (PCORI) and NIDDK. She has served on data monitoring committees for Novo Nordisk. She has editorial income from Elsevier and royalty income from UpToDate.

Outline

- Background and rationale
  - A pragmatic question at the crux of the cardiac-kidney-metabolic health axis
- The PRECIDENTD Trial
- Lessons from the PRECIDENTD feasibility phase
  - Preliminary findings from the feasibility phase
  - Implications for pragmatic trials and clinical care

Background and rationale

USE OF GLUCOSE-LOWERING MEDICATIONS IN THE MANAGEMENT OF TYPE 2 DIABETES



Diabetes Care. 2022;46(Supplement_1):S140-S157. doi:10.2337/dc23-S009

Which class is better for which patient?

Patient or provider preference or priority	SGLT2 inhibitor	GLP-1 receptor agonists
MI, stroke, or death	+++	+++
Heart Failure	+++	+
Weight Loss	+	+++
Kidney disease benefit	+++	++
Route	Oral	Subcutaneous or oral
Considerations that may prompt the use of the alternate class	• Severely reduced kidney function • Prior amputation • History of recurrent genital fungal infection • History of DKA • History of fracture	• Persistent nausea • History of gastroparesis • Active gallbladder disease

Das SR, Everett BM, et al. ACC ECDP JACC 2020. pp. 1117–45. doi: 10.1016/j.jacc.2020.05.037

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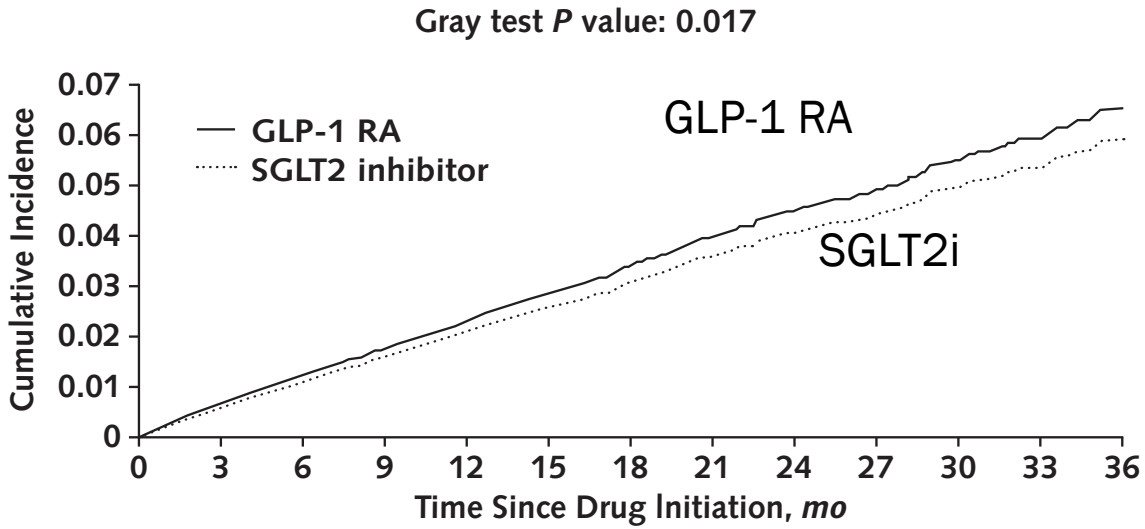
Observational Analyses:
SGLT2i vs. GLP-1RA in Patients with Established CVD

Composite CV Outcome

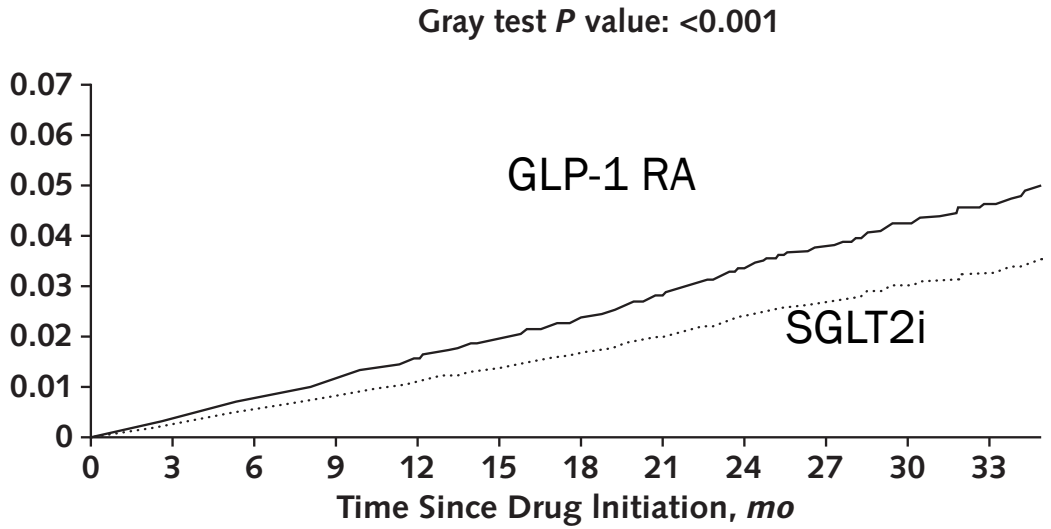
Hospitalization for Heart Failure

Patients with history of CVD



GLP-1 RA	52901	45918	27704	19288	14071	10834	8269	6213	4713	3612	2726	1921	1344
SGLT2 inhibitor	52901	46023	29108	20961	15387	12035	9321	7167	5506	4289	3319	2451	1827

HR 0.90 (0.82-0.98)

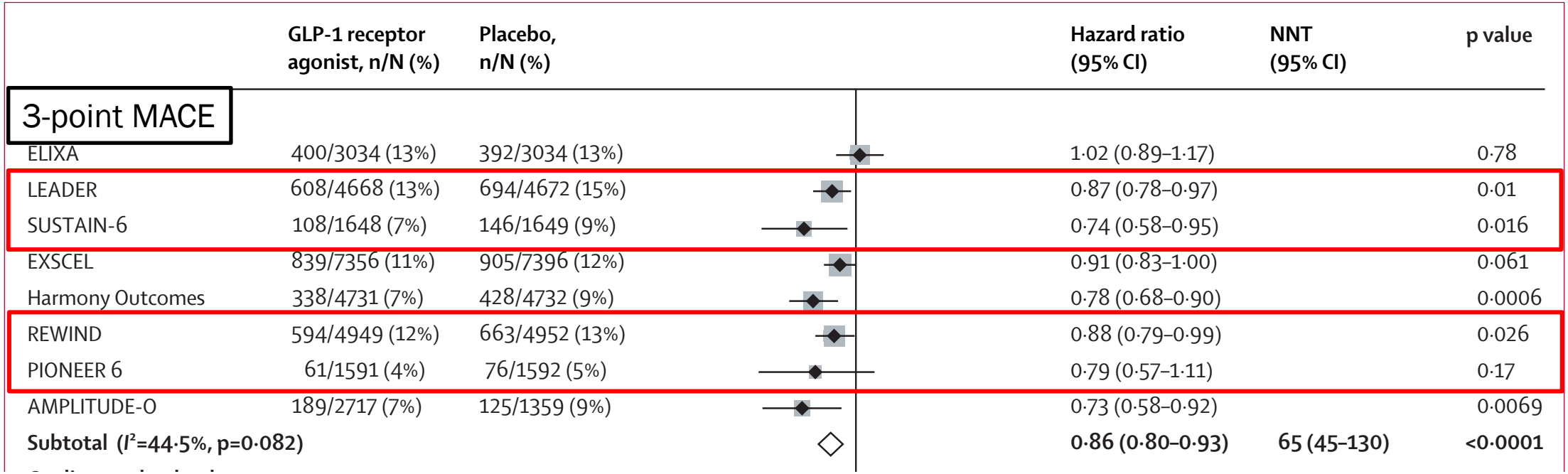


52901	46004	27775	19346	14129	10902	8333	6256	4740	3631	2748	1942
52901	46119	29240	21092	15502	12147	9403	7253	5585	4368	3382	2502

HR 0.71 (0.64-0.79)

Patorno, Glynn, Wexler, Everett, Kim et al. Ann Intern Med. doi:10.7326/M21-0893

Meta-analysis of placebo-controlled randomized trials
GLP-1RA: Hazard ratio for MI, stroke, CV Death



	GLP-1 receptor agonist, n/N (%)	Placebo, n/N (%)	Hazard ratio (95% CI)	NNT (95% CI)	p value
3-point MACE					
ELIXA	400/3034 (13%)	392/3034 (13%)	1·02 (0·89–1·17)		0·78
LEADER	608/4668 (13%)	694/4672 (15%)	0·87 (0·78–0·97)		0·01
SUSTAIN-6	108/1648 (7%)	146/1649 (9%)	0·74 (0·58–0·95)		0·016
EXSCEL	839/7356 (11%)	905/7396 (12%)	0·91 (0·83–1·00)		0·061
Harmony Outcomes	338/4731 (7%)	428/4732 (9%)	0·78 (0·68–0·90)		0·0006
REWIND	594/4949 (12%)	663/4952 (13%)	0·88 (0·79–0·99)		0·026
PIONEER 6	61/1591 (4%)	76/1592 (5%)	0·79 (0·57–1·11)		0·17
AMPLITUDE-O	189/2717 (7%)	125/1359 (9%)	0·73 (0·58–0·92)		0·0069
Subtotal (I^2=44·5%, p=0·082)			**0·86 (0·80–0·93)**	**65 (45–130)**	**<0·0001**

HR 0.86 (0.80-0.93)

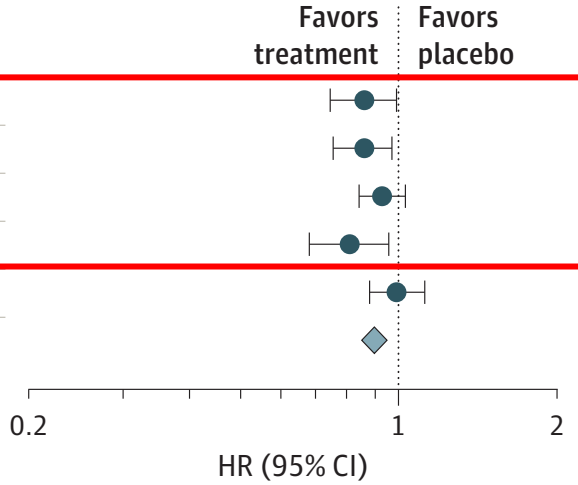
Sattar et al. Lancet Diabetes Endocrinol 2021 9: 653–62

Meta-analysis of placebo-controlled randomized trials SGLT2i: Hazard ratio for MI, stroke, CV Death

Figure 1. Effects of Sodium-Glucose Cotransporter 2 Inhibitors on Major Adverse Cardiovascular Events—Composite of Myocardial Infarction, Stroke, or Cardiovascular Death

A Overall MACEs

	Treatment		Placebo					
	No./total No.	Rate/1000 patient-years	No./total No.	Rate/1000 patient-years	Hazard ratio (95% CI)	Favors treatment	Favors placebo	Weight, %
EMPA-REG OUTCOME	490/4687	37.4	282/2333	43.9	0.86 (0.74-0.99)			15.72
CANVAS program	NA/5795	26.9	NA/4347	31.5	0.86 (0.75-0.97)			20.12
DECLARE-TIMI 58	756/8582	22.6	803/8578	24.2	0.93 (0.84-1.03)			32.02
CREDENCE	217/2202	38.7	269/2199	48.7	0.80 (0.67-0.95)			10.92
VERTIS CV	735/5499	40.0	368/2747	40.3	0.99 (0.88-1.12)			21.23
Fixed-effects model ($Q = 5.22$; $df = 4$; $P = .27$; $I^2 = 23.4\%$)					0.90 (0.85-0.95)			



HR 0.90 (0.85-0.95)

McGuire et al. *JAMA Cardiol*. 2021;6(2):148-158. doi:10.1001/jamacardio.2020.4511

Inescapable bias hampers observational studies
Could pragmatic trials be a possible solution?

- Sources of bias
  - Allocation bias
  - Time-lag bias
- Other issues: short duration on medication (6-8 months)

- One solution?
  - Pragmatic randomized trials
  - The randomization step eliminates bias inherent to observational trials

    … while not solving all problems!

GLP-1RA vs. SGLT2i

Funded by PCORI through
Phased Large Awards for Comparative Effectiveness Research (PLACER) Mechanism

Feasibility Phase: 1.5 years
Full Phase: 5 years

PRECIDENTD Specific Aims

Aim 1: Head-to-head evaluation of SGLT2i versus GLP-1 RA for the the prevention of major adverse cardiovascular and kidney events and death

Aim 2: Compare SGLT2i and GLP-1RA on the burden of adverse events of special interest, measures of global health and treatment satisfaction

Currently in the full study phase after a pilot phase that previously included a combination arm

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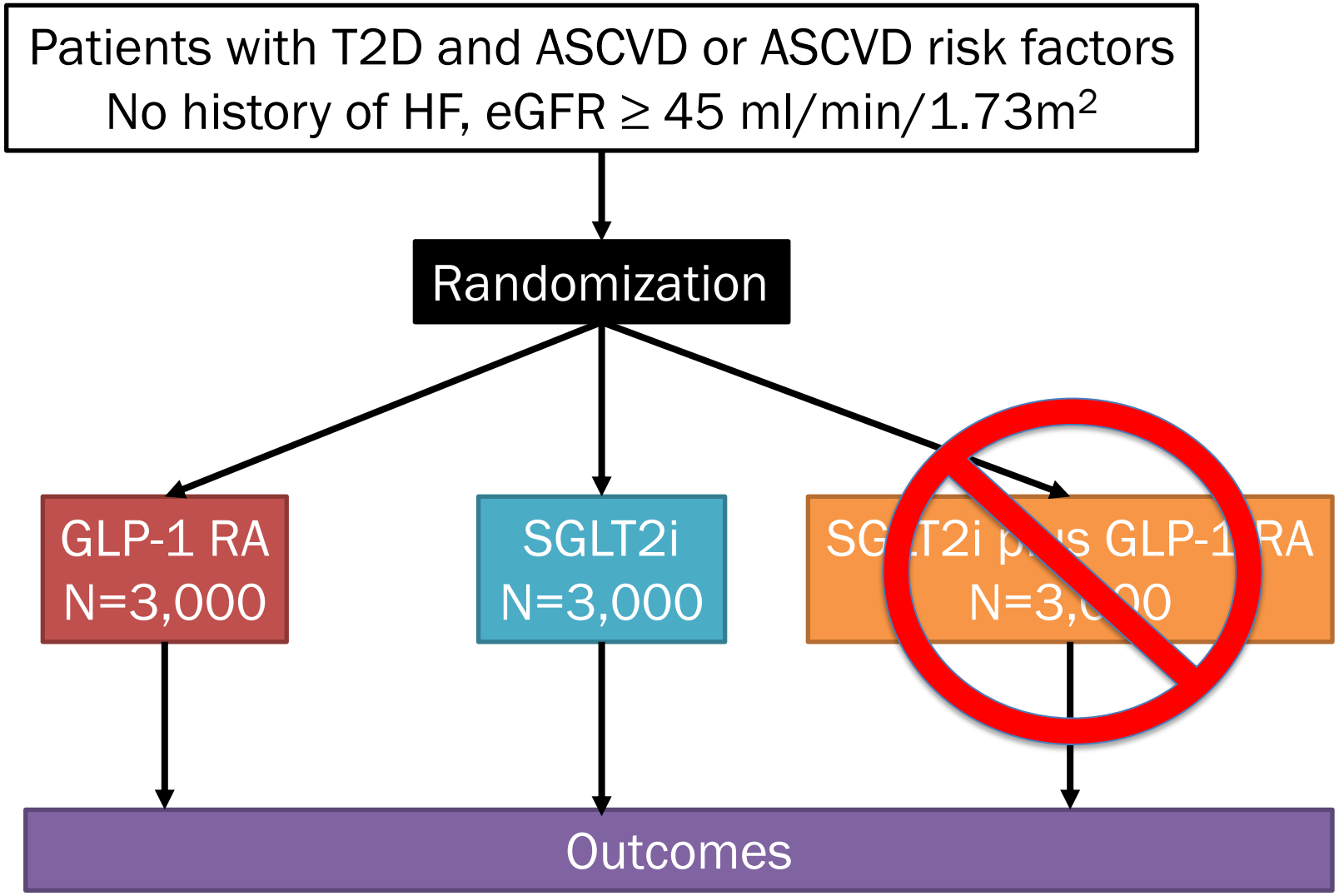
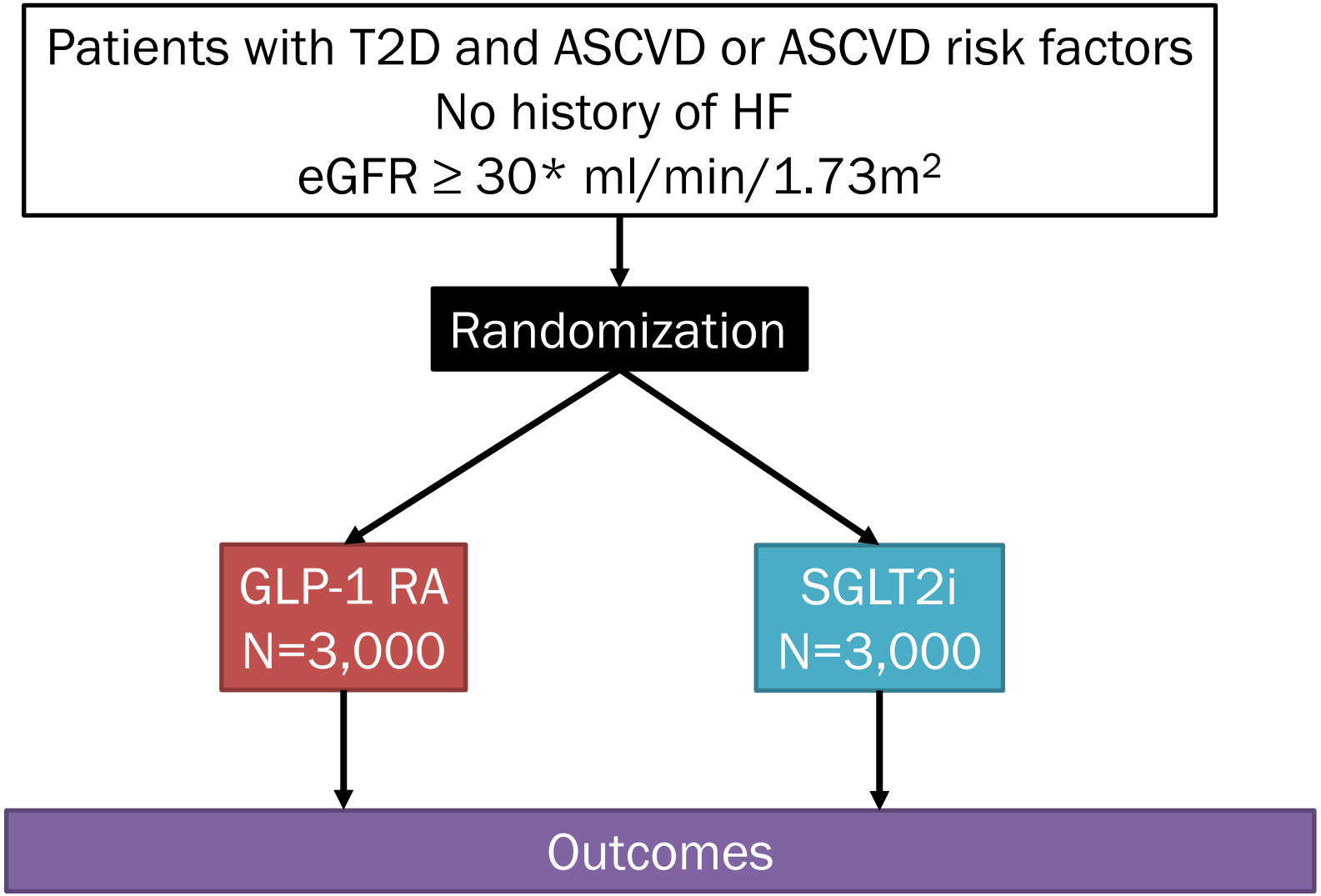
Original study design – feasibility phase



PRECIDENTD: Full trial study design



*Post-FLOW; final IRB review pending

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Intervention

- Random allocation to SGLT2i or GLP-1 RA

- Site investigator will write a prescription for whichever drug in the assigned class is covered by the patient's pharmacy benefit plan and help start the participant on medication

- Patient fills preferred medication within class through their own pharmacy/insurance

The conversation…

Clinician:

- "There are two new medications recommended for people with ASCVD and type 2 diabetes."
- "Both will reduce your risk of major cardiac events, like heart attack, stroke, and death, and also help lower HbA1c and weight."

Patient:

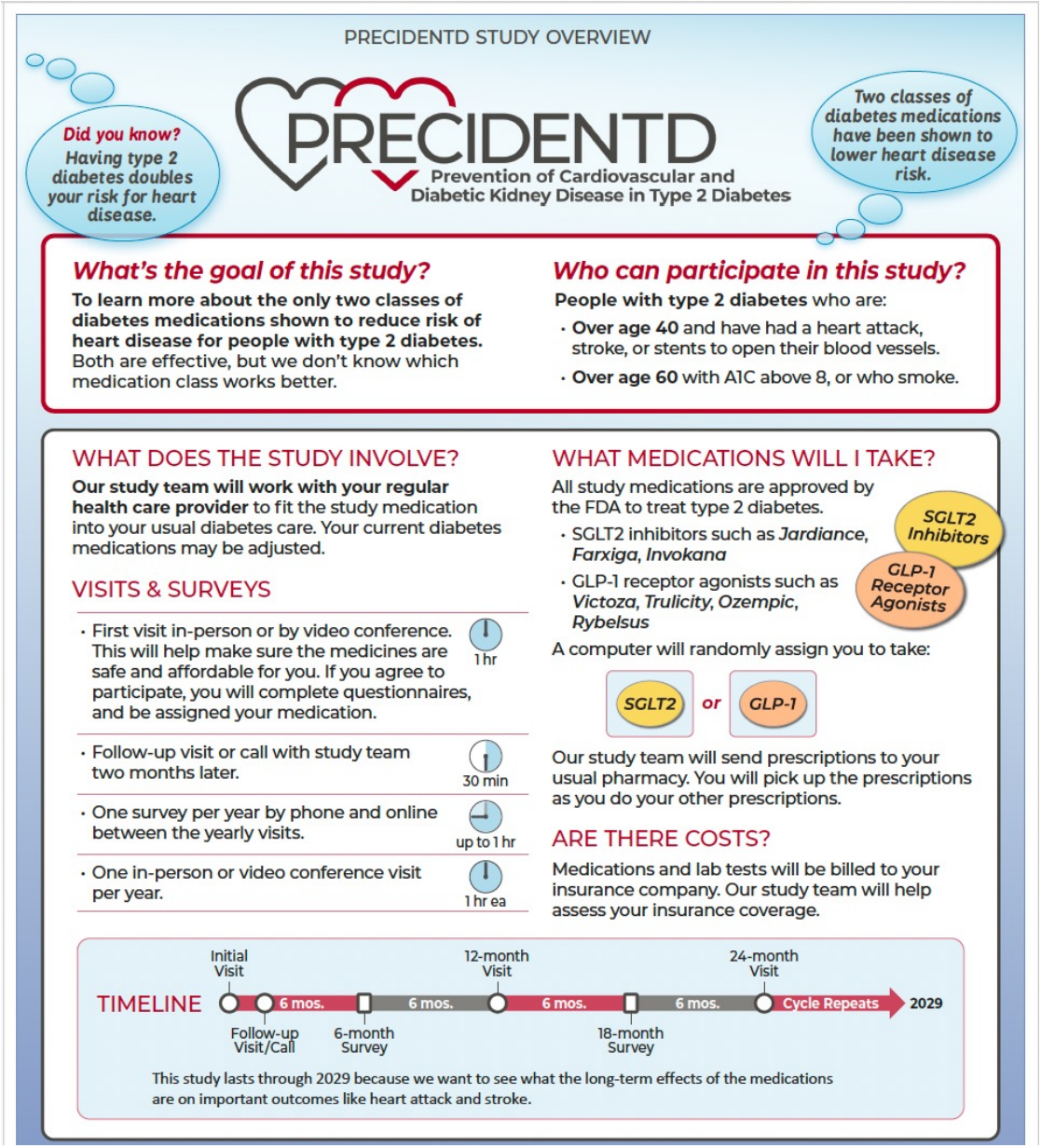
- "Which one should I take? Which one is better for my heart? What would you recommend?"

Clinician:

- "Right now, we don't know which one is better."
- "Would you be willing to help us answer that question?"

Patient, provider, and stakeholder engagement is crucial

- Engagement strategies
  - Community Engagement Studios
  - Center for Effective Health Communication
  - MEMOTEXT interactive text messaging to assess adherence
- Outstanding team
  - Lindsay Mayberry PhD, Lyndsay Nelson PhD, and team at Vanderbilt



Partnership and engagement: keys to the success of this pragmatic trial

- What will study team do?
  - Recruit
  - Randomize
  - Prescribe
  - Educate the patient and perform initial medication titration
  - Communicate with usual diabetes care provider at all clinical touchpoints through the EHR
  - Collect outcomes
- What will usual care providers do?
  - Refer patients
  - Collaborate in medication prescribing
  - Attempt to maintain participant on the assigned study medication regimen while adjusting other diabetes medications as needed for safety.

Engagement for recruitment, consistent messaging, usability, process improvement, adherence (MEMOTEXT) and so much more

PRECIDENTD: A key test of pragmatic trials

Patient Identification in a Pragmatic Trial

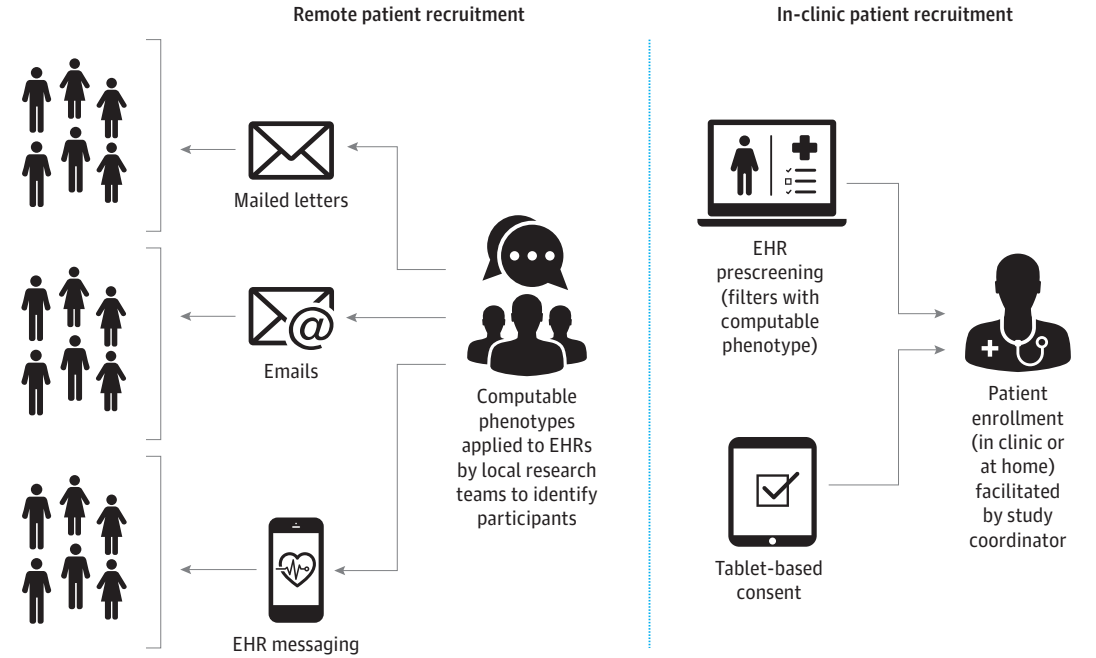
"Computable Phenotype" for use in PCORnet common data model

- Code adjustment for local data conventions
- "Stale" data – typically updated every 3 months or longer
- All patients, regardless of involvement with the health system, are weighted equally
- Not possible to concurrently identify eligible patients when they are in a clinic (e.g., cardiology or primary care)

"EHR screening" model

- Addresses many of these concerns
- Can facilitate "MyChart" or similar direct-to-patient messaging
- Requires independent coding and IT resources at each site

Figure 1. Recruitment Approaches



Marquis-Gravel G, et al. JAMA Cardiol. 2020 Mar 18. doi: 10.1001/jamacardio.2020.0116

Informed Consent in a Pragmatic Trial

- **Obtaining informed consent is time-consuming, challenging, and individualized**
  - **Nothing about it is pragmatic!**

- PRECIDENTD views the study as a partnership with patients and potential study participants
  - In all trials, participants donate their time and energy
  - In PRECIDENTD, they also pay for their study medicine
  - The goal of answering the primary study question must be shared by everyone involved, including study participants

- The study must support the time and effort of the study investigators, coordinators, and participants in order to be successful

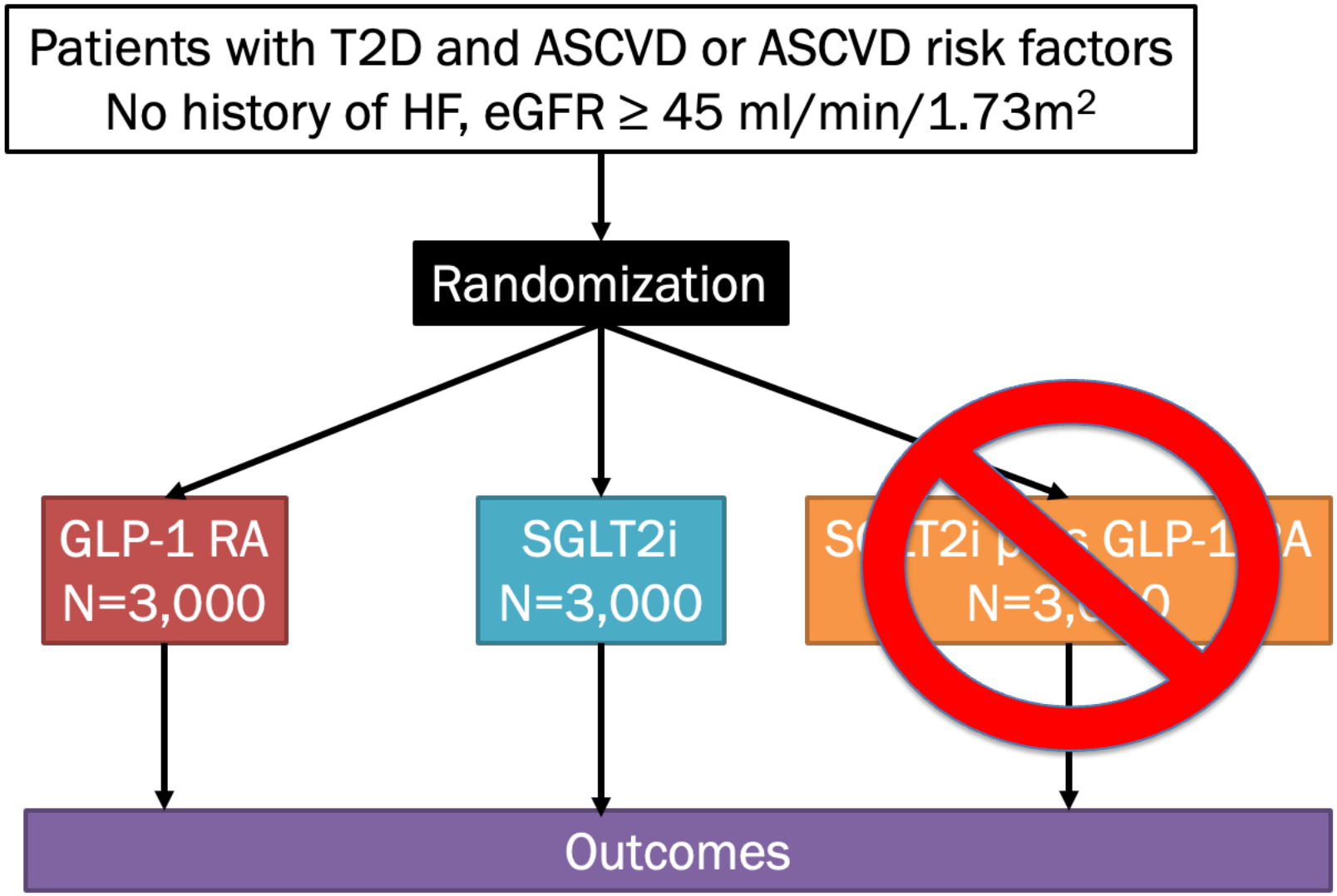
Outcome ascertainment in a Pragmatic Trial

- The dream
  - Collect outcomes through PCORnet common data model
  - Pitfalls:
    - Missing data (out-of-network events)
    - Lack of patient-reported outcomes
    - Non PCORnet sites cannot participate

- The reality: Belt-and-suspenders approach
  - PCORnet outcome queries AND
  - Site and patient-reported outcomes through REDCap electronic data capture system, validated through electronic health record review

Lessons from the feasibility phase

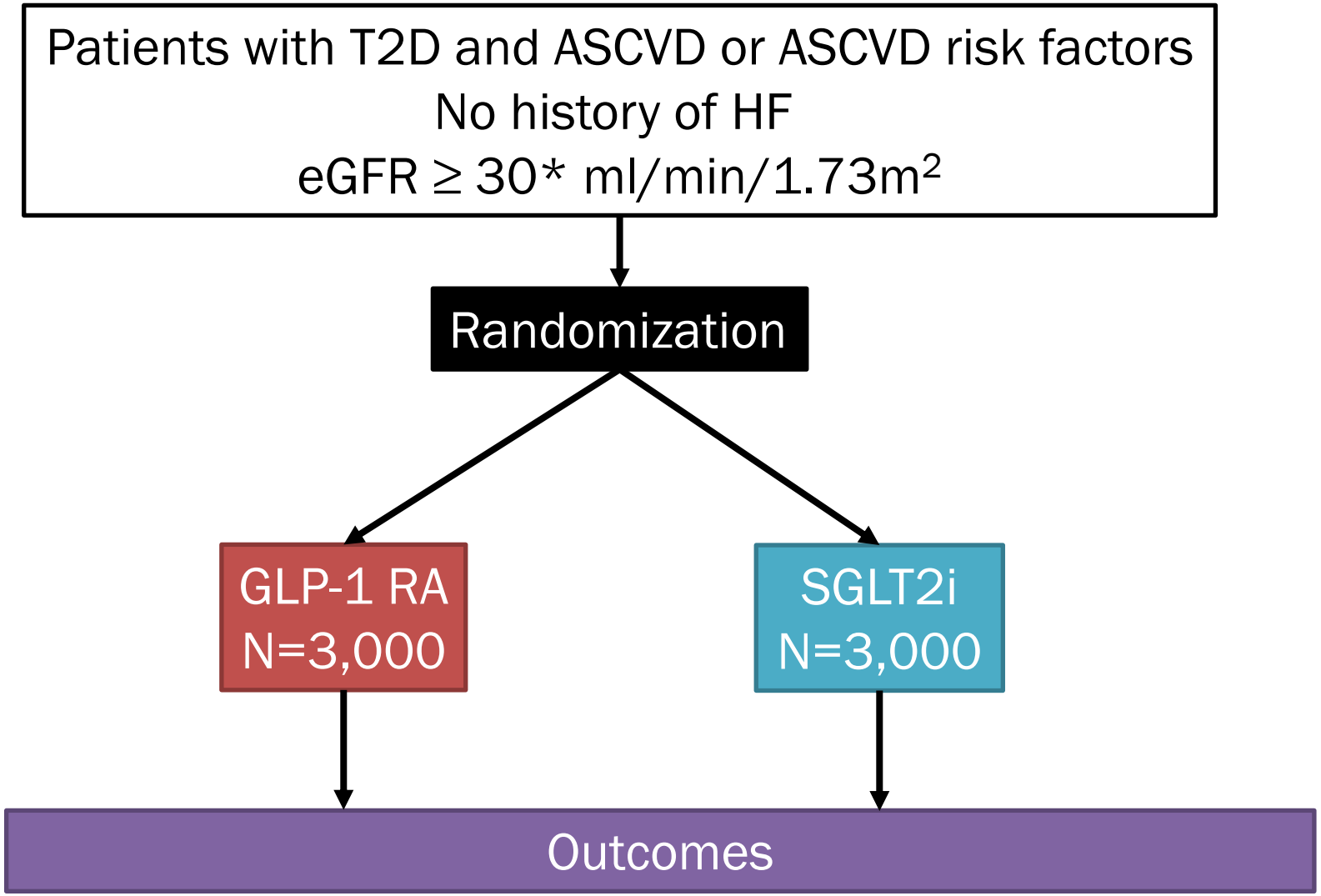
Original study design – feasibility phase



Three Major Challenges to Reaching Enrollment Goals

- ✅ Delays in IRB approval
- ✅ Site payments are not sufficient to support coordinator effort
- ✅ Study drug cost
  - Enrollment
  - Adherence
  - Cost issues may be particularly acute in the combination therapy arm

PRECIDENTD: Full trial study design



*Post-FLOW; final IRB review pending

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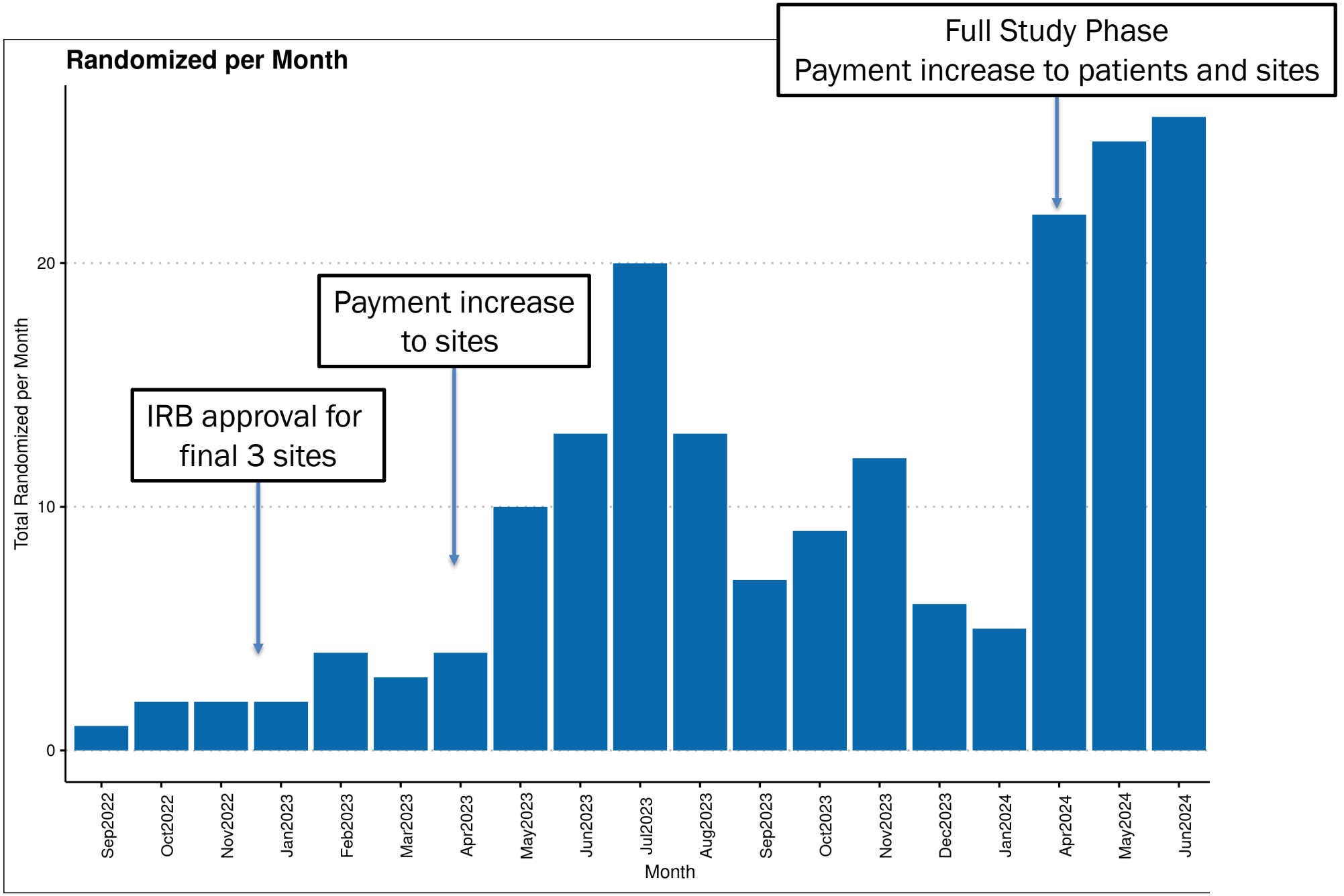
How did we arrive at this suggested trial modification? Stakeholder feedback (patients, sites, and professional leaders)

- Combination therapy presents unique challenges for a pragmatic trial
  - Cost and adherence
- Ongoing trials may be able to address combination vs. monotherapy through secondary analyses
  - e.g. recently published SMART-C meta-analysis*
- Monotherapy comparison
  - Relevant for primary care physicians and patients
  - No other large trial is testing this question
  - Feasible to answer with 6,000 patients randomized (rather than 9,000)

**Lancet Diabetes Endocrinol 2024* (July 8) *https://doi.org/10.1016/S2213-8587(24)00155-4*

Pros and cons of feasibility to full phase mechanism

- In theory:
  - Feasibility phase, with limited funding, is designed to demonstrate feasibility while allowing minor modifications for a full trial phase
- In practice:
  - Yes, this is true.
- But:
  - Constrained funding in feasibility phase may hamper growth of the trial
  - The practical challenges of even minor changes in study design in a bureaucratic research environment are real


Randomized per Month
Full Study Phase
Payment increase to patients and sites
Payment increase
to sites
IRB approval for
final 3 sites
Total Randomized per Month
0
10
20
Sep2022
Oct2022
Nov2022
Jan2023
Feb2023
Mar2023
Apr2023
May2023
Jun2023
Jul2023
Aug2023
Sep2023
Oct2023
Nov2023
Dec2023
Jan2024
Apr2024
May2024
Jun2024
Month

Feasibility Phase: Baseline Characteristics

	Monotherapy (N=113)	Dual Therapy (N=60)	Total (N=173)
Cohort– n(%)			
Primary	37 (32.7%)	21 (35.0%)	58 (33.5%)
Secondary	76 (67.3%)	39 (65.0%)	115 (66.5%)
Age Group– n(%)			
<65	46 (40.7%)	23 (38.3%)	69 (39.9%)
$\geq$ to 65	67 (59.3%)	37 (61.7%)	104 (60.1%)
Age at Screening			
N	113 (100.0%)	60 (100.0%)	173 (100.0%)
Median (IQR)	66 (62, 72)	68 (62, 74.2)	67 (62, 72)
Weight (lbs)			
N	113 (100.0%)	60 (100.0%)	173 (100.0%)
Median (IQR)	205 (179, 236)	200.5 (173.2, 240)	204 (175, 237)
BMI			
N	113 (100.0%)	60 (100.0%)	173 (100.0%)
Median (IQR)	32.1 (27.6, 36.5)	32.4 (27.9, 38.1)	32.3 (27.7, 36.8)
Gender– n(%)			
Male	64 (56.6%)	29 (48.3%)	93 (53.8%)
Female	49 (43.4%)	31 (51.7%)	80 (46.2%)
Non-binary	0	0	0
Other	0	0	0

Feasibility Phase: Baseline self-reported race, ethnicity, education

	Monotherapy (N=113)	Dual Therapy (N=60)	Total (N=173)
Race– n(%)			
Am. Indian/Alaska Native	0	0	0
Asian	6 (5.4%)	3 (5.0%)	9 (5.3%)
Black/African-American	32 (28.8%)	12 (20.0%)	44 (25.7%)
Hawaiian/Pacific Islander	0	0	0
White/Caucasian	71 (64.0%)	43 (71.7%)	114 (66.7%)
Multi-Race	0	1 (1.7%)	1 (0.6%)
Prefer Not to Answer	1 (0.9%)	0	1 (0.6%)
Unknown	1 (0.9%)	0	1 (0.6%)
Other	0	1 (1.7%)	1 (0.6%)
Hispanic– n(%)			
Yes	3 (2.7%)	0	3 (1.7%)
No	105 (92.9%)	59 (98.3%)	164 (94.8%)
Unknown	4 (3.5%)	1 (1.7%)	5 (2.9%)
Prefer not to Answer	1 (0.9%)	0	1 (0.6%)
Education– n(%)			
< 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%)
Bachelor's Degree	32 (28.3%)	9 (15.0%)	41 (23.7%)
Graduate Degree	20 (17.7%)	22 (36.7%)	42 (24.3%)

Feasibility Phase: Baseline medical comorbidities

Medical History	Monotherapy (N=113)	Dual Therapy (N=60)	Total (N=173)
Hospitalized for Heart Failure > 12 months ago	14 (12.4%)	10 (16.7%)	24 (13.9%)
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%)
Blockages of Heart Blood Vessels[1]	53 (46.9%)	28 (46.7%)	81 (46.8%)
Blockages of Blood Vessels in Brain or Neck[2]	3 (2.7%)	1 (1.7%)	4 (2.3%)
Blockages of Blood Vessels in Legs[3]	5 (4.4%)	2 (3.3%)	7 (4.0%)
CABG[4]	18 (15.9%)	9 (15.0%)	27 (15.6%)
Atrial Fibrillation	18 (15.9%)	10 (16.7%)	28 (16.2%)
Aortic Stenosis			
Yes	8 (7.1%)	0	8 (4.6%)
No	98 (86.7%)	58 (96.7%)	156 (90.2%)
Unknown	7 (6.2%)	2 (3.3%)	9 (5.2%)
Diabetic Neuropathy	41 (36.3%)	20 (33.3%)	61 (35.3%)
Treated for Diabetic Eye Disease	3 (2.7%)	5 (8.3%)	8 (4.6%)

Feasibility Phase: Baseline diabetes medication use

	Monotherapy (N=113)	Dual Therapy (N=60)	Total (N=173)
Insulin Use	28 (24.8%)	16 (26.7%)	44 (25.4%)
Metformin	77 (68.1%)	45 (75.0%)	122 (70.5%)
Sulfonylurea or Glinide	21 (18.6%)	11 (18.3%)	32 (18.5%)
DPP-4 Inhibitor	8 (7.1%)	5 (8.3%)	13 (7.5%)
GLP-1 Receptor Agonists	33 (29.2%)	21 (35.0%)	54 (31.2%)
SGLT2 Inhibitors	25 (22.1%)	10 (16.7%)	35 (20.2%)
Other Glucose Lowering Medication	11 (9.7%)	7 (11.7%)	18 (10.4%)

Feasibility Phase: Baseline cardiac medication use

	Monotherapy (N=113)	Dual Therapy (N=60)	Total (N=173)
Statins	95 (84.1%)	49 (81.7%)	144 (83.2%)
ACE Inhibitor	39 (34.5%)	20 (33.3%)	59 (34.1%)
ARBs	34 (30.1%)	23 (38.3%)	57 (32.9%)
Thiazide Diuretic	26 (23.0%)	11 (18.3%)	37 (21.4%)
Loop Diuretic	23 (20.4%)	12 (20.0%)	35 (20.2%)
Mineralocorticoid Antagonist	11 (9.7%)	6 (10.0%)	17 (9.8%)
Beta Blocker	55 (48.7%)	30 (50.0%)	85 (49.1%)
Other Blood Pressure Medications	27 (23.9%)	16 (26.7%)	43 (24.9%)
Injectable Cholesterol Medication	8 (7.1%)	5 (8.3%)	13 (7.5%)
Other Lipid Lowering Medications	23 (20.4%)	12 (20.0%)	35 (20.2%)
Aspirin Use	60 (53.1%)	37 (61.7%)	97 (56.1%)
Other Anti-Platelet Drugs	15 (13.3%)	6 (10.0%)	21 (12.1%)
Anticoagulant	16 (14.2%)	13 (21.7%)	29 (16.8%)

Feasibility Phase: Health insurance and affordability

	Monotherapy (N=113)	Dual Therapy (N=60)	Total (N=173)
Health Insurance– n(%)			
Yes	112 (99.1%)	60 (100.0%)	172 (99.4%)
No	1 (0.9%)	0	1 (0.6%)
Type of Health Insurance[1]– n(%)			
Employer/Union	34 (21.5%)	19 (23.8%)	53 (22.3%)
Personally Purchased	15 (9.5%)	9 (11.2%)	24 (10.1%)
Medicare	67 (42.4%)	35 (43.8%)	102 (42.9%)
Medicaid	15 (9.5%)	8 (10.0%)	23 (9.7%)
Other	26 (16.5%)	8 (10.0%)	34 (14.3%)
Missing	1 (0.6%)	1 (1.2%)	2 (0.8%)
Affordability of Medication– n(%)			
Yes	113 (100.0%)	60 (100.0%)	173 (100.0%)
No	0	0	0
Unknown	0	0	0

[1] Type of health insurance is not unique and is shown as the top four types of health insurance plus insurance missing, the rest are categorizes as Other

Adherence in a Pragmatic Trial: How many pick up their new study medicine?

- Unpublished outcome data that we cannot share in this forum

- However, rates medication adherence were substantially lower in the combination therapy arm compared to monotherapy arms
  - Expected initial pick-up: 30% lower in combination therapy arm
  - Pick-up rate at 10 weeks: 40% lower in combination therapy arm
  - Pick-up rate at 4 months: 30% lower in combination therapy arm

- Visit adherence decreased along with medication adherence and was lower in the combination therapy arm

Summary

- Comparative effectiveness of SGLT2 inhibitors and GLP-1 receptor agonists for cardiac and kidney outcomes is a major question in cardiac-kidney-metabolic health

- More broadly, comparative effectiveness of on-patent medications is crucial, yet not mandated, with little incentive (and some disincentive) for pharmaceutical companies to participate

- PRECIDENTD will answer this pressing clinical question, and test one approach to evaluating the comparative effectiveness of expensive new therapies

The PRECIDENTD Team

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Brendan Everett, MD
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Elaine Zaharris
Amy Casarella
Doris Chen
Todd Davison
Meg Perry
Ted Silva

Feasibility Phase Vanguard Clinical sites

Site	PI
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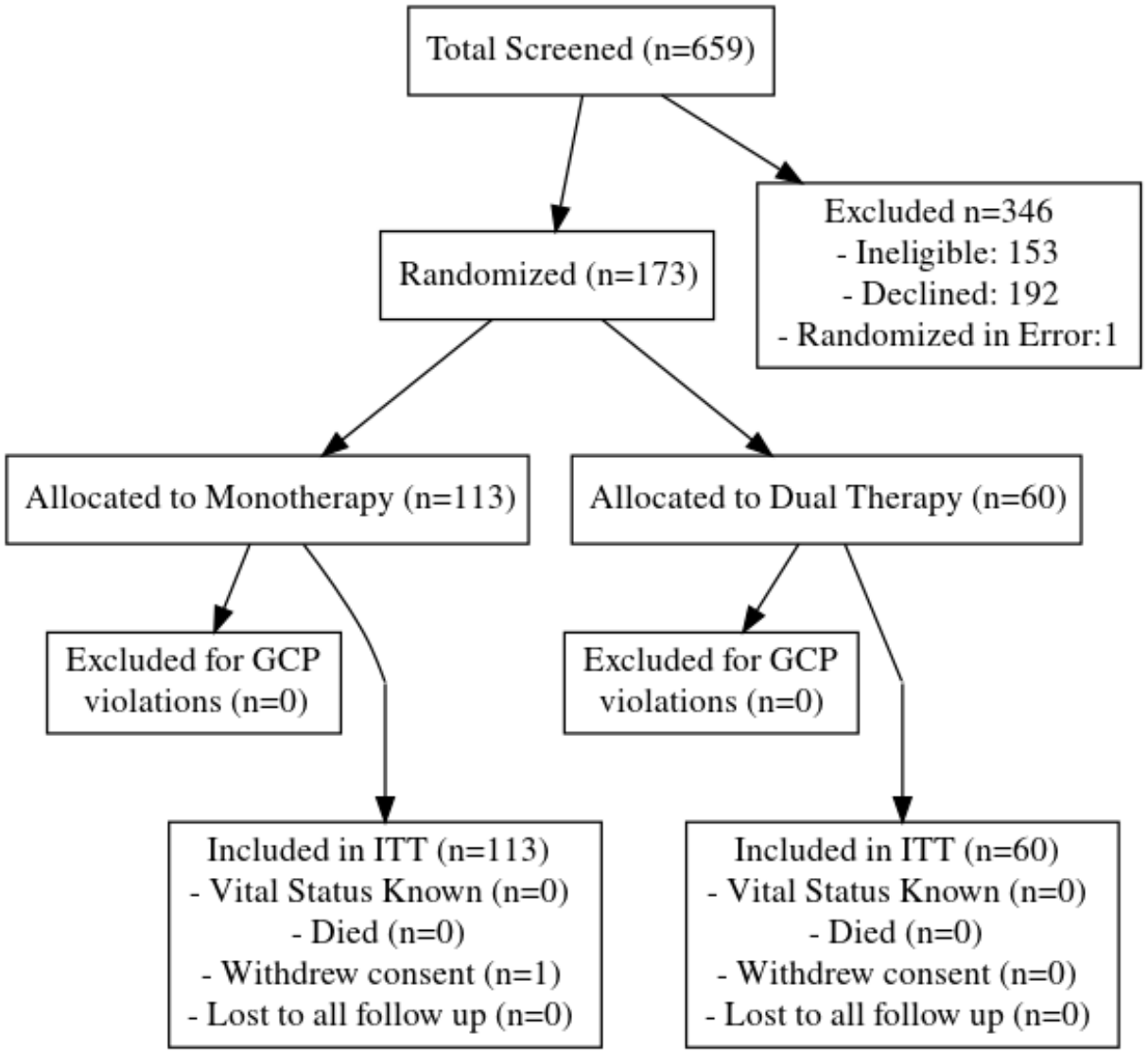
Medical University of South Carolina	Harsha Karanchi, MD
Duke	Schuyler Jones, MD
Vanderbilt	Leslie Maheny, MD
University of Missouri	Camila Manrique- Acevedo, MD
Medical College of Wisconsin	Jake Decker, MD
Essentia	Katie Benziger, MD

Questions and Discussion

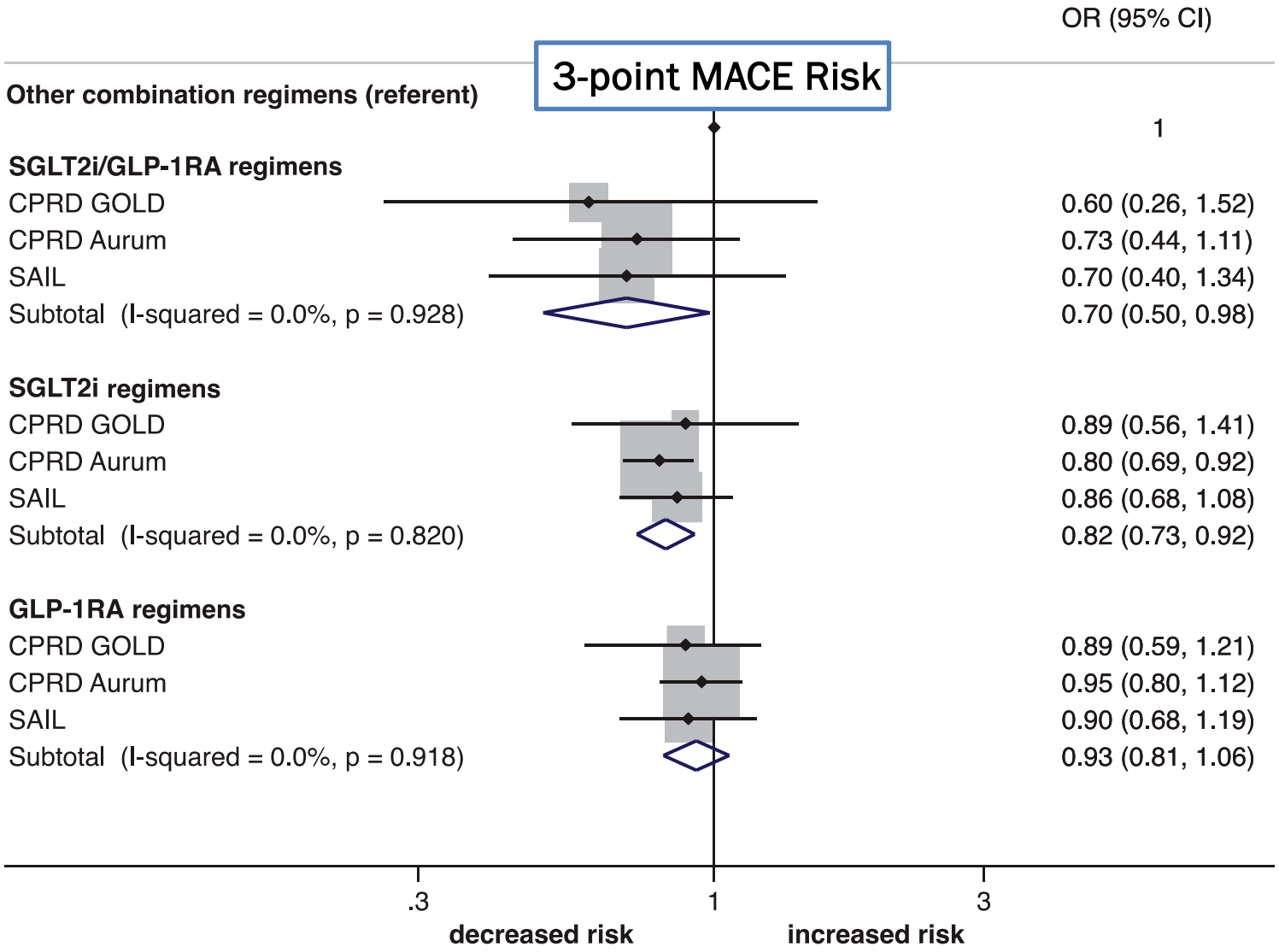
Feasibility Phase Enrollment and Baseline Characteristics

1.1 Consort Diagram for Feasibility Stage



SGLT2i, GLP-1RA, or the combination in patients without CVD
MACE outcome

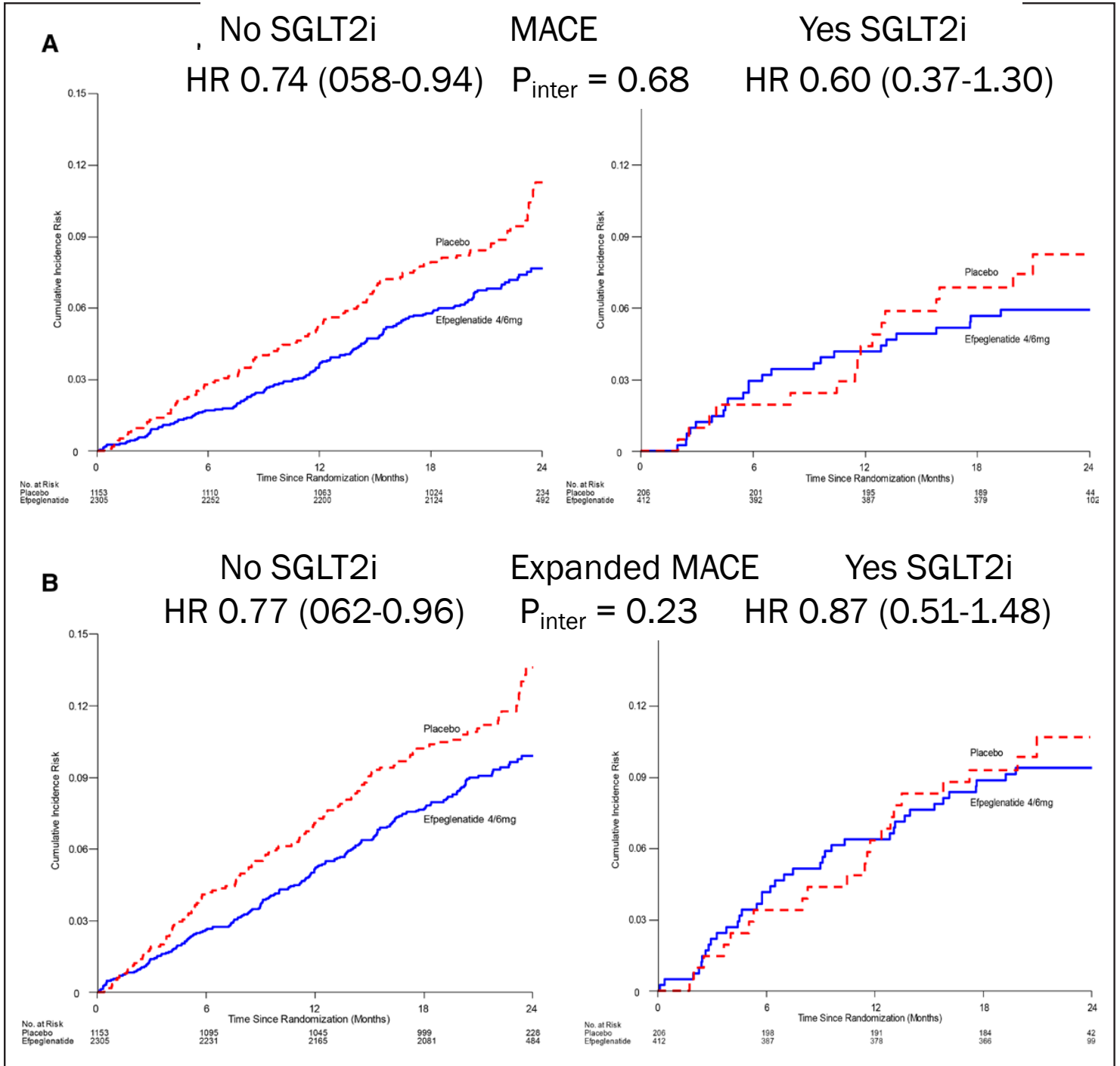
- Nested case-control data from England and Wales
- Calculated odds ratio for 3-point MACE associated with SGLT2i + GLP-1RA, SGLT2i, or GLP-1 RA regimens compared to other regimens
- There were 53 total events in the combination SGLT2i/GLP-1 RA regimen group



Wright et al. Diabetes Care 2022. https://doi.org/10.2337/dc21-1113

Randomly allocated GLP-1 RA on top of baseline SGLT2i: Data from AMPLITUDE-O

- Randomly allocated efpeglenitide had similar benefits regardless of baseline SGLT2i use
- Population had about 90% prevalence of CVD at baseline
- Similar benefits observed for MACE, expanded MACE, renal composite, MACE + death, and HHF



Lam et al. *Circulation*. 2022;145:565–574.
DOI: 10.1161/CIRCULATIONAHA.121.057934

Currently, SGLT2 inhibitors and GLP-1 receptor agonists are underutilized in patients at high risk

- Fewer than one in three patients with ASCVD, CKD, or heart failure are currently prescribed these medications
- Barriers
  - Lack of familiarity with medication
  - Need for education / titration
  - Cost to patient
  - Prior authorization

- Appropriate use is improving with time
  - Insurance coverage improving
- Study teams will address barriers
  - Teach patients
  - Pre-screen and troubleshoot for cost issues
  - Use systems to reduce burden of prior authorization