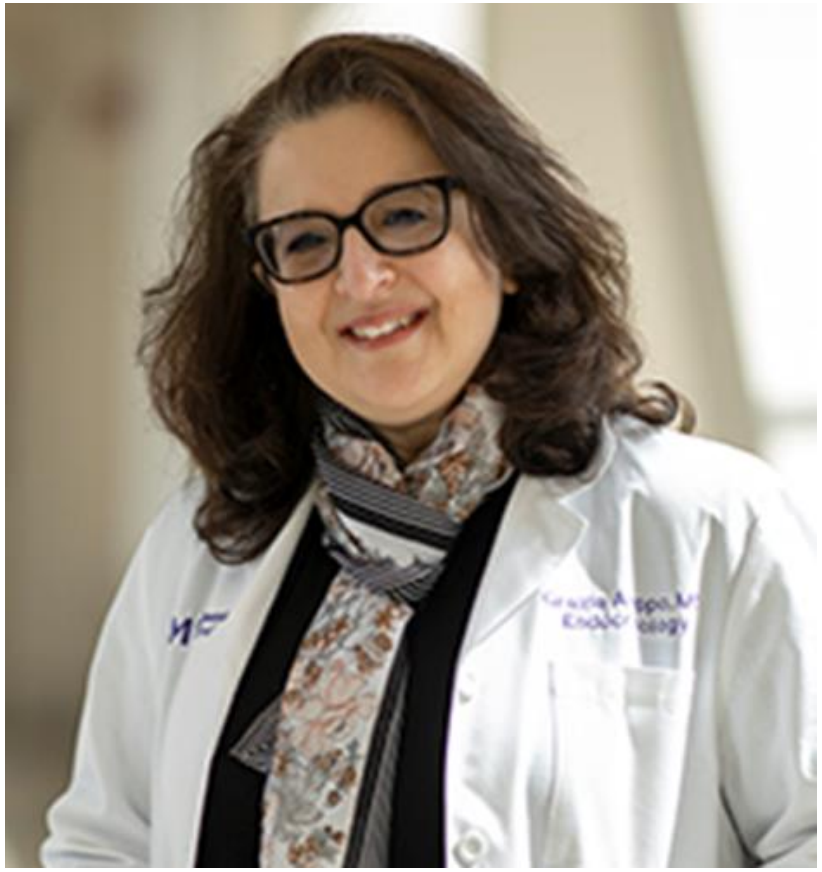
Updates on Inhaled Insulin



Grazia Aleppo, MD

Northwestern Medicine®

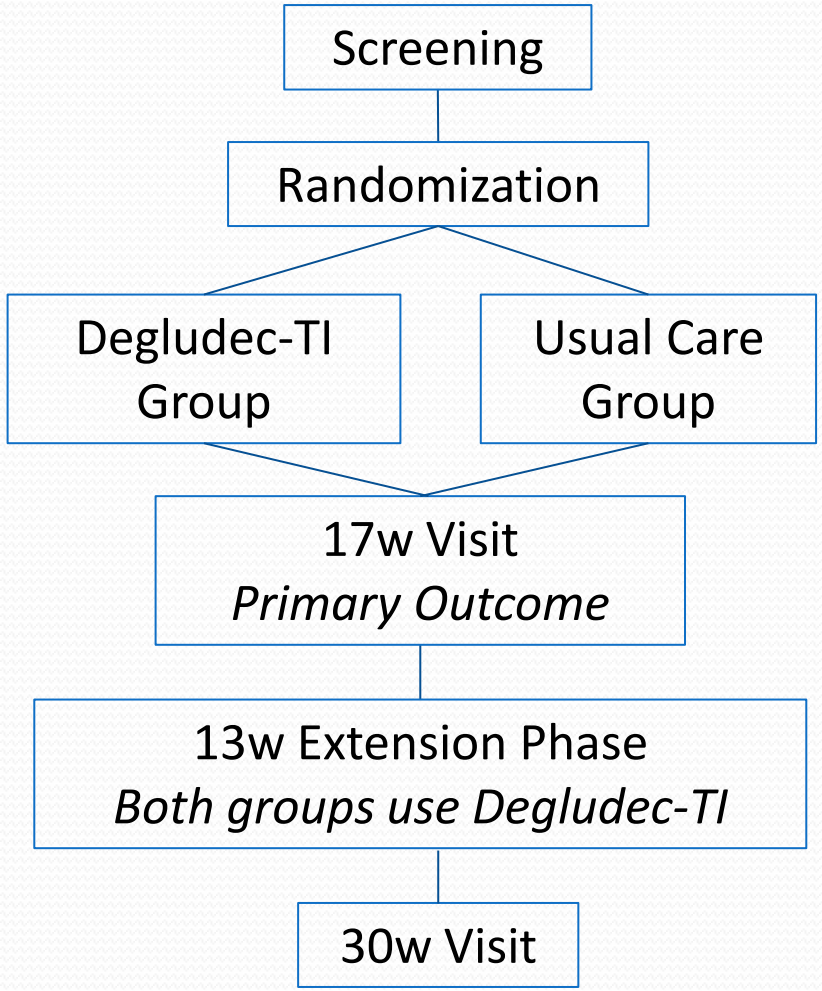
T1D Exchange

The Efficacy and Safety of Inhaled Insulin Used with Insulin Degludec Compared with Automated Insulin Delivery or Multiple Daily Insulin Injections in Adults with Type 1 Diabetes

Grazia Aleppo, MD
Professor of Medicine
Feinberg School of Medicine, Northwestern University

INHALE-3 Protocol Overview

- Study Design: Randomized Controlled Trial
- 1:1 random assignment to:
  - Degludec + technosphere insulin (TI), Dexcom G7
  - Usual care (AID, SAP, or MDI), personal CGM
- 17-wk RCT
  - First 4 wks used for dose titration
- 13-wk extension
  - Both groups use Degludec-TI



Hirsch IB, et al. Diabetes Care. 2024 Sep 1;47(9):1682-1687
Hirsch IB et al. Diabetes Care, 2024, in press

Eligibility Criteria/Baseline Procedures

- Key Inclusion Criteria
  - Age >18 years old
  - Type 1 diabetes for at least 6m
  - HbA1c <11.0% (point-of care)
  - Same insulin delivery method for 3mos: AID, SAP, MDI
  - TDI 20-100 units
  - Using CGM on regular basis

- Blinded Dexcom G6 Pro for 14d
  - *Participants continued to use their personal CGM and insulin delivery method*
- Blood draw for central lab HbA1c, FEV_1
- PROs
- Randomization to:
  - Degludec-TI group (with study Dexcom G7 CGM)
  - Usual Care group (continuation of pre-study insulin delivery and personal CGM)
- Meal Challenge using either RAA insulin or TI at baseline and 17 weeks

Hirsch IB, et al. Diabetes Care. 2024 Sep 1;47(9):1682-1687
Hirsch IB et al. Diabetes Care, 2024, in press

TI Group

Degludec dose

- Dosage titrated Q 3-5d day 1-10, then weekly through 4w (and ongoing through trial), targeting fasting glucose of 90-120 mg/dL without hypoglycemia

4-Unit Cartridge

8-Unit Cartridge

12-Unit Cartridge

Hirsch IB, et al. Diabetes Care. 2024 Sep 1;47(9):1682-1687
Hirsch IB et al. Diabetes Care, 2024, in press

TI

<u>Initial</u> Dose Based on Typical RAA Insulin for Amount of Carbs or Size of Meal
Converting from RAA units to bioequivalent "Afrezza Units"
Round # of RAA units to nearest whole number
Multiply by 2
Round down to nearest 4-unit cartridge

RAA Dose (Units)	TI Dose ("Afrezza Units")
≤3	4
4-5	8
6-7	12
8-9	16
10-11	20
≥12	24

TI Titration

- Week 1-4, meal dose titrated based on 1hr post-prandial CGM
  - If glucose >140 mg/dL, dose increased by 4 Afrezza units
  - If glucose >200 mg/dL dose increased by 8 Afrezza units
  - If pre-meal glucose 140-200 mg/dL, increase dose by 4 units
  - If pre-meal glucose >200 mg/dL, increase dose by 8 units
- Correction dose to be given 60-90min after prior dose if >140 mg/dL:
  - 4 units for 140-200 mg/dL
  - 8 units for >200 mg/dL during day
  - 4 units at bedtime or overnight

Hirsch IB, et al. Diabetes Care. 2024 Sep 1;47(9):1682-1687
Hirsch IB et al. Diabetes Care, 2024, in press

Study Outcomes

Efficacy

- Primary outcome: HbA1c at 17 wks, tested for non-inferiority
- CGM metrics: TIR, TITR, mean glucose, TAR, TBR
- Weight change
- PROs

Safety

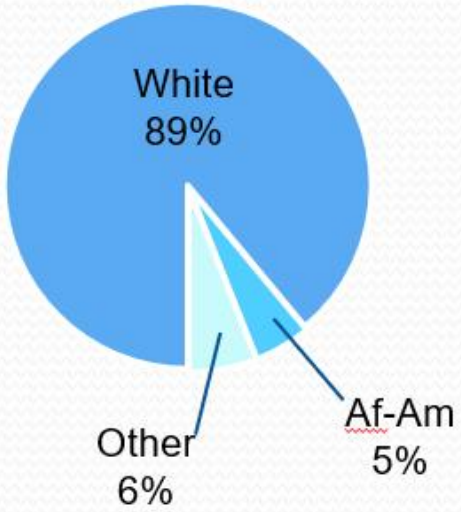
- Severe hypoglycemia
- DKA and other SAEs
- CGM measured time <54 mg/dL and events <54 mg/dL
- Change in FEV_1
- Bronchospasm, asthma exacerbation, hypersensitivity reaction

Hirsch IB, et al. Diabetes Care. 2024 Sep 1;47(9):1682-1687
Hirsch IB et al. Diabetes Care, 2024, in press

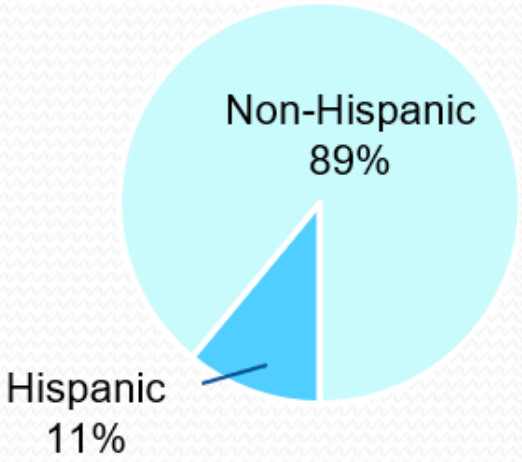
Baseline Characteristics (N=123)

Age *mean*	45 yrs (18-77)
Female	54%
Mean Diabetes Duration	23 yrs (1-64)
Education < Bachelors Degree	42%
Income <100K	41%
Private Insurance	81%
BMI *mean*	27.9 kg/m^2 (≥30, 31%)

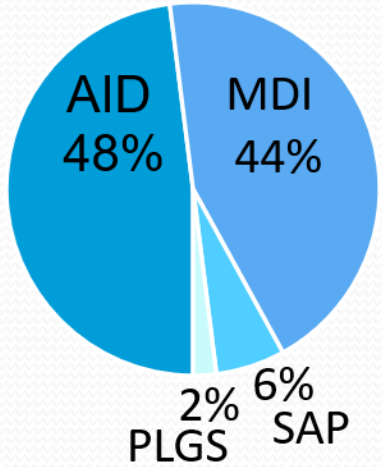
Race



Ethnicity



Insulin Delivery Method



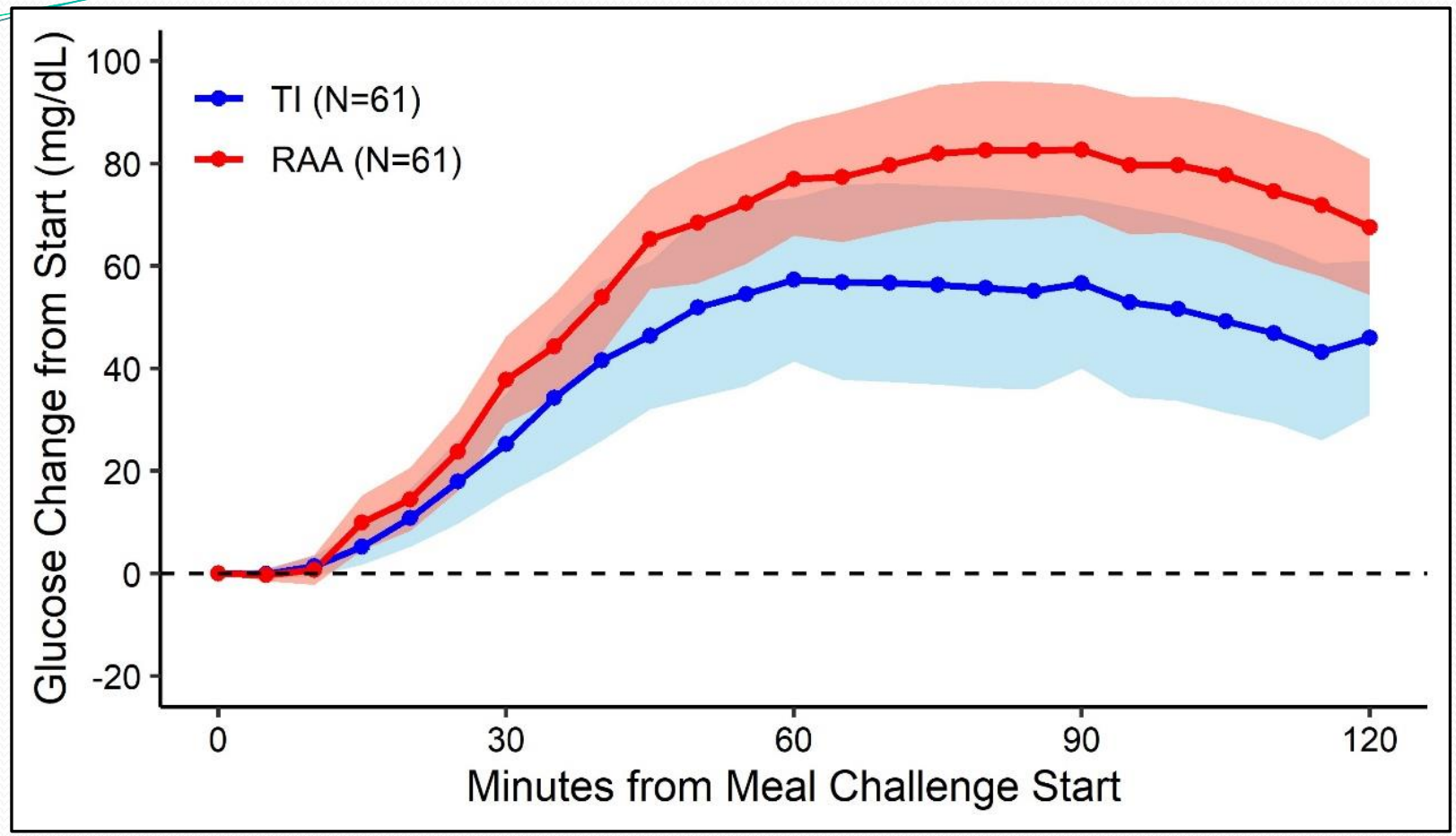
Total Daily Insulin Dose

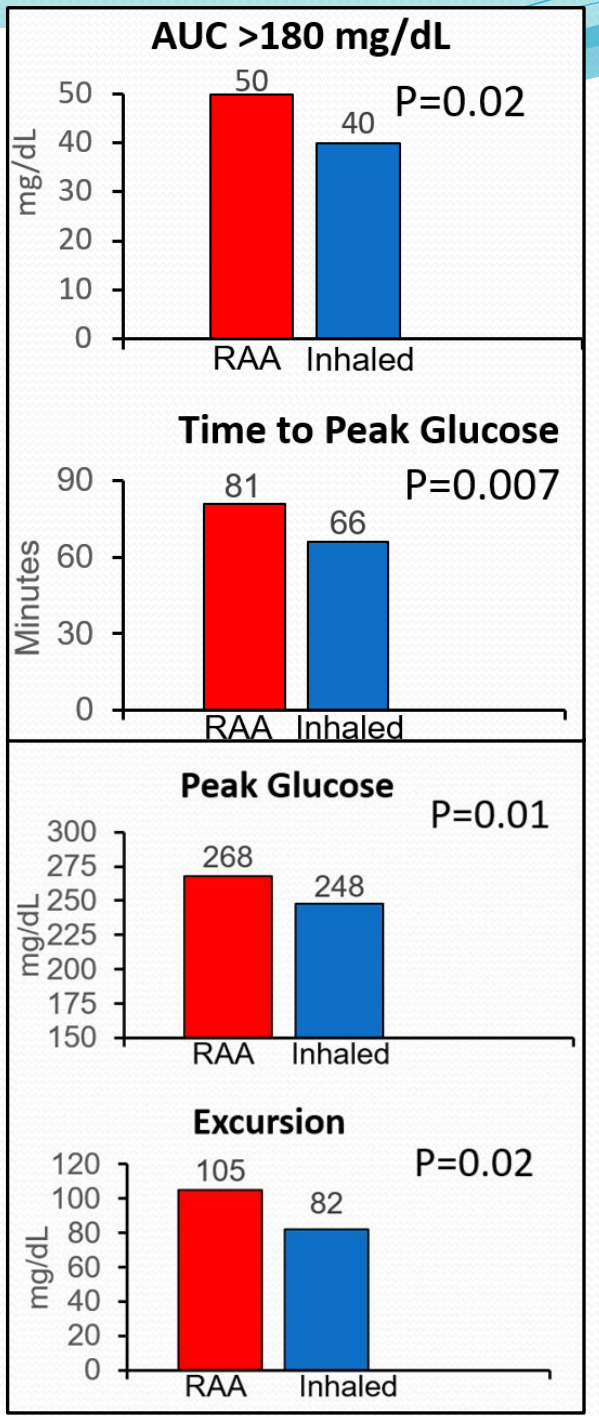
0.6 ± 0.2 units/kg/day

Bolus: Basal Ratio = 50%

Hirsch IB, et al. Diabetes Care. 2024 Sep 1;47(9):1682-1687
Hirsch IB et al. Diabetes Care, 2024, in press

Baseline Meal Challenge





Boost, 37 gm CHO, TI at start of meal or RAA 5-15 min prior to meal

AID continued (TI group: Control-IQ in sleep mode)

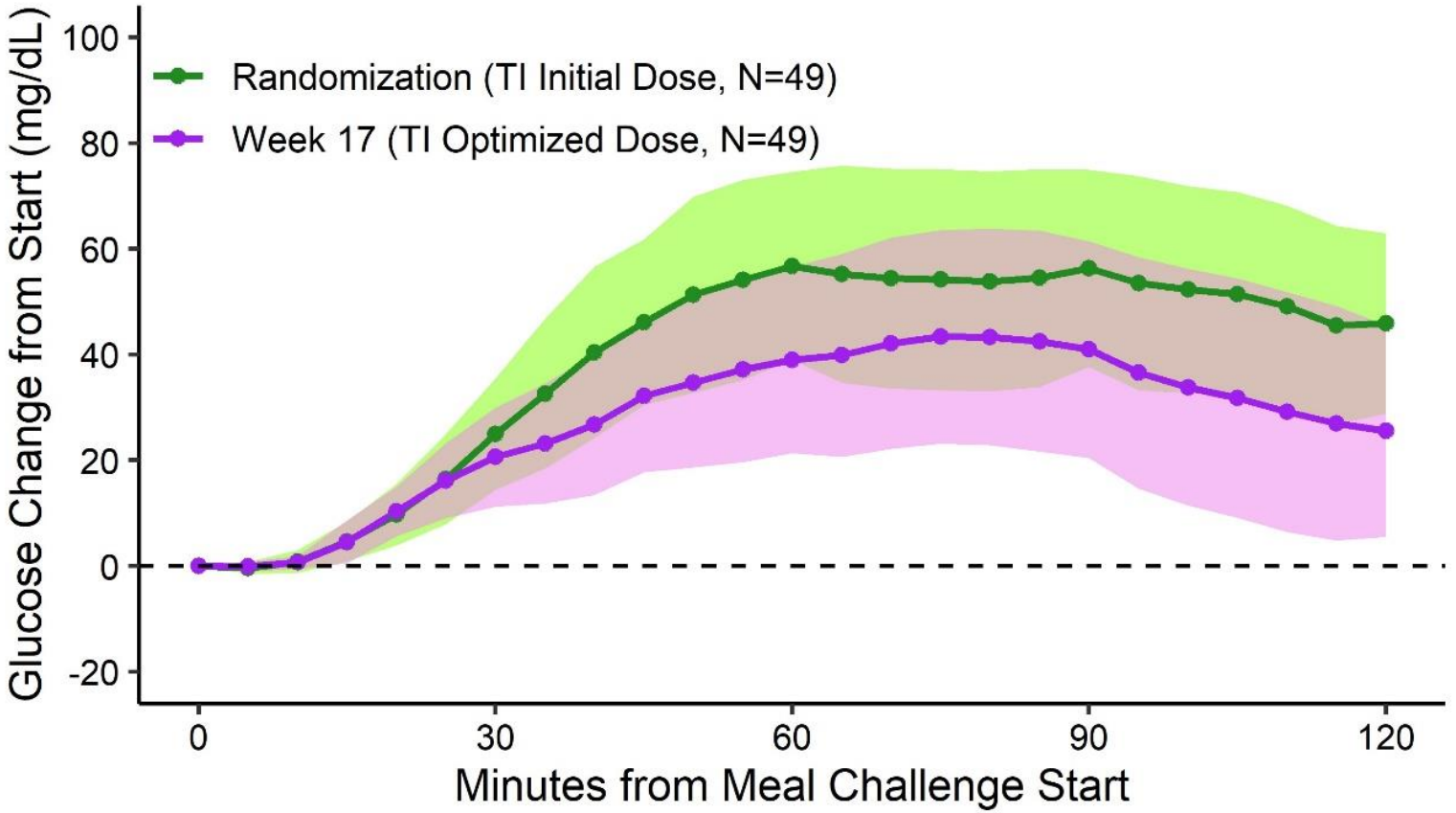
BGM every 15-30 min through 2 hrs

Blinded Dexcom G6 Pro used for analyses

Hirsch IB, et al. Diabetes Care. 2024 Sep 1;47(9):1682-1687

Hirsch IB et al. Diabetes Care, 2024, in press

Meal Challenge with TI at Baseline and 17 Weeks (N=49)



Ratio of TI dose (Afrezza units) at 17w : baseline

Mean ± SD	1.6 ± 1.4
Median (IQR)	1.5 (0.7-2.0)

Mean AUC >180 mg/dL

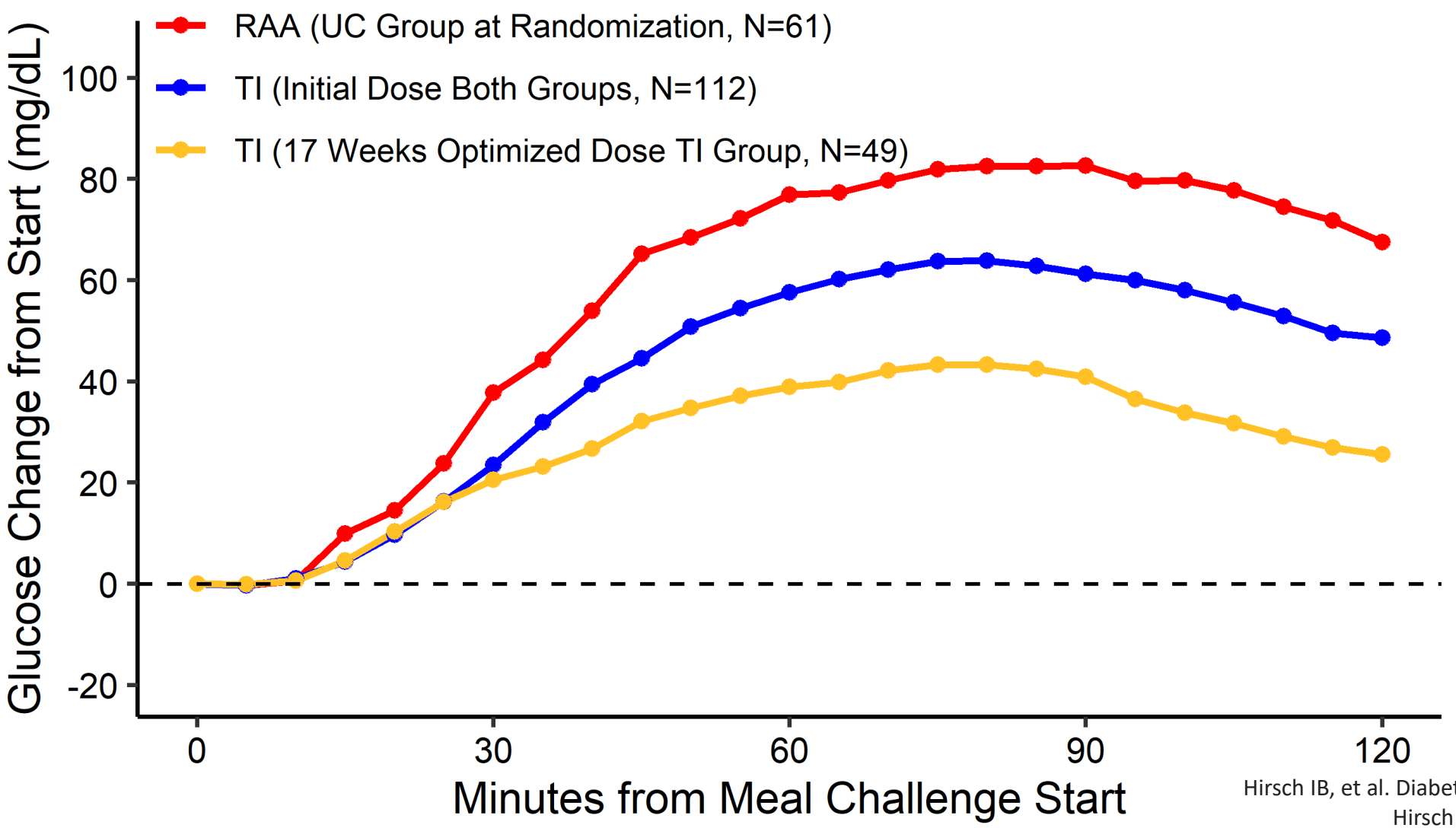
35 mg/dL vs. 41 mg/dL

Difference= -7 mg/dL (95% CI -19 to 4)

P=0.20

Hirsch IB, et al. Diabetes Care. 2024 Sep 1;47(9):1682-1687
Hirsch IB et al. Diabetes Care, 2024, in press

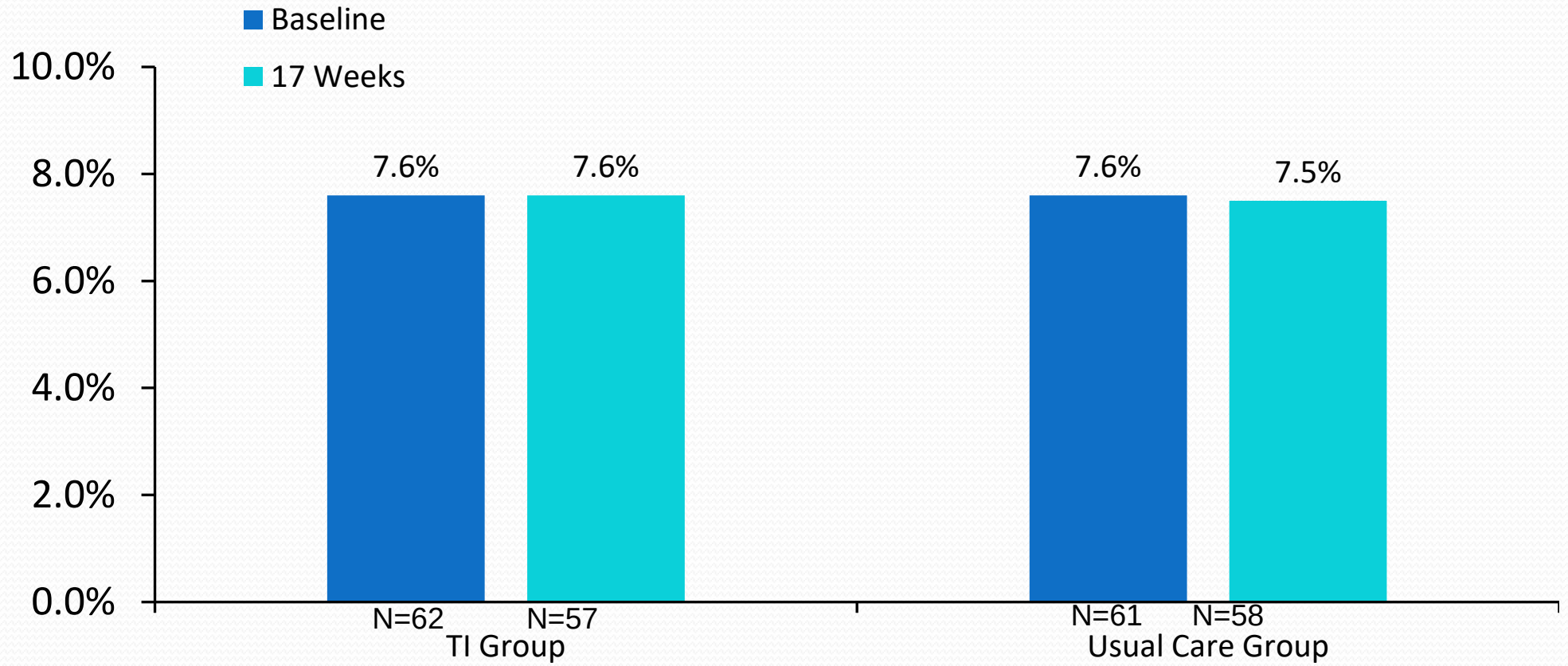
Combining Both Meal Challenges



The post-meal spike is mitigated with dosing optimization

Hirsch IB, et al. Diabetes Care. 2024 Sep 1;47(9):1682-1687
Hirsch IB et al. Diabetes Care, 2024, in press

Primary Endpoint: HbA1c



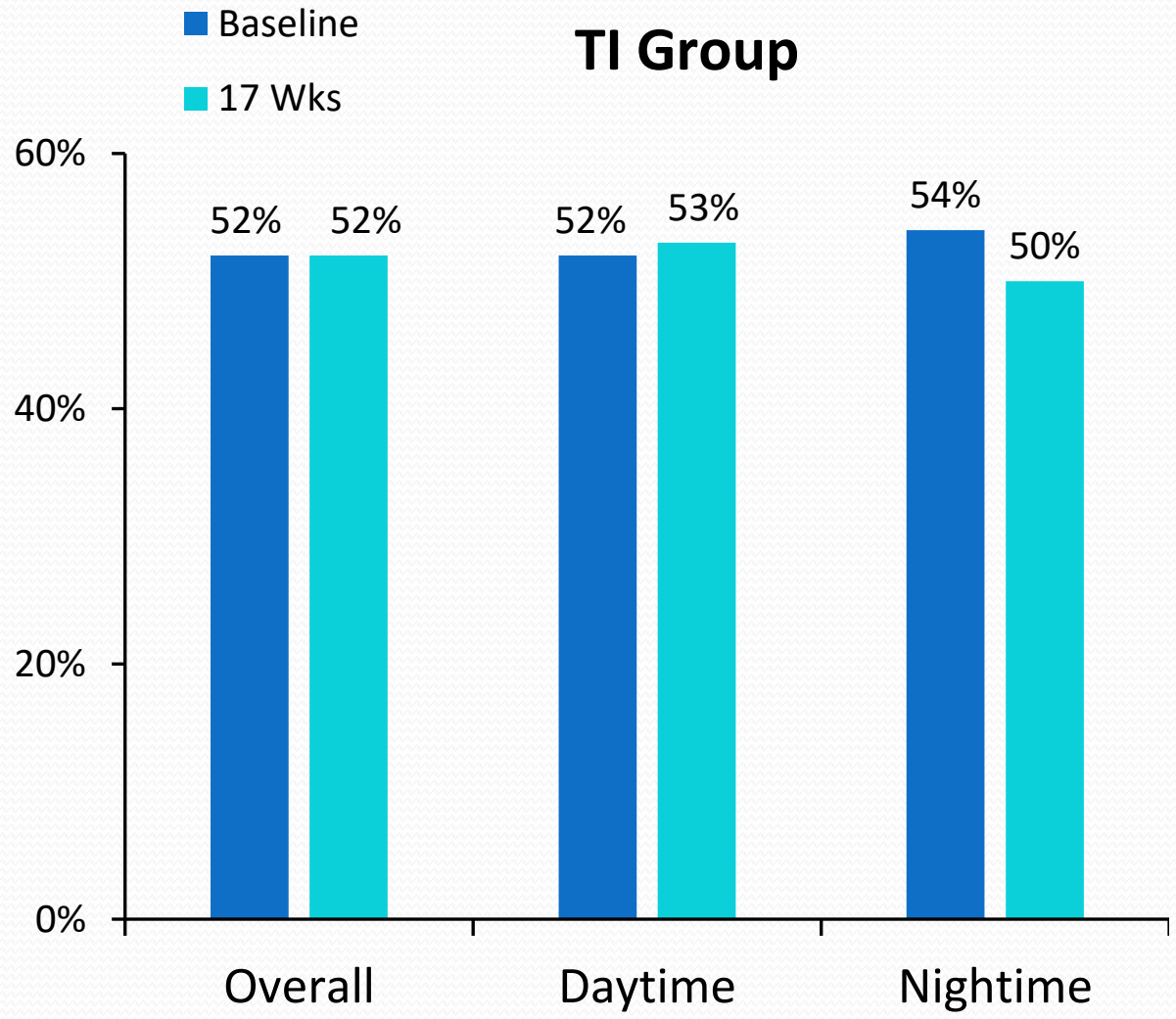
Intent to Treat Analysis

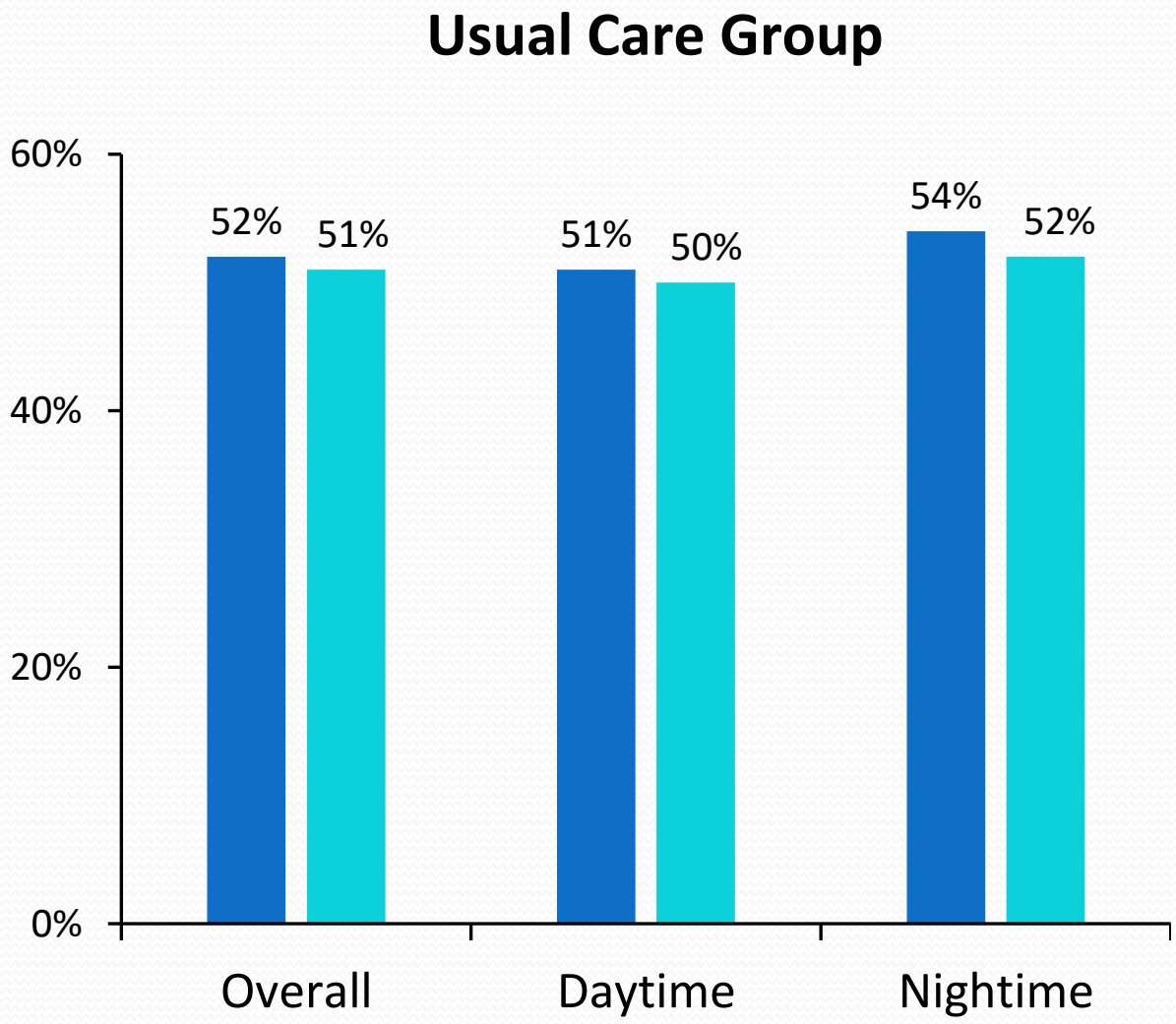
Difference 0.11% 95% CI -0.10 to 0.33

P=0.01 for non-inferiority (0.4% non-inferiority margin)

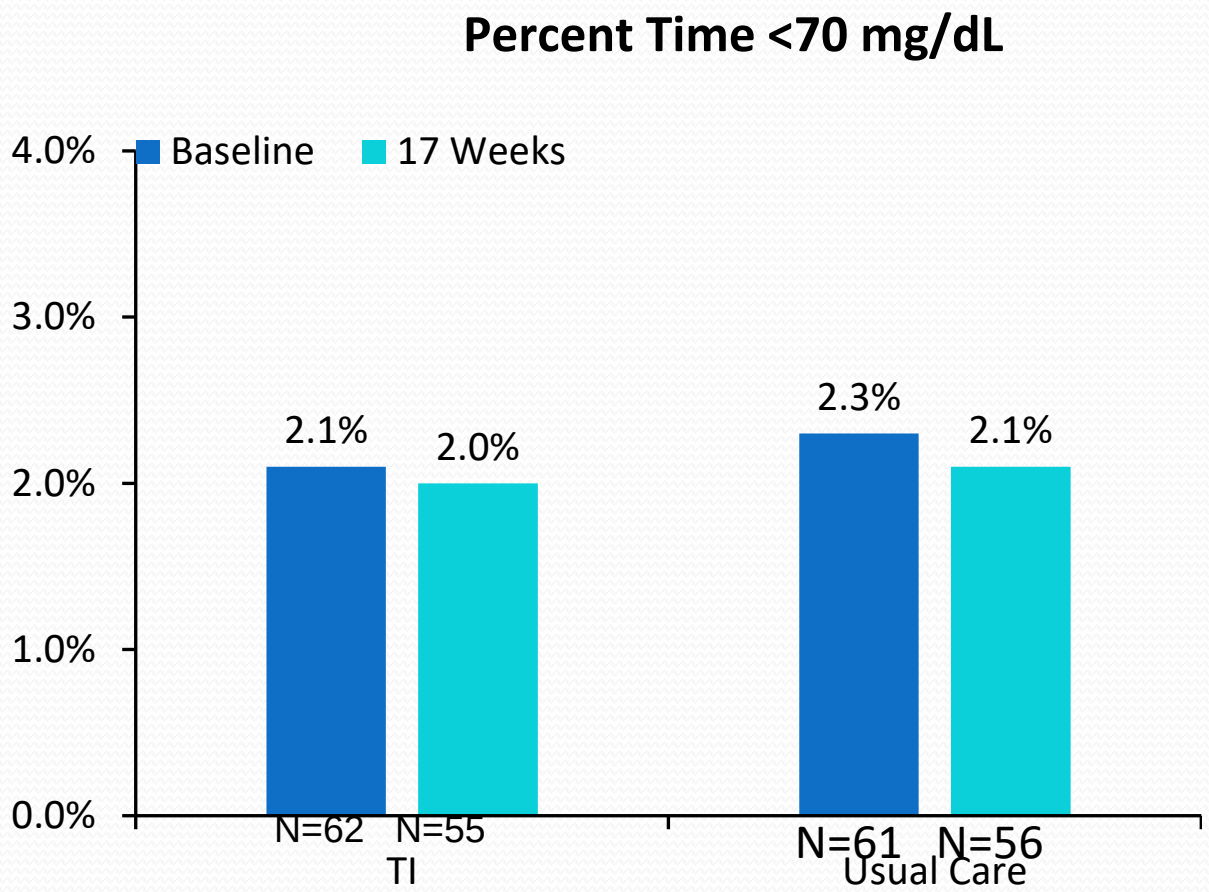
Hirsch IB, et al. Diabetes Care. 2024 Sep 1;47(9):1682-1687
Hirsch IB et al. Diabetes Care, 2024, in press

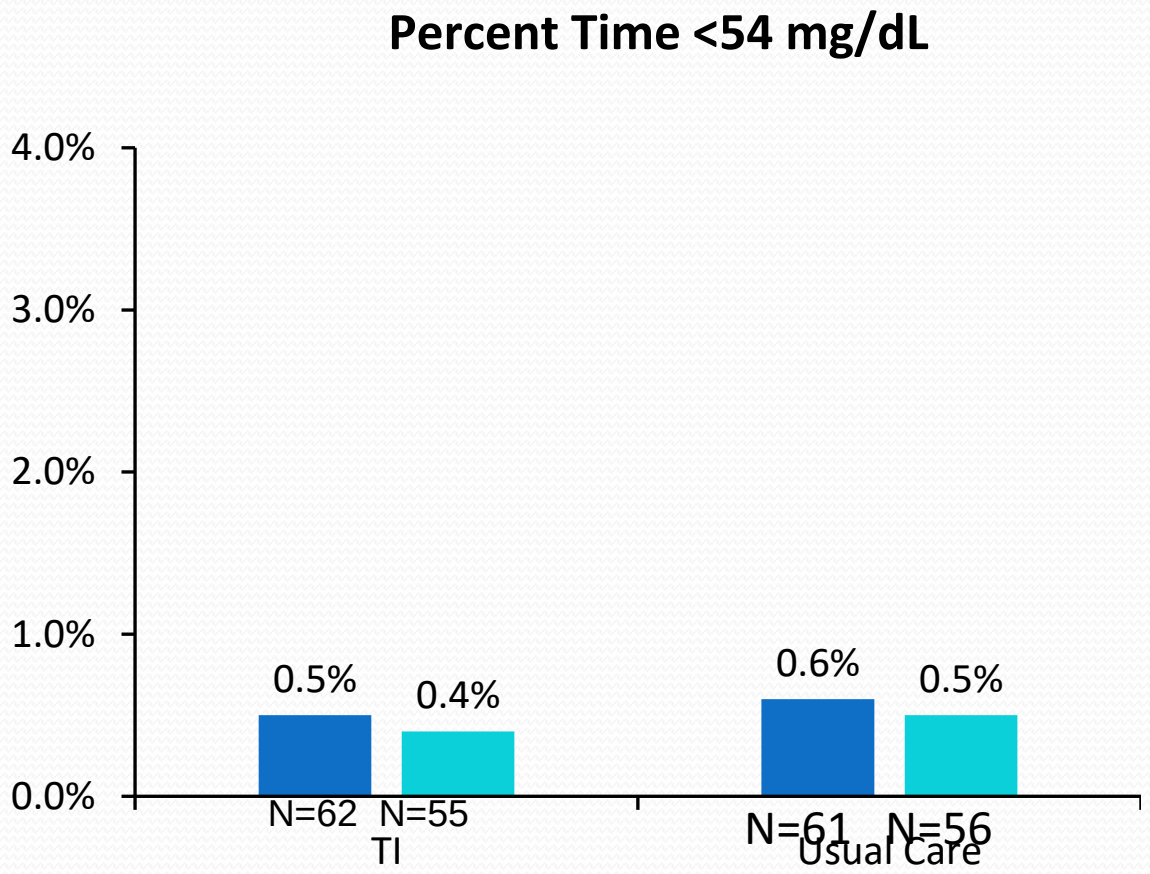
CGM Metrics: Time in Range 70-180 mg/dL





CGM Metrics: Hypoglycemia

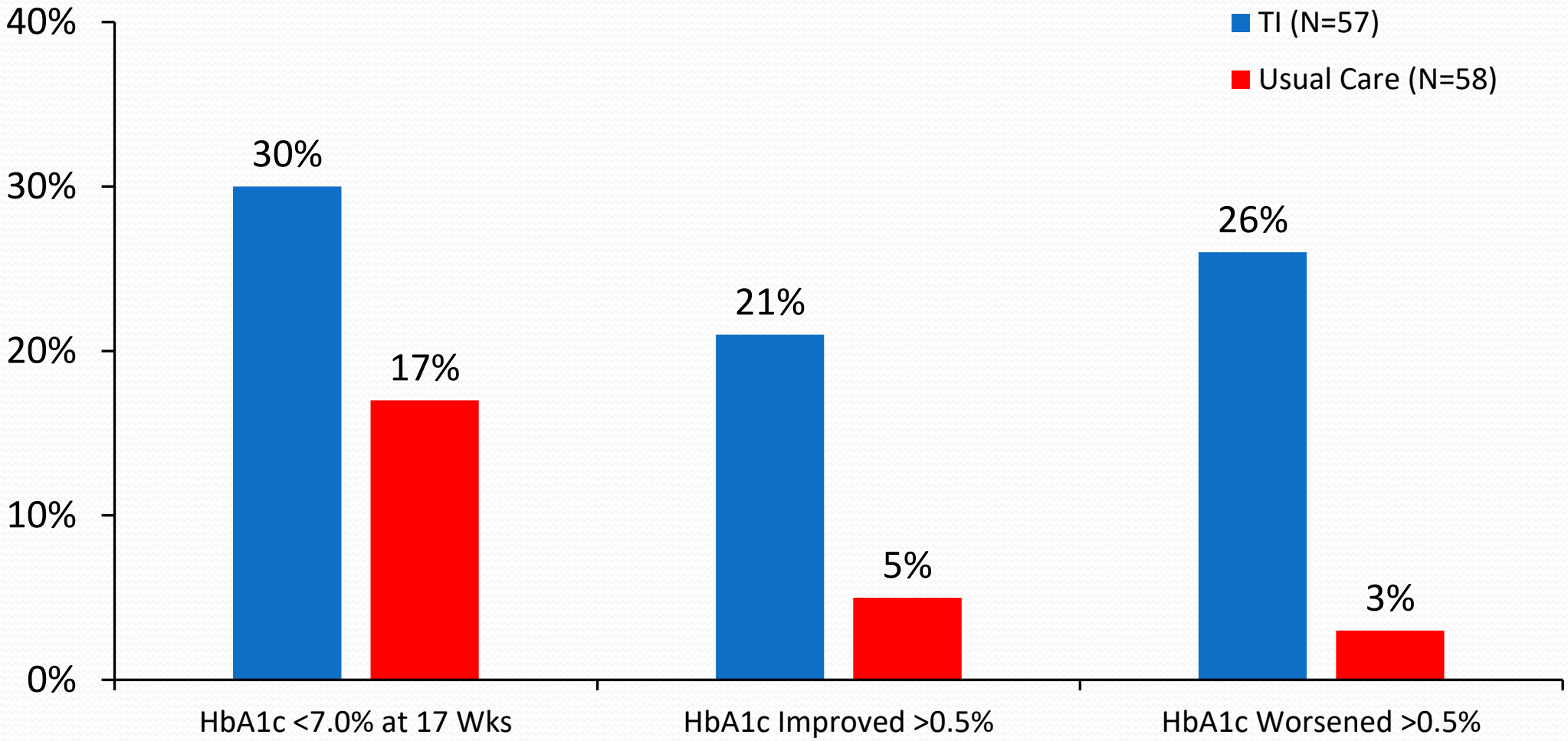




Time<54 mg/dL: trt grp difference = 0.0% (95% CI -0.3% to +0.3%)

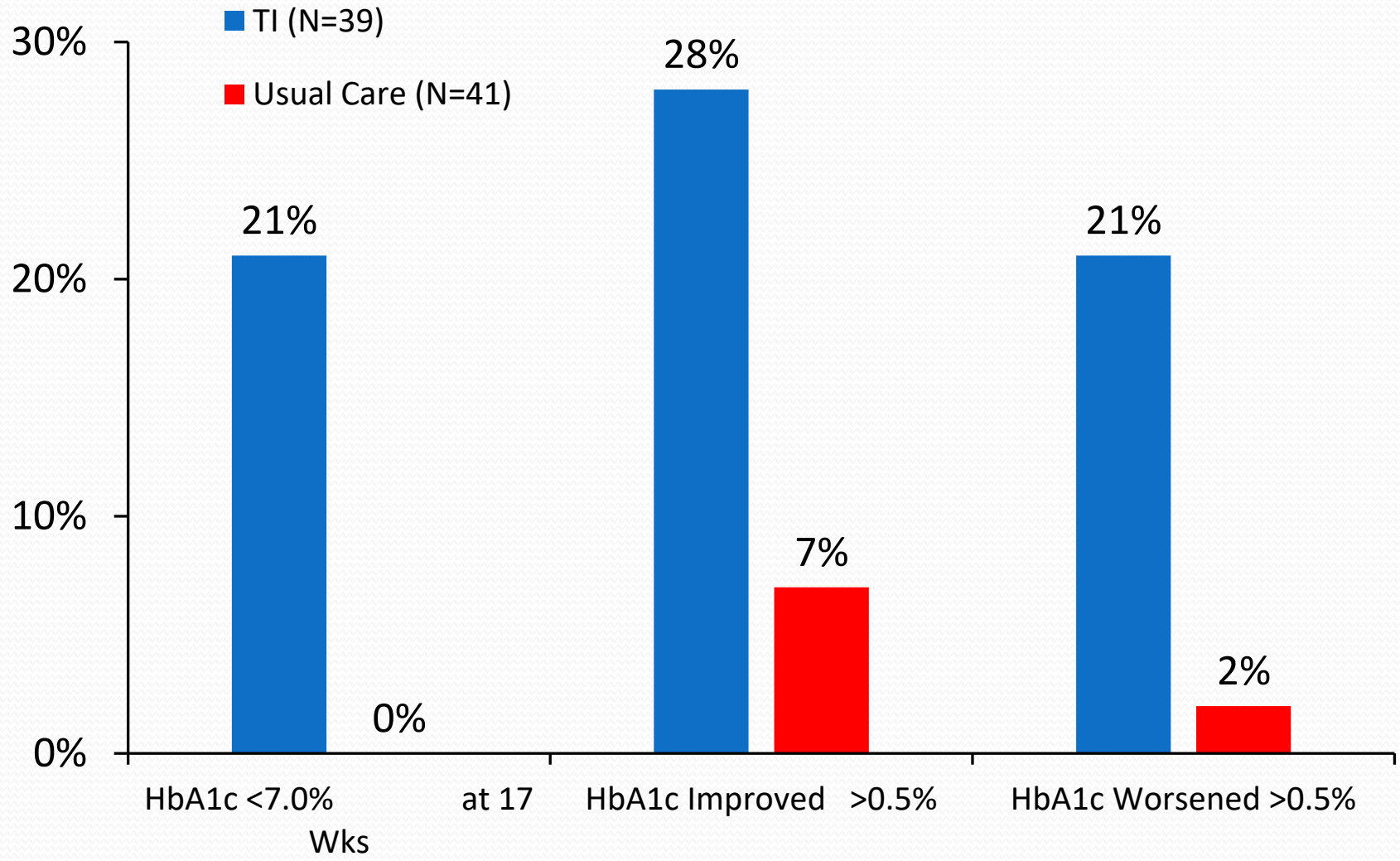
P value for non-inferiority = 0.002

HbA1c Secondary Endpoints



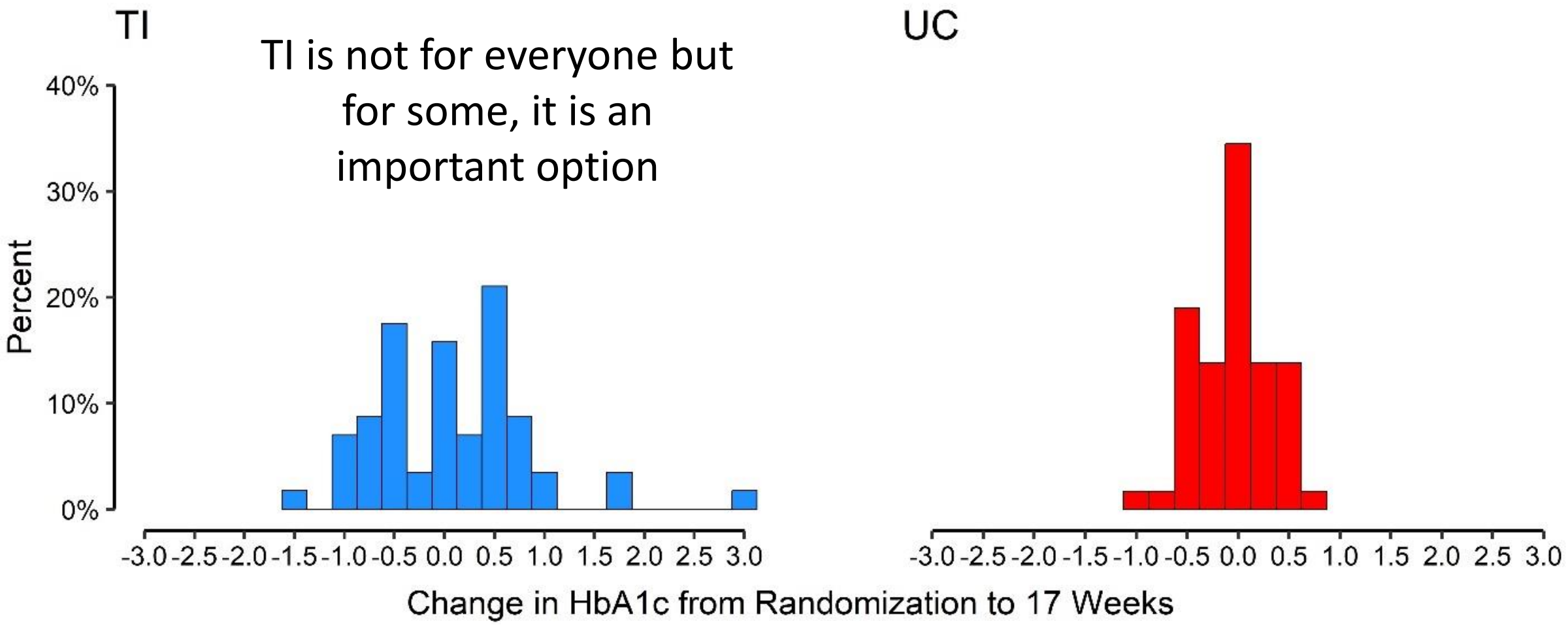
Hirsch IB, et al. Diabetes Care. 2024 Sep 1;47(9):1682-1687
Hirsch IB et al. Diabetes Care, 2024, in press

HbA1c Outcomes in Participants with Baseline HbA1c >7.0%

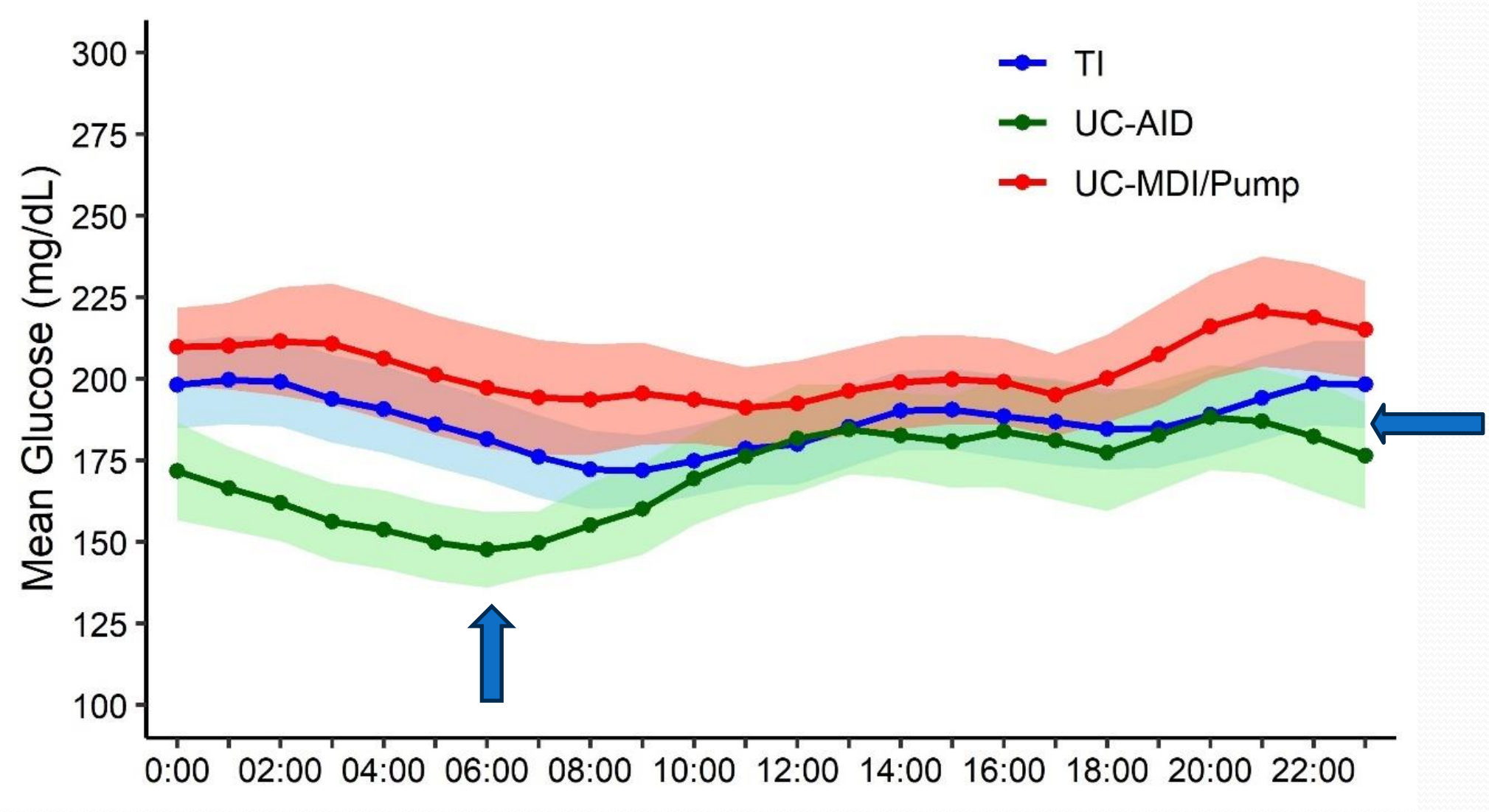


Distribution of Change in HbA1c from Baseline to 17 Weeks

TI is not for everyone but for some, it is an important option



Mean Glucose by Hour of the Day at 17 Weeks



An “Afrezza Unit” Can Not Be Compared to an Injectable RAA Unit

- At randomization, we estimated 2 Afrezza Units would be bioequivalent to ~one RAA unit
- Titrated dose after 17w: 2.5-3 times higher than RAA at baseline
- With degludec, 17w basal:bolus ratio ~30/70

	Randomization	17 weeks
	N = 49	N = 49
Afrezza/RAA Ratio (mean ± SD)	1.8 ± 0.3	2.8 ± 1.9
Median (Quartiles)	2.0 (1.6, 2.0)	2.4 (1.3, 3.5)

Take-home point: we need to understand appropriate dosing for TI and basal

The Most Important Learnings From INHALE-3

- Using TI may be good option for patients engaged in their diabetes self-management and want to reduce hyperglycemia even further
- Using TI may be good option for patients who want an alternative to a pump
- To maximize benefit of TI, need to repeat inhalation at 1-3 hours after a meal if glucose is trending >140

Thank You