ACC. 24 TRIALS

- *Madjid Chinikar, MD*
- *Ehsan Khalilipur, MD*
- *Armin Elahifar, MD*

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- **AEGIS-II** -- Effect of CSL112 on Recurrent Myocardial Infarction (MI) and Cardiovascular (CV) Death DOI: 10.1056/NEJMoa2400969

- **ARISE-HF** -- A Selective Aldose Reductase Inhibitor For the Treatment of Diabetic Cardiomyopathy

- **BE ACTIVE** -- Gamification, Financial Incentives, or Both to Increase Physical Activity Among Patients at High Risk of Cardiovascular Events

- **Bridge – TIMI 73a** -- Olezarsen in patients with hypertriglyceridemia at high cardiovascular risk

- **CRESCENT** -- Mandibular Advancement versus CPAP for BP Reduction In OSA and high cardiovascular Risk

- **DanGer Shock** -- Microaxial Flow Pump or Standard Care in Infarct-Related Cardiogenic Shock

- **DEPOSITION** -- Topical Tranexamic Acid to Reduce Seizures in Cardiac Surgery

- **Full REVASC** -- FFR-Guided Complete or Culprit-Only PCI in Patients With Myocardial Infarction

- **HUDDLE** -- Prevalence of Cardiovascular Disease (CVD) and Risk Factors Among National Football League (NFL) Alumni

- **IVUS-DCB** -- Comparison of IVUS-guided vs. Angiography-guided Angioplasty for the Outcomes of DCB in the Treatment of Femoropopliteal Artery Disease

- **PREVENT** -- Preventive Percutaneous Coronary Intervention (PCI) vs. Optimal Medical Therapy (OMT) Alone For the Treatment of Vulnerable Atherosclerotic Coronary Plaques

- **PROACT** -- Can we prevent chemotherapy-related heart damage in patients with breast cancer and lymphoma?

- **RELIEVE-HF** -- Interatrial Shunt In Patients with HFrEF and HFpEF

- **TACT2** -- Chelation Therapy Does Not Improve Post-MI Outcomes in Patients With DM

- **TACTiC** -- Evaluation of a Technology Assisted Web Application to Qualify for Nonprescription Statin Administration

- **Target BP I** -- Effect of Alcohol-mediated Renal Denervation on Blood Pressure in the Presence of Antihypertensive Drugs

- **TRAVERSE** -- Transseptal vs. Retrograde Aortic Ventricular Entry to Reduce Systemic Emboli

- **ULTIMATE-DAPT** -- One-month Ticagrelor Monotherapy After PCI in Acute Coronary Syndromes

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AEGIS-II

Effect of CSL112 on Recurrent Myocardial Infarction (MI) and Cardiovascular (CV) Death

Phase Three, Global, Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial

OBJECTIVE: To evaluate the effects of CSL112 (Apo A-1) therapy on the incidence of CV death and recurrent MI.

18,219
PATIENTS

INCLUSION CRITERIA:
Adult patients with type 1 MI with multivessel coronary artery disease, and either drug-treated diabetes or two additional risk factors.

4 WEEKLY INFUSIONS OF CSL112 (Apo A-1)

VS.

PLACEBO

PRIMARY ENDPOINT

THE COMPOSITE OF CV DEATH, ALL MI OR STROKE FROM RANDOMIZATION THROUGH 90 DAYS vs. PLACEBO.
4.9% (CSL112) vs. **5.2% (PLACEBO)** **(HR, 0.93, P=0.24)**

SECONDARY ENDPOINTS

ANALYSIS OF THE INDIVIDUAL COMPONENTS OF THE PRIMARY ENDPOINT THROUGH 90 DAYS, 180 DAYS AND 365 DAYS.

THE INCIDENCE OF CV DEATH OR ANY MI WAS NUMERICALLY LOWER IN THE CSL112 GROUP THROUGHOUT THE FOLLOW-UP PERIOD: HR, 0.91, 0.89 AND 0.92, RESPECTIVELY.

CONCLUSION

Although the primary endpoint findings were neutral, data suggest that treatment with CSL112 is well tolerated and may result in lower rates of CV death and MI.

Povsic TJ, Korjian S, Bahit MC, et al. Effect of CSL112 on Recurrent Myocardial Infarction and Cardiovascular Death: Insights from the AEGIS-II Trial. *NEJM* 2024. Presented at ACC.24.

Developed and reviewed by Raymond Yeow, MD, and Kent Brummel, MD

AMERICAN COLLEGE of CARDIOLOGY®

ARISE-HF

A Selective Aldose Reductase Inhibitor For the Treatment of Diabetic Cardiomyopathy

Multicenter, Multinational, Randomized, Placebo-Controlled Double-Blind Trial

OBJECTIVE: To assess the efficacy of AT-001 compared with placebo for stabilization of exercise capacity in patients with type 2 diabetes (T2D) and diabetic cardiomyopathy.

691
PATIENTS

INCLUSION CRITERIA:
Patients with treated T2D with an HbA1c ≤7.5%, diabetic cardiomyopathy with stage B heart failure, and Peak VO_2 <75% of predicted.

LOW-DOSE AT-001 (1,000 MG BID) ARM (N=230)

HIGH-DOSE AT-001 (1,500 MG BID) ARM (N=231)

VS.

PLACEBO (N=230)

PRIMARY ENDPOINT

CHANGE IN PEAK VO_2 FROM BASELINE TO 15 MONTHS:
HIGH-DOSE AT-001 (-0.03 ML/KG/MIN) VS. **PLACEBO (-0.34 ML/KG/MIN)**
BETWEEN-GROUP DIFFERENCE: 0.30 ML/KG/MIN (P=0.21).

CONCLUSION

Treatment with AT-001 at 15 months was safe but did not result in a significant difference in peak VO_2 among patients with well-controlled T2D and diabetic cardiomyopathy with reduced exercise capacity.

Januzzi JL Jr, Butler J, Del Prato S, et al. A Selective Aldose Reductase Inhibitor for the Treatment of Diabetic Cardiomyopathy: A Randomized Clinical Trial. *JACC* 2024. Presented at ACC.24.

Developed and reviewed by: Ashwini Kerkar, MD, and Kent Brummel, MD

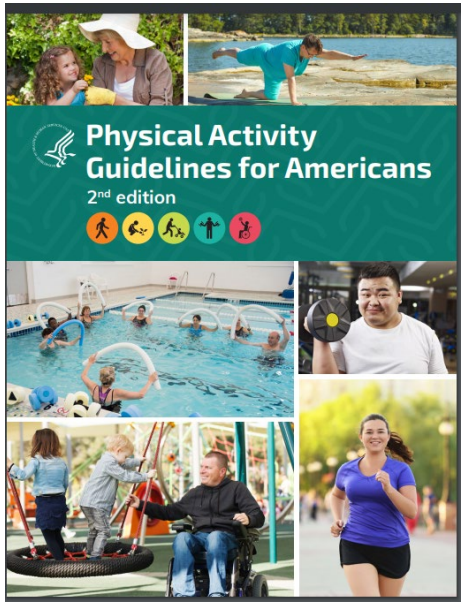
Penn Medicine

Gamification, Financial Incentives, or Both to Increase Physical Activity Among Patients at High Risk of Cardiovascular Events:
The BE ACTIVE Randomized Controlled Trial

Alexander Fanaroff

Mitesh Patel, Neel Chokshi, Samantha Coratti, David Farraday, Laurie Norton, Charles Rareshide, Jingsan Zhu, Tamar Kleiman, Julia Szymczak, Louise Russell, Dylan Small, Kevin Volpp

Physical activity



- Many benefits
  - ↓ all cause and CV mortality
  - ↓ risk of heart disease and stroke
  - ↓ risk of hypertension, diabetes, hyperlipidemia
- CDC recommends 150 minutes/week of moderate to vigorous physical activity, but few exercise that much – especially older adults at highest risk for CVD
- In short-term studies:
  - Gamification increases physical activity
  - Financial incentives increase physical activity
- But it is not certain how long these effects last, or which approach is better

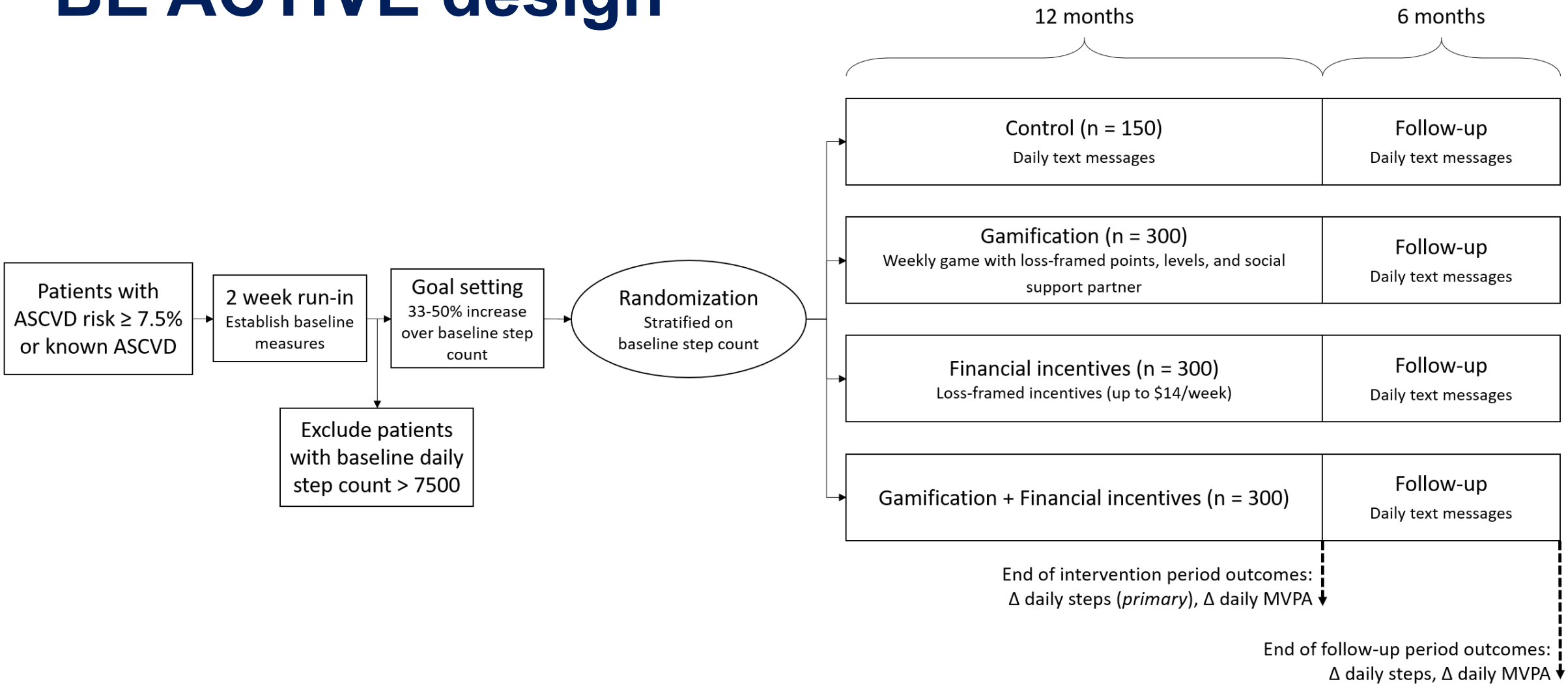
Objectives

- To determine the effectiveness of behaviorally-designed gamification, loss-framed financial incentives, or the combination versus control for increasing physical activity over a 12-month intervention and 6-month follow-up period

Design: Patient population

- Age > 18
- 10-year ASCVD event risk > 7.5% or established vascular disease
- Have a Penn Medicine PCP
- Able to provide informed consent
- Own device (smartphone or tablet) able to transmit data from the wearable
- Not participating in another physical activity study
- No reason an 18-month physical activity program is unsafe or infeasible
- Baseline step count < 7500

BE ACTIVE design



Way To Health

Evidence Based Patient Engagement

- Automated patient communication
- Device integration
- Clinical Trials
- Behavioral Economics
- Gamification
- Customizable Rules Engine

Design: gamification

- Each week, participants are endowed with 70 points
- Each day a participant does not meet his/her step goal, he/she loses 10 points
- At the end of each week, points will determine whether participants move up or down a level based on weekly point total (> or < 40)
- Daily text messages note the number of points the participant has
- Participants start in the middle level
- After 8 weeks, participants in lower levels restarted back at middle and offered a chance to reset goals
- Weekly emails to support partner

Design: financial incentives

- Each week, $14 is put in each participant's virtual account
- Every day they don't meet their step goal, they lose $2; if they meet their goal, they keep their money

Power calculations

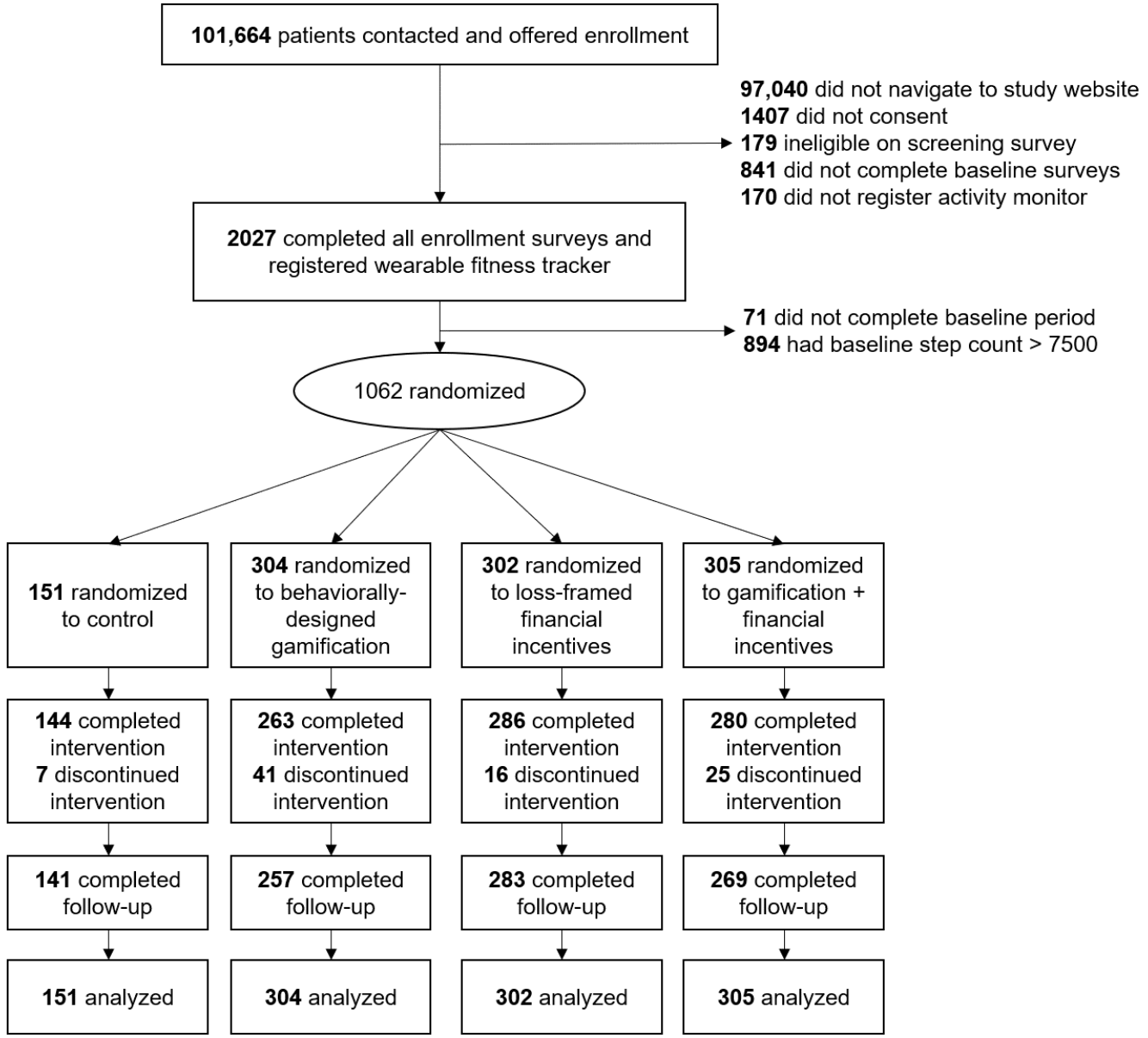
- Powered for 6 comparisons between arms keeping the familywise error rate < 0.05
  1. Three intervention arms vs. control – Bonferroni adjustment of type 1 error rate with two-sided α = 0.017
  2. Only intervention arms significant versus control were compared with each other, with same adjustment of type 1 error rate
- With 300 patients in the intervention arm and 150 patients in the control arm, we estimated 93% power to detect a difference of 1000 steps and 85% power to detect a difference of 750 steps, assuming a 10% drop-out rate

Methods

- All randomly assigned patients were included in the intention-to-treat analysis
- Multiple imputation for days with missing step count or values < 1000
  - Sensitivity analyses using only captured data without imputation
- Generalized linear mixed effect regression models to evaluate changes from baseline in daily steps and minutes of MVPA
- Powered to compare all 3 interventions vs. control using Bonferroni adjustment of type 1 error rate with two-sided α = 0.017
  - Intervention arms significant versus control were compared with each other, with same adjustment of type 1 error rate
  - 93% power to detect a difference of 1000 steps and 85% power to detect a difference of 750 steps

Participant flow

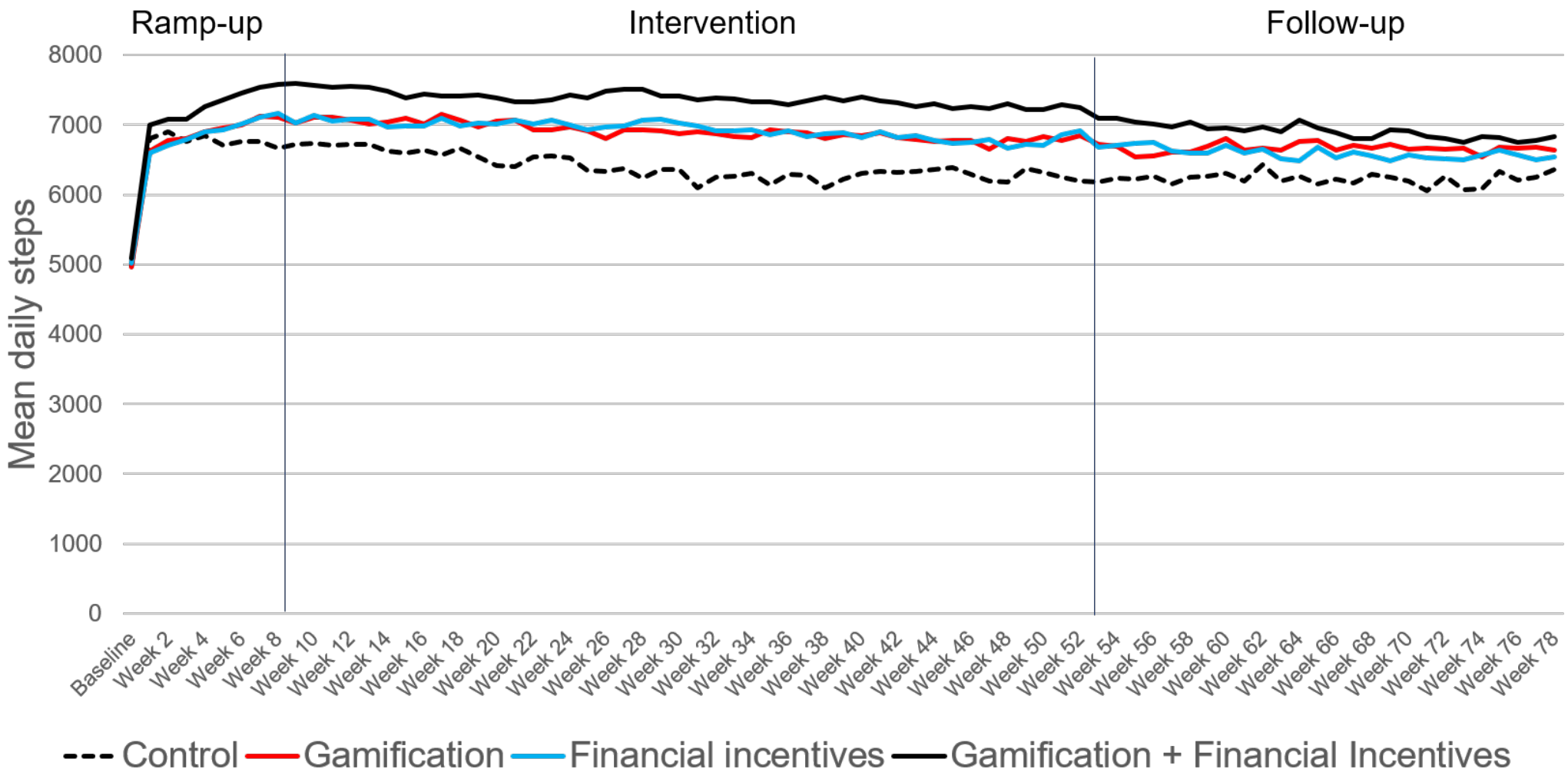
- 91.6% (n = 973) completed the 12-month intervention
- 89.4% (n = 950) completed the 18-month study



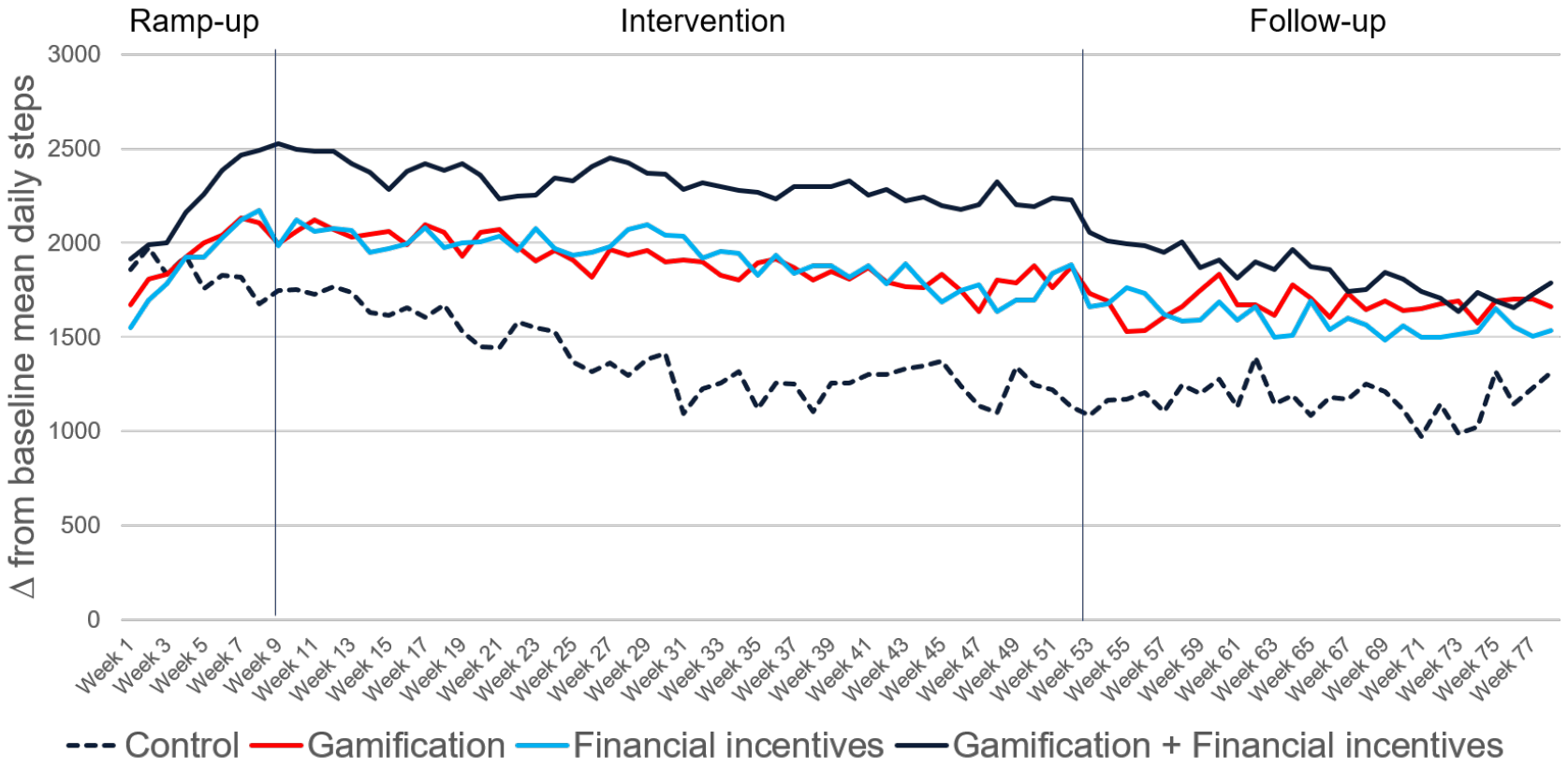
Baseline characteristics

	Control	Gamification	Incentives	Combination
Age	66.6	67.2	66.4	66.6
Black	27%	25%	27%	22.3%
Annual household income < $50k	32%	20%	24%	20%
Diabetes	25%	21%	22%	25%
Hyperlipidemia	51%	54%	56%	51%
Hypertension	62%	62%	64%	60%
Smoking	7%	3%	4%	4%
Baseline step count	4980	4958	5018	5081
Step goal increase	1855	1890	1890	1826

Change in daily steps



Change from baseline daily steps



Main intervention period

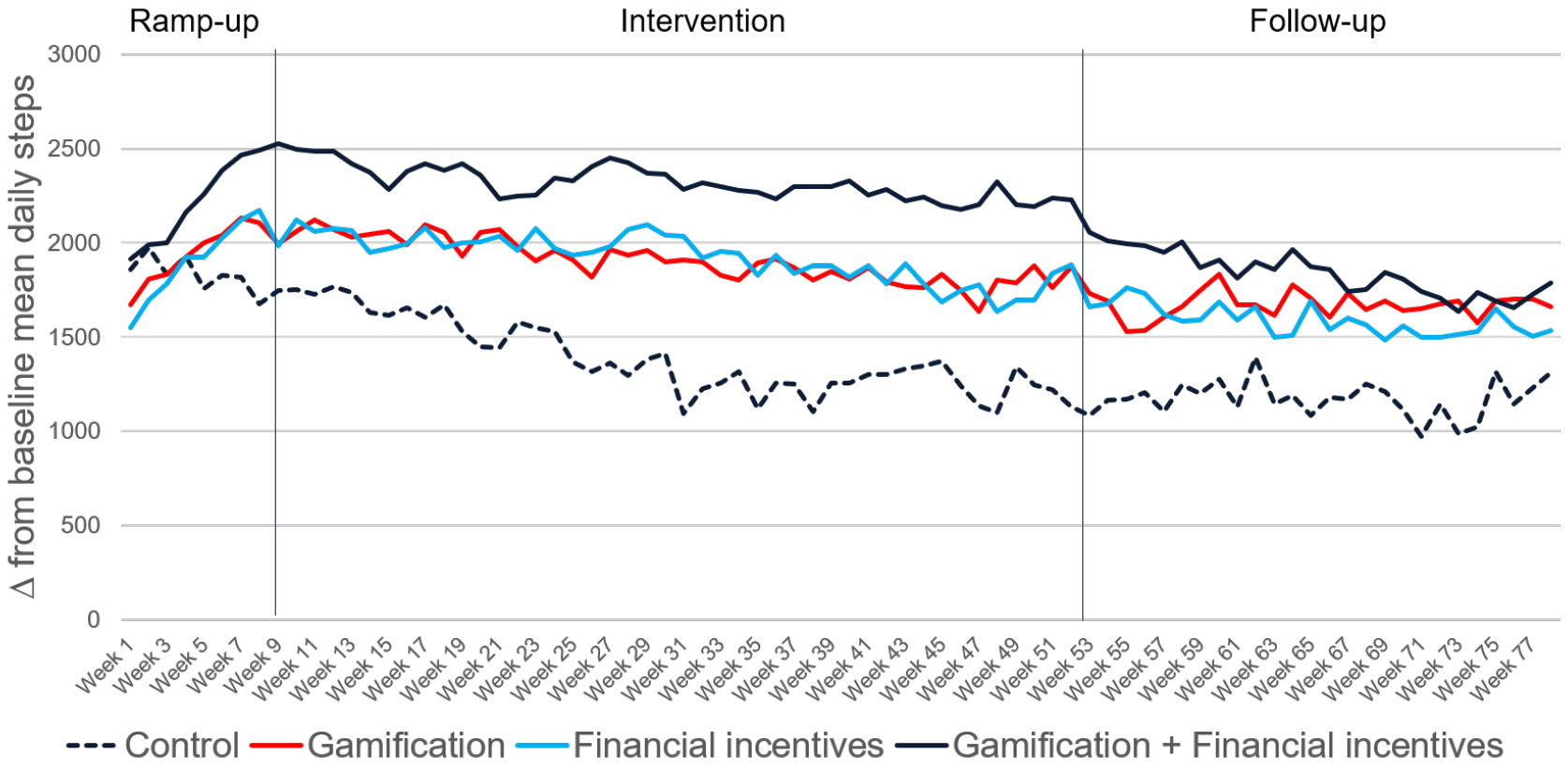
Control: +1418
from baseline

Gamification +1954
from baseline (+538 over control)

$ Incentives: +1915
from baseline (+492 over control)

Combination: +2297
from baseline (+868 over control)

Change from baseline daily steps



Follow-up period

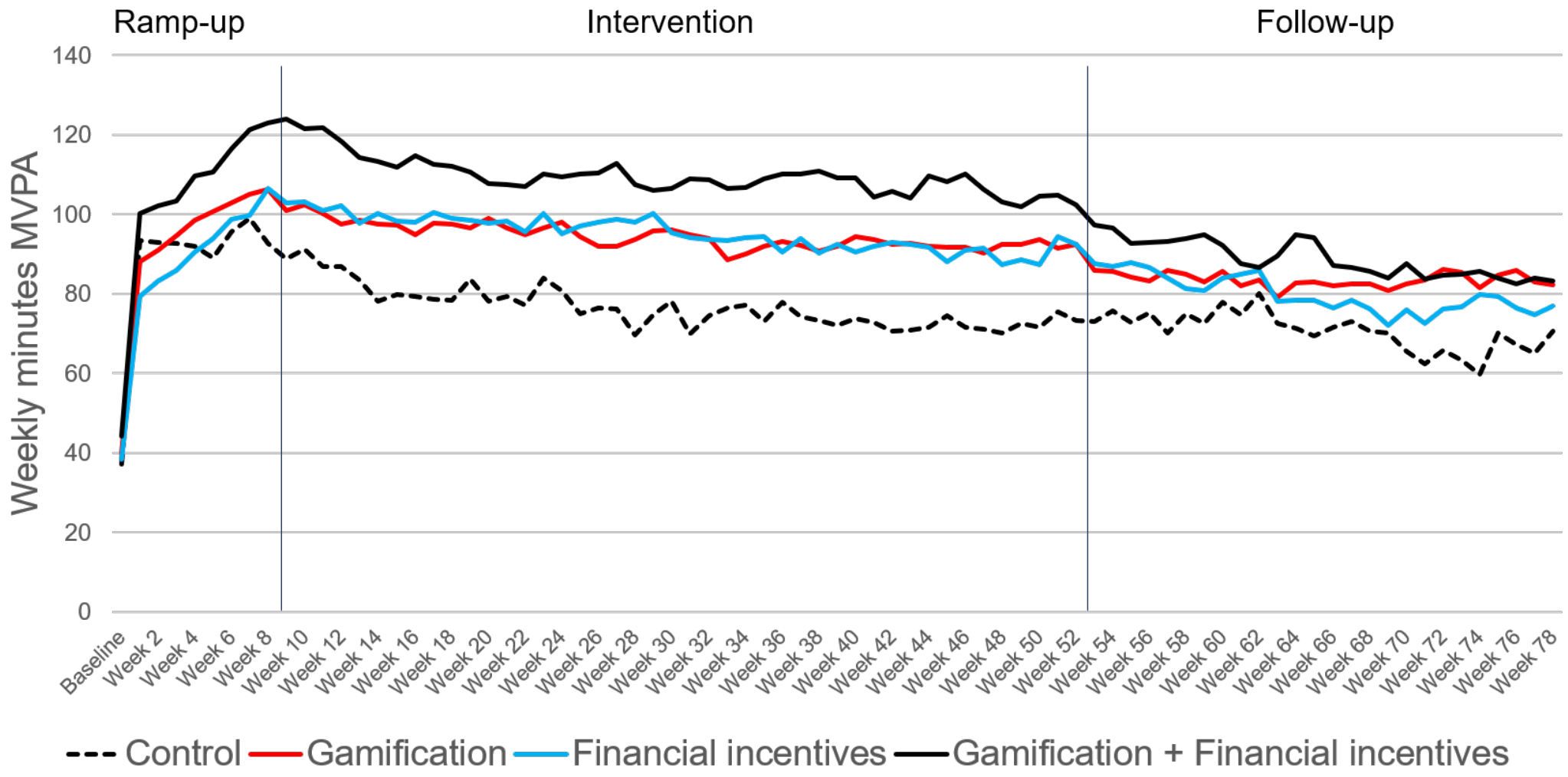
Control: +1245
from baseline

Gamification +1708
from baseline (+460 over control)

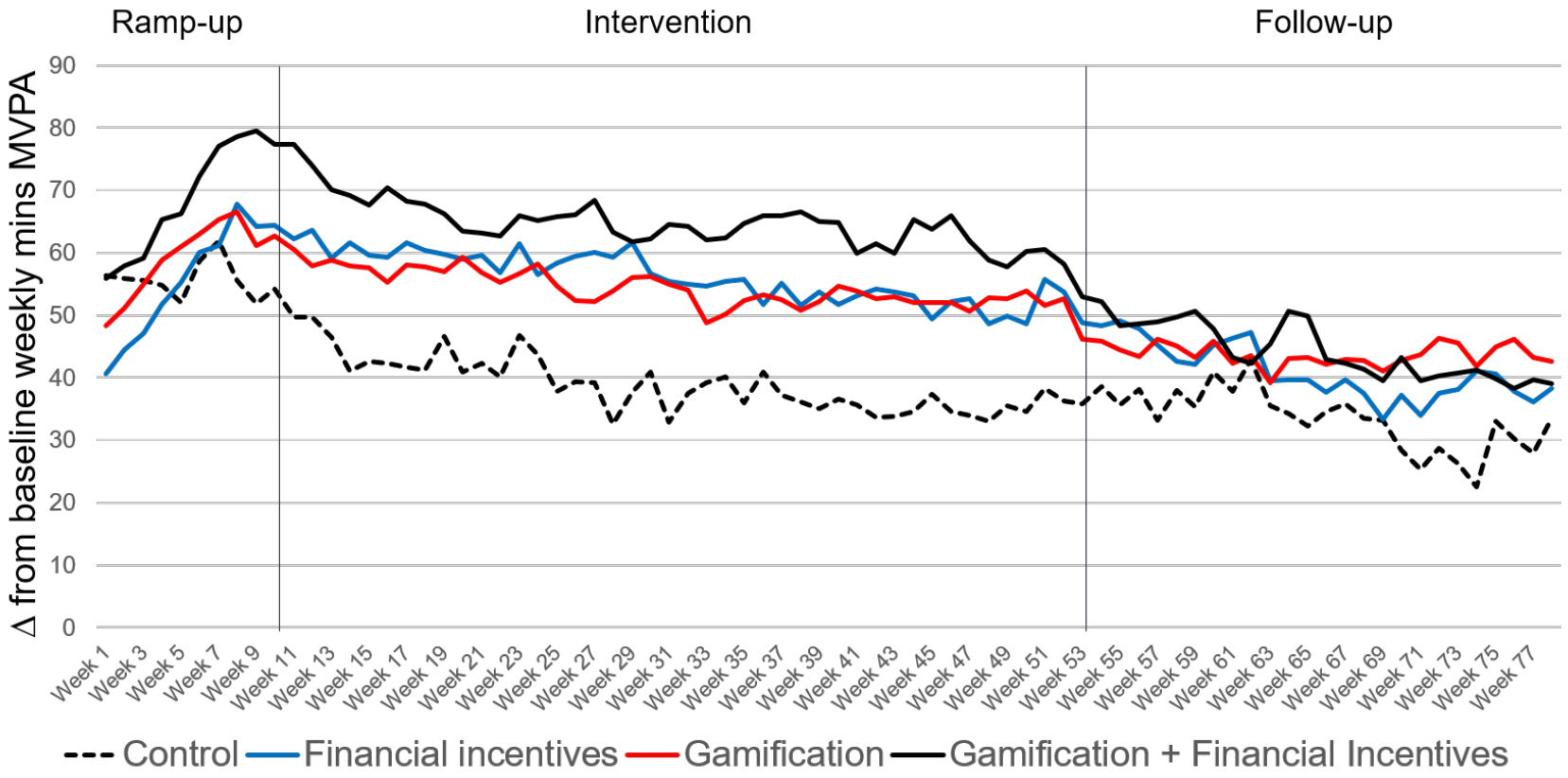
$ Incentives: +1576
from baseline (+328 over control)

Combination: +1831
from baseline (+576 over control)

Change in weekly MVPA



Change from baseline weekly minutes MVPA



Main intervention period

Control: +40

from baseline

Gamification +55

from baseline (+15 over control)

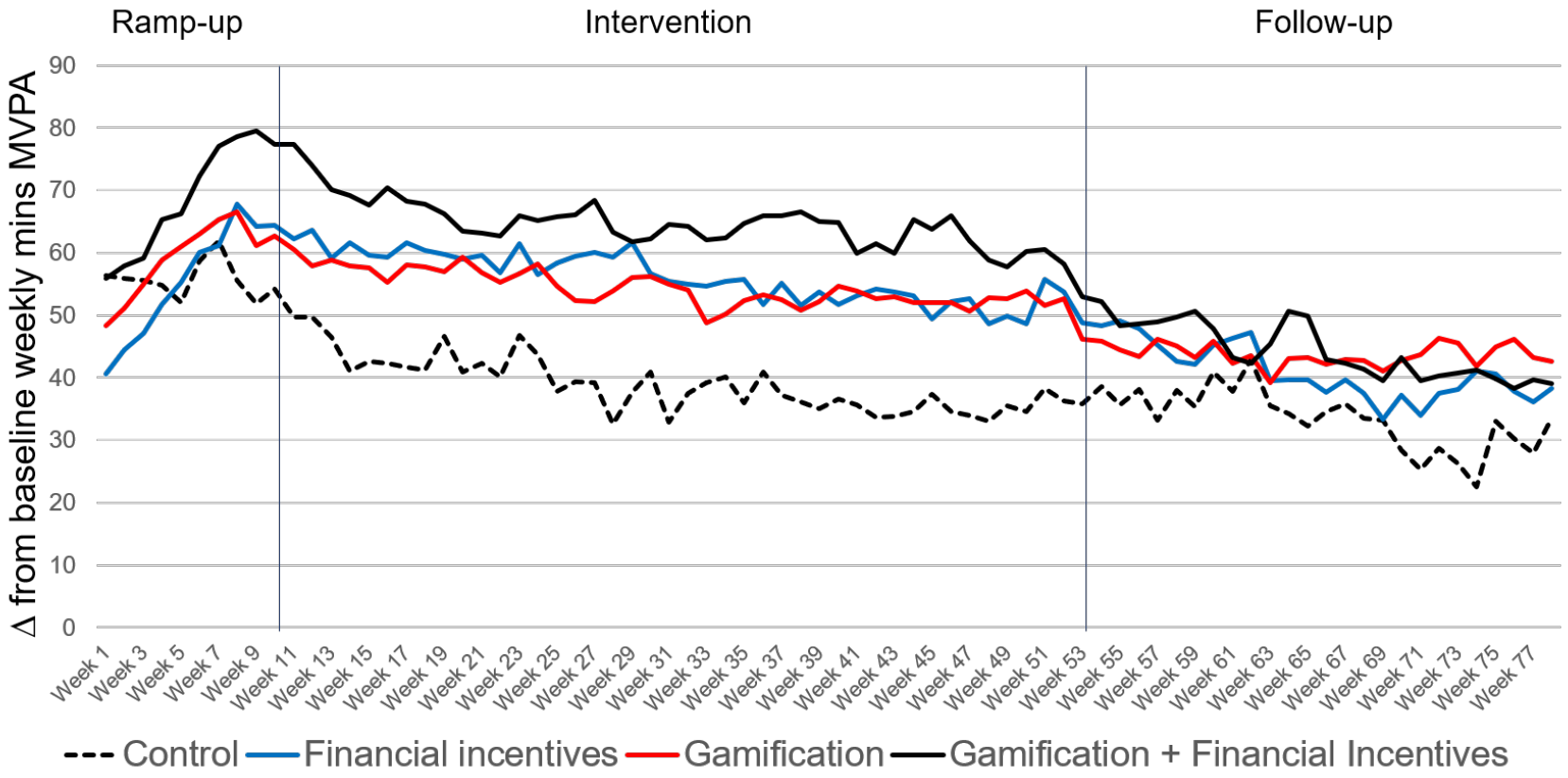
$ Incentives: +57

from baseline (+17 over control)

Combination: +65

from baseline (+26 over control)

Change from baseline weekly minutes MVPA



Follow-up period

Control: +37
from baseline

Gamification +51
from baseline (+11 over control)

$ Incentives: +51
from baseline (+8 over control)

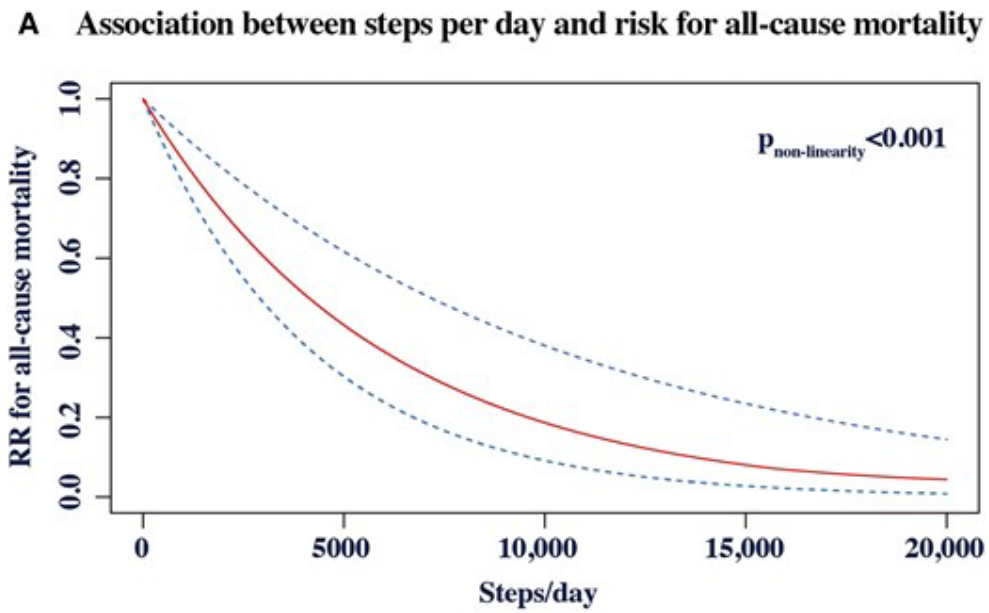
Combination: +58
from baseline (+13 over control)

Limitations

- Participants volunteered to participate
  - Many more invited than ultimately participated and results may not be fully generalizable
- Used commercial devices rather than research grade accelerometers
  - Pragmatic, doesn’t add bias, but may be less accurate
- Did not measure the effect of the intervention on clinical outcomes
  - Dedicated clinical trials needed

Implications

- In observational studies, there is an inverse association between steps per day and outcomes (mortality, CV events)
  - From baseline 5000 steps per day
    - 1700-step increase → ~1.2 years longer life expectancy
    - 500-step increase → ~ 0.4 years longer life expectancy
- ***These highly scalable, automatically delivered interventions increase physical activity over long-term periods in patients at high risk for CV events and could improve outcomes***



Thank you!

Patients and families

Study team

Alexander Fanaroff, Mitesh Patel, Neel Chokshi, Samantha Coratti, David Farraday, Laurie Norton, Charles Rareshide, Jingsan Zhu, Tamar Kleiman, Julia Szymczak, Louise Russell, Dylan Small, Kevin Volpp

DSMB

Phillip Greenland, William Yancey, Judy Zhong

AMERICAN COLLEGE of CARDIOLOGY®

BE ACTIVE

Effect of Gamification, Financial Incentives, or Both to Increase Physical Activity Among Patients at High Risk of Cardiovascular (CV) Events

Single-Center, Pragmatic, Randomized, Controlled Trial

OBJECTIVE: To evaluate the effect of behavioral economic approaches on physical activity levels in patients with elevated risk of CV disease.

1,062
PATIENTS

INCLUSION CRITERIA:
Patients with clinical atherosclerotic CV disease or 10-year risk of myocardial infarction, stroke or CV death ≥7.5%.

ATTENTION CONTROL (N=151) vs. **GAMIFICATION (N=304)** vs. **FINANCIAL INCENTIVES (N=302)** vs. **GAMIFICATION + FINANCIAL INCENTIVES (N=305)**

PRIMARY ENDPOINT

CHANGE IN DAILY STEPS FROM BASELINE THROUGH 12 MONTHS (ADJUSTED DIFFERENCE)

CONTROL: 1,418

GAMIFICATION: 538 (95% CI, 186.2-89.9; P=0.0027)

FINANCIAL INCENTIVES: 491.8 (95% CI, 139.6-844.1; P=0.0062)

COMBINED APPROACH: 868 (95% CI, 516.3-1219.7; P<0.0001)

CONCLUSION

In patients at increased risk of CV disease, gamification and financial incentives, especially when combined, resulted in increased physical activity over 12 months, and this was sustained over six months of post intervention follow-up.

Fanaroff AC, Patel MS, Chokshi N, et al. Effect of Gamification, Financial Incentives, or Both to Increase Physical Activity Among Patients at High Risk of Cardiovascular Events. The BE ACTIVE Randomized Controlled Trial. Circulation 2024. Presented at ACC.24.

Developed and reviewed by: Heather Wheat, MD, and Kent Brummel, MD

ACC.24

Bridge – TIMI 73a

Olezarsen in patients with hypertriglyceridemia at high cardiovascular risk

Brian Bergmark, MD

For the Bridge–TIMI 73 Investigators

AMERICAN COLLEGE of CARDIOLOGY

Background

Reducing triglyceride-rich lipoproteins (TRL) remains an unmet clinical need

- Elevated TRLs are associated with ↑ CV risk
- TRLs are at least as atherogenic as LDL
- Hypertriglyceridemia has direct clinical consequences, particularly when severe

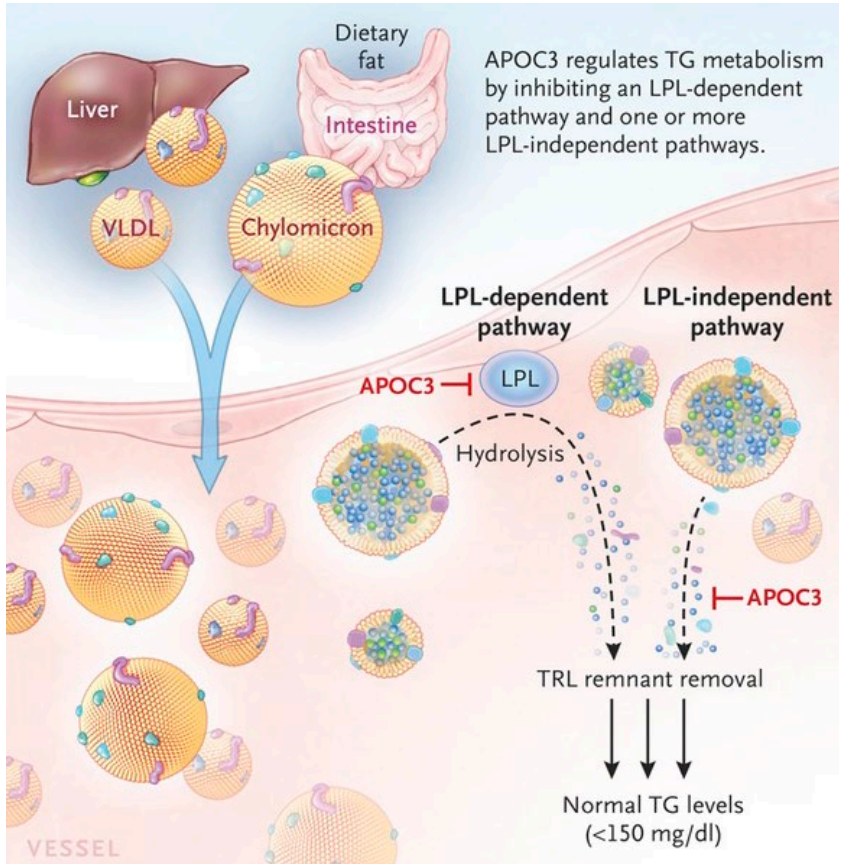
Apolipoprotein C-III

- Synthesized primarily in the liver
- Inhibits lipoprotein lipase
- ↑ triglyceride levels

Loss of function mutations in *APOC3*

- ↓ triglyceride levels
- ↓ CV risk

Olezarsen is a $GalNAc_3$-conjugated antisense oligonucleotide targeting *APOC3* mRNA

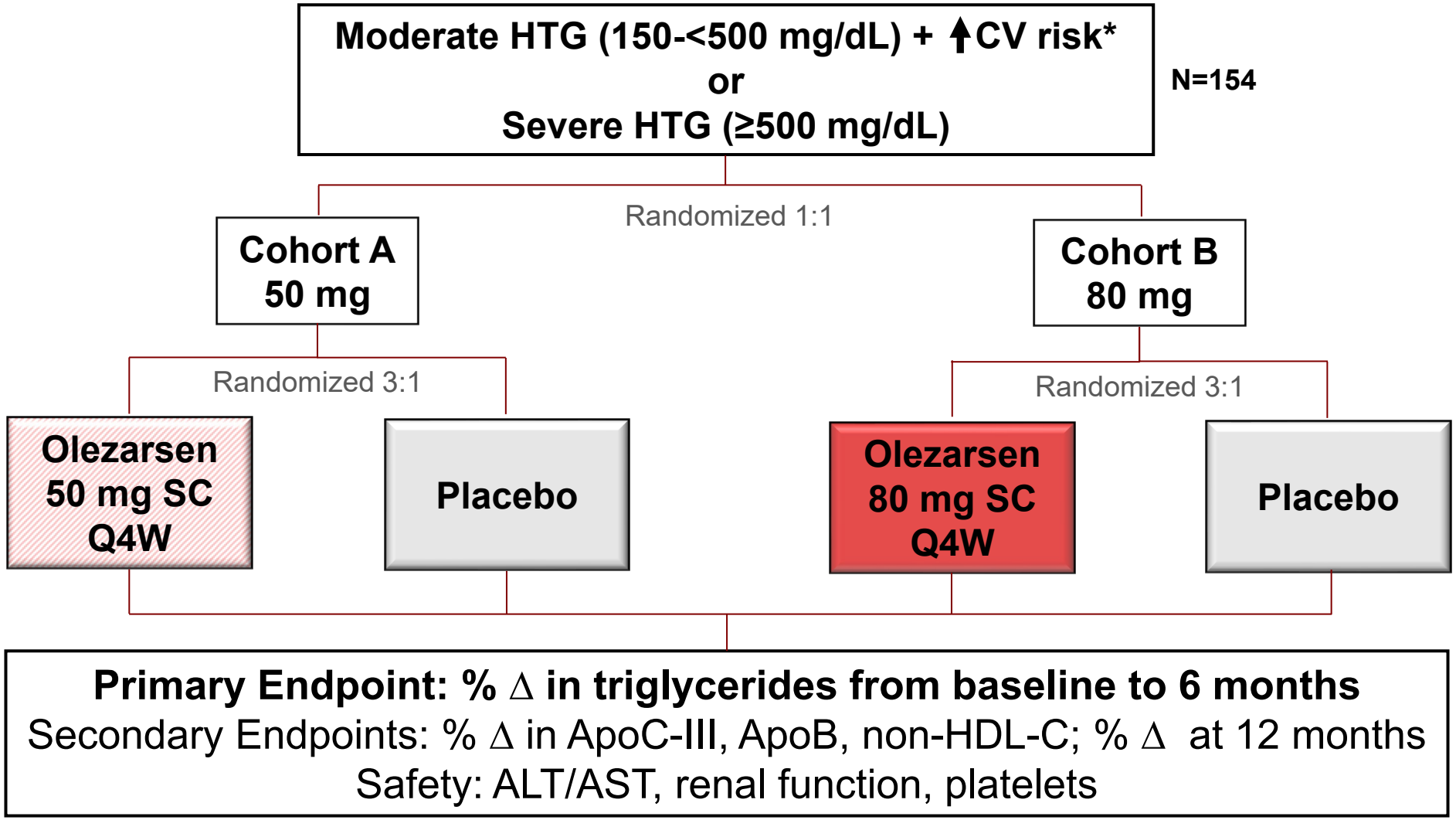


Gaudet D. *N Engl J Med*. 2014;371:2200-6
Alexander VJ, et al. *Eur Heart J*. 2019;40:2785-96
Tardif JC, et al. *Eur Heart J*. 2022;43:1401-12

Objective

Assess the efficacy and safety of olezarsen in patients with moderate hypertriglyceridemia and elevated CV risk or with severe hypertriglyceridemia

Trial Design



* ↑ **CV risk:** Established ASCVD or increased ASCVD risk (T2DM or ≥2 risk factors)

Trial Organization

TIMI Study Group

Marc Sabatine (Chair)
Robert Giugliano (Sr Investigator)
P. Fish & A. Jevne (Ops)
Brian Bergmark (PI)
Nicholas Marston (Investigator)
S. Murphy, E. Goodrich, S. Zhang (Stats)

Sponsor: Ionis

Sotirios Tsimikas (SVP, Global CV Dev)
Ewa Karwatowska-Prokopczuk (VP, CV Med)
Thomas Prohaska (Director, Clin Dev)
Vickie Alexander (Executive Director, Clin Dev)

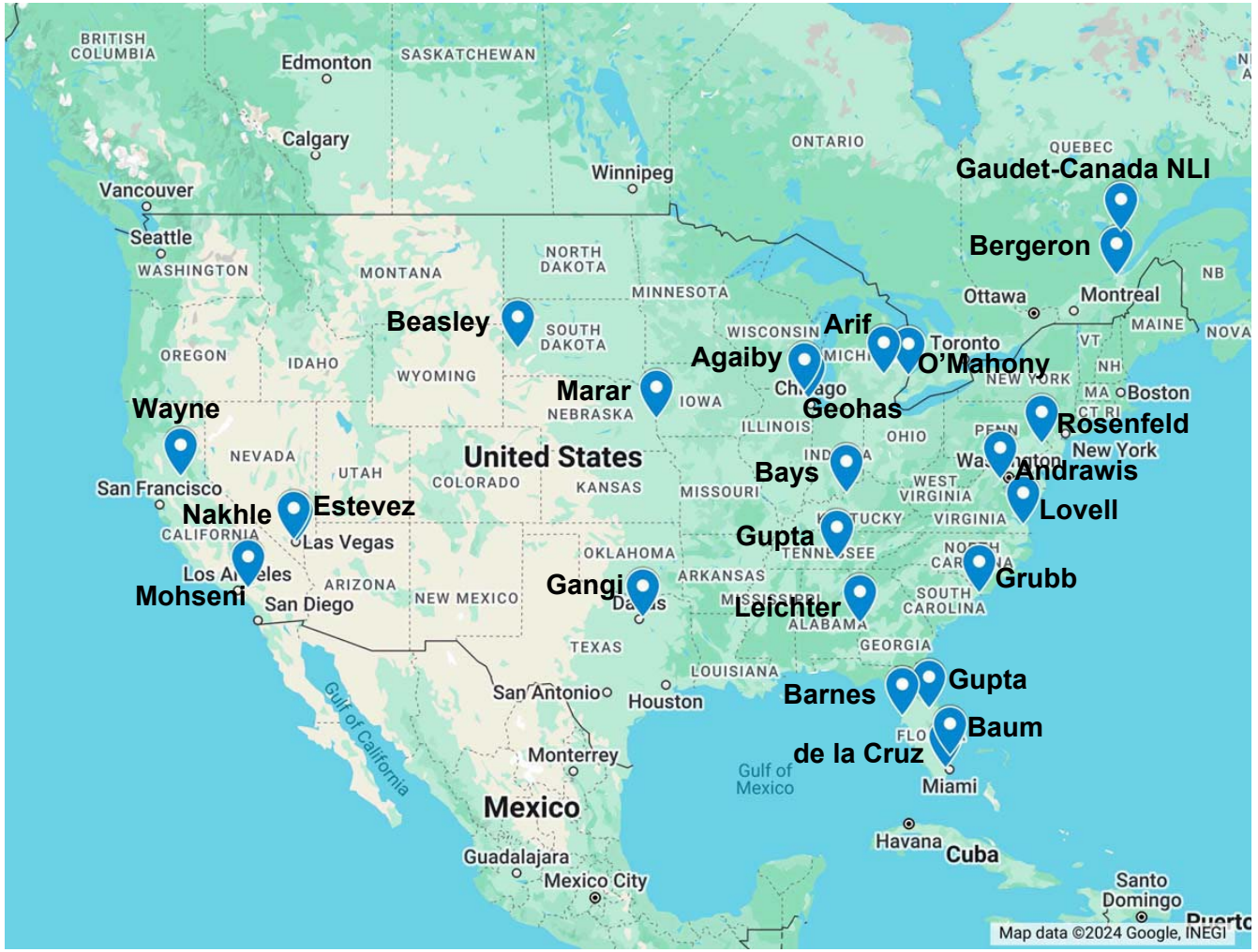
Independent Data Monitoring Committee

Richard Becker (Chair)
Jamie Dwyer
Willis Maddrey
Charles Davis (Statistician)
François Mach

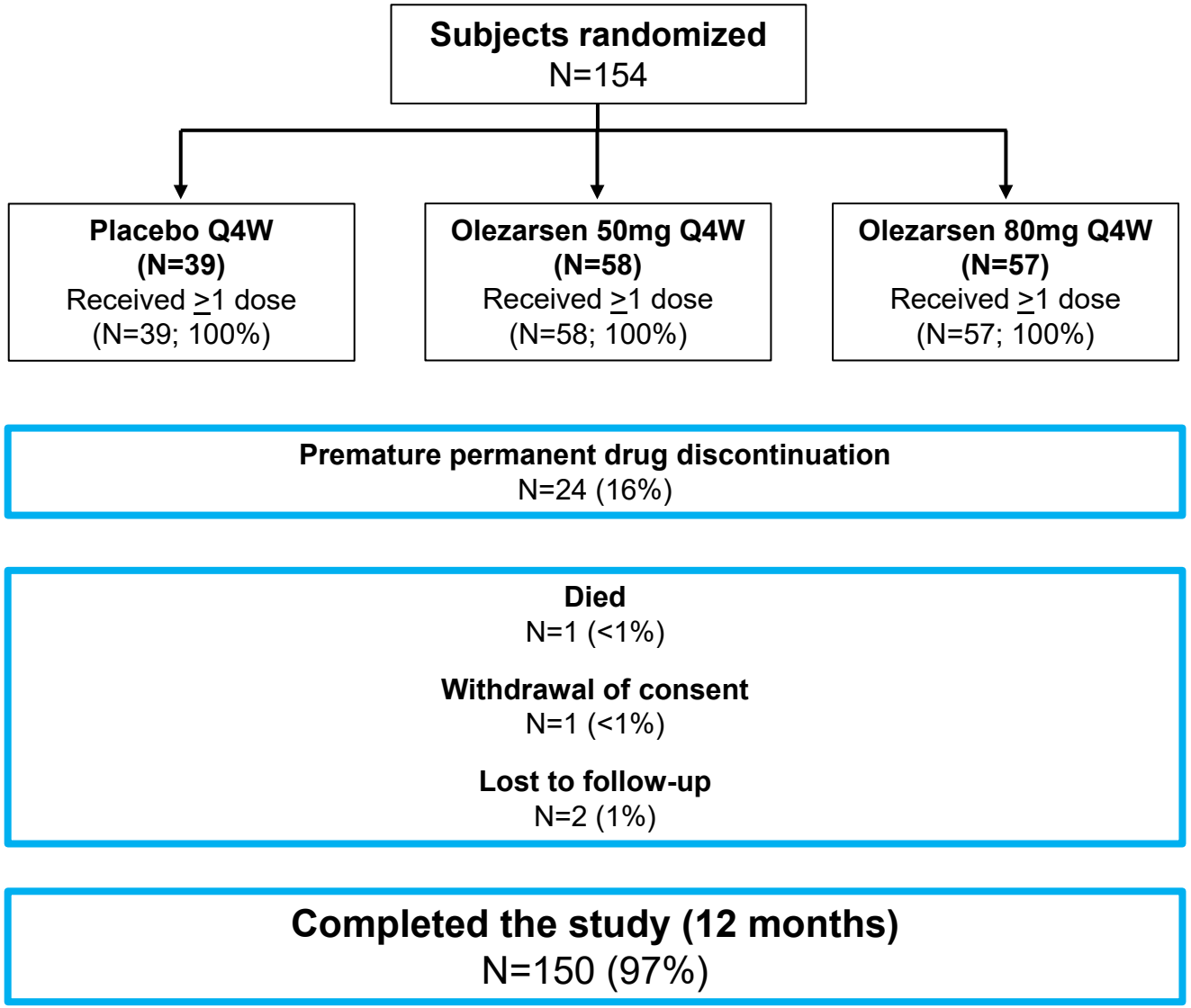
Bridge-TIMI 73a was supported by a grant from Ionis Pharmaceuticals to Brigham and Women's Hospital.

Enrollment

June – September 2022 | **24** Sites | **154** Patients



Follow-up

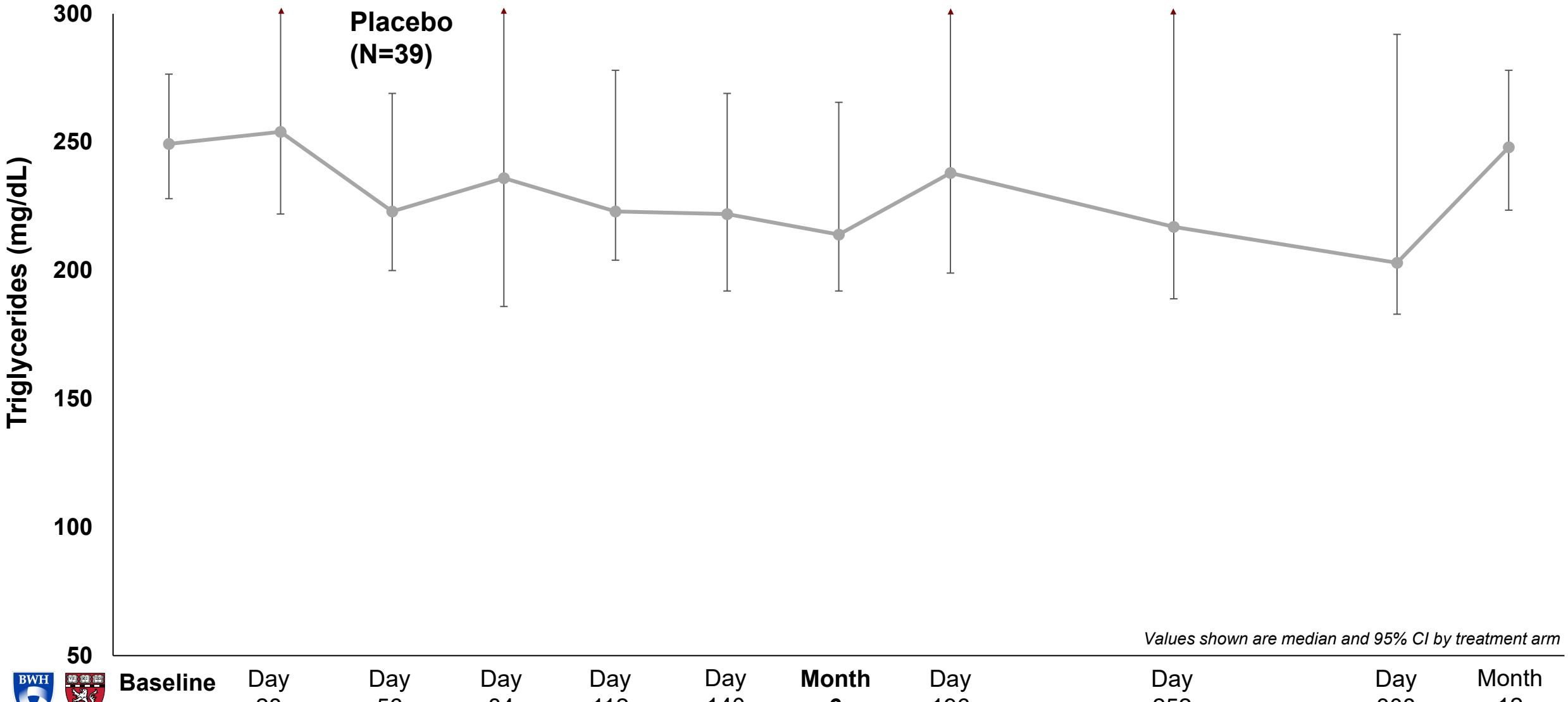

Subjects randomized
N=154
Placebo Q4W
(N=39)
Received ≥1 dose
(N=39; 100%)
Olezarsen 50mg Q4W
(N=58)
Received ≥1 dose
(N=58; 100%)
Olezarsen 80mg Q4W
(N=57)
Received ≥1 dose
(N=57; 100%)
Premature permanent drug discontinuation
N=24 (16%)
Died
N=1 (<1%)
Withdrawal of consent
N=1 (<1%)
Lost to follow-up
N=2 (1%)
Completed the study (12 months)
N=150 (97%)

Baseline Characteristics

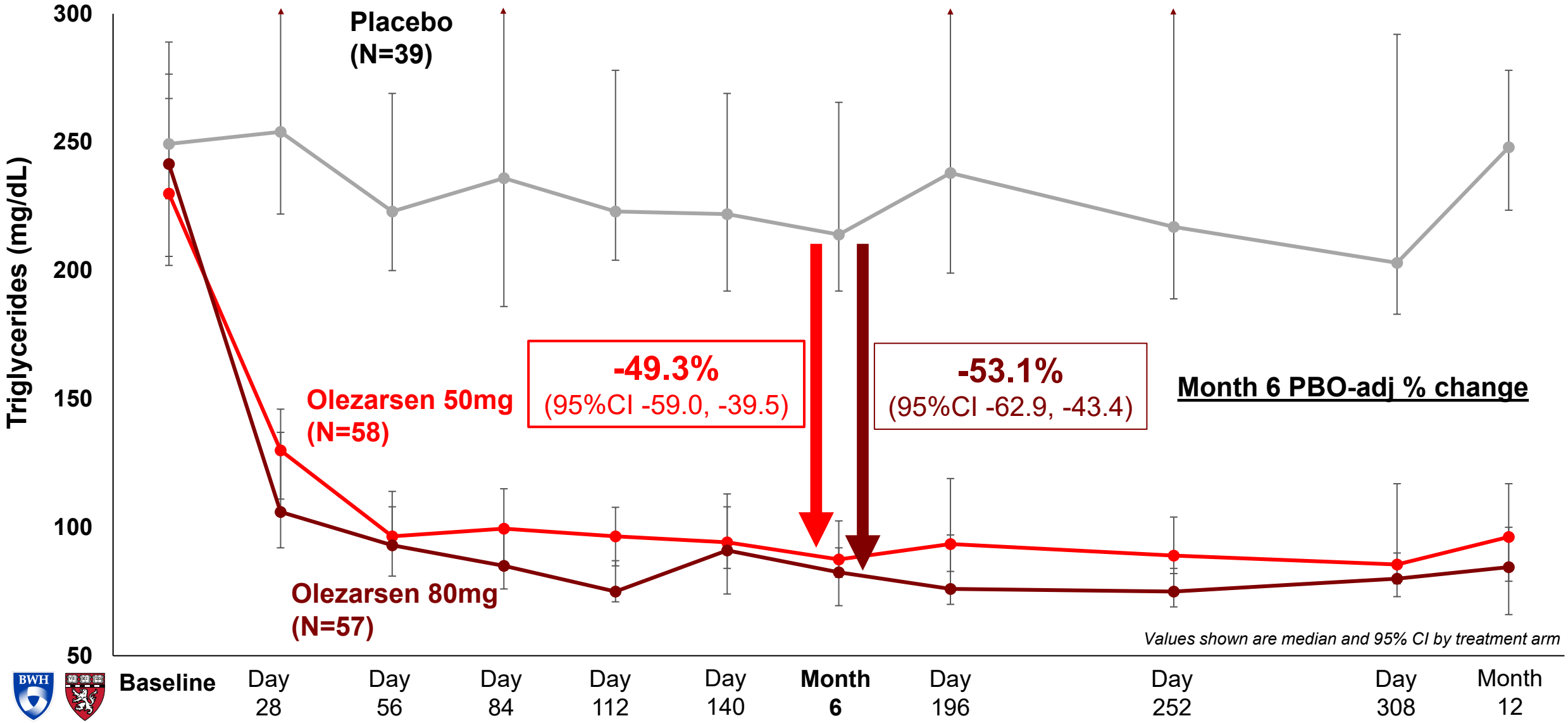
Clinical characteristics	Total N=154
Age (yrs)	62 (55-70)
Female sex	42%
Race/Ethnicity	
White	92%
Hispanic/Latino	38%
Black	8%
Hispanic/Latino	33%
Asian	1%
BMI (kg/m^2)	33 (29-37)
Prior pancreatitis	1%
Diabetes mellitus	68%

Values shown are % or median (IQR)

Olezarsen Efficacy



Olezarsen Efficacy

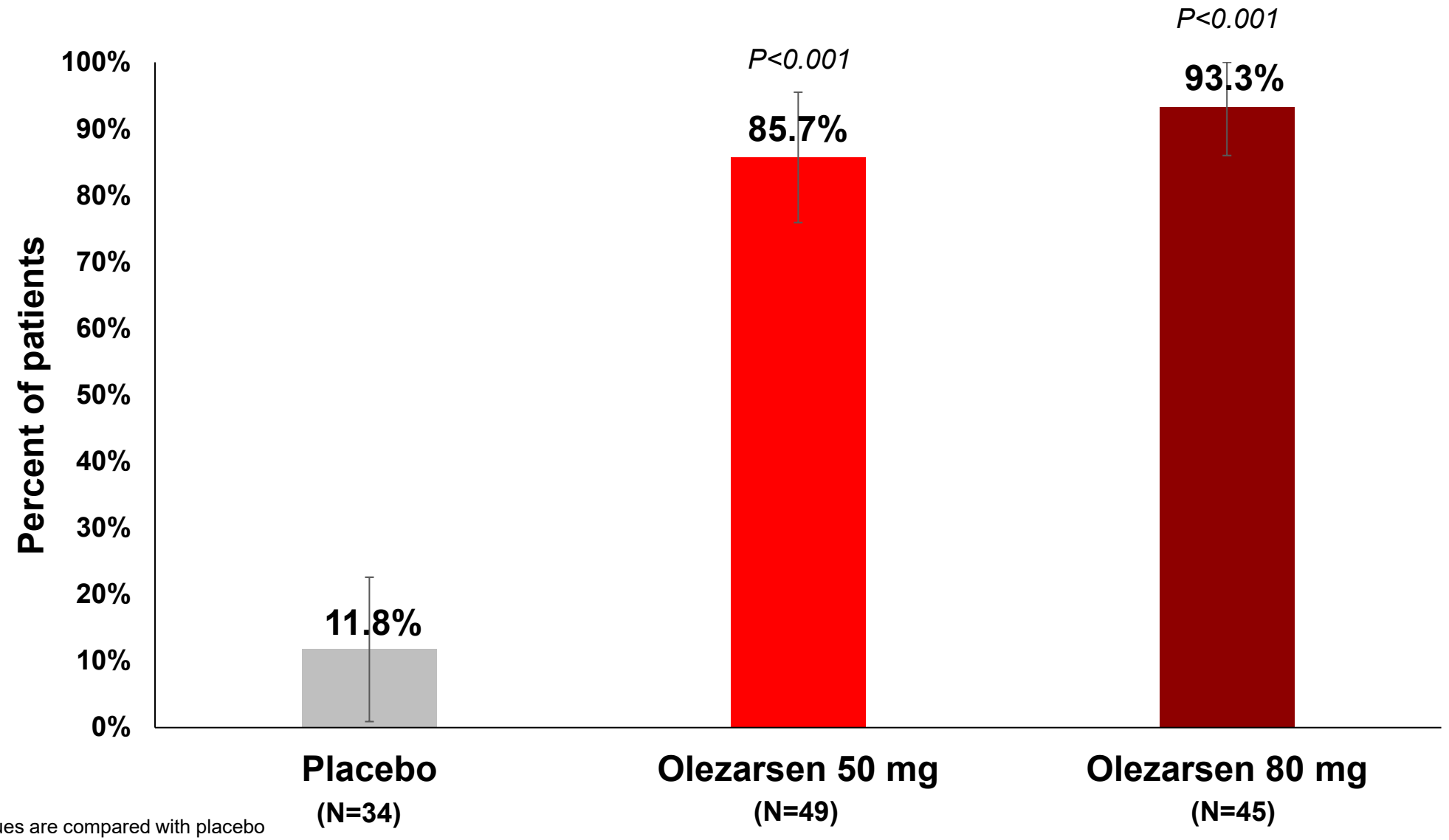


Lipid changes at 6 months

Values shown are placebo-adjusted LSM % changes and 95% CI at 6 months

Achieved TG<150 mg/dL at 6 months

In patients with moderate hypertriglyceridemia at baseline



P values are compared with placebo

Key Safety Parameters

	Placebo N=39	Olezarsen 50 mg N=58	P-value vs Placebo	Olezarsen 80 mg N=57	P-value vs Placebo
Treatment-emergent adverse events					
Any	29 (74.4)	42 (72.4)	0.83	38 (66.7)	0.42
Leading to drug discontinuation	0 (0)	7 (12.1)	0.04	3 (5.3)	0.27
Serious	2 (5.1)	4 (6.9)	>0.99	7 (12.3)	0.30
Leading to drug discontinuation	0 (0)	1 (1.7)	>0.99	1 (1.8)	>0.99
Pancreatitis	0	0	--	0	--
Hepatic abnormalities					
ALT ≥ ULN	1 (2.6)	27 (46.6)	<0.001	21 (36.8)	<0.001
AST ≥ ULN	4 (10.3)	18 (31.0)	0.03	21 (36.8)	0.004
ALT or AST ≥3x ULN	0	4 (6.9)	0.15	1 (1.8)	>0.99
Total bilirubin ≥2x ULN	0	0	--	0	--
Alkaline phosphatase ≥2x ULN	0	0	--	0	--

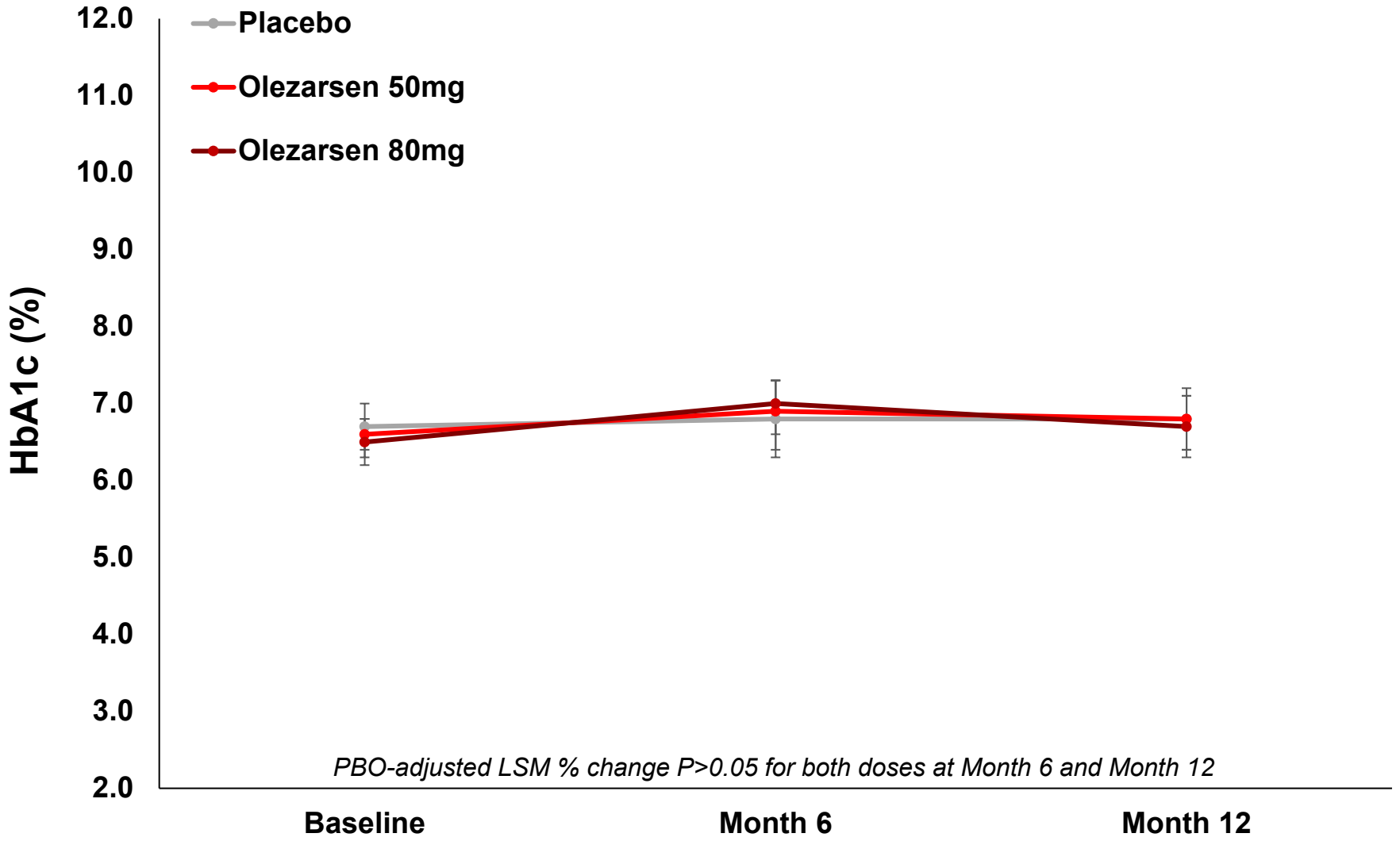
Treatment phase safety data shown

Key Safety Parameters

	Placebo N=39	Olezarsen 50 mg N=58	P-value vs Placebo	Olezarsen 80 mg N=57	P-value vs Placebo
Renal abnormalities					
eGFR decline ≥30%	8 (20.5)	6 (10.3)	0.16	4 (7.0)	0.06
eGFR decline ≥50%	0	0	--	0	--
UPCR ≥1000 mg/g	4 (10.3)	4 (6.9)	0.71	3 (5.3)	0.44
Platelet count					
<140K/uL	1 (2.6)	10 (17.2)	0.05	10 (17.5)	0.03
<100K/uL	1 (2.6)	0	0.40	3 (5.3)	0.64
<75K/uL	0	0	--	0	--

Treatment phase safety data shown

Additional Safety



Olezarsen Program

Mod HTG + CV risk *or* Severe HTG	**Bridge-TIMI 73a**	**Essence-TIMI 73b** • 1478 patients • Coronary CTA substudy
Severe HTG	**CORE-TIMI 72a** • 540 patients • Hepatic MRI substudy	**CORE2-TIMI 72b** • 390 patients • Hepatic MRI substudy
	Open Label Extension	

Limitations

The number of patients with severe hypertriglyceridemia was small, limiting the ability to assess olezarsen's lipid and clinical effects in these patients

Trials of olezarsen in patients with severe hypertriglyceridemia are ongoing

Treatment beyond one year was not evaluated

Open label extension programs with olezarsen are underway

These findings cannot necessarily be applied to patients with specific genetic syndromes or secondary causes of hypertriglyceridemia

Olezarsen's effects in patients with familial chylomicronemia syndrome (Balance trial) will be presented at 9:45 am today in room B313A

Summary and Conclusions

In patients with largely moderate hypertriglyceridemia and elevated cardiovascular risk, olezarsen 50 mg or 80 mg monthly significantly reduced triglyceride levels

- *TG effect was greater than is possible with currently available treatments*
- *There were no major safety concerns in this phase 2b trial*

Olezarsen led to meaningful reductions in apolipoprotein B and non-high-density lipoprotein cholesterol, markers of atherogenic risk

Thank you

The NEW ENGLAND JOURNAL of MEDICINE

ACC.24

Mandibular Advancement versus CPAP for BP Reduction In OSA and high Cardiovascular Risk

Chi-Hang Ronald LEE, MBBS MD

Professor, NUS Yong Loo Lin School of Medicine

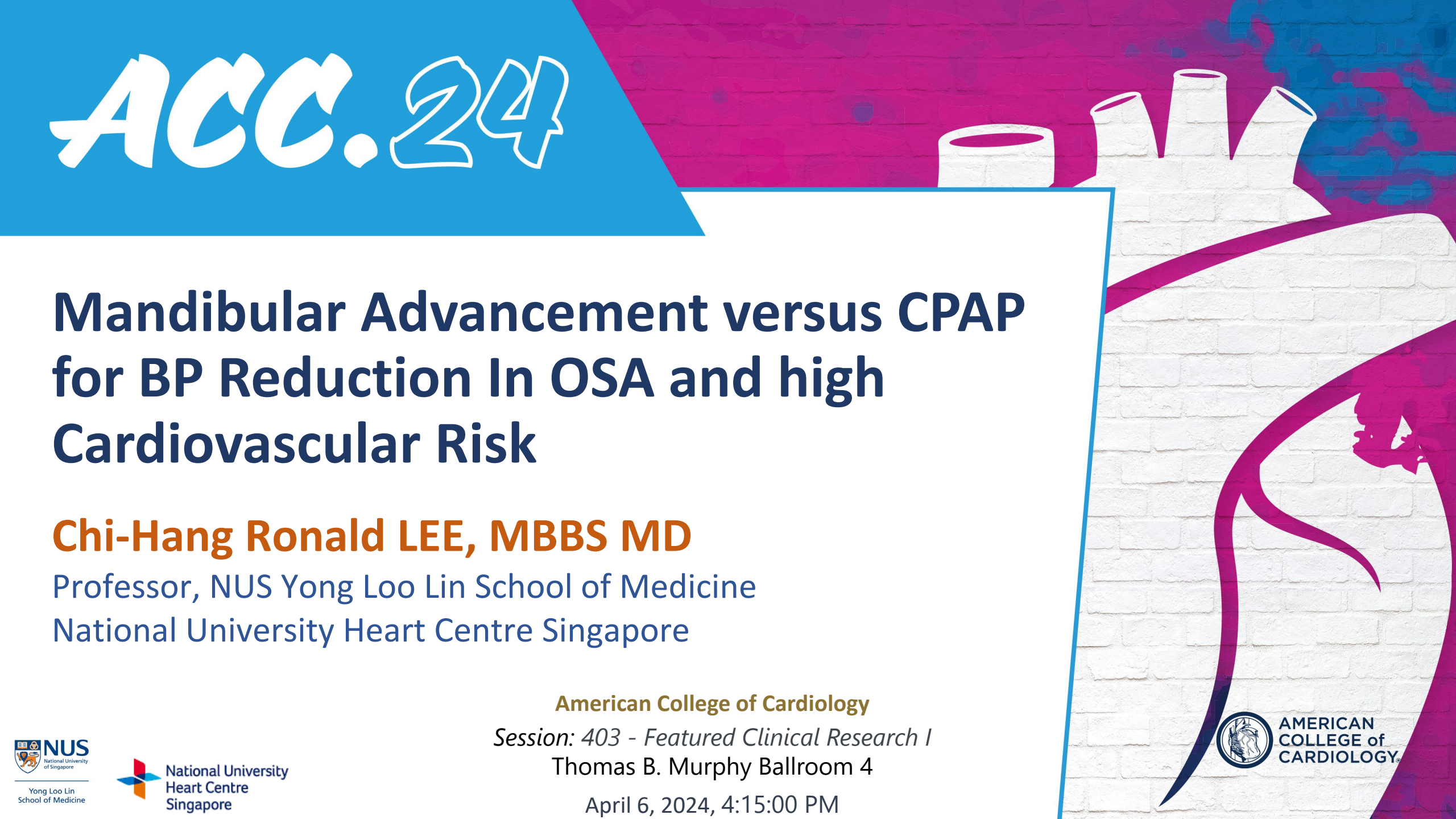
National University Heart Centre Singapore

American College of Cardiology

Session: 403 - Featured Clinical Research I

Thomas B. Murphy Ballroom 4

April 6, 2024, 4:15:00 PM



NUS National University of Singapore

Yong Loo Lin School of Medicine

National University Heart Centre Singapore

AMERICAN COLLEGE of CARDIOLOGY

Disclosure

None declared

CRESCENT is an investigator-initiated trial funded by the Singapore Ministry of Health. Manufacturers of the MAD and CPAP had no role in the trial design, data collection or analysis

Hypertension, OSA and CPAP

- Hypertension is a major risk factor for cardiac and cerebrovascular diseases[1]
- OSA is an under-diagnosed and modifiable cause of hypertension[2]
- Hypertension guidelines[3] and scientific statements[4] recommend screening and treatment of OSA in patients with hypertension
- CPAP is the first-line treatment – deliver PAP via a nasal or oronasal interface to maintain airway patency during sleep
- However, many patients either decline to use CPAP or find it challenging to stick to the treatment[5]

[1]J Am Coll Cardiol. 2020;76(25):2982-3021. [2]Lancet. 2021;398(10296):249-261.
[3]J Am Coll Cardiol. 2018;71(19):e127-e248. [4]Circulation. 2021;144(3):e56-e67.
[5]Chest. 2021;159(1):382-389.

What is MAD?

- MAD (oral appliance) reduces airway collapsibility by advancing the mandible during sleep
- MAD improves sleepiness and QoL, and better accepted and tolerated
- Unknown if treating OSA using MAD is effective in reducing BP due to limitations of early studies[6-11]

- CRESCENT trial - compare the effectiveness of MAD vs CPAP in reducing BP in patients with moderate-to-severe OSA, hypertension, and high CV risk

[6]*Am J Respir Crit Care Med. 2004;170(6):656-664.* [7]*Thorax. 2007;62(4):354-359.*
[8]*Am J Respir Crit Care Med. 2013;187(8):879-887.* [9]*Sleep Breath. 2014;18(4):749-759.*
[10]*Heart Vessels. 2019;34(10):1692-1702.* [11]*J Clin Sleep Med. 2022;18(6):1547-1555.*

CRESCENT – design summary

- **Non-inferiority:** non-inferiority margin was set at +1.5 mmHg based on a RCT comparing CPAP vs sham CPAP[12]
- **Null hypothesis:** CPAP is more effective in reducing mean arterial BP by 1.5 mmHg
- **Sample size:** detect the non-inferiority of MAD with respect to CPAP based on a statistical power of 90%, a 2.5% type-1 error rate, and 20% attrition rate, a sample size of 220 participants was needed
- **Primary outcome:** change in 24-hour mean arterial BP from baseline to 6 m

[12]*Lancet. 2002;359(9302):204-210.*

CRESCENT – protocol summary

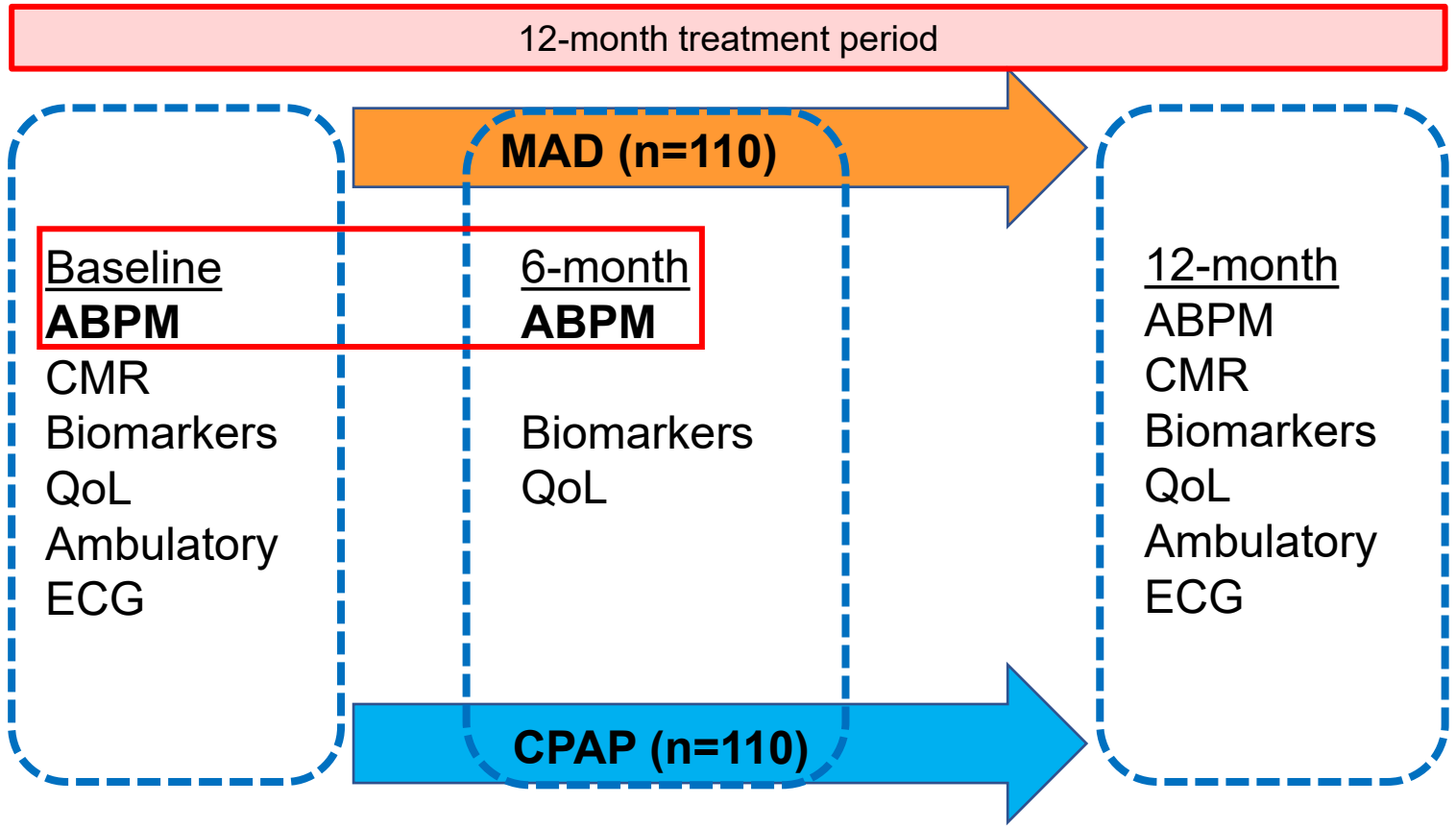
INCLUSION CRITERIA[13]
1. Age ≥ 40 years
2. Chinese
3. Essential hypertension, on ≥ 1 medication for BP control
4. *High cardiovascular risk, as defined by ≥ one of the following:
(a) DM
(b) stroke
(c) significant CAD
(d) chronic kidney disease
(e) age of ≥ 75 years old

EXCLUSION CRITERIA
Known OSA on treatment
Secondary hypertension
Contraindications to MAD
Hypertensive crisis, ACS, or acute HF in the past 30 days

Recruitment
October 2019 - December 2022

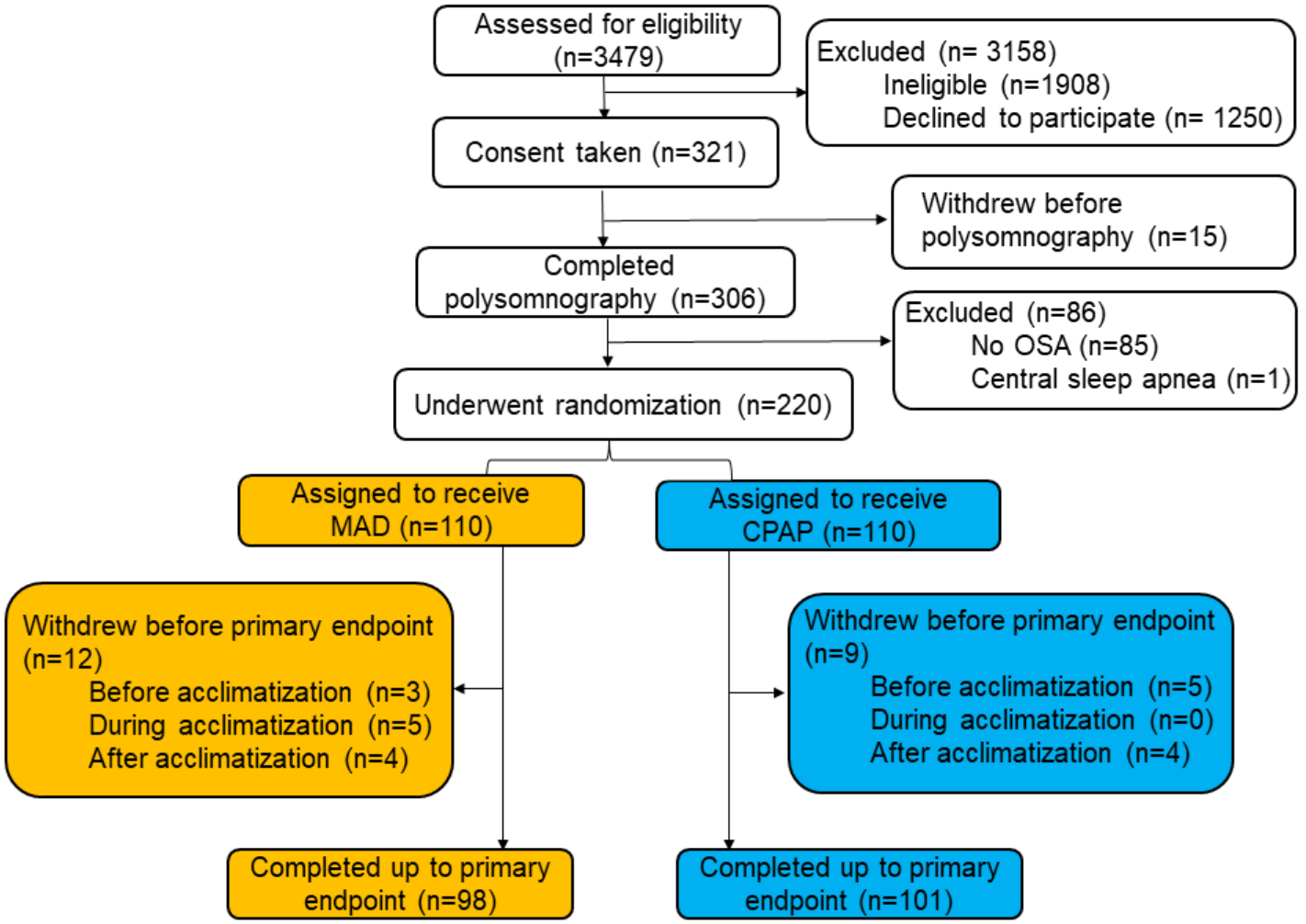
Polysomnogram → Moderate-to-severe OSA

Exclude: non-OSA and Central Sleep Apnea



[13] *BMJ Open* 2023;13:e072853.

CONSORT diagram



***Overall withdrawal: 9.5% - less than the 20% anticipated**

Key baseline characteristics balanced

	MAD (n=110)	CPAP (n=110)
Age (years), median (IQR)	61.5 (56.0-66.0)	61.0 (55.0-65.0)
Male sex, n (%)	96 (87.3)	92 (83.6)
BMI (kg/m^2), median (IQR)	27.6 (25.4-30.5)	27.4 (25.2-30.6)
Number of BP medications, n (%)		
1	27 (24.6)	42 (38.2)
2	53 (48.2)	41 (32.3)
3	22 (20.0)	22 (20.0)
≥4	8 (7.3)	5 (4.0)
24-h SBP (mmHg), median (IQR)	125 (118-132)	125 (118-132)
DM	65 (59.1)	65 (59.1)
Previous CVA/TIA	8 (7.3)	8 (7.3)
Chronic kidney disease	9 (8.2)	8 (7.3)
Previous MI	32 (29.1)	33 (30.0)
Previous PCI	51 (46.4)	57 (51.8)
Previous CABG	11 (10.0)	12 (10.9)

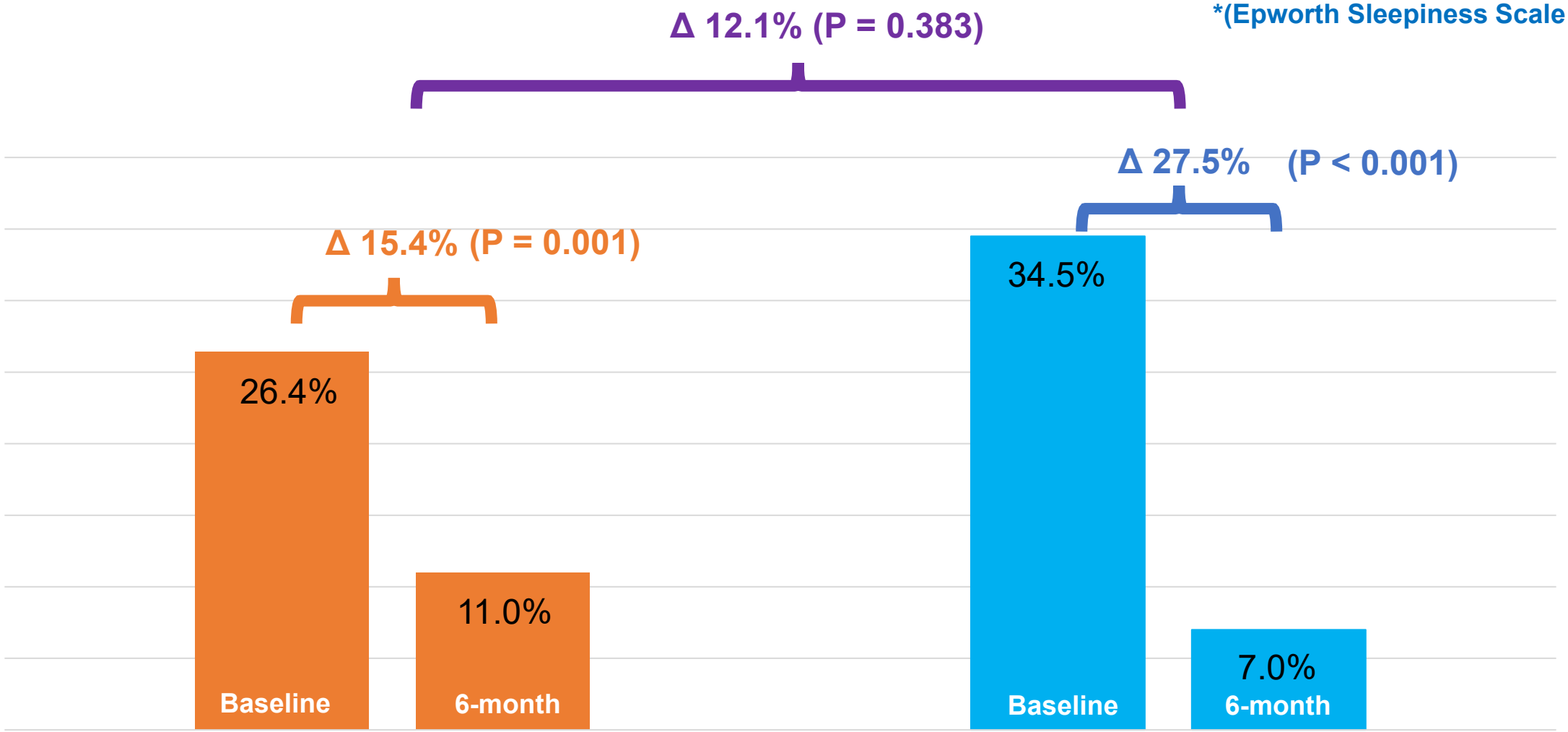
Device adherence (over 6 months)

	MAD (n=85)	CPAP (n=98)
Device adherence		
*≥ 4 hours per night in ≥ 70% of the night, n (%)	59 (69.4)	63 (64.3)
Average usage ≥ 4 hours per night, n (%)	64 (75.3)	68 (68.7)
Average usage ≥ 6 hours per night, n (%)	48 (**56.5**)	23 (**23.2**)

* American Academy of Sleep Medicine (AASM) recommendation for improvement in clinical symptoms

Excessive Daytime Sleepiness*

*(Epworth Sleepiness Scale >10/24)

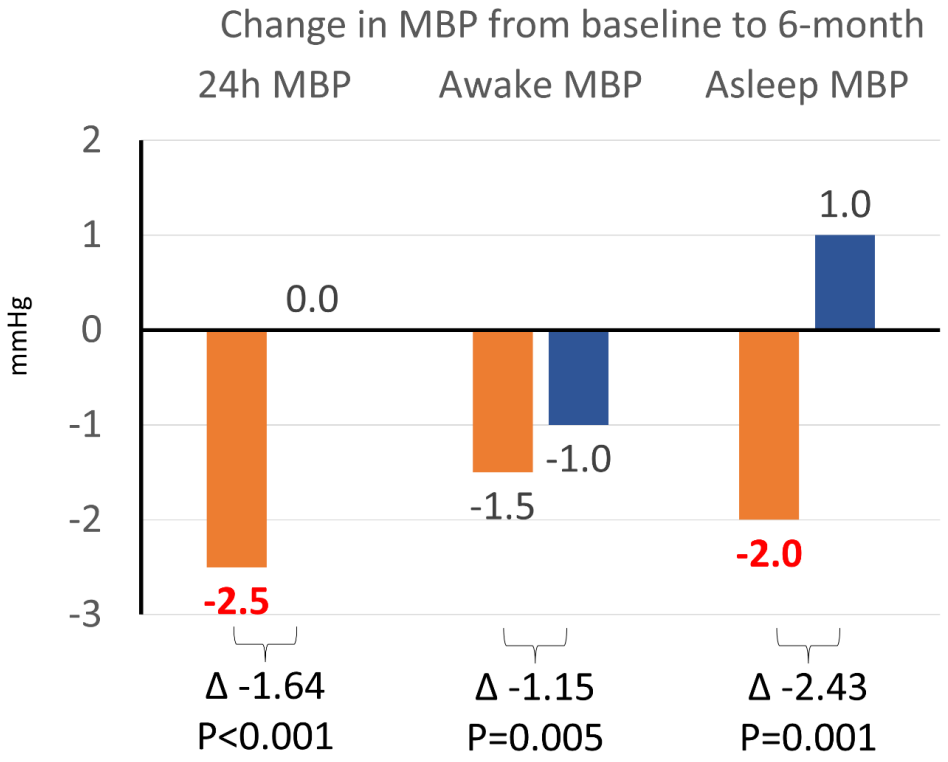


Change in BP from baseline to 6-month

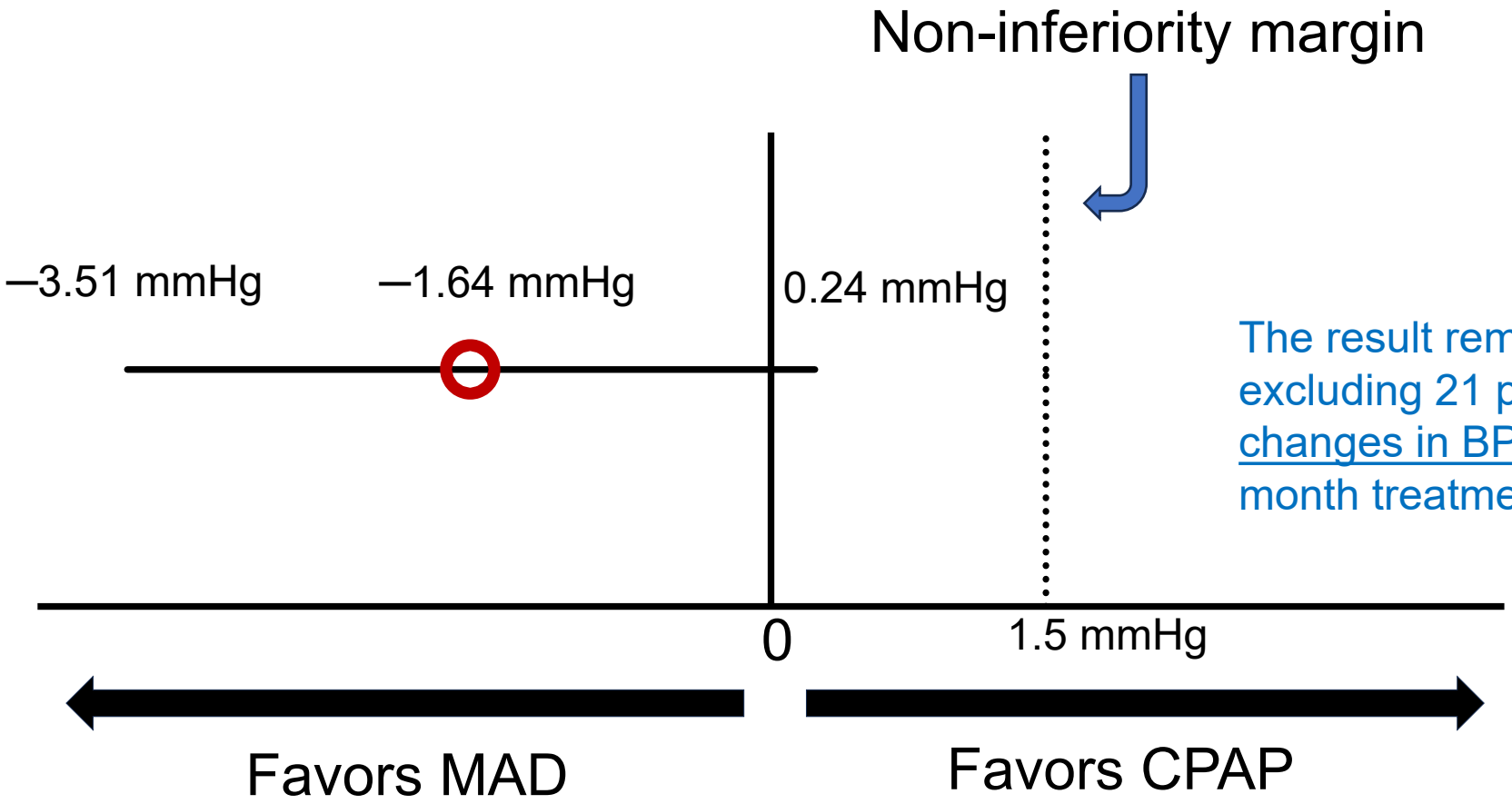
In this cohort of OSA participants with relatively well-controlled BP at baseline…

MAD vs. **CPAP**

Mean arterial BP



Effect size in relation to margin



The result remains the same after excluding 21 participants who had changes in BP medication during the 6-month treatment period.

The non-inferiority of MAD against CPAP is demonstrated because the confidence interval does not exceed the predefined margin of 1.5 mmHg (dotted line).

Awake vs Asleep BP

	MAD		CPAP		Difference (95% CI) in BP changes (mmHg)	p value ANOVA
	Baseline	6-month	Baseline	6-month		
Awake BP – not wearing the device						
SBP	126 (121-135)	124 (117-134)	129 (119-136)	127 (119-136)	**-1.83 (-4.56 to 0.90)**	0.009
DBP	82 (77-88)	81 (75-85)	81 (75-88)	81 (74-88)	**-0.83 (-2.66 to 1.00)**	0.007
Asleep BP – wearing the assigned device						
SBP	122 (113-131)	118 (110-129)	121 (113-129)	120 (111-131)	**-2.85 (-6.14 to 0.44)**	0.005
DBP	77 (71-84)	75 (69-81)	75 (70-82)	76 (70-83)	**-2.26 (-4.59 to 0.06)**	0.001

Summary

- The CRESCENT compared the effectiveness of MAD versus CPAP for BP reduction. All participants had hypertension and high CV risk
- MAD was non-inferior to CPAP for reducing 24-h mean arterial BP at 6-m follow-up
- The between-group difference in BP reduction favored MAD and was most pronounced for asleep BPs
- Both the MAD and CPAP were effective in improving daytime sleepiness

Acknowledgement

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Ching-Hui **Sia**, MBBS, Chieh-Yang **Koo**, MBBS, Serene **Wong**, MBBS,
Aiping **Chua**, MBBS, Chin-Meng **Khoo**, MBBS, William **Kong**, MBBS, PhD,
Calvin W. **Chin**, MD, PhD, Pipin **Kojodjojo**, MBBS; PhD, Philip E. **Wong**, MBBS,
Mark Y. **Chan**, MBBS; PhD, A. Mark **Richards**, MD, PhD,
Peter A. **Cistulli**, MBBS; PhD, Chi-Hang **Lee,** MBBS, MD

J Am Coll Cardiol. 2024 (in press)

AMERICAN COLLEGE of CARDIOLOGY®

CRESCENT

Mandibular Advancement (MAD) vs. Continuous Positive Airway Pressure (CPAP) For Blood Pressure (BP) Reduction in Obstructive Sleep Apnea (OSA)

Randomized, Open-Label, Noninferiority Trial

OBJECTIVE: To compare the effectiveness of MAD vs. CPAP in reducing BP in patients with moderate-to-severe OSA, hypertension and high cardiovascular risk.

220
PATIENTS

INCLUSION CRITERIA:
Ethnic Chinese adults living in Singapore with OSA and essential hypertension taking at least one BP lowering medication and at high cardiovascular risk.

NONINFERIORITY MAD (N=110)

VS.

CPAP (N=110)

PRIMARY ENDPOINT

DIFFERENCE BETWEEN 24-HOUR MEAN ARTERIAL BP AT BASELINE AND SIX-MONTH FOLLOW-UP

MAD GROUP: -2.5 MM HG; P=0.003 vs. **CPAP GROUP: 0.0 MM HG; P=0.374**

BETWEEN-GROUP DIFFERENCE: -1.6 MM HG (95% CI, -3.51-0.24); NONINFERIORITY P<0.001; SUPERIORITY P=0.086

CONCLUSION

MAD is noninferior to CPAP for reducing 24-hour mean arterial BP at six-month follow-up in participants with hypertension and increased cardiovascular risk.

Ou Y-H, Colpani JT, Cheong CS, et al. Mandibular Advancement vs. CPAP for Blood Pressure Reduction in Patients with Obstructive Sleep Apnea. Presented at ACC.24.

Developed and reviewed by: Stephanie Spehar, MD, and Kent Brummel, MD

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DanGer Shock

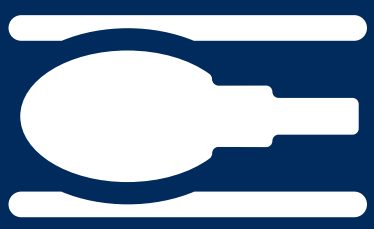
Microaxial Flow Pump or Standard Care in Infarct-Related Cardiogenic Shock

International, Multicenter, Randomized, Open-Label Trial

OBJECTIVE: To assess the efficacy of temporary mechanical support with a microaxial flow pump (Impella CP) in patients with STEMI complicated by cardiogenic shock.

355
PATIENTS

INCLUSION CRITERIA:
Patients with STEMI and cardiogenic shock, defined as hypotension, elevated lactic acid and left ventricular ejection faction <45%.



IMPELLA CP
(N=179)

VS.

STANDARD CARE
(N=176)

PRIMARY ENDPOINT

DEATH FROM ANY CAUSE WAS REDUCED WITH THE IMPELLA CP (45.8%) vs. STANDARD CARE (58.5%)

(HAZARD RATIO, 0.74; 95% CI, 0.55-0.99; P=0.04)

SECONDARY ENDPOINT

COMPOSITE SAFETY ENDPOINT (SEVERE BLEEDING, LIMB ISCHEMIA, HEMOLYSIS, DEVICE FAILURE OR WORSENING AORTIC REGURGITATION)

IMPELLA CP 24% vs. **STANDARD CARE 6.2%**
(RELATIVE RISK, 4.74; 95% CI, 2.36-9.55)

CONCLUSION

The use of the Impella CP microaxial flow pump in patients with STEMI and cardiogenic shock led to lower mortality than standard care at 180 days, but with significantly more serious complications.

Møller J, Engstrøm T, Jensen LO, et al. Microaxial Flow Pump or Standard Care in Infarct-Related Cardiogenic Shock. *NEJM* 2024. Presented at ACC.24.

Developed and reviewed by: Kent Brummel, MD

DEPOSITION

Topical Tranexamic Acid to Reduce Seizures in Cardiac Surgery

Dr. Andre Lamy on behalf of DEPOSITION Investigators
Population Health Research Institute, Hamilton, Canada

Funding: Canadian Institutes of Health Research

Population Health Research Institute
HEALTH THROUGH KNOWLEDGE

Disclosure

- None

Background

- Perioperative bleeding in cardiac surgery is associated with morbidity and mortality
- IV antifibrinolytics are standard of care: tranexamic acid (TxA)
- IV TxA increases the risk of seizure

Problem

- Anesthesiologists decrease the dose of TxA to prevent seizures
- It may increase the risk of bleeding
- Giving TxA directly on the source of bleeding (topical) has been tested in various type of surgery
- Promising alternative in our pilot study

Question

- In patients undergoing on-pump cardiac surgery, does topical tranexamic acid (intra-pericardial) compared to the usual intravenous tranexamic acid administration

  -reduce the risk of in-hospital seizure without increasing red blood cell transfusion?

Design

- Randomized controlled trial
- Double dummy to maintain blinding
  - Each patient received 2 syringes (up to 10g) for intravenous use and 2 syringes (up to 10g) for topical use
  - Investigator initiated trial
- Sample size: 3800 patients
- Funding: Canadian Institute of Health Research

Eligibility criteria

- Included patients
  - ≥18 yrs undergoing cardiac surgery with cardiopulmonary bypass
  - Median sternotomy
- Excluded patients (too low or too high risk of bleeding)
  - Minimally invasive surgery or off-pump CABG
  - Bleeding disorder
  - eGFR <30 ml/min
  - Pre-operative hemoglobin >170 g/L or <110 g/L or thrombocytopenia (<50,000 platelets per µL)
  - Expected circulatory arrest
  - Active endocarditis

Intervention and Follow-up

- Patients randomized to receive
  - TXA 1-10 g IV bolus or placebo at start and during surgery
  - TXA 1-10 g topical or placebo at end of surgery (Protamine)

- Follow-up
  - until discharge or 10 days, whichever occurred first

Outcomes

- Primary outcome
  - Seizure
- Secondary outcome
  - Red blood cell transfusion
- Tertiary outcomes: blood products transfusion, composite (death, MI, stroke), reoperation for bleeding or tamponade, ICU length of stay

Statistics

- Primary outcome hypothesis
  - Topical TXA superior to IV TXA for seizure
  - Fisher's exact test with 2-sided P <0.05
- Secondary outcome hypothesis
  - Topical TXA noninferior to IV TXA for red blood cell transfusion
    - upper bound of 1-sided 97.5% CI for HR needed to fall below 1.15
    - 1-sided P <0.025

Enrollment

- Second pre-specified interim analysis by DSMB (75%)
- DSMB recommended to stop the trial for safety
- Operations Committee reviewed the data and stop enrollment in the trial on November 28,2023
- 3242 patients enrolled out of 3800

Baseline characteristics

Characteristics	Topical TXA (N=1624)	Intravenous TXA (N=1618)
Age – (mean yrs)	66.3	65.7
Male	77%	78%
History of		
Myocardial infarction	38%	40%
Diabetes	30%	29%
Stroke	4%	4%
Seizure history	0.9%	0.4%
Elective surgery	65%	64%

Surgical characteristics

Characteristics	Topical TXA (N=1624)	Intravenous TXA (N=1618)
CABG only	69%	70%
Valve only	13%	12%
Ascending aorta only	1%	1%
Mixed	16%	15%
Cardio-pulmonary bypass time (mins)	88.7	88.6
Cross-clamp time (mins)	66.2	66.0

Compliance and Follow-up

- In both TXA and placebo groups
  - 96.5% of patients received active treatment allocation

- Follow-up: 100% of participants completed

Primary outcome

Outcome	Topical TXA n=1624 no. (%)	Intravenous TXA n=1618 no. (%)	RR (95% CI)	P value
Seizure	4 (0.2)	11 (0.7)	0.36 (0.12-1.14)	0.07

- Fisher's exact test

Post Hoc Primary outcome

Outcome	Topical TXA n=1624 no. (%)	Intravenous TXA n=1618 no. (%)	RR (95% CI)	P Value¶
Seizure*	4 (0.2)	11 (0.7)	0.36 (0.12-1.14)	0.07
Any seizure	4 (0.2)	14 (0.9)	0.29 (0.09-0.86)	0.02

*patients with seizure and stroke were excluded

¶ Fisher's exact test

Post Hoc Primary outcome

Outcome Stroke	Topical N=22 no. (%)	Intravenous n=12 no. (%)	RR (95% CI)	P value
Any seizure	0 (0)	3 (25%)	-	0.04

- Fisher's exact test

Post Hoc Primary outcome

Outcome	Close chambers n=2268 no. (%)	Open chambers n=940 no. (%)	RR (95% CI)	P value
Seizure	7 (0.3)	8 (0.9)	0.36 (0.13-0.99)	0.04
Any seizure	8 (0.4)	10 (1.1)	0.33 (0.13-0.84)	0.01

- Chi-square

Secondary outcome

Outcome	Topical TXA n=1624 no. (%)	Intravenous TXA n=1618 no. (%)	RR (95% CI)	P value
RBC transfusion	570 (35.1)	433 (26.8)	1.31 (1.18-1.46)	< 0.001

One-side value for non-inferiority P=0.007

Tertiary outcome

Outcome	Topical TXA n=1624 no. (%)	Intravenous TXA n=1618 no. (%)	RR (95% CI)
Any blood products	756 (46.6)	583 (36.0)	1.29 (1.19-1.40)
Reoperation bleeding	63 (3.9)	46 (2.8)	1.37 (0.94-1.98)
ICU LOS (hr) –median	24	24	-
MACE	40 (2.5)	31 (1.9)	1.29 (0.81-2.04)

Post Hoc Tertiary outcome

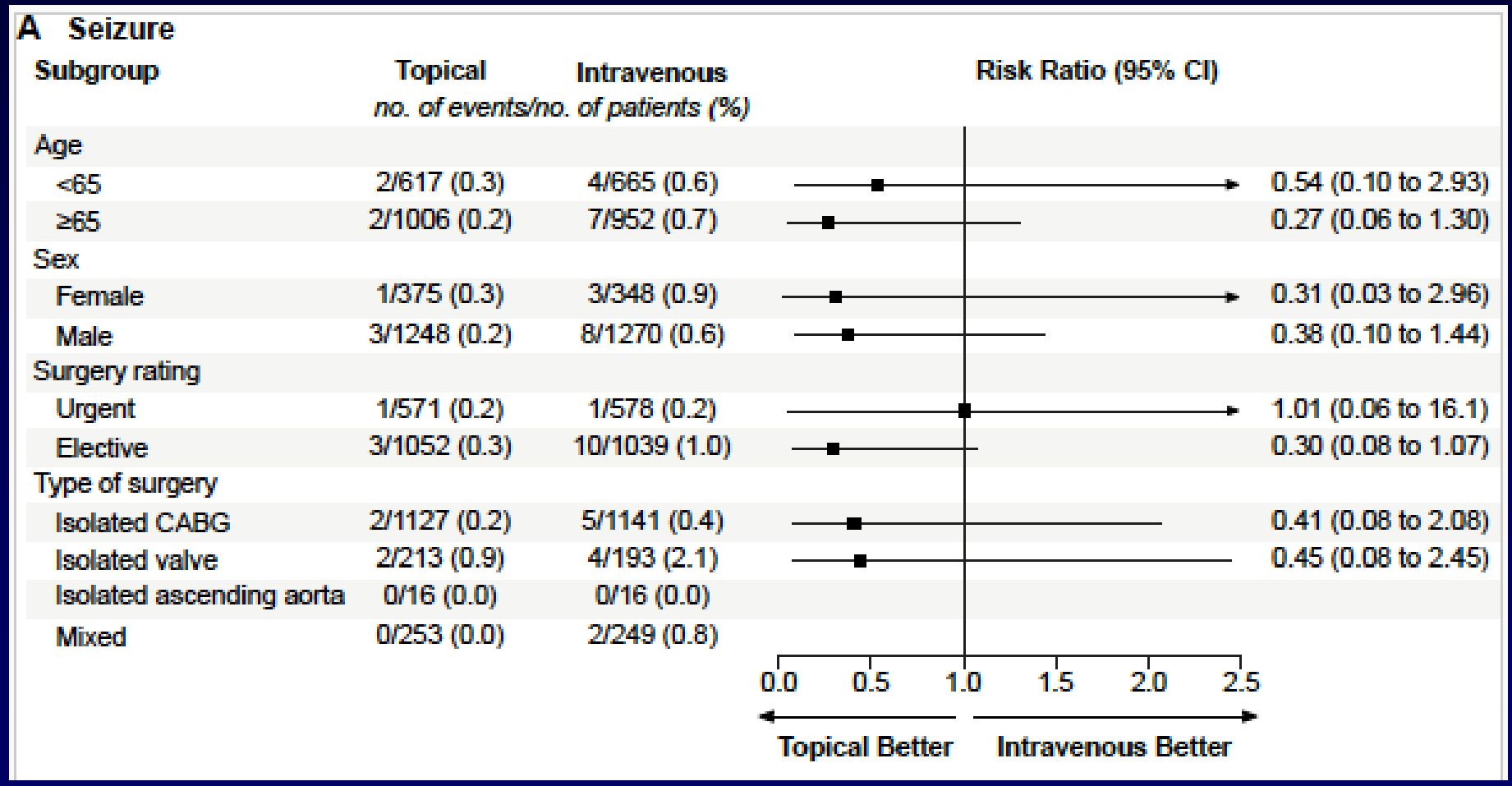
Outcome	Topical TXA n=1618 no. (%)	Intravenous TXA n=1608 no. (%)	RR (95% CI)	P value	P value *
KDIGO stage 1	322 (19.9)	330 (20.5)	0.95 (0.92-0.99)	0.02	0.45
KDIGO stage 2	7 (0.4)	5 (0.3)	1.37 (0.44-4.27)	0.59	0.51
KDIGO stage 3	24(1.5)	10 (0.6)	2.35 (1.14-4.83)	0.02	0.12
Dialysis	19 (1.2)	6 (0.4)	3.16 (1.26-7.88)	0.01	0.05

* Controlled for bleeding

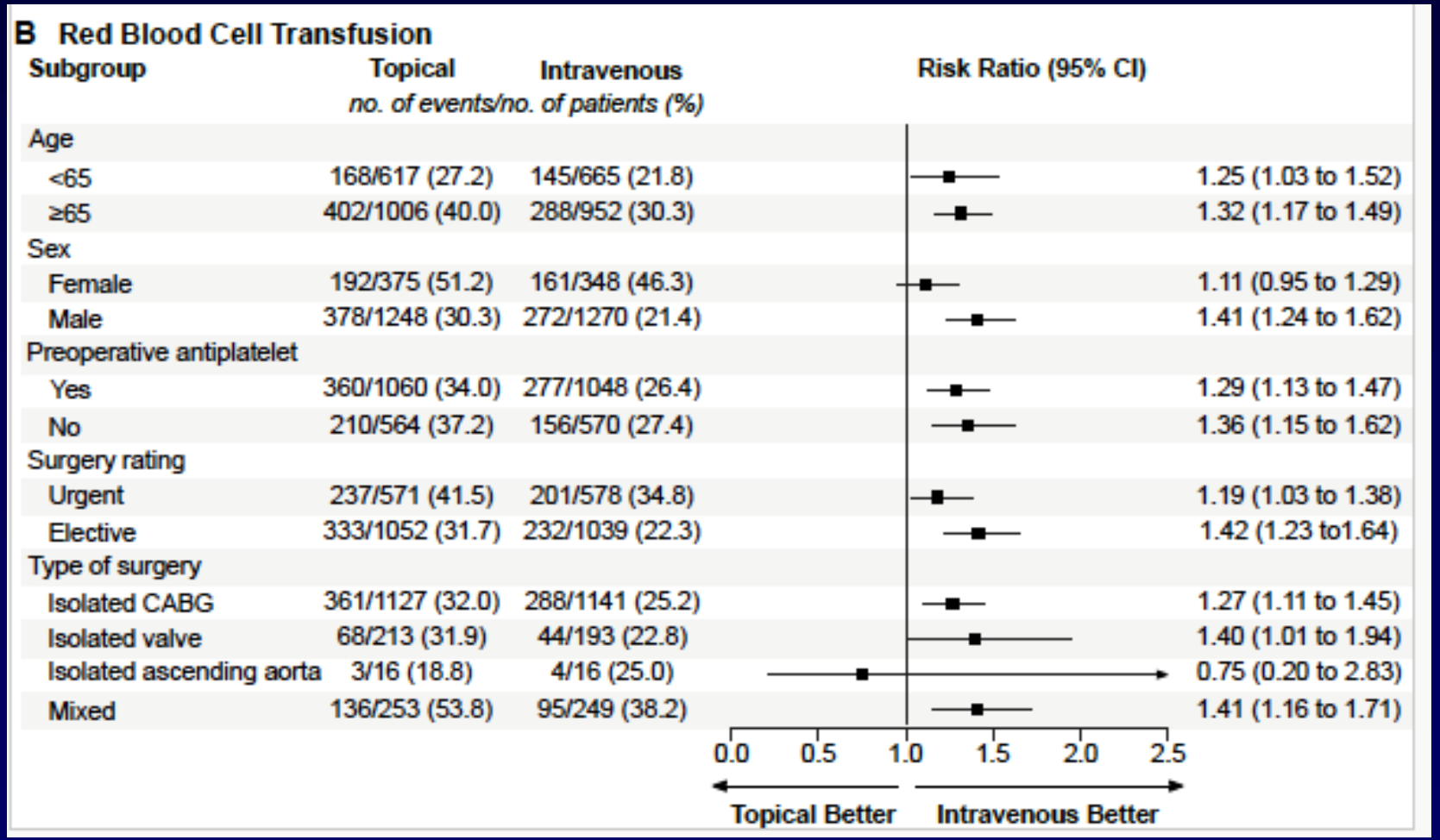
Intravenous dosage and Outcomes

Intravenous TXA n=1618 no. (%)	Group n=	Seizure no. (%)	Any Seizure no. (%)	RBC transfusion no. (%)
0 to 36mg/kg	612	5 (0.8)	5 (0.8)	164 (26.8)
36.1 to 60mg/kg	621	4 (0.6)	5 (0.8)	154 (24.8)
>60.1 mg/kg	355	2 (0.6)	4 (1.1)	110 (31.0)

Subgroup Seizure



Subgroup RBC transfusion

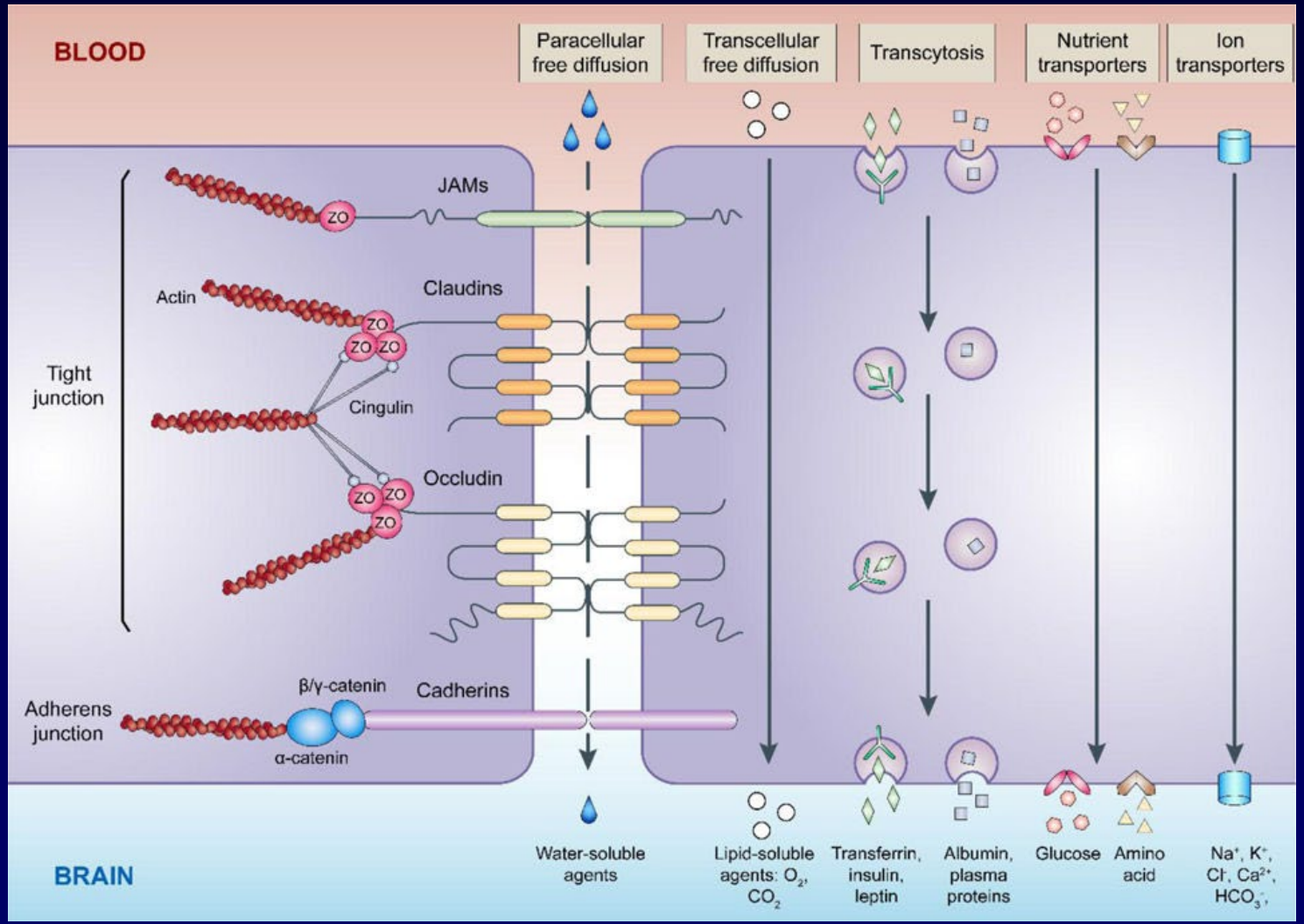


Conclusions of our trial

Topical vs. Intravenous TXA cardiac surgery

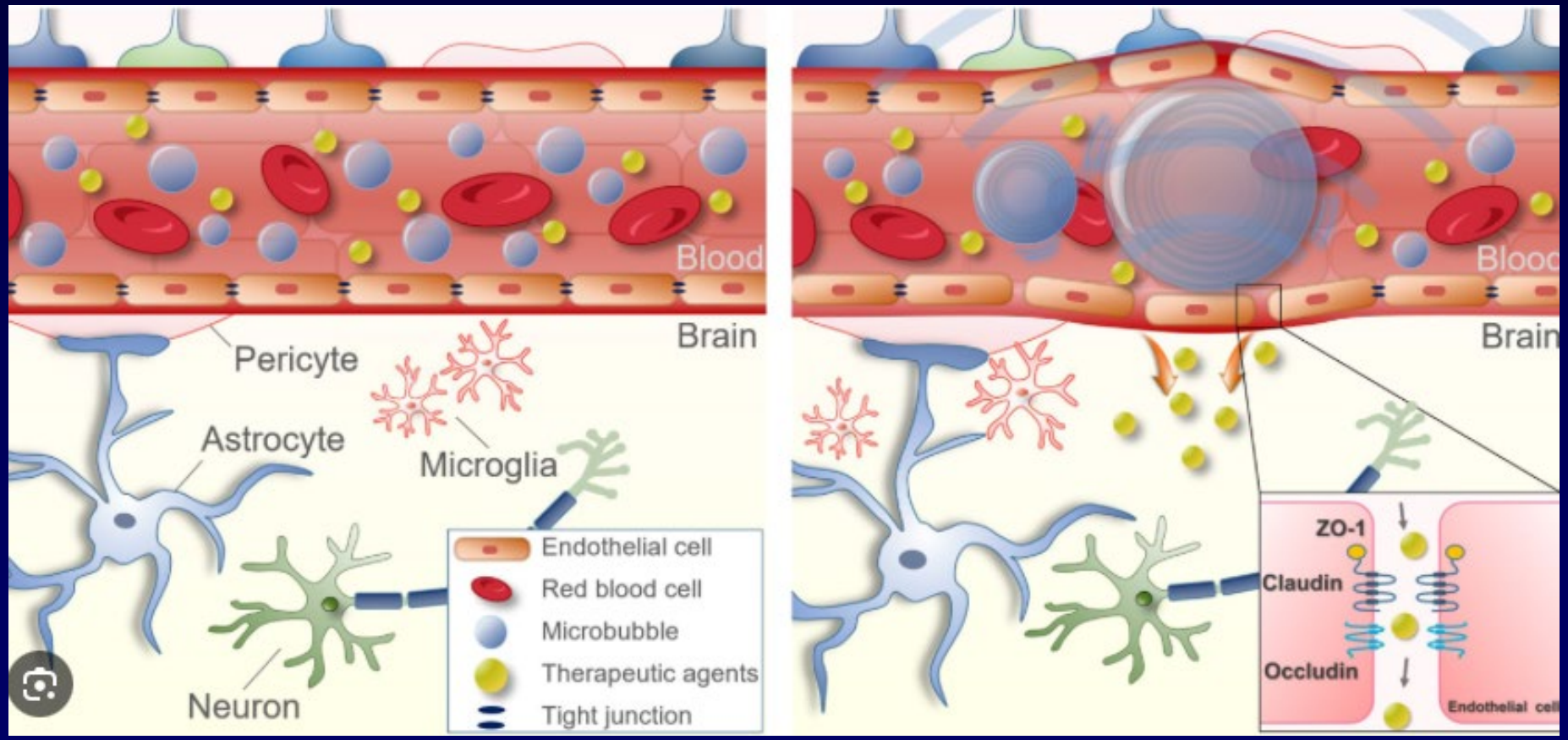
- Topical TXA does not reduce risk of seizure
- Topical TXA increases the risk of transfusion

How does TxA cross the blood-brain barrier?



Jiang X, et al. Prog Neurobiol. 2018

Micro-bubbles and Focused ultrasound

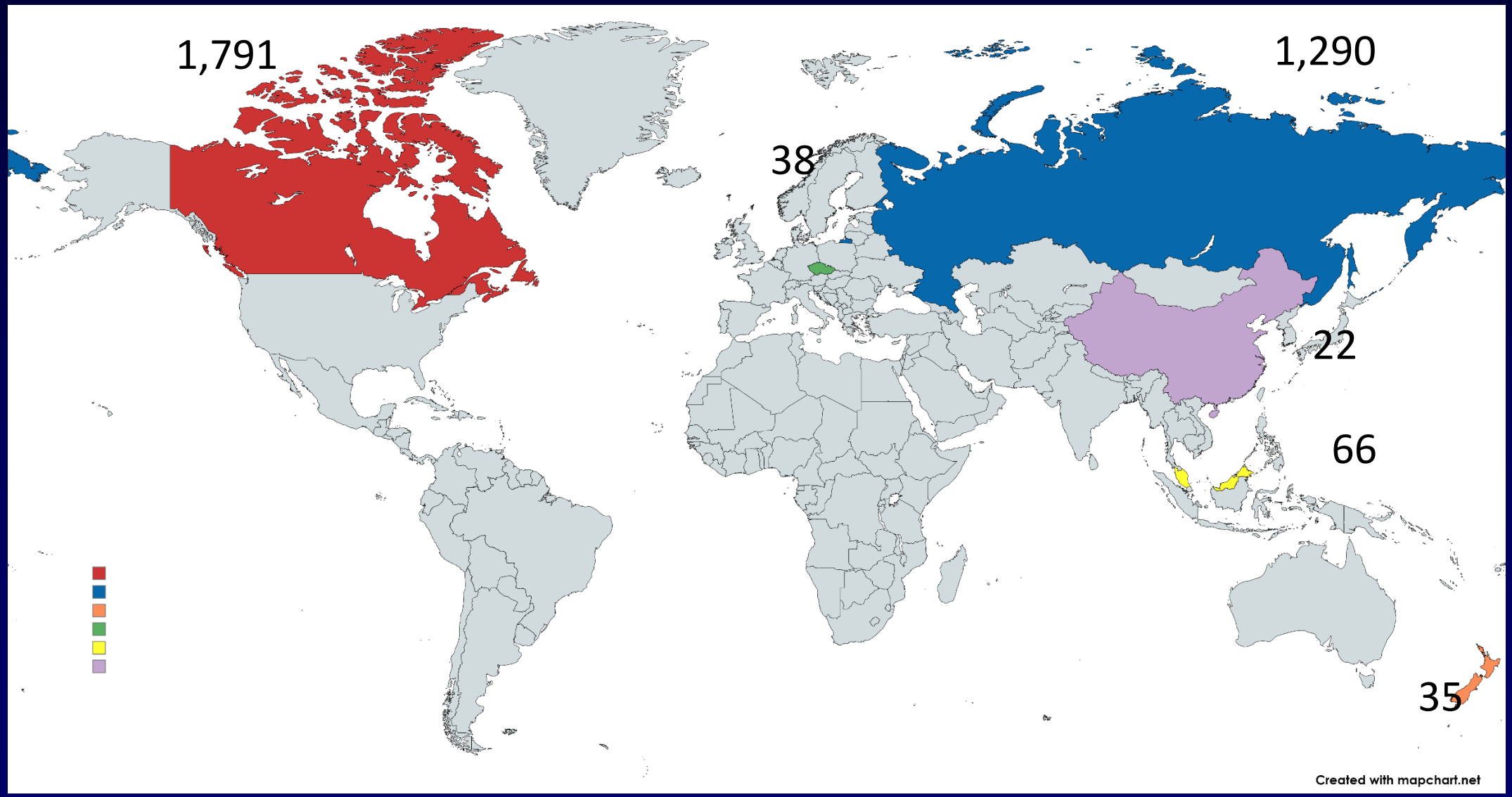


Further hypotheses

- Mechanism of seizure is more complex
  - Not only related to dose of IV TxA
  - Probably mediated by embolism of air or debris
  - Presence or absence of TxA at the time of embolism could be the mechanism: timing
  - Easily available tests for TxA levels are needed

- Thank you.

3242 patients randomized
16 centres in 6 countries



Glycine receptors

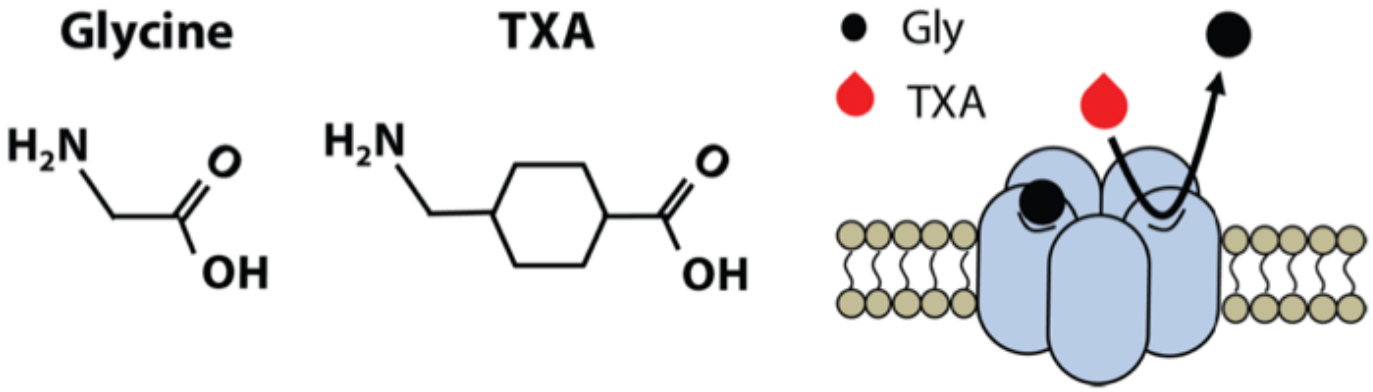
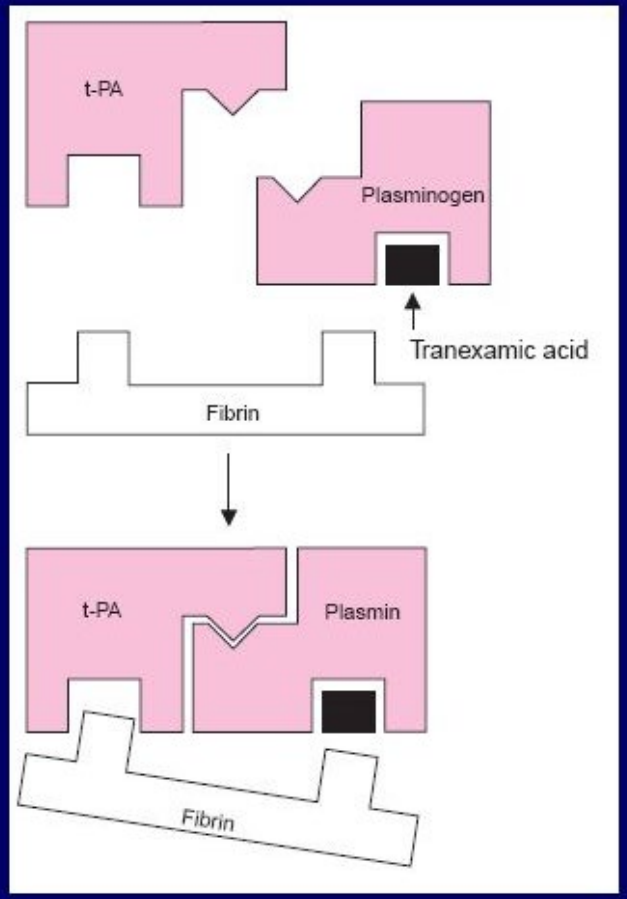


Figure 2.4 TXA is a competitive antagonist of glycine receptors.

Glycine and TXA are structural analogues suggesting that TXA competes for the glycine binding site of the glycine receptor.

Tranexamic acid and bleeding



- **Tranexamic Acid (TXA)** is a synthetic derivative of the amino acid lysine.
  - It has a very high affinity for the lysine binding sites of plasminogen.
  - It blocks these sites and prevents binding of plasmin to the fibrin surface, thus exerting its antifibrinolytic effect.

ACC.24

FULL REVASC

FFR-Guided Complete or Culprit-Only PCI in Patients with Myocardial Infarction

Felix Böhm, MD, PhD

Karolinska Institute and Danderyd Hospital, Stockholm, Sweden

On behalf of the FULL REVASC Trial Executive and Steering Committees and Investigators

AMERICAN COLLEGE of CARDIOLOGY

Disclosures

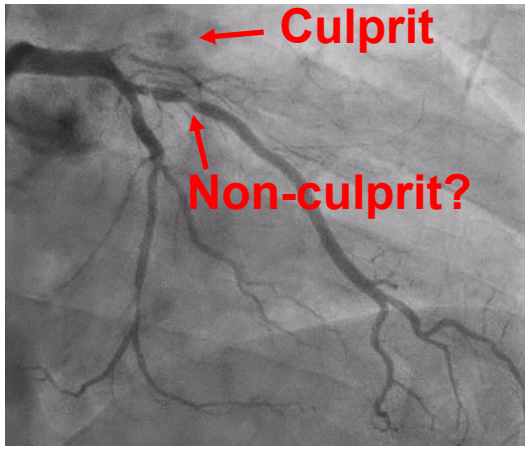
- Funded by the Swedish Research Council, the Swedish Heart-Lung Foundation and Region Stockholm with additional unrestricted grants from Abbott and Boston Scientific.
- Coordinated by Uppsala Clinical Research Center, Sweden

Background

FULL REVASC

- Around half of patients undergoing primary PCI to the culprit lesion in STEMI have multivessel disease with 1 or more angiographically significant non-culprit lesions.

- Fractional Flow Reserve (FFR) has been shown to be of benefit in chronic coronary syndromes.[1-3]



- There is uncertainty regarding how to best manage non-culprit lesions in STEMI:
  - FFR-guided complete revascularization?
  - Conservative management with guideline-directed medical therapy alone?

- Previous RCT's have shown that non-culprit lesion PCI reduces repeat revascularization, but the effect on hard endpoints like death and MI have been variable,[4-7] and the benefit of FFR-guided complete revascularization on hard endpoints remains unclear.

- The FULL REVASC Trial was designed to address this evidence gap.

1. Tonino et al, NEJM, 2009
2. De Bruyne et al, NEJM, 2014
3. Zimmerman et al, Eur Heart J. 2015
4. Wald et al, NEJM 2013
5. Gershlick et al, JACC 2015
6. Engstrom et al, Lancet 2015
7. Smits et al, NEJM 2017

Primary objective

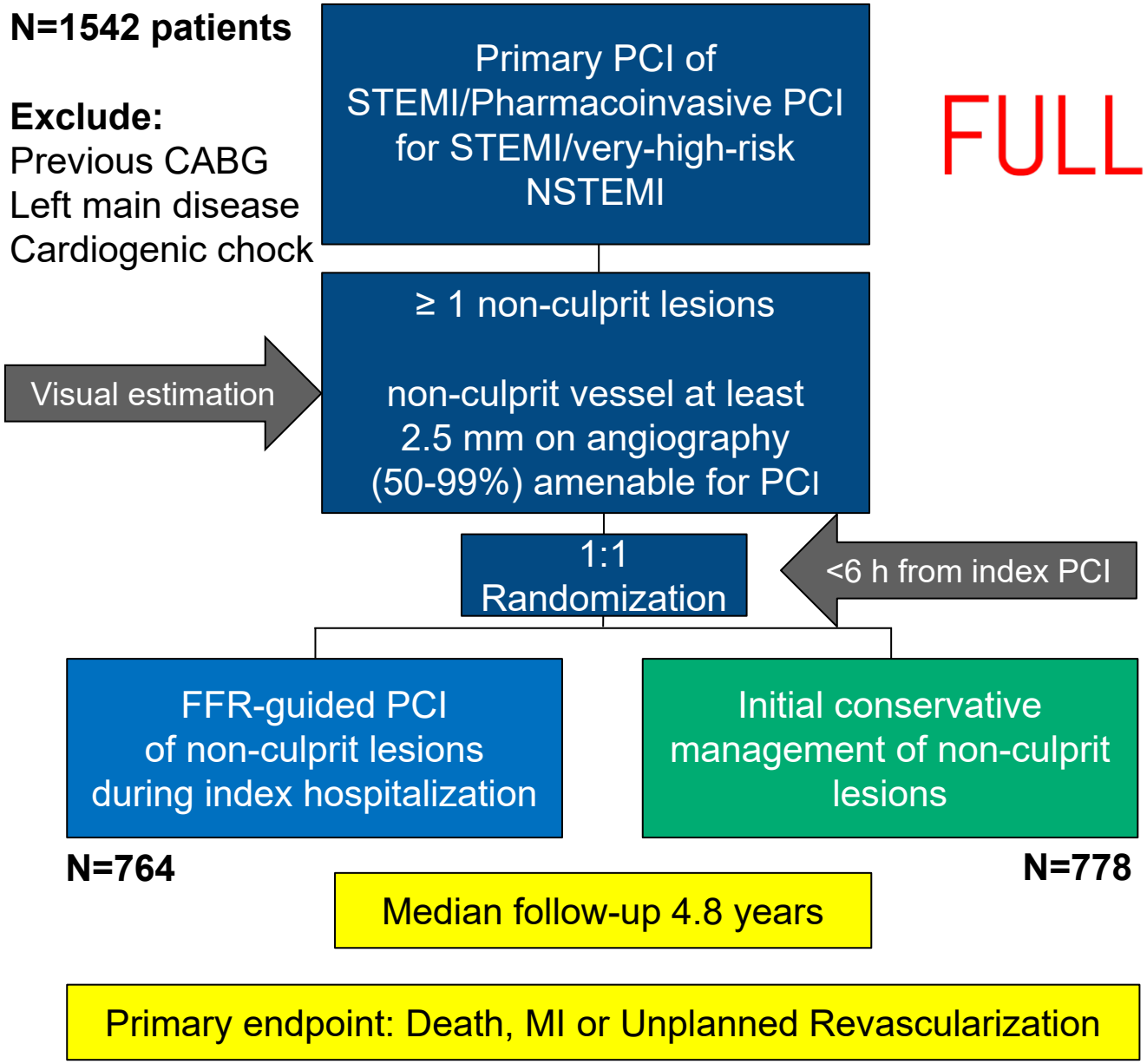
In patients with STEMI and multivessel disease, who had undergone culprit-lesion PCI, the objective was:

To determine whether a strategy of FFR-guided complete revascularization during the index hospitalization was superior to culprit-lesion-only PCI to reduce the composite of all-cause death, new myocardial infarction, or unplanned revascularization.

Trial design

N=1542 patients

Exclude:
Previous CABG
Left main disease
Cardiogenic chock

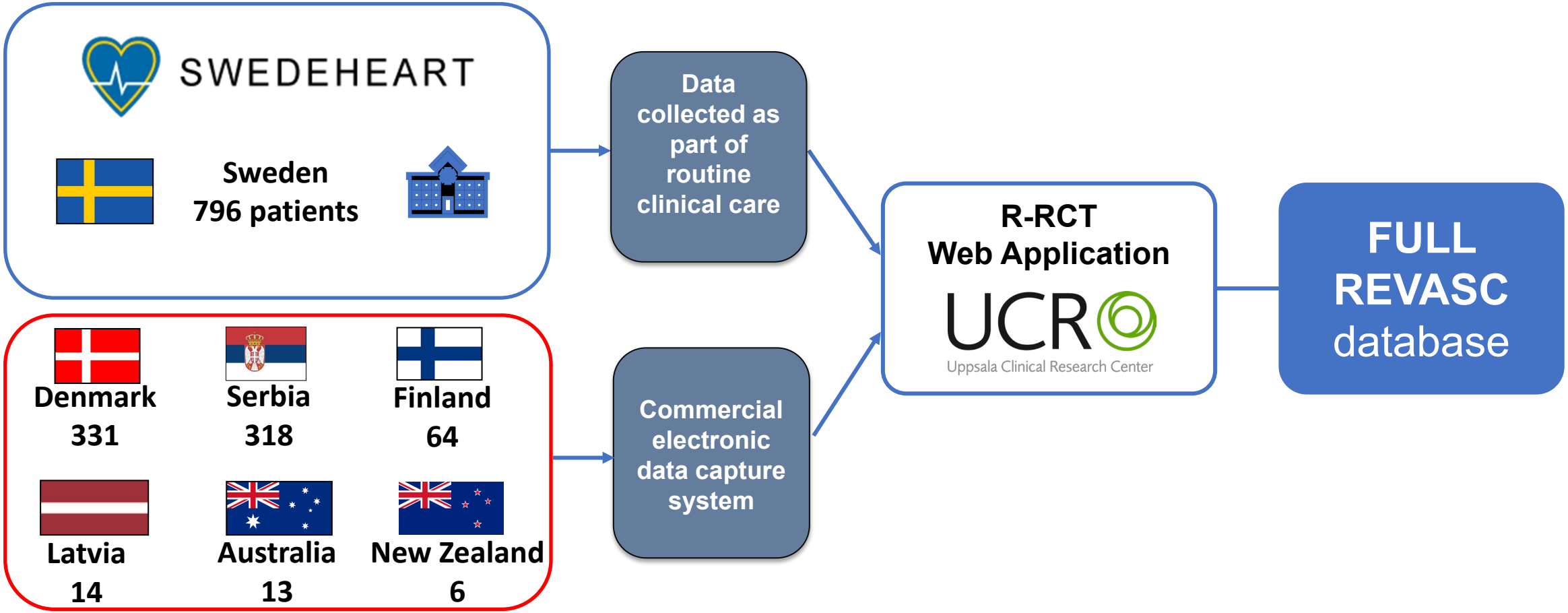


FULL REVASC

Multinational RRCT hybrid

32 centers, 7 countries

FULL REVASC



Study Power and Follow-up

- **Study Power:** Original plan: 4052 patients, 80% power for HRR of 0.75 for death or MI.
  - After COMPLETE, inclusion in the study was halted for feasibility and ethical reasons.
  - Adjusted plan: 1542 patients, 74% power for HRR for death, MI or unplanned revascularization.

- **Recruitment period:** August 8, 2016 - September 11, 2019

- **Analysis:** Intention-to-treat, Cox-proportional hazard models

- **Follow-up (vital status):** 100%. No patient lost to follow-up.

- **Crossovers during Index Hospitalization:** From *Complete revasc* to *Culprit-Only* = 4.1%
  From *Culprit-Only* to *Complete revasc* = 0.4%

Baseline characteristics

FULL REVASC

	Complete N=764	Culprit-only N=778
Age (yrs)	65.0	65.7
Female sex (%)	21.3	26.0
BMI (kg/m²)	27.6	27.6
Diabetes (%)	16.0	16.3
Prior MI (%)	9.5	6.8
Current smoker (%)	35.8	33.6
Hypertension (%)	50.3	52.2
Dyslipidemia (%)	23.3	22.2
Prior PCI (%)	9.3	8.1
Sx onset to Culprit PCI ≤6 h (%)	71.4	74.6
6-12 h (%)	16.1	14.4
>12 h (%)	12.5	11.0

	Complete N=764	Culprit-only N=778
Killip class II-IV (%)	4.6	4.8
ECG to Culprit PCI (h)	1.13	1.12
Peak creatinine - µmol/L	91.1	90.1
Discharge Meds (%)		
Aspirin	97.5	97.6
P2Y12 inhibitor		
Any	98.4	98.3
Ticagrelor	88.9	87.1
Clopidogrel	9.5	11.2
Beta blocker	81.6	80.8
ACEi/ARB	79.8	78.5
Statin	97.6	96.9

Baseline characteristics

FULL REVASC

	Complete N=764	Culprit-only N=778
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Female sex (%)	21.3	26.0
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Procedural characteristics

FULL REVASC

	Complete N=764	Culprit-only N=778
Indication for PCI (%)		
STEMI - Primary	88.2	88.7
STEMI - Pharmacoinvasive	2.7	3.2
Very-high-risk NSTEMI	9.0	8.1
Radial access (%)	93.2	93.4
Residual diseased vessels		
1	73.8	70.6
≥2	26.2	29.4
Non-Culprit Lesion Location		
Left main	0.3	0.3
LAD	51.4	56.0
Proximal LAD	21.1	20.2
Circumflex	44.2	43.2
RCA	30.1	29.9

	Complete N=764	Culprit-only N=778
Non-culprit lesion stenosis (%)		
50-69%	34.9	41.8
70-89%	47.6	42.2
90-99%	17.3	15.9
100% (+ other NCL)	5.5	4.5
Number of stents (median)	2.0	1.0
Total stent length (median)	43.0	28.0
Largest stent Ø (median)	4.0	3.0
FFR ≤0.80 in NCL (%)	47.3	
Any vessel with FFR≤0.80 per patient (%)	60.3	
Lowest FFR per patient	0.76	
PCI in NCL if FFR≤0.80 (%)	94.1	

Procedural characteristics

FULL REVASC

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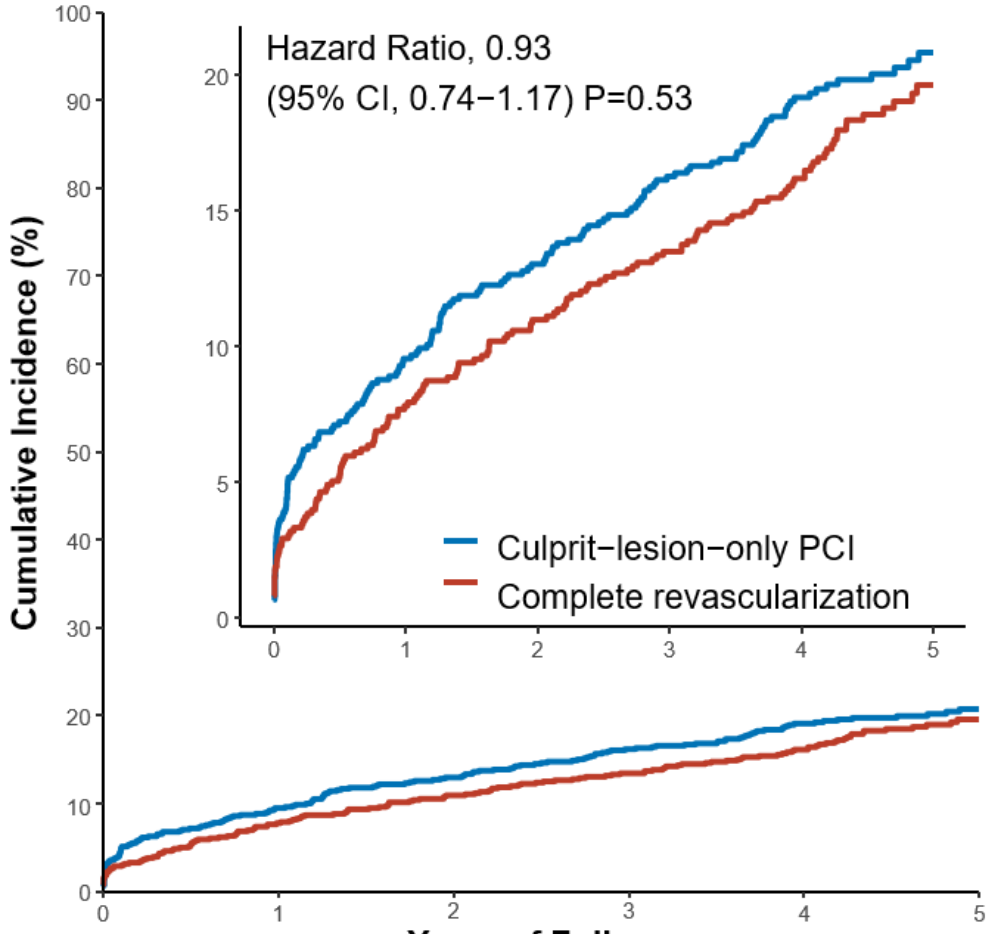
Lowest FFR per patient	0.76	
PCI in NCL if FFR≤0.80 (%)	94.1	

Complete revascularization was achieved in 94.1% after FFR-guided non-culprit lesion PCI

Primary Endpoint
Death, MI or Unplanned Revasc

FULL REVASC

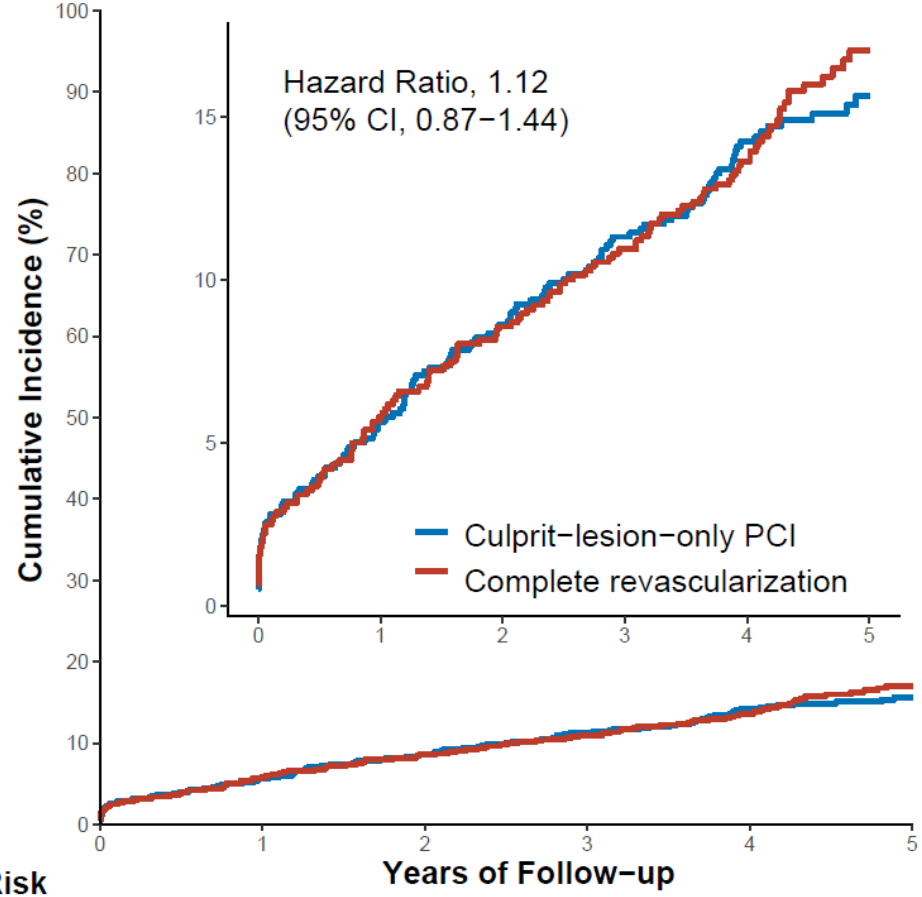


No. at Risk						
Culprit Only	778	705	676	651	552	245
Complete	764	699	675	656	573	232

Key secondary endpoints

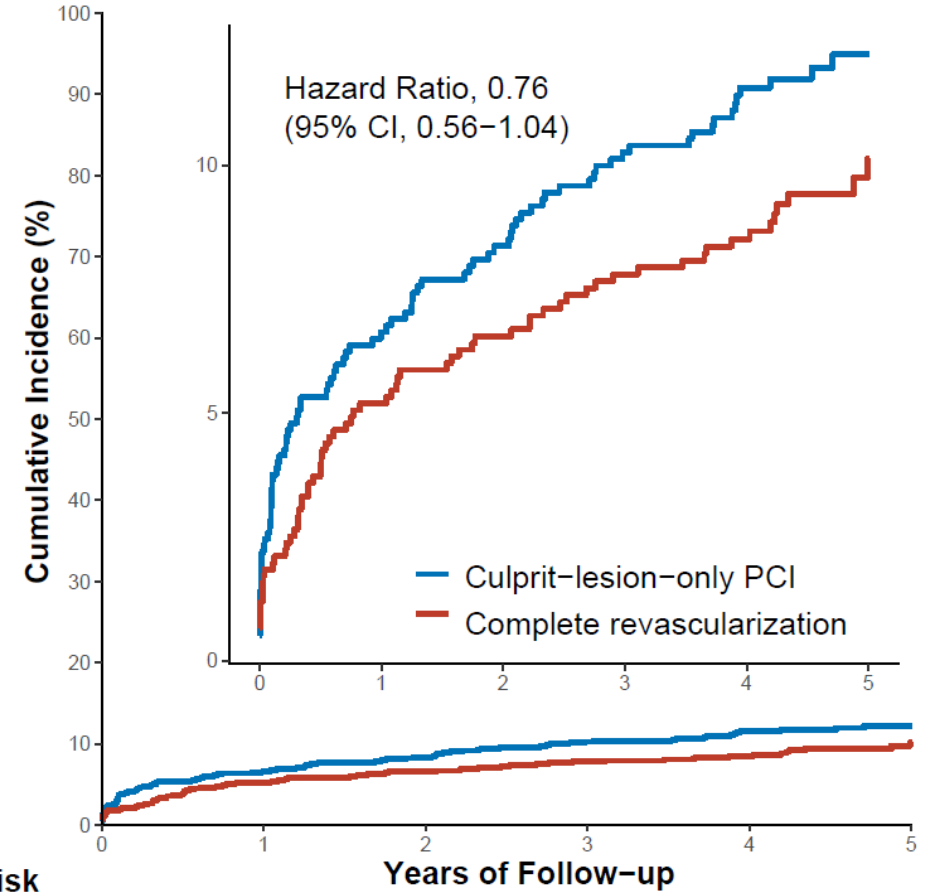
FULL REVASC

Death or MI



No. at Risk						
Culprit only	778	735	710	689	586	263
Complete	764	714	693	675	589	241

Unplanned Revasc



No. at Risk						
Culprit only	778	708	681	658	560	249
Complete	764	702	681	663	582	240

Efficacy Outcomes

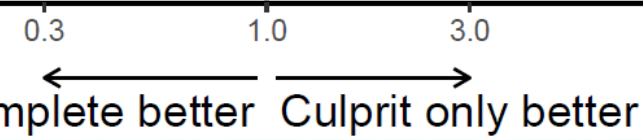
FULL REVASC

Outcome	Complete (N = 764)	Culprit only (N = 778)	Hazard Ratio (95% CI)	P-value
	number of patients (%)			
Primary outcome				
Death, MI, or unplanned revascularization	145 (19.0)	159 (20.4)	0.93 (0.74-1.17)	0.93
Key secondary outcomes				
Death or myocardial infarction	126 (16.5)	119 (15.3)	1.12 (0.87-1.44)	0.37
Unplanned revascularization	70 (9.2)	91 (11.7)	0.76 (0.56-1.04)	0.092
Other secondary outcomes				
Death from any cause	76 (10.0)	72 (9.3)	1.15 (0.83-1.58)	0.41
Death from cardiovascular causes	32 (4.2)	40 (5.1)	0.87 (0.55-1.39)	0.56
Myocardial infarction	61 (8.0)	58 (7.5)	1.09 (0.76-1.57)	0.62
Any revascularization (planned or unplanned)	78 (10.2)	128 (16.5)	0.59 (0.45-0.78)	0.00027
CV death, MI, or unplanned revascularization	104 (13.6)	132 (17.0)	0.80 (0.62-1.03)	0.085

Main subgroup analyses

FULL REVASC

Subgroup	Complete	Culprit only	Hazard Ratio for Primary Outcome (95% CI)
	no. of events (%)		
Age (years, median)			
Below 66	55(14.1)	61(16.7)	0.84(0.58−1.21)
66 or above	90(24.1)	98(23.8)	0.99(0.74−1.32)
Sex			
Male	122(20.3)	115(20.0)	1.02(0.79−1.32)
Female	23(14.1)	44(21.8)	0.65(0.39−1.08)
Diabetes mellitus			
No	110(17.2)	129(19.8)	0.86(0.67−1.11)
Yes	35(28.7)	30(23.6)	1.25(0.77−2.03)
Degree of stenosis			
50−69%	40(16.1)	54(18.1)	0.92(0.61−1.38)
70−89%	70(19.5)	59(18.3)	1.09(0.77−1.54)
90−99%	35(22.6)	46(29.7)	0.69(0.45−1.08)
Severity of coronary disease (vessels)			
1−2	96(17.9)	94(18.1)	0.98(0.74−1.31)
3	49(21.6)	65(25.0)	0.87(0.60−1.26)
Nonculprit proximal LAD			
No	111(18.6)	117(19.2)	0.97(0.75−1.26)
Yes	34(20.5)	42(24.7)	0.81(0.51−1.27)



FULL REVASC

Safety and Other Outcomes

Outcome	Complete (N = 764)	Culprit only (N = 778)	Hazard Ratio (95% CI)	P-value
	number of patients (%)			
Stent thrombosis	19 (2.5)	7 (0.9)	2.80 (1.18-6.67)	0.02
Restenosis	32 (4.2)	18 (2.3)	1.84 (1.03-3.28)	0.039
Target vessel revascularization	66 (8.6)	43 (5.5)	1.57 (1.07-2.31)	0.021
Contrast-associated acute kidney injury	89 (11.7)	91 (11.8)	0.99 (0.73-1.35)	0.96
Stroke	22 (2.9)	22 (2.8)	1.03 (0.57-1.87)	0.91
Major bleeding	19 (2.5)	17 (2.2)	1.18 (0.61-2.28)	0.61
Rehospitalization for heart failure	23 (3.0)	26 (3.3)	0.97 (0.55-1.70)	0.92

Recent RCTs

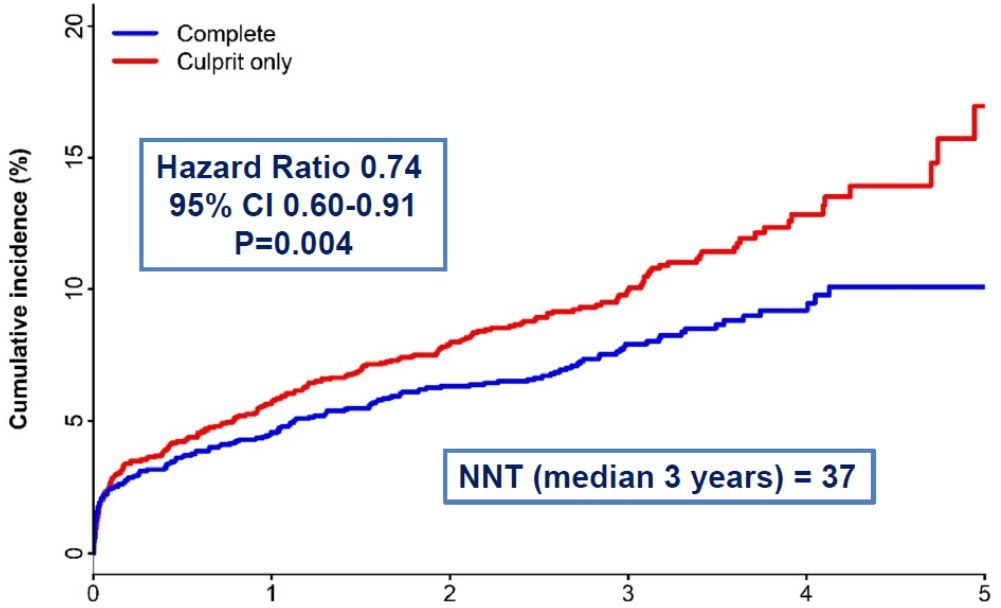
COMPLETE: Angio-guided Complete Revasc

FIRE: Physiology-guided Complete Revasc

FULL REVASC

COMPLETE:

CV Death or New MI

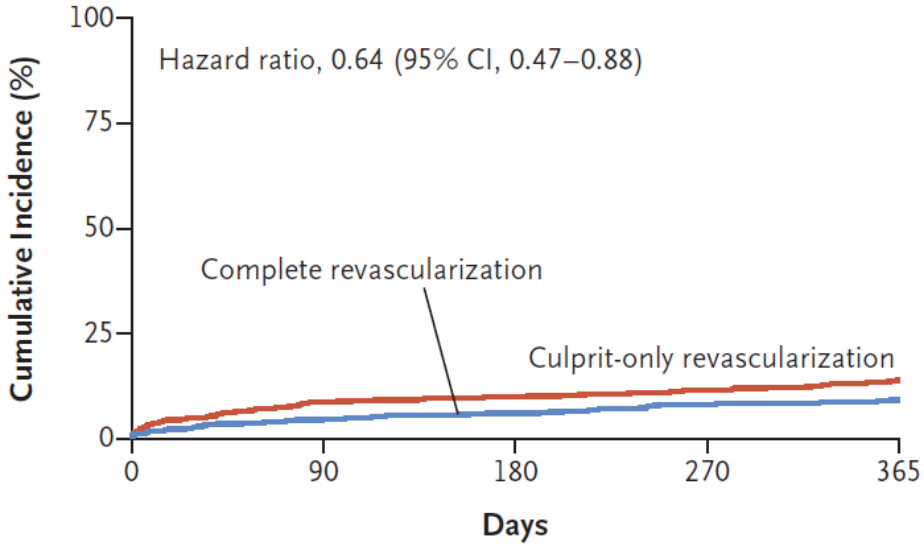


No. at Risk						
Complete	2016	1904	1677	938	337	70
Culprit only	2025	1897	1666	933	310	59

Mehta et al, NEJM, 2019

FIRE:

CV Death or New MI



No. at Risk					
Culprit-only revascularization	725	654	634	618	592
Complete revascularization	720	675	659	641	627

Biscaglia et al, NEJM, 2023

Conclusions

FULL REVASC

In patients with STEMI/very-high-risk NSTEMI and multivessel disease:

- Compared with Culprit-lesion-only PCI, FFR-guided complete non-culprit revascularization:
  - **Did not reduce Death, MI or Unplanned Revasc** (HR 0.93; p=0.53)
  - **Did not reduce Death or MI** (HR 1.12; p=0.37)
  - **Did not reduce Unplanned Revasc** (HR 0.76; p=0.092)

- There was a benefit of reducing any revascularization (planned and unplanned), but higher incidence of stent thrombosis by the Complete strategy.

- There were no apparent differences in stroke, bleeding, heart failure or acute kidney injury.

Acknowledgments

FULL REVASC

Executive Committee

Felix Böhm, Study PI
Stefan James, Study Chair
Thomas Engstrøm, NC Denmark
Goran Stankovic, NC Serbia
Andreas Rück, NC Sweden
Oscar Angerås, Sweden
Mika Laine, NC Finland
Andrejs Ērglis, NC Latvia
Carl Schultz, NC Australia
Madhav Menon, NC New Zealand

Sponsor Leadership

Marcus Ståhlberg, Frieder Braunschweig, Per Mattsson, Anders Ahlsson,
Eva Wallgren, Raquel Binisi

We thank all investigators, study coordinators and participants

International Steering Committee

Executive Committe and:

Sammy Zwackman
Dario Hauer
Mehmet Hamid
Fredrik Calais
Thomas Kellerth
Jörg Lauermann
Jonas Andersson
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Rickard Linder
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Bo Lindvall
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Evald Høj Christiansen
Lisette Okkels Jensen
Olli Kajander
Robert Masar
Ilija Srdanovic
Aleksandar Neskovic
Barry Kneale

UCR Central Coordinating Center

Azar Pettersson, Ulla Nässander Schikan, Susanne Johansson, Anna Stendahl, Åsa Michelgård Palmquist, Ollie Östlund, Henrik Renlund, Karin Jensevik Eriksson, Manuela Zamfir, Åsa Eck, Kathrina Felix, David Karlsson, Stefano Caramuta, Malin Lundgren, Caroline Moberg, Malin Thoudal, Karin Renlund Grausne, Anna Dahlstedt, Lan Vu Thi, Vinaykoumar Kontham, Karolina Östlund, Ida Björkgren, Swanthe Lindgren, Malin Nord, Annika Edberg, Helena Pettersson, Susanna Thörnqvist, Rebecka Ekhamn, Matts Högberg, Sahid Hasan, Maria Eriksson-Svensson, Jonas Oldgren

Data Monitoring Board

Nils Johnson, Bernard de Bruyne, William Fearon,
Nico Pijls, Ollie Östlund

Adjudication Committee

Claes Held (Chair), Kai Eggers, Christina Christersson, Nina Johnston, Christer Lidell, Kasper Andersen, Gabriel ArefalkRobert Sevcik, Gianluigi Savarese, Oscar Braun, Rickard Linder

ClinicalTrials.gov number, NCT02862119. fullrevasc.se

ACC.24

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

AMERICAN COLLEGE of CARDIOLOGY®

HUDDLE

Prevalence of Cardiovascular Disease (CVD) and Risk Factors Among National Football League (NFL) Alumni

Multi-City, Cross-Sectional Study

OBJECTIVE: To estimate the perceived (through prescreening questionnaires) and actual prevalence of CVD and associated risk factors and provide education in an understudied population through screening events.

285
PATIENTS

INCLUSION CRITERIA:
Former NFL players who were aged ≥50 years

MEDICAL HISTORY | BLOOD PRESSURE (BP) | ECG | TRANSTHORACIC ECHOCARDIOGRAM (TTE)

PRIMARY ENDPOINT

SCREENING DEMONSTRATED:
HYPERTENSION (HTN) IN 255/284 (89.8%)
ABNORMAL ECG IN 131/285 (46.1%)
STRUCTURAL ABNORMALITIES ON TTE IN 176/285 (61.8%)

SECONDARY ENDPOINTS

KNOWLEDGE GAP:
SELF-REPORTED HTN 37.5% vs. **89.8%**
ON SCREENING (83.8% WITH BP ≥130/80 MM HG)

RISK PREDICTION:
INDEPENDENT ASSOCIATION ON MULTIVARIABLE ANALYSIS BETWEEN HTN AT SCREENING AND STRUCTURAL CARDIAC ABNORMALITIES ON TTE (ODDS RATIO, 2.02; P=0.04).

FOLLOW-UP:
RECOMMENDED TO 76.7% ON 30-DAY CALL

CONCLUSION

There is a high prevalence of HTN among former NFL players with a significant discrepancy between awareness and observed prevalence. Early TTE screening may be of benefit in this population, particularly in those with HTN.

Okoh AK, Amponsah MKD, Cheffet-Walsh S, et al. Prevalence of Cardiovascular Disease and Risk Factors Among National Football League Alumni and Family Members. Presented at ACC.24.

Developed and reviewed by: Scott Ketcham, MD, and Kent Brummel, MD

ACC.24

Comparison of IVUS-guided vs. Angiography-guided Angioplasty for the Outcomes of DCB in the Treatment of Femoropopliteal Artery Disease

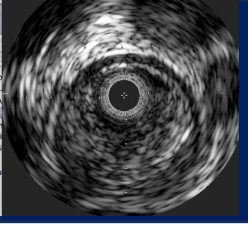
Young-Guk Ko, MD. **on behalf of IVUS-DCB Investigators**

Professor, Division of Cardiology

Severance Cardiovascular Hospital

Yonsei University, Seoul, Korea

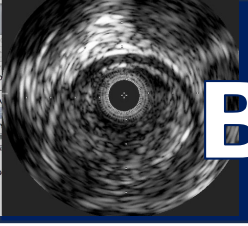
AMERICAN COLLEGE of CARDIOLOGY



Disclosures

- This study was funded by Medtronic Inc. and Korea United Pharmaceutical, and supported by the Cardiovascular Research Center, Seoul, Korea.

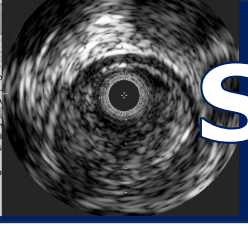
- Drs. YG Ko and D Choi received research grants from Medtronic, Korea United Pharm, Cook Medical, Boston Scientific, Otsuka Korea, Dong-A ST, Samjin Pharm, and Cordis.



Background

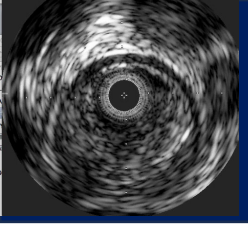
- Drug-coated balloons (DCBs) have demonstrated favorable clnical outcomes in treating femoropopliteal artery disease.
- However, challenges such as vessel recoil, residual stenosis, and arterial dissection remain significant limitations of DCB treatment .
- Thus, improved vessel preparation and post-DCB optimization are needed to enhance endovascular treatment (EVT) outcomes.
- Intravascular ultrasound (IVUS) provides detailed information on vessel dimensions and plaque characteristics.
- However, there have been limited clinical data on the benefit of IVUS in the EVT of femoropopliteal artery disease using DCBs.

Zeller T, EuroIntervention 2022;18:e940.
Lee SJ, J Am Coll Cardiol Intv. 2023;16:1640.
Allan RB, J Am Coll Cardiol Intv. 2022;15(5):536



Study Purpose

To investigate the clinical advantages of IVUS-guided DCB angioplasty for femoropopliteal artery disease by comparing the outcomes of IVUS-guided versus angiography-guided DCB angioplasty.



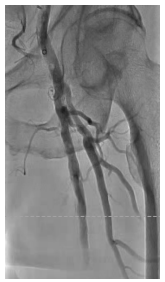
Study Design

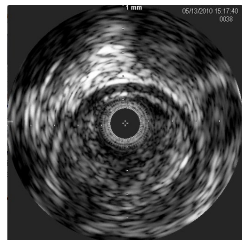
- *IIT*
- *Multicenter RCT*
- *To test superiority of IVUS guidance*

Patients with symptomatic femoropopliteal artery disease
- Rutherford category 2~5
- N = 237 from 7 centers in Korea

1:1 randomization

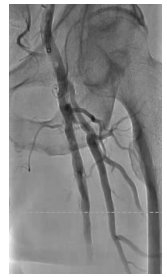
Stratified by the enrolling site and lesion length with a cutoff of 150 mm





IVUS Guidance (n=119)

Angiography Guidance (n=118)

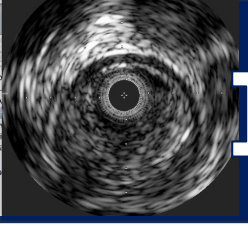


cross-over (n=1)

cross-over (n=2)

Angioplasty using DCBs (IN.PACT, Medtronic)

Primary endpoint: Primary patency at 12 months



Institutions and Investigators

- Severance Hospital, Seoul, Korea

  Young-Guk Ko, Seung-Jun Lee, Chul-Min Ahn, Donghoon Choi

- NHIS Ilsan Hospital, Goyang, Korea

  Ji Yong Jang

- Sejong General Hospital, Incheon, Korea

  Tae-Hoon Kim, Ha-Wook Park

- Chungnam National University Hospital, Daejeon, Korea

  Jae-Hwan Lee, Jae-Hyeong Park

- Busan Veterans Hospital, Busan, Korea

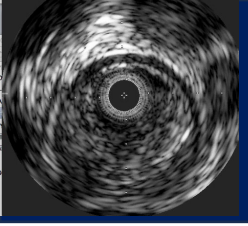
  Su Hong Kim

- Yongin Severance Hospital, Yongin, Korea

  Eui Im

- Soonchunhyang University Cheonan Hospital, Cheonan, Korea

  Sang-Ho park



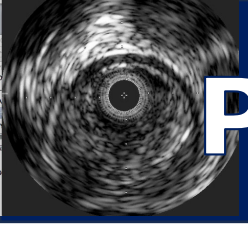
Key Inclusion & Exclusion Criteria

Inclusion criteria

- Age ≥19 years
- Symptomatic femoropopliteal artery disease (Rutherford 2~5)

Exclusion criteria

- Acute limb ischemia
- Age >85 years
- Life expectancy <1 year
- Previous bypass surgery or stenting in the target femoropopliteal artery
- Untreated inflow lesions

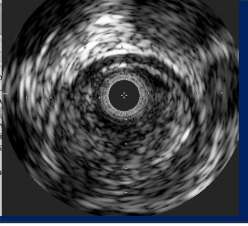


Primary & Secondary Endpoints

- Primary endpoint:
  - Primary patency defined as the absence of clinically-driven target lesion revascularization (CD-TLR) or binary restenosis on imaging studies (DUS, CT, angiography) at 12-month follow-up.

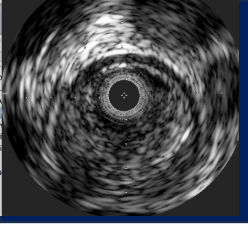
- Secondary endpoints:
  - Freedom from CD-TLR
  - Sustained clinical improvement (improved Sx ≥1 Rutherford category, no CD TLR)
  - Sustained hemodynamic improvement (improved ABI ≥ 0.15, no CD TLR)
  - Mortality
  - Major amputations
  - Major bleeding

Eur Heart J. 2007;28:798



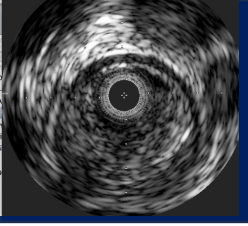
Procedures

- Randomization was performed after successful wire passage
- All lesions were routinely predilated except for cases treated with vessel prep using atherectomy.
- Pretreatment and post lesion optimization as well as the choice of device sizes were left to operators' discretion.
- IVUS was performed before and after the use of DCBs and the final treatment.
- No specific IVUS goals were recommended for the IVUS-guidance group.
- All lesions were treated with IN.PACT DCBs.
- DAPT was required for at least 90 days post procedure.
- All procedural and follow-up images were analyzed at central core labs by independent experts.



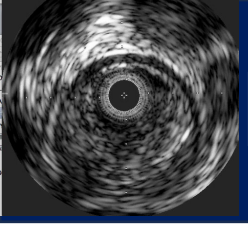
Baseline Clinical Characteristics

	IVUS Guidance (n=119)	Angiography Guidance (n=118)	P value
Age, years	69.0 ± 9.1	70.2 ± 8.6	0.31
Men	102 (85.7)	100 (84.7)	0.98
Body mass index, kg/m^2	23.8 ± 3.4	23.4 ± 3.1	0.32
Hypertension	94 (78.0)	99 (83.8)	0.44
Diabetes mellitus	71 (59.7)	79 (67.5)	0.26
Dyslipidemia	84 (70.6)	86 (72.9)	0.80
Chronic kidney disease	29 (24.4)	19 (16.1)	0.16
End-stage kidney disease on dialysis	14 (11.8)	8 (6.8)	0.27
Current smoker	37 (31.1)	41 (34.7)	0.76
CAD	45 (37.8)	31 (26.3)	0.08
Prior stroke	14 (11.8)	14 (11.9)	0.99
Prior peripheral revascularisation	18 (15.1)	18 (15.3)	0.99
Prior limb amputation	5 (4.2)	4 (3.4)	0.99
Clinical presentation			
Claudication	89 (74.8)	86 (72.9)	0.66
CLTI	39 (25.2)	32 (27.1)	
Pre-procedural ABI	0.64 ± 0.21	0.63 ± 0.21	0.74



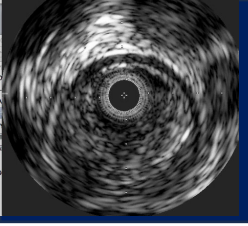
Lesion Characteristics

	IVUS Guidance (n=119)	Angiography Guidance (n=118)	P value
TASC II lesion type			
A/B	39 (32.8)	40 (33.9)	0.96
C/D	80 (67.2)	78 (66.1)	
Lesion length, mm	204.9 ± 103.1	214.5 ± 102.9	0.48
Reference vessel diameter, mm	5.0 ± 0.7	5.0 ± 0.7	0.79
Minimal lumen diameter, mm	0.36 ± 0.65	0.47 ± 0.68	0.20
Total occlusion	78 (66.7)	68 (58.1)	0.23
Severe calcification (PACCS grade 4)	38 (31.9)	30 (25.4)	0.34
Popliteal involvement	11 (9.2)	10 (8.5)	>0.99
Poor distal runoff (0 or 1 vessel)	30 (25.2)	36 (30.5)	0.44



Procedural Data

	IVUS Guidance (n=119)	Angiography Guidance (n=118)	P value
Subintimal approach	31 (26.5)	31 (26.5)	>0.99
Atherectomy	41 (35.0)	38 (32.5)	0.78
Pre-balloon diameter, mm	5.0 ± 0.9	4.5 ± 1.1	<0.001
Pre-balloon length, mm	122.3 ± 57.5	119.1 ± 62.8	0.69
Pre-balloon maximal pressure, mmHg	11.8 ± 3.6	8.9 ± 2.7	<0.001
Total number of DCBs	2.0 ± 0.8	2.0 ± 0.8	0.75
Maximal DCB diameter, mm	5.8 ± 0.7	5.8 ± 0.7	0.95
Mean DCB diameter, mm	5.4 ± 0.6	5.4 ± 0.6	0.92
Adjuvant post-dilatation	31 (26.1)	16 (13.6)	0.03
Maximal post-balloon pressure, mmHg	13.7 ± 2.9	9.6 ± 4.0	0.001
Bailout stenting	24 (20.5)	17 (14.5)	0.30
Post-procedural minimal lumen diameter, mm	3.90 ± 0.59	3.71 ± 0.73	0.03
Post-procedural diameter stenosis, %	21.5 ± 12.0	25.4 ± 13.3	0.02

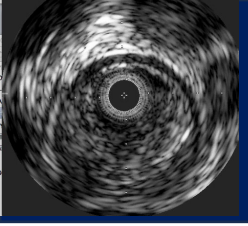


Immediate Procedural Outcomes

IVUS-DCB

	IVUS Guidance (n=119)	Angiography Guidance (n=118)	P value
Technical success*	91 (76.5)	72 (61.0)	0.02
Procedural success†	88 (73.9)	71 (60.2)	0.03
Dissection type	70 (59.8)	68 (58.1)	0.67
A	8 (10.7)	15 (20.3)	
B	35 (46.7)	29 (39.2)	
C	20 (26.7)	18 (24.3)	
D	5 (6.7)	5 (6.8)	
E	2 (2.7)	1 (1.4)	
Distal embolisation	0	0	–
Target lesion perforation	1 (0.9)	1 (0.9)	>0.99
Access site complications	2 (1.7)	2 (1.7)	>0.99
Post-procedure ABI	0.99 ± 0.13	0.93 ± 0.15	0.001

**defined as residual stenosis of <30% without flow compromise; †defined as technical success without any acute complications*

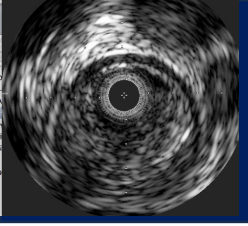


Clinical Outcomes at 12 months

IVUS-DCB

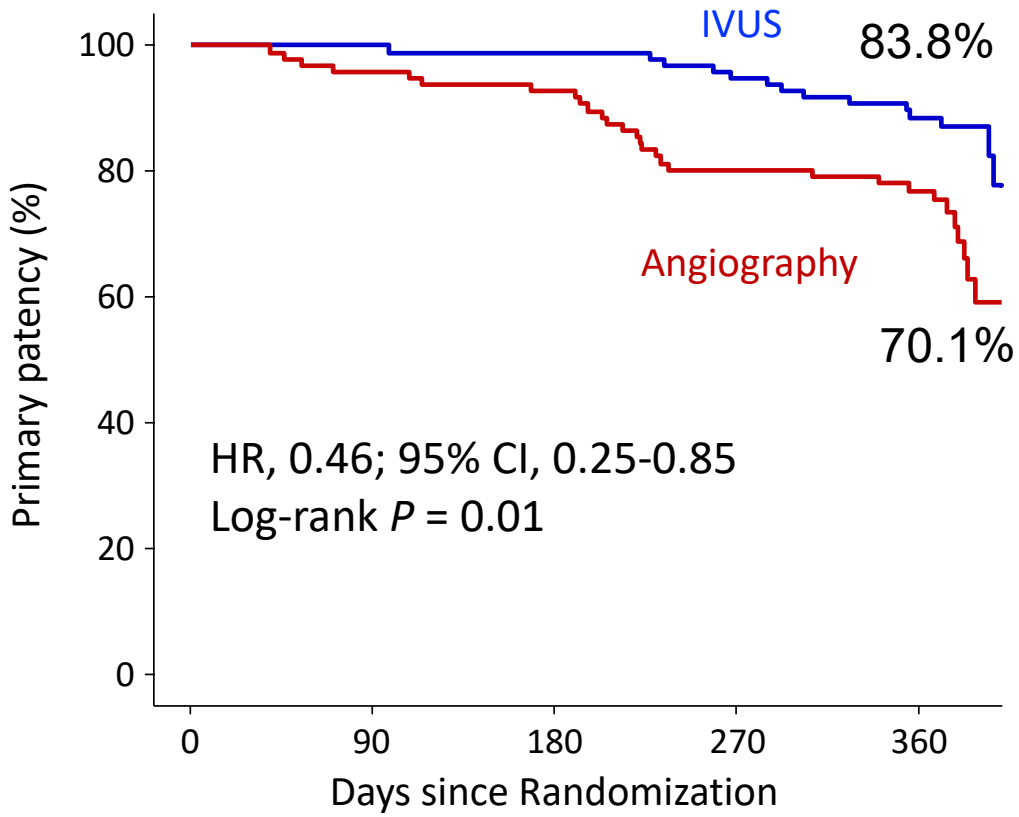
Outcomes	Event No. / Total. No (%)		Risk Difference[a] (95% CI)	Hazard Ratio[b] (95% CI)	P value
	IVUS (n=119)	Angiography (n=118)			
Primary endpoint					
Primary patency*	83.8 (83/99)	70.1 (68/97)	13.7 (2.1 – 25.4)	0.46 (0.25–0.85)	0.01
Secondary endpoints					
Freedom from CD TLR	92.4 (110/119)	83.0 (98/118)	9.4 (1.1 – 17.7)	0.41 (0.19-0.90)	0.03
Sustained clinical improvement	89.1 (106/119)	76.3 (90/118)	12.8 (3.3 – 22.3)	0.45 (0.23-0.86)	0.02
Sustained hemodynamic improvement	82.4 (98/119)	66.9 (79/118)	15.4 (4.5 – 26.3)	0.52 (0.31-0.89)	0.02
Major amputation of target limb	0/119	0/118	–	–	–
All-cause death	6.7 (8/119)	7.6 (9/118)	−0.9 (−7.5 – 5.7)	1.21 (0.44–3.34)	0.72
Cardiovascular death	2.5 (3/119)	2.5 (3/118)	0.0 (−4.0 – 4.0)	1.45 (0.29–7.24)	0.65
Major bleeding	1.7 (2/119)	2.5 (3/118)	−0.9 (−4.5 – 2.8)	0.69 (0.11–4.18)	0.61

**Imaging follow-up rate at 12 months: 82.7%*



Primary patency at 12 months

ITT analysis

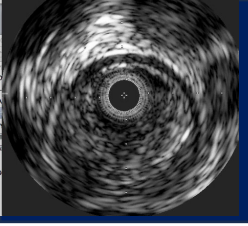


No. at Risk					
IVUS Guidance	99	99	98	94	69
Angio Guidance	97	93	90	76	57

PP analysis

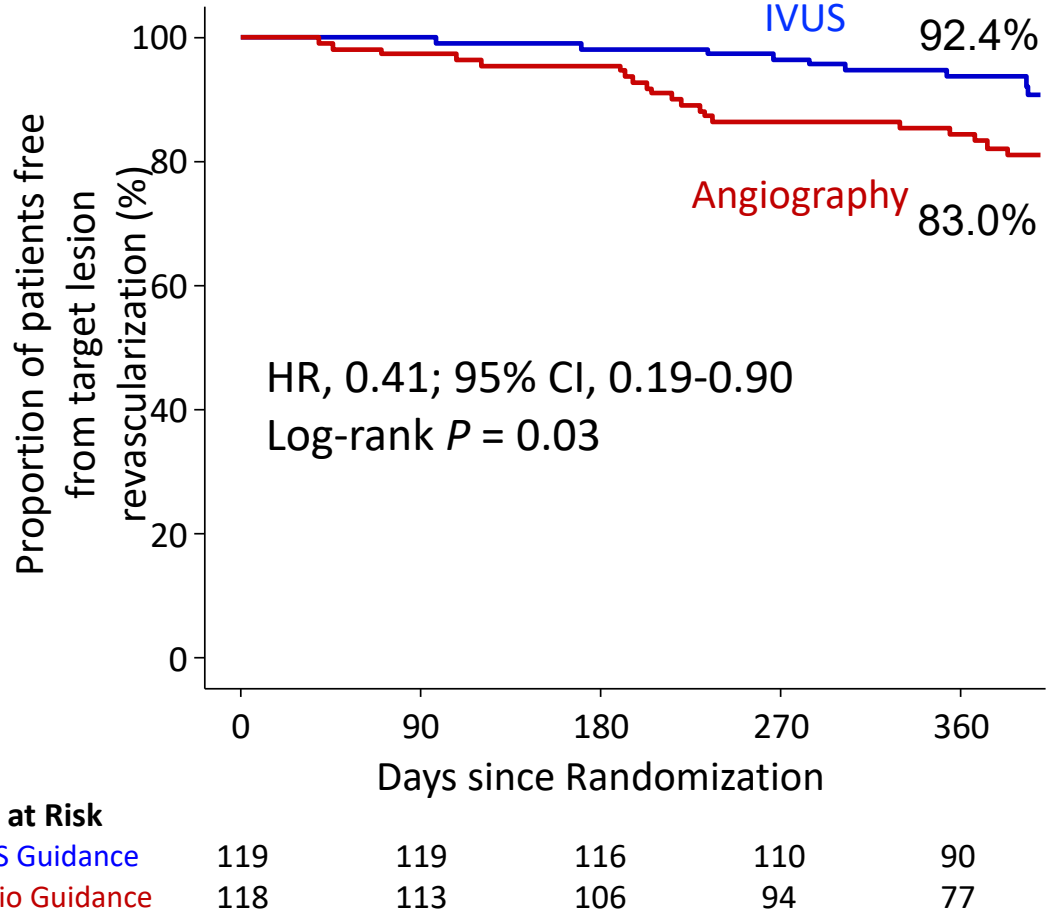
IVUS: 83.7% (82/98) vs.
Angiography: 70.8% (68/96)

HR 0.48 (0.26-0.88)
P = 0.02



Freedom from CD-TLR

ITT analysis

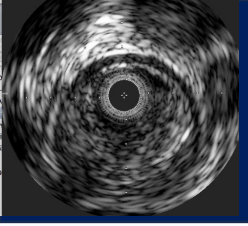


No. at Risk					
IVUS Guidance	119	119	116	110	90
Angio Guidance	118	113	106	94	77

PP analysis

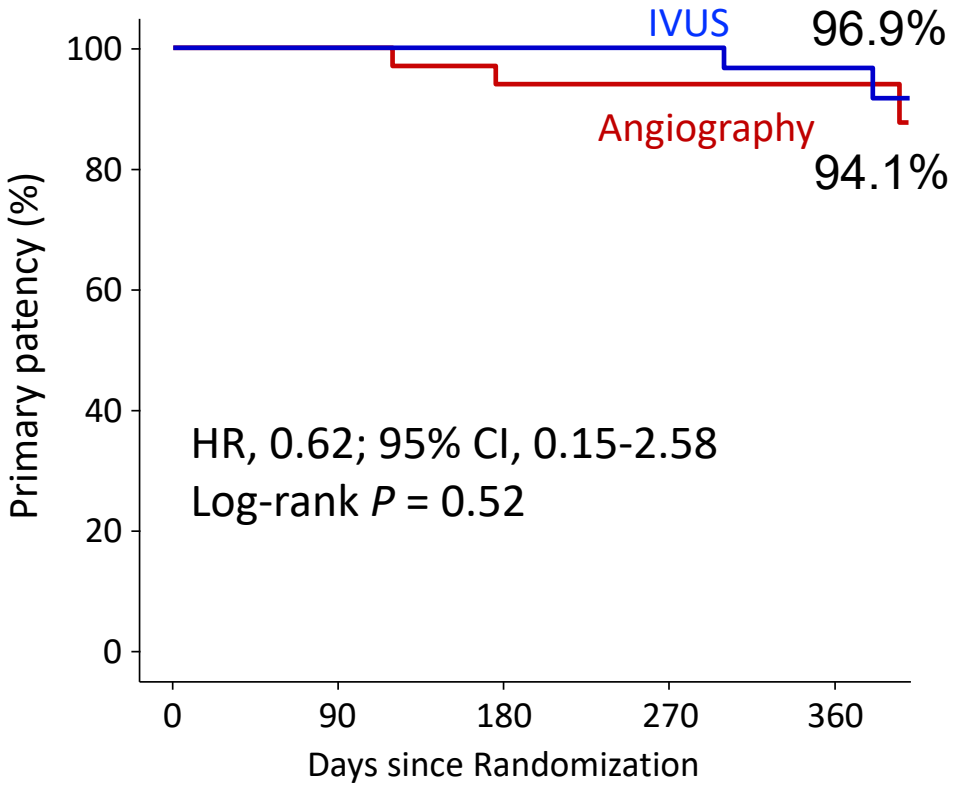
IVUS: 92.4% (109/118) vs.
Angiography: 83.6% (97/116)

HR 0.43 (0.20-0.96)
P = 0.04



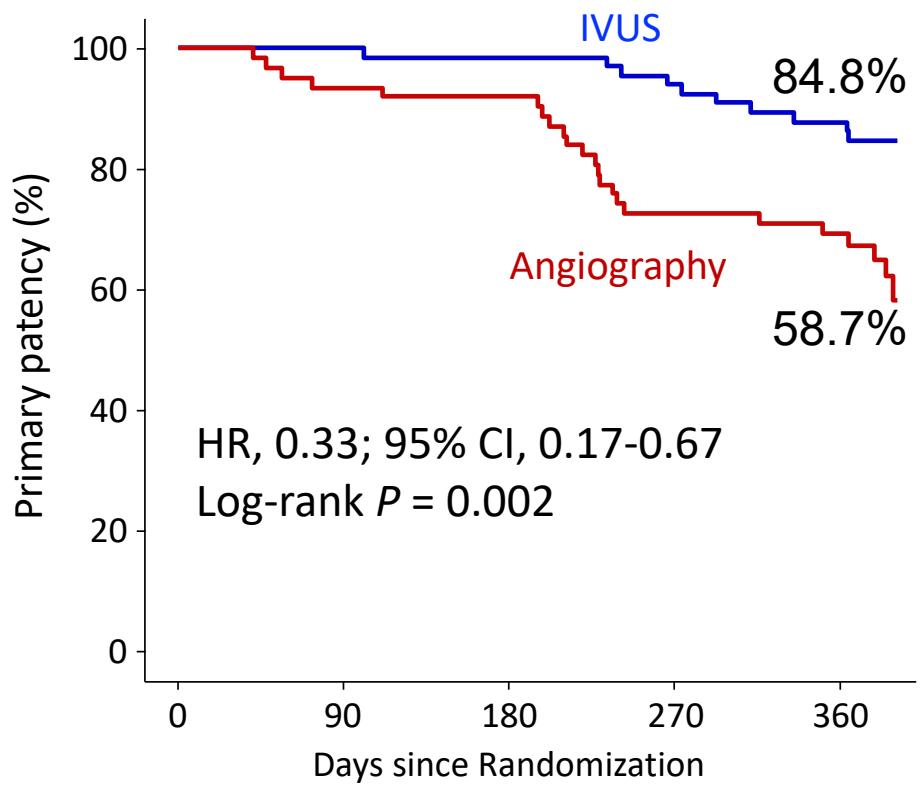
Primary Patency According to TASC II Lesion Types

TASC-II type A/B

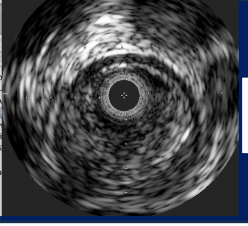


No. at Risk					
IVUS Guidance	32	32	32	31	21
Angio Guidance	34	34	32	31	24

TASC-II type C/D

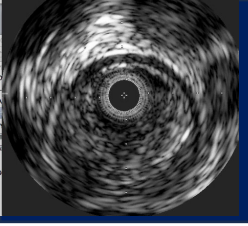


No. at Risk					
IVUS Guidance	67	67	66	62	48
Angio Guidance	63	59	58	45	31



Predictors of Restenosis

	Univariate		Multivariate			
			Model 1		Model 2	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Lesion length ≥200 mm	2.96 (1.50-5.87)	0.002	2.36 (1.14-4.91)	0.02	2.15 (1.07-4.34)	0.03
Total occlusion	2.32 (1.12-4.84)	0.02	1.43 (0.62-3.29)	0.40	1.59 (0.69-3.70)	0.28
Subintimal recanalization	2.57 (1.42-4.64)	0.001	1.91 (1.02-3.60)	0.04	1.43 (0.73-2.80)	0.30
Use of IVUS	0.46 (0.25-0.85)	0.01	0.40 (0.21-0.75)	0.004	-	-
Post-procedural MLD (per 0.1 mm decrease)	1.14 (1.09-1.20)	<0.001	-	-	1.13 (1.07-1.18)	<0.001



Conclusions

- IVUS guidance significantly improved the outcomes of DCB angioplasty for FPA disease in terms of primary patency, freedom from CD TLR, and sustained clinical and hemodynamic improvement at 12 months.
- The benefit of IVUS guidance for primary patency after DCB treatment was more evident in complex FPA lesions.

AMERICAN COLLEGE of CARDIOLOGY®

PREVENT

Preventive Percutaneous Coronary Intervention (PCI) vs. Optimal Medical Therapy (OMT) Alone For the Treatment of Vulnerable Atherosclerotic Coronary Plaques

Investigator-Initiated, Multicenter, Open-Label, Randomized, Controlled Trial

OBJECTIVE: To evaluate the effects of preventive PCI with OMT vs. OMT alone on major adverse cardiovascular events in patients with non–flow-limiting, high-risk, vulnerable plaques.

1,606
PATIENTS

INCLUSION CRITERIA:
Adults with non–flow limiting (fractional flow reserve >0.80) vulnerable coronary plaques identified by intracoronary imaging.

PCI + OMT
(N=803)

VS.

OMT
(N=803)

PRIMARY ENDPOINT

COMPOSITE OF DEATH FROM CARDIAC CAUSES, TARGET-VESSEL MYOCARDIAL INFARCTION (MI), ISCHEMIA-DRIVEN TARGET-VESSEL REVASCULARIZATION, OR HOSPITALIZATION FOR UNSTABLE OR PROGRESSIVE ANGINA ASSESSED AT TWO YEARS.

3 PATIENTS (0.4% IN PCI GROUP) vs. **27 PATIENTS (3.4% IN OMT GROUP)**

SECONDARY ENDPOINT

DEATH FROM ANY CAUSE:
HAZARD RATIO (HR), 0.61 (95% CI, 0.35-1.06)

COMBINED DEATH FROM ANY CAUSE, ALL MIs, ANY REVASCULARIZATION: HR, 0.69 (95% CI, 0.50-0.95)

CONCLUSION

In patients with non–flow limiting vulnerable coronary plaques, preventive PCI reduced major adverse cardiac events arising from high-risk vulnerable plaques compared with OMT alone.

Park S-J, Ahn J-M, Kang D-Y, et al. Preventive Percutaneous Coronary Intervention Versus Optimal Medical Therapy Alone For The Treatment Of Vulnerable Atherosclerotic Coronary Plaques (PREVENT): A Multicentre, Open-Label, Randomised Controlled Trial. Presented at ACC.24.

Developed and reviewed by: Raymond Yeow, MD, and Kent Brummel, MD

ACC.24

PROACT: Can we prevent chemotherapy-related heart damage in patients with breast cancer and lymphoma?

Dr David Austin

Chief Investigator, PROACT

Consultant Cardiologist, Academic Cardiovascular Unit

The James Cook University Hospital, Middlesbrough, UK

@ACUSouthTees @akaplatini

SOUTH TEES Academic Cardiovascular Unit

Newcastle University

AMERICAN COLLEGE of CARDIOLOGY

Disclosures

- Research grants within last 24 months: Kancera, Astra Zeneca
- Consultancy fees/honoraria within last 24 months: Philips Volcano

Newcastle University

FUNDED BY NIHR | National Institute for Health and Care Research

SOUTH TEES Academic Cardiovascular Unit

Preventing cardiac damage in patients treated for breast cancer and lymphoma: a phase 3 Randomised, Open label, blinded endpoint superiority trial of enalapril to prevent Anthracycline-induced CardioToxicity

Registration: Clinicaltrials.org: NCT03265574

https://research.ncl.ac.uk/proact/

Background

- Anthracyclines are widely used in cancer treatment
- Anthracycline cardiotoxicity is dose dependent and associated with myocardial injury
- Prevention of cardiotoxicity is key to reducing the life-long impact of cancer treatment in the increasing population of cancer survivors
- The absence of myocardial injury during or immediately after anthracycline treatment has a high negative predictive value for clinical cardiotoxicity
- ACE inhibitors may be protective against anthracycline toxicity
- **Aim:** To establish the effectiveness of the ACE inhibitor enalapril in the prevention of anthracycline cardiotoxicity in patients with breast cancer and non-Hodgkin lymphoma (NHL)

Key design features of PROACT

- Multi-center randomized controlled trial
- Blinded end point analysis at core laboratories (PROBE design)
- Enriched population receiving high dose anthracyclines (≥300mg/m^2 doxorubicin-equivalent)
- Fair test of enalapril - aimed to titrate to 10mg bd
- End points consistent with current understanding of anthracycline cardiotoxicity
  - Now enshrined in ESC Cardio-oncology guideline (2022)

Blinded, Core lab assessed end points

Primary end point:

- Myocardial injury defined as cTnT ≥14ng/L

Secondary end points:

- Myocardial Injury defined as cTnI >26.2ng/L
- Left ventricular global longitudinal strain (LV GLS) >15% relative decline from baseline
- Left ventricular ejection fraction (LVEF) >10% absolute decline from baseline

hs Trop I
BHF Cardiovascular Biomarker Lab,
University of Edinburgh

hs Trop T
Royal Victoria Infirmary,
Newcastle Upon Tyne

Echocardiographic Core lab
The James Cook University Hospital,
Middlesbrough

Inclusion

Adult patients due to receive 6 cycles (≥ 300mg/m^2 doxorubicin-equivalent) of anthracycline chemotherapy

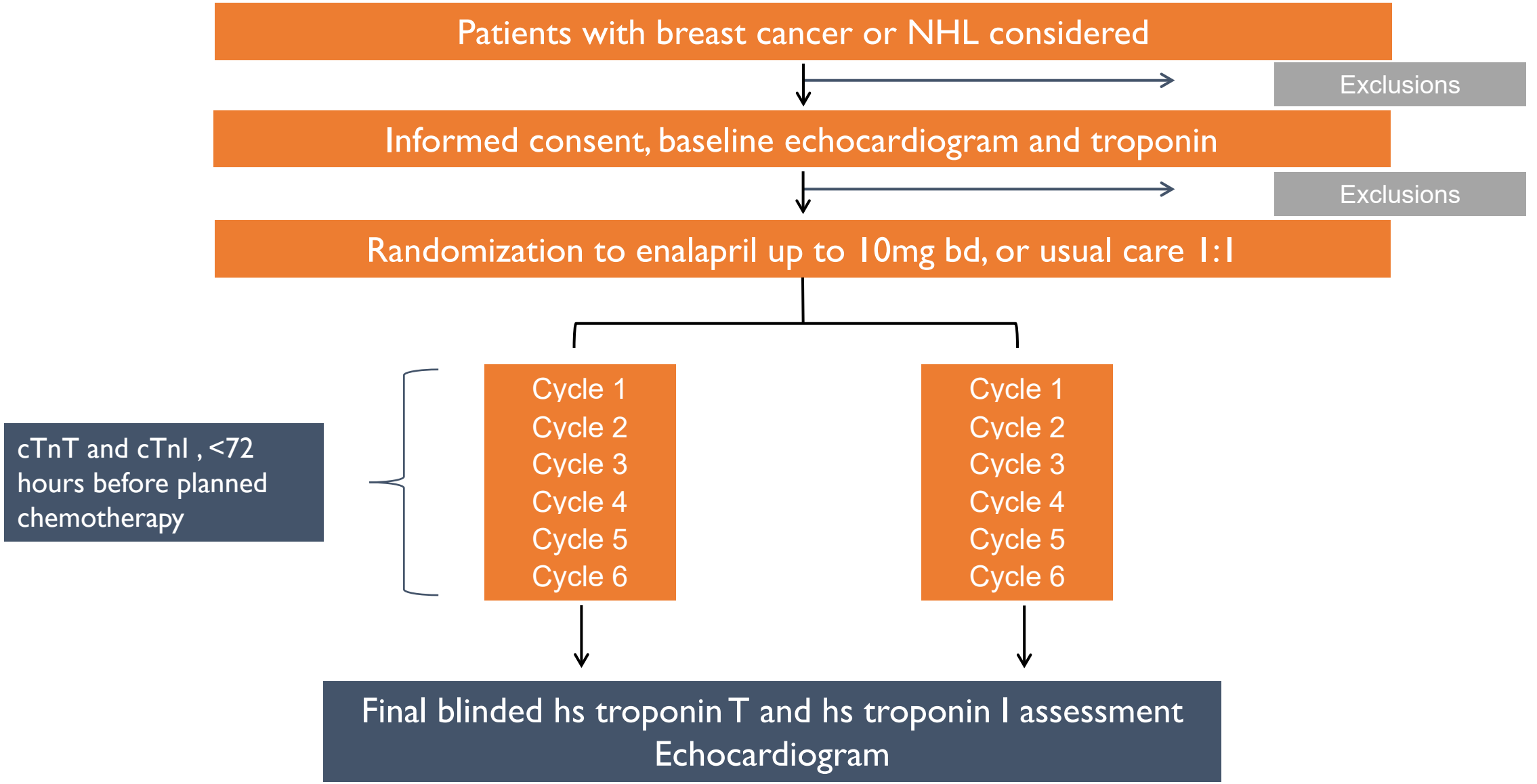
- **EC 90** (432mg/m^2 doxorubicin-equivalent)
- **FEC 75** (360mg/m^2 doxorubicin-equivalent)
- **R-CHOP** (300mg/m^2 doxorubicin-equivalent)

Key exclusion

- Myocardial injury at baseline
- LVEF <50% on echo
- Contraindications to enalapril
- Already taking agents acting on RAAS

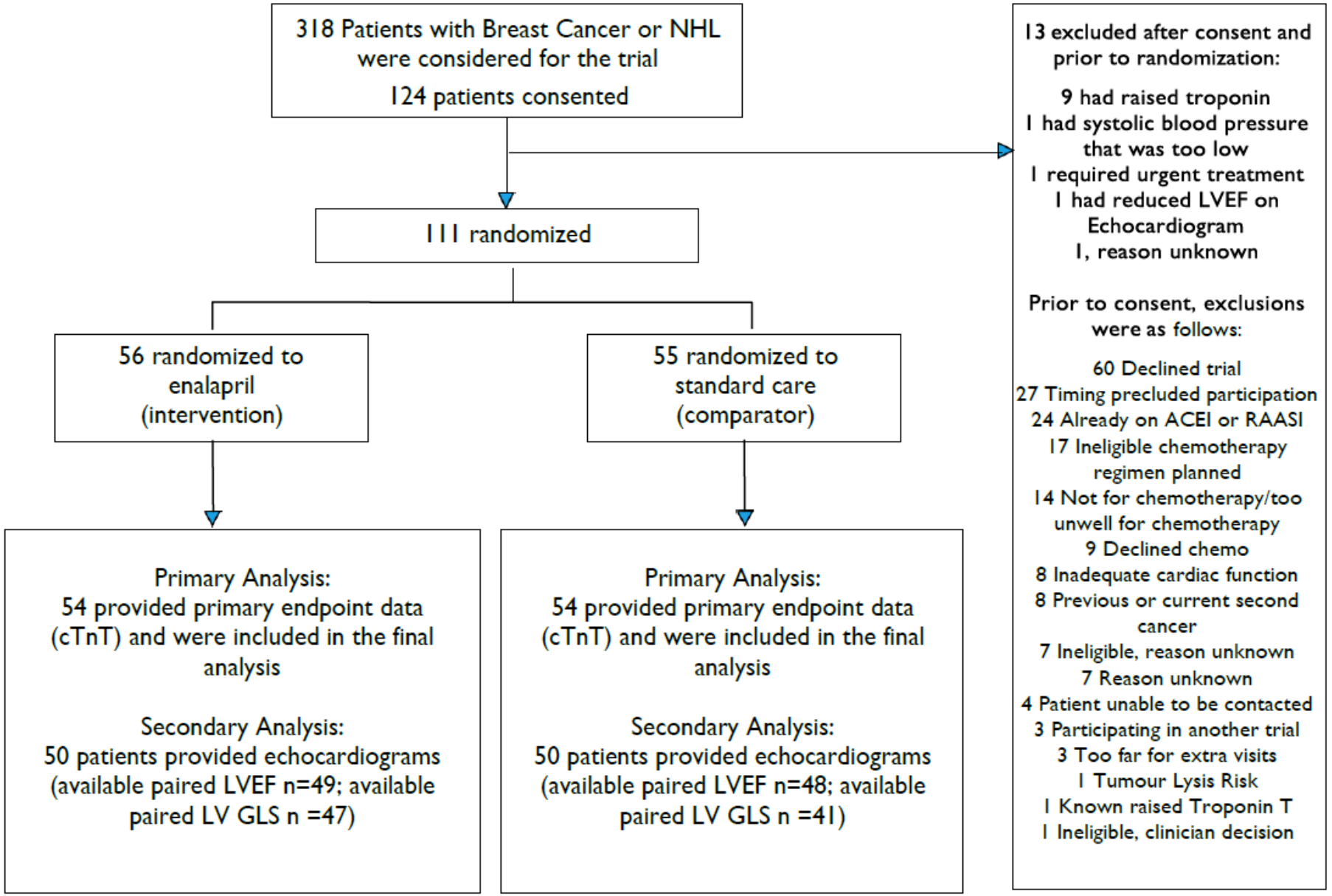
Power calculation

- Based on pilot data (FEC 75) and consultation with oncology, cardiology and two patient groups
- Assumption that 47% of patients would exhibit myocardial injury
- For enalapril to be considered effective, the myocardial injury would be reduced to 20% of patients
- At **90%** power, **140** patients would be needed (plus attrition)
- Due to complex recruitment challenges, including COVID 19, the power was reduced to **80%**, and a **minimum of 106 patients** (plus attrition) was required with the same assumptions


Patients with breast cancer or NHL considered
Exclusions
Informed consent, baseline echocardiogram and troponin
Exclusions
Randomization to enalapril up to 10mg bd, or usual care 1:1
cTnT and cTnI , <72 hours before planned chemotherapy
Cycle 1
Cycle 2
Cycle 3
Cycle 4
Cycle 5
Cycle 6
Cycle 1
Cycle 2
Cycle 3
Cycle 4
Cycle 5
Cycle 6
Final blinded hs troponin T and hs troponin I assessment
Echocardiogram

- North Tyneside General Hospital, Northumbria
- Freeman Hospital, Newcastle upon Tyne
- Sunderland Royal Hospital, Sunderland
- County Durham and Darlington
- University Hospital of North Tees, Stockton
- The James Cook University Hospital, Middlesbrough
- Castle Hill Hospital, Hull
- Blackpool Victoria Hospital, Blackpool
- Clatterbridge Hospital, Liverpool
- Weston Park Hospital, Sheffield
- Royal Berkshire Hospital, Reading
- Kent and Canterbury Hospital, Canterbury
- Derriford Hospital, Plymouth

Recruitment: October 2017 to March 2023


318 Patients with Breast Cancer or NHL were considered for the trial
124 patients consented
111 randomized
56 randomized to enalapril (intervention)
55 randomized to standard care (comparator)
Primary Analysis:
54 provided primary endpoint data (cTnT) and were included in the final analysis
Secondary Analysis:
50 patients provided echocardiograms (available paired LVEF n=49; available paired LV GLS n =47)
Primary Analysis:
54 provided primary endpoint data (cTnT) and were included in the final analysis
Secondary Analysis:
50 patients provided echocardiograms (available paired LVEF n=48; available paired LV GLS n =41)
13 excluded after consent and prior to randomization:
9 had raised troponin
1 had systolic blood pressure that was too low
1 required urgent treatment
1 had reduced LVEF on Echocardiogram
1, reason unknown
Prior to consent, exclusions were as follows:
60 Declined trial
27 Timing precluded participation
24 Already on ACEI or RAASI
17 Ineligible chemotherapy regimen planned
14 Not for chemotherapy/too unwell for chemotherapy
9 Declined chemo
8 Inadequate cardiac function
8 Previous or current second cancer
7 Ineligible, reason unknown
7 Reason unknown
4 Patient unable to be contacted
3 Participating in another trial
3 Too far for extra visits
1 Tumour Lysis Risk
1 Known raised Troponin T
1 Ineligible, clinician decision

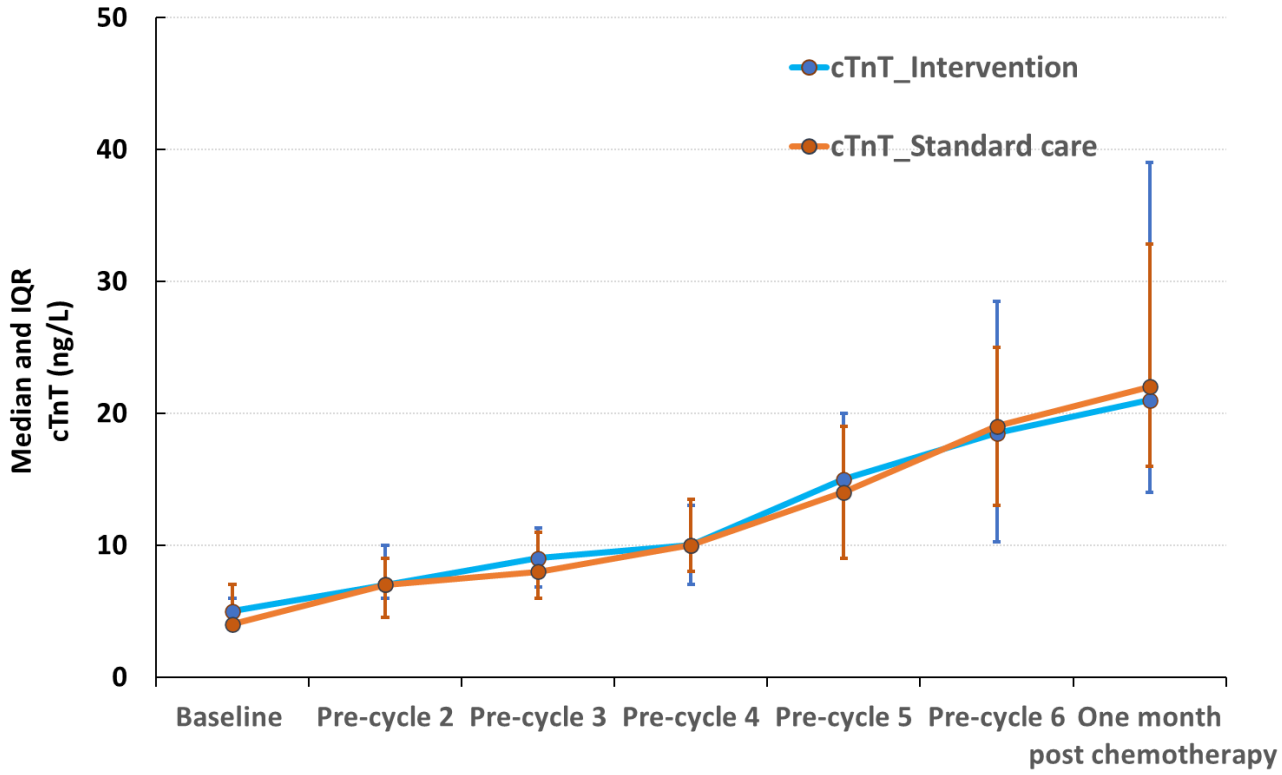
Key findings

- Average age: 58 years old
- Predominantly white British, >75% female population
- Breast cancer 62% NHL 38%
- Chemotherapy regimens well balanced
- Received chemotherapy dose was **328mg/m² doxorubicin–equivalent**
- Enalapril titrated to 20mg in >75% of patients, **mean 17.7mg**

Characteristics		Enalapril (n = 56)	Standard care (n = 55)
Demographic			
Age at randomization, mean (SD)		58 (11)	58 (12)
Female, no. (%)		45 (80.4)	41 (74.5)
Ethnicity	White	55 (98.2)	52 (94.5)
	Non white	1 (1.8)	3 (5.5)
Body Mass Index, mean (SD)		28.3 (4.8)	28.2 (5.5)
Clinical history, no (%)			
Breast cancer		35 (62.5)	34 (61.8)
Non-Hodgkin Lymphoma		21 (37.5)	21 (38.2)
NYHA functional class			
	I	48 (85.7)	48 (88.9)
	II	8 (14.3)	6 (11.1)
ECOG performance status scale			
	Grade 0	49 (87.5)	48 (87.3)
	Grade 1	6 (10.7)	7 (12.7)
	Grade 2	1 (1.8)	0 (0.0)
Coronary Heart Disease		2 (3.6)	2 (3.6)
Diabetes		5 (8.9)	3 (5.5)
Hypertension		12 (21.4)	5 (9.1)
Current or ex-smoker		29 (51.7)	18 (32.7)
Chemotherapy regimen, No (%)			
	FEC75	8 (14.3)	9 (16.4)
	EC90	27 (48.2)	25 (45.5)
	(R-)CHOP	21 (37.5)	21 (38.2)

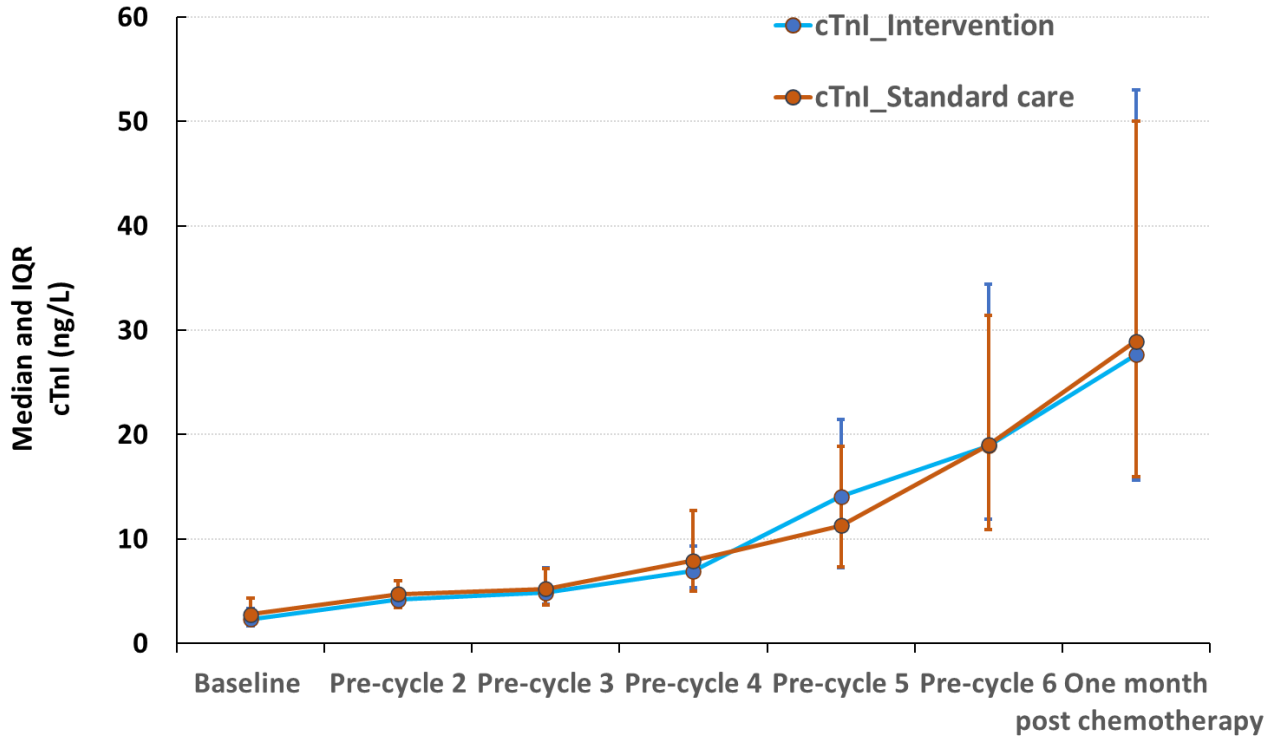
Troponin T: primary endpoint

Indicator	Groups	Total n/N (%)	Adjusted Odds Ratio (95% CI)	P value
cTnT	Enalapril	**42/54 (78)**	**0.65 (0.23-1.78)**	**0.405**
	Standard care	**45/54 (83)**		

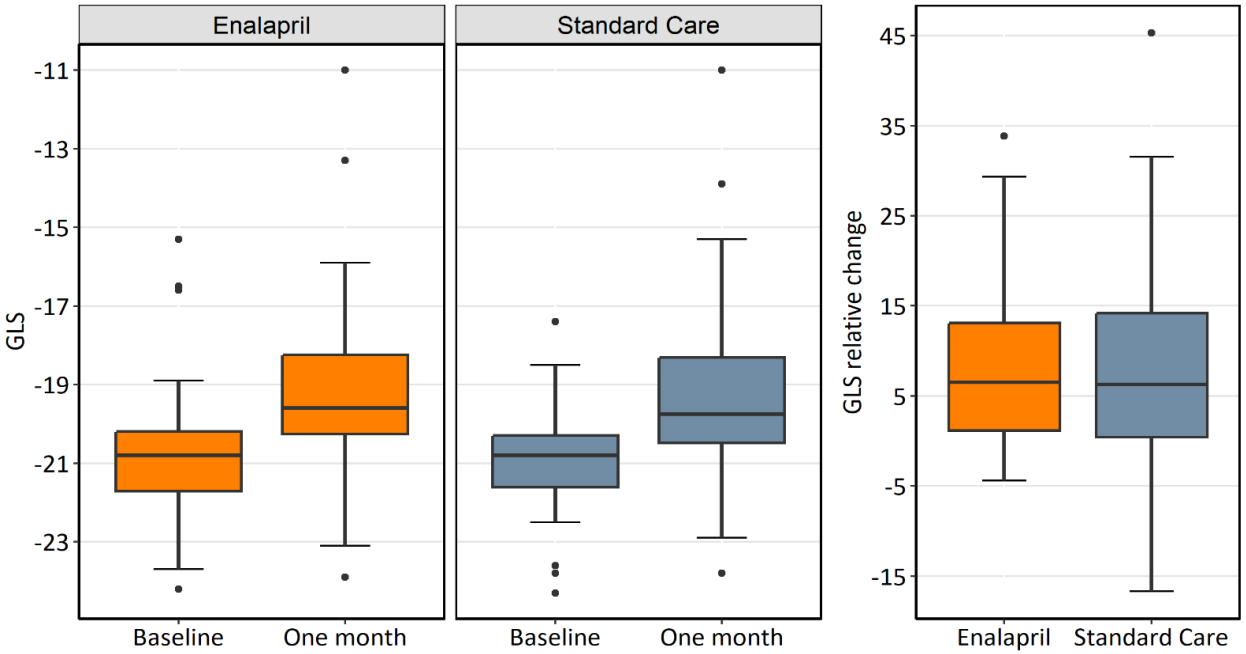


Troponin I: secondary endpoint

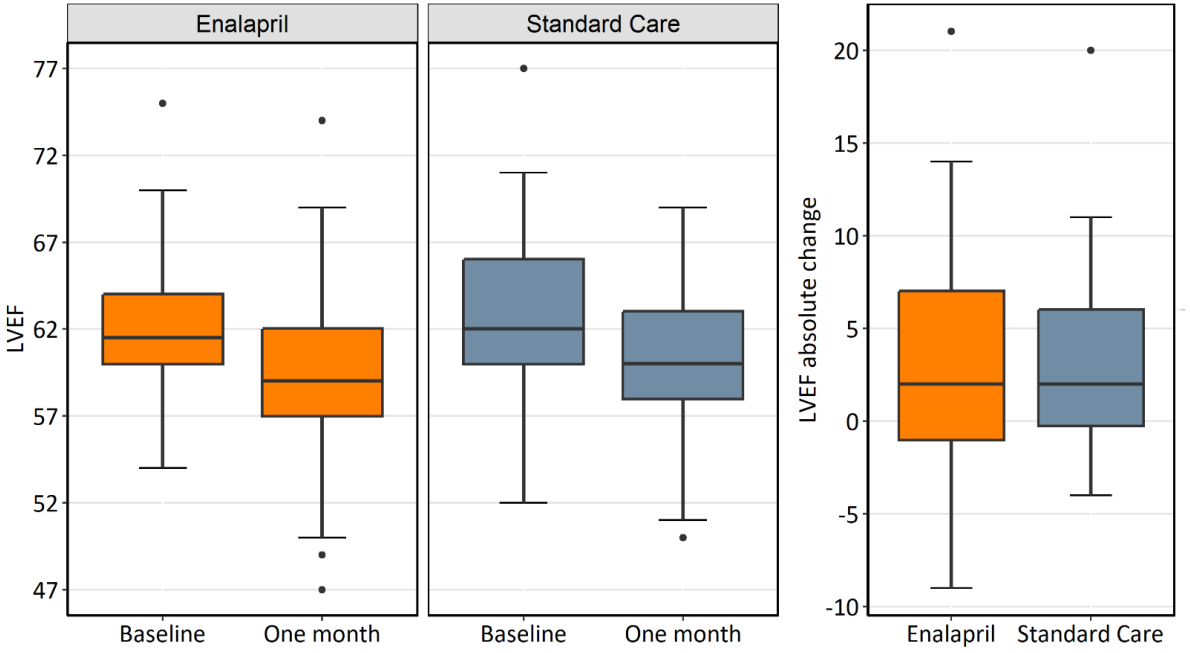
Indicator	Groups	Total n/N (%)	Adjusted Odds Ratio (95% CI)	P value
cTnI	Enalapril	**25/53 (47)**	**1.10 (0.50-2.38)**	**0.819**
	Standard care	**24/53 (45)**		



Cardiac function: LV GLS



Cardiac function: LV EF



Indicator	Groups	Total n/N (%)	Adjusted Odds Ratio (95% CI)	p
LV GLS	Enalapril	10/47 (21)	0.95 (0.33-2.74)	0.921
	Standard care	9/41 (22)		

Indicator	Groups	Total n/N (%)	Adjusted Odds Ratio (95% CI)	p
LVEF	Enalapril	2/49 (4)	4.89 (0.40-674.62	0.236
	Standard care	0/48 (0)		

Key findings

- **81%** of patients had myocardial injury on cardiac troponin T criteria
- **46%** of patients had myocardial injury on cardiac troponin I criteria
- Cardiac troponin T and cardiac troponin I did not give equivalent results

- **21%** had a >15% relative decrease in LV GLS
- **2%** had a >10% reduction in LV EF to <50%

- Enalapril did not affect myocardial injury or cardiac function outcomes

Limitations

- Open label
- Challenging recruitment
  - Included NHL patients
  - Power 90% to 80% during COVID 19 pandemic
- Echocardiographic assessment at an early post chemotherapy stage – further clinical and echo follow up is on going

Conclusion

Adding enalapril to standard care was not superior to standard care alone in the prevention of cardiotoxicity in patients receiving high-dose anthracycline based chemotherapy

Newcastle University

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NIHR | National Institute for Health and Care Research

SOUTH TEES
Academic
Cardiovascular Unit

Acknowledgments

- PROACT trial participants
- Local PIs and site teams
- Newcastle Clinical Trials Unit
- Durham University and Teesside University statistics
- Core lab teams

- Trial Steering Committee
  - Chairs:

    Prof Helena Earl

    Dr Colette Jackson
- Independent Data Monitoring Committee
  - Chair: Dr Alex Lyon
- Sponsor: South Tees NHS Foundation Trust

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Research for Patient Benefit (PB-PG-0815-20061)

Newcastle University

SOUTH TEES Academic Cardiovascular Unit

ACC.24

A Double-blind, Randomized Placebo-Procedure-Controlled Trial of an Interatrial Shunt In Patients with HFrEF and HFpEF: **Principal Results from the RELIEVE-HF Trial**

Gregg W Stone MD

for the RELIEVE-HF study group

@GreggWStone

AMERICAN COLLEGE of CARDIOLOGY

RELIEVE-HF

Background

- Heart failure (HF) is characterized by increased left atrial pressure and pulmonary venous congestion
- Left atrial pressure rises with exercise and fluid overload and may be difficult to regulate pharmacologically
- An inter-atrial shunt (IAS) may provide an autoregulatory mechanism to decrease left atrial pressure and improve HF symptoms and prognosis
- In pilot studies, the **Ventura IAS (V-Wave Ltd.)** reduced filling pressures, improved cardiac structure and function, and provided symptomatic relief and functional improvement in patients with HFrEF and HFpEF

RELIEVE-HF

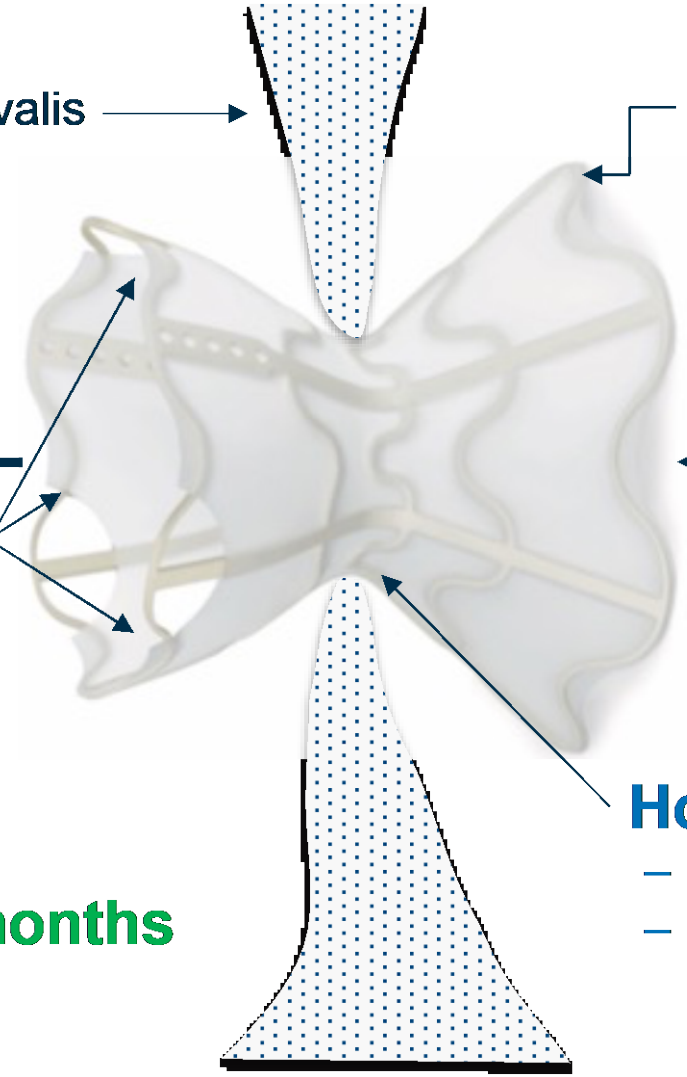
Objectives and Trial Design

- We therefore sought to determine the safety and effectiveness of the V-Wave Ventura IAS device in symptomatic HF patients with any LVEF in a randomised, double-blind, placebo-procedure-controlled, multicenter trial

- Given uncertainty as to whether the response to an IAS would vary according to systolic function, stratified randomizations were performed in patients with reduced (≤40%) and preserved (>40%) LVEF

RELIEVE-HF

V-Wave Ventura Inter-atrial Shunt



Fossa ovalis

Nitinol frame

14F delivery system
Over-the-wire, retrievable

Full ePTFE encapsulation
- Channels flow
- Prevents late lumen loss

Right Atrium

Left Atrium

Exit hood
- Blocks route of paradoxical emboli transit in RA

Hourglass shape
- Secure and atraumatic retention
- 5.1 mm orifice, Venturi efficiency

- **DAPT 6 months**

Length: 12mm; LA diameter: 14mm; RA diameter: 11mm;
Neck diameter: 5.1mm; Qp/Qs: approximately 1.2:1

RELIEVE-HF

Key Inclusion Criteria

1. Ischemic or non-ischemic cardiomyopathy with **any LVEF** and documented HF for at least 6 months
2. NYHA class II, III, or ambulatory IV functional class despite maximally-tolerated class I GDMT and cardiac rhythm management device therapy for HF as assessed by a central eligibility committee
3. HF hospitalization within the prior 12 months and/or an elevated (BMI-adjusted) BNP/NT-proBNP (both required for NYHA II)
4. 6MWT ≥100 meters - ≤450 meters
5. Written, informed consent

RELIEVE-HF

Key Clinical Exclusion Criteria

1. Resting SBP <90 or >160 mmHg or intractable HF
2. Severe pulmonary hypertension defined as PASP >70 mmHg by echo/Doppler or PVR >4.0 WU on RHC that cannot be reduced by vasodilator therapy
3. RV dysfunction defined as TAPSE <12 mm or RVFAC ≤25% on TTE
4. LVEDD >8 cm on TTE
5. ASD, PFO, APVR, corrected CHD, severe valve lesions
6. Transseptal procedure for another indication planned within 6 months

Final Key Exclusion Criteria After RHC and TEE/ICE

- performed just prior to randomization -

1. Anatomical anomaly that precludes implanting the IAS across the fossa ovalis (FO) including:

   Minimal FO thickness >6 mm or length <10 mm; ASD or PFO with >trace shunting; atrial septal aneurysm; intracardiac thrombus

2. Hemodynamic, heart rhythm, or respiratory instability including:

   Mean PCWP <7 mmHg or >35 mmHg; RAP ≥ LAP (or PCWP) when LAP (PCWP) is ≥7 mmHg; CI <1.5 L/min/m^2; severe pulmonary HTN as previously defined, SBP <90 or >160 mmHg; need for IV vasopressor or inotrope medication; malignant arrhythmias; acute respiratory distress or hypoxemia

RELIEVE-HF Primary Effectiveness Endpoint

- **Comparison between groups of the hierarchical composite ranking of:**
  - All-cause death
  - Cardiac transplantation or left ventricular assist device (LVAD) implantation
  - All HF hospitalizations
  - All outpatient worsening HF events
  - Change in KCCQ-OS from baseline to 12 months (5-point minimum difference)
- **Analyzed by the Finkelstein-Schoenfeld method when the last enrolled patient reaches 12 months with longest FU to 24 months, expressed as the win ratio**
- A single interim analysis of the primary effectiveness outcome with adaptive sample size re-estimation by an independent third party was planned when 200 enrolled patients completed 6-month follow-up. To prevent inflation of type-1 error the final FS statistic is derived from data weighted differently before and after the interim analysis.*

*Cui L, Hung HMJ, Wang S-J. Biometrics 1999;55:853-857

RELIEVE-HF Primary Safety Endpoint

- Device-related or procedure-related MACNE (all-cause death, stroke, systemic embolism or need for open cardiac surgery or major endovascular surgical repair) at 30 days in the IAS group, compared against an OPC of 11%

- Numerous additional secondary safety and effectiveness endpoints were pre-specified
- All primary and secondary endpoints will be tested in the randomized strata of patients with reduced and preserved LVEF

Patient Flow

1136 patients were screened for enrollment at **113 sites** in **11 countries** (USA, Canada, Israel, Germany, Spain, Switzerland, Belgium, Poland, The Netherlands, Australia, and New Zealand

Roll-in cases
N=97
Shunt implanted

Enrolled
N=605
at 101 sites

Ineligible
N= 531
All inclusion criteria not met (n=212)
Exclusion criteria present (n=182)
Not approved by eligibility committee (n=17)
Failed final eligibility assessment in the cath lab (n= 60)
Withdrew consent during screening (n=33)
Incomplete screening or other (n= 24)
Death during screening (n=3)

Randomized
N=508
at 94 sites
between Oct 24, 2018 and Oct 19, 2022

Randomized 1:1
Stratified by core lab LVEF ≤40% vs. >40% and site

Inter-atrial shunt
N=250

Placebo-procedure
N=258

Patients and all post-cath lab personnel were blinded

	30-d FU	12-mo FU (primary endpoint minimum)	24-mo FU (eligible pts)
Inter-atrial shunt	N=250/250 (100%)	N=249/250 (99.6%)	N=150/151 (99.3%)
Placebo-procedure	N=258/258 (100%)	N=256/258 (99.2%)	N=133/137 (97.1%)
Lost-to-FU / Withdrew	0 / 0	0 / 1	0 / 1
Lost-to-FU / Withdrew	0 / 0	0 / 2	0 / 4

Post-procedure patients not on OAC were treated with open-label aspirin (75-100 mg per day) for 2 years + study drug clopidogrel (75 mg per day in the IAS group vs. matching placebo in the control group) for 6 months

Median follow-up 22.0 (13.3, 23.9) months

RELIEVE-HF

Baseline Characteristics (1)

	Shunt group (N=250)	Placebo group (N=258)
Age, years	74.0 (67.0, 79.0)	72.0 (65.0, 78.0)
Sex, male	162 (64.8%)	157 (60.9%)
Body mass index, kg/m²	30.0 (25.6, 34.9)	30.3 (26.2, 36.0)
Diabetes mellitus	124 (49.6%)	125 (48.4%)
Hypertension	209 (83.6%)	216 (83.7%)
Hyperlipidemia	201 (80.4%)	195 (75.6%)
Current or previous smoker	133 (53.2%)	137 (53.1%)
Prior stroke or TIA	43 (17.2%)	48 (18.6%)
COPD	43 (17.2%)	52 (20.2%)
Ischemic cardiomyopathy	114 (45.6%)	120 (46.5%)
Non-ischemic cardiomyopathy	136 (54.4%)	138 (53.5%)
At least one HFH in the prior year	128 (51.2%)	127 (49.2%)
Known CAD	169 (67.6%)	160 (62.0%)
Prior MI	104 (41.6%)	103 (39.9%)
Prior PCI	103 (41.2%)	96 (37.2%)
Prior CABG	65 (26.0%)	58 (22.5%)

RELIEVE-HF

Baseline Characteristics (2)

	Shunt group (N=250)	Placebo group (N=258)
History of atrial fibrillation or flutter	170 (60.8%)	159 (61.2%)
- Baseline rhythm is atrial fib or flutter	76 (30.4%)	64 (24.8%)
ICD or CRT-D	115 (46.0%)	123 (47.7%)
CRT-D or CRT-P	70 (28.0%)	59 (22.9%)
NYHA class II	9 (3.6%)	7 (2.7%)
NYHA class III	239 (95.6%)	251 (97.3%)
NYHA class IV	2 (0.8%)	0 (0.0%)
KCCQ overall summary score	52.1 (35.4, 66.9)	50.8 (34.6, 66.4)
Six-minute walk distance, m	264.8 (195.5, 325.0)	270.9 (198.0, 330.0)
LVEF (biplane, core lab assessment), %	45.4 (33.4, 58.9)	45.3 (33.3, 57.4)
- ≤40% (reduced LVEF)	101/250 (40.4%)	105/258 (40.7%)
- >40% (preserved LVEF)	149/250 (59.6%)	153/258 (59.3%)
BNP (pg/mL)	237.9 (117.2, 412.5)	221.0 (101.0, 518.3)
NT-proBNP(pg/mL)	1939.4 (1066.0, 3259.0)	1596.6 (852.0, 2868.1)
eGFR, mL/min/1.73 m^2	45.5 (37.5, 59.8)	48.5 (37.2, 60.8)
- <60 mL/min/1.73 m^2	188 (75.2%)	188 (72.9%)

RELIEVE-HF

Baseline TTE (core-lab)

	Shunt group (N=250)	Placebo group (N=258)
LVEDV (biplane), mL	123.3 (87.0, 175.5)	126.0 (96.0, 181.5)
LVESV (biplane), mL	66.3 (37.5, 115.5)	70.0 (40.5, 117.0)
LAV (biplane), mL	78.5 (63.5, 103.0)	76.0 (59.5, 101.0)
SV, mL	54.0 (41.0, 67.0)	54.0 (44.0, 67.0)
SVI, mL/m^2	26.7 (21.7, 31.9)	27.5 (21.8, 33.0)
CO, L/min	3.7 (2.9, 4.6)	3.8 (3.1, 4.7)
CI, L/min/m^2	1.8 (1.5, 2.2)	1.9 (1.5, 2.3)
RV FAC, %	37.7 (33.3, 42.9)	37.5 (33.3, 42.9)
TAPSE, mm	16.5 (14.0, 20.0)	17.0 (14.0, 19.0)
PASP, mmHg	32.0 (24.0, 41.0)	32.0 (25.0, 40.0)
RVEDAI, cm^2/m^2	9.8 (8.2, 11.9)	10.4 (8.4, 12.4)
IVC diameter max, cm	1.6 (1.2, 2.0)	1.6 (1.2, 1.9)
MR moderate or greater	49 (19.6%)	38 (14.7%)
TR moderate or greater	50/247 (20.2%)	45/257 (17.5%)

RELIEVE-HF

Baseline Right Heart Catheterization

	Shunt group (N=250)	Placebo group (N=258)
HR, bpm	67.0 (60.0, 75.0)	68.0 (60.0, 77.0)
SBP, mmHg	116.0 (104.0, 133.0)	115.0 (103.0, 134.0)
DBP, mmHg	64.0 (57.0, 73.0)	65.0 (59.0, 73.0)
Mean RAP, mmHg	9.0 (6.0, 12.0)	9.0 (6.0, 11.0)
Systolic PAP, mmHg	37.0 (30.0, 45.0)	37.0 (31.0, 44.0)
Mean PAP, mmHg	25.0 (21.0, 31.0)	25.0 (20.0, 30.0)
PVR, WU	2.1 (1.5, 3.1)	2.0 (1.4, 2.8)
PCWP, mmHg	15.5 (12.0, 20.0)	16.0 (12.0, 21.0)
CO, L/min	4.2 (3.4, 5.3)	4.3 (3.6, 5.3)
CI, L/min/m^2	2.1 (1.8, 2.6)	2.2 (1.8, 2.6)

RELIEVE-HF

Procedural Details

	Shunt group (N=250)	Placebo group (N=258)	Difference [95% CI]
Procedure duration, minutes	80 (59, 100)	43 (30, 55)	35.5 [31.0, 40.0]
Fluoroscopy time, minutes	14 (10, 21)	4 (2, 7)	9.9 [8.9, 10.9]
Contrast administered, mL	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)
Heparin administered, units	9000 (7000, 12,000)	-	-
Activated clotting time, secs	291 (246, 342)	-	-
Shunt implant attempt	250 (100%)	1 (0.4%)*	-
- Shunt implanted successfully	250 (100%)	1 (0.4%)	-
Hospital duration post procedure, days	1 (1, 1)	1 (1, 1)	0.0 [0.0, 0.0]

*Site randomization error

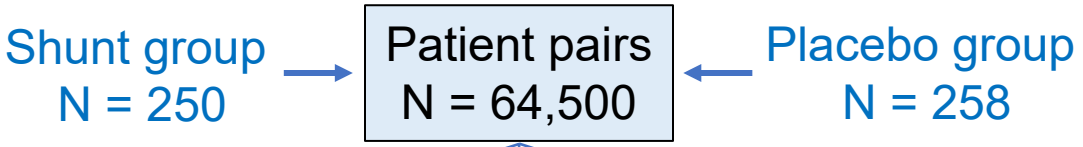
RELIEVE-HF Primary Safety Endpoint

- Device-related or procedure-related MACNE (all-cause death, stroke, systemic embolism or need for open cardiac surgery or major endovascular surgical repair) at 30 days in the IAS group, compared against an OPC of 11%

Within 30 days, MACNE occurred in 0 (0.0%) of 250 patients in the IAS group (upper 1-sided 97.5% CL = 1.5%), which is below the 11% performance goal, P<0.0001 using an exact binomial test

MACNE occurred in 0 (0.0%) IAS-treated patients through 2-year FU

RELIEVE-HF Primary Effectiveness Endpoint



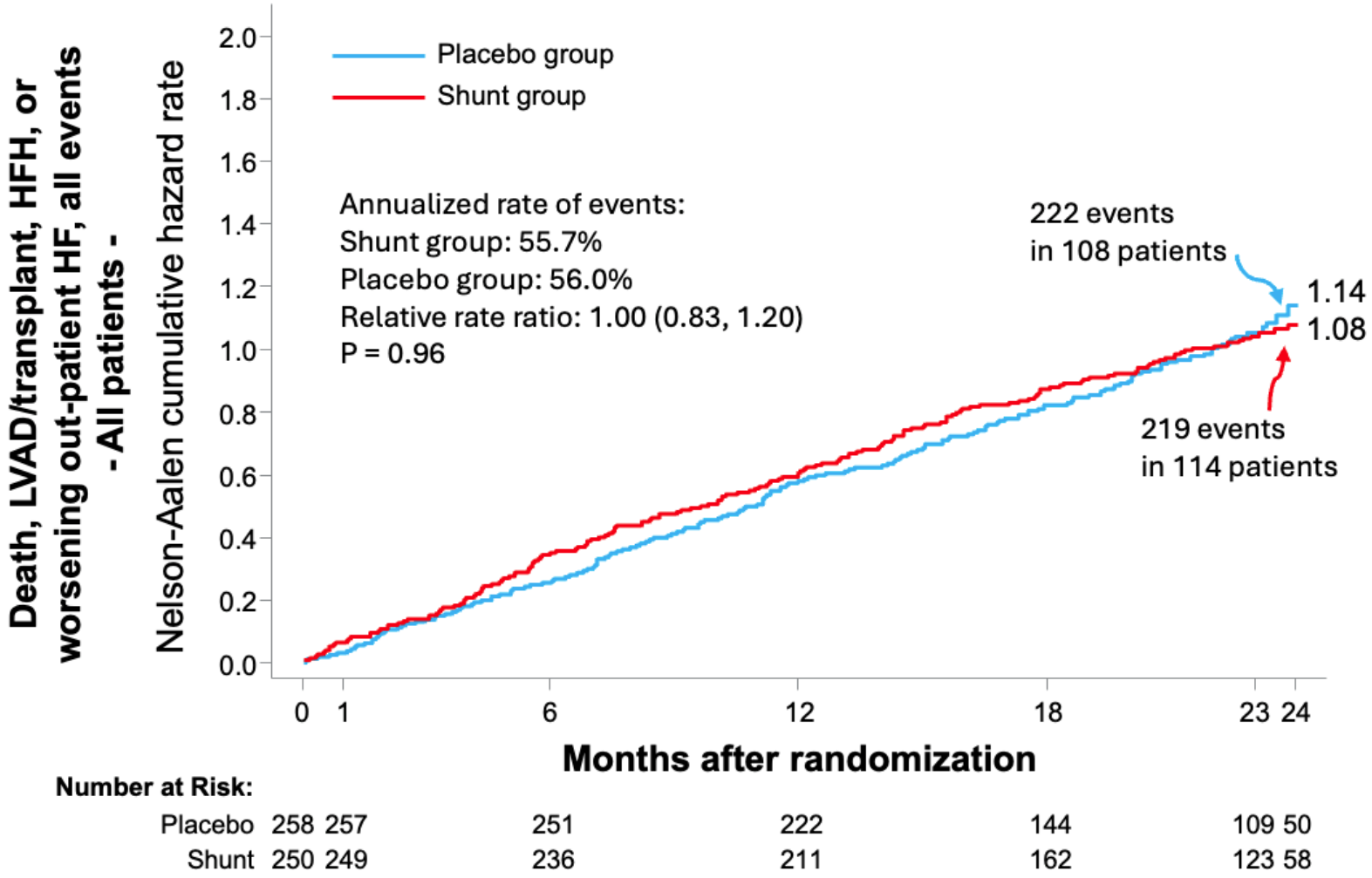
Shunt group outcomes	Wins	Ties	Losses	% of decisions
Level 1: All-cause death	5424	51,461	7615	21.4%
Level 2: Cardiac transplantation or LVAD implantation	1177	50,122	162	2.2%
Level 3: Heart failure hospitalizations	9264	30,271	10,587	32.5%
Level 4: Out-patient worsening heart failure events	3921	22,488	3862	12.8%
Level 5: Change in KCCQ from baseline by at least 5 points	8876	3533	10,079	31.1%

Total wins = 28,662, total losses = 32,305
Win ratio (unweighted) = 28,662/32,305 = 0.89 (0.72, 1.09)
Win ratio (phase weighted for interim analysis) = 0.86 (0.61, 1.22); **p=0.20**

RELIEVE-HF

Risk of all Cardiovascular Events

- All-cause death, LVAD/HT, all HFHs, and all out-patient worsening HF events -



RELIEVE-HF

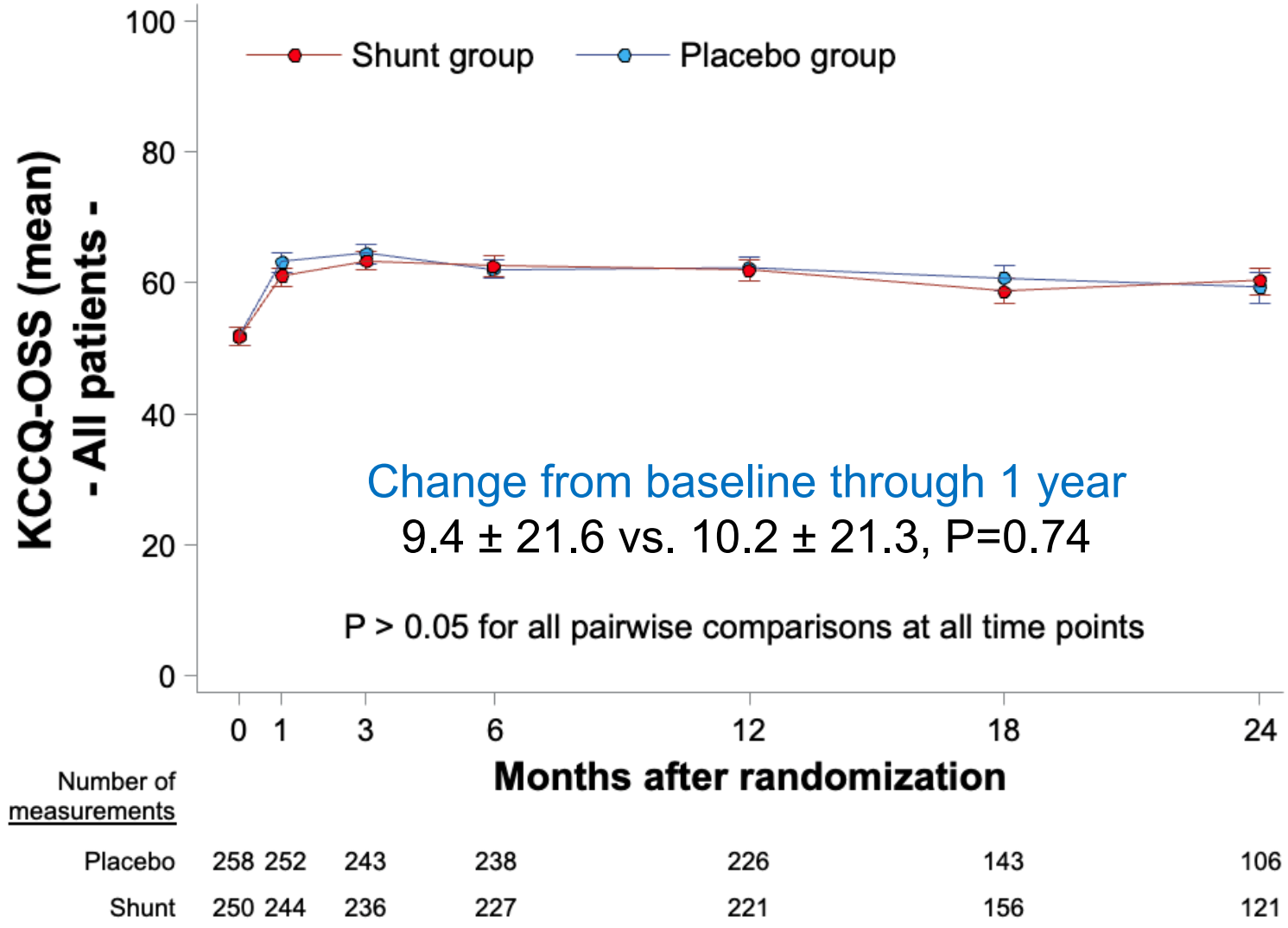
Risk of all Cardiovascular Events

- All-cause death, LVAD/HT, all HFHs, and all out-patient worsening HF events -

2-year rates	Shunt group (N=101)	Placebo group (N=108)	RR or HR (95% CI)	P-value
All events[1]	219/392.7 (55.7%/year)	222/396.1 (56.0%/year)	1.00 (0.83, 1.20)	0.96
All-cause death[2]	35 (15.6%)	27 (13.7%)	1.31 [0.79, 2.16]	0.30
LVAD/HT[2]	2 (0.8%)	2 (1.1%)	1.01 [0.14, 7.14]	1.00
All HFHs[1,3]	128/392.7 (32.6%/year)	125/396.1 (31.6%/year)	1.09 [0.79, 1.50]	0.60
All out-pt WHFs[1,3]	55/392.7 (14.0%/year)	64/396.1 (16.2%/year)	0.88 [0.61, 1.26]	0.48

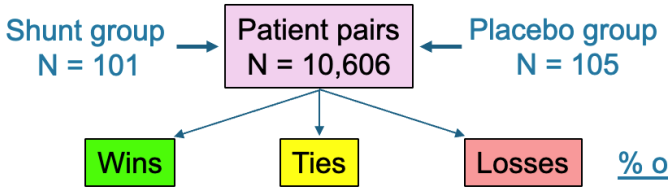
[1]Total no. of events/total no. of patient-years of follow-up (annualized rate) with relative rate ratio (95% CI)
[2]Time-to-first event analysis – n events (Kaplan-Meier estimated rate) with HR (95% CI) from a Cox model
[3]HR (95% CI) from a joint frailty model accounting for the competing risk of death

Change in KCCQ-OSS Over Time



Primary Effectiveness Outcome by LVEF

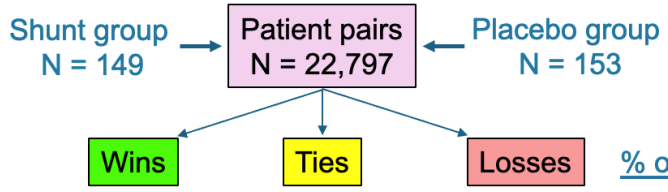
LVEF ≤40% (n=206)



Shunt group outcomes	Wins	Ties	Losses	% of decisions
Level 1: All-cause death	1543	7908	1154	26.7%
Level 2: Cardiac transplantation or LVAD implantation	466	7384	58	5.2%
Level 3: Heart failure hospitalizations	1670	4304	1410	30.5%
Level 4: Outpatient worsening heart failure events	506	3227	571	10.7%
Level 5: Change in KCCQ from baseline by at least 5 points	1339	501	1387	27.0%

Total wins = 5524; Total losses = 4580
Win ratio (unweighted) = 5524/4580 = 1.21 (0.87, 1.67)
Win ratio (phase weighted for interim analysis) = 1.40 [0.80, 2.46]

LVEF >40% (n=302)



Shunt group outcomes	Wins	Ties	Losses	% of decisions
Level 1: All-cause death	914	19014	2869	17.7%
Level 2: Cardiac transplantation or LVAD implantation	0	19014	0	0%
Level 3: Heart failure hospitalizations	3067	11637	4310	34.5%
Level 4: Outpatient worsening heart failure events	1590	8628	1419	14.1%
Level 5: Change in KCCQ from baseline by at least 5 points	3238	1418	3972	33.7%

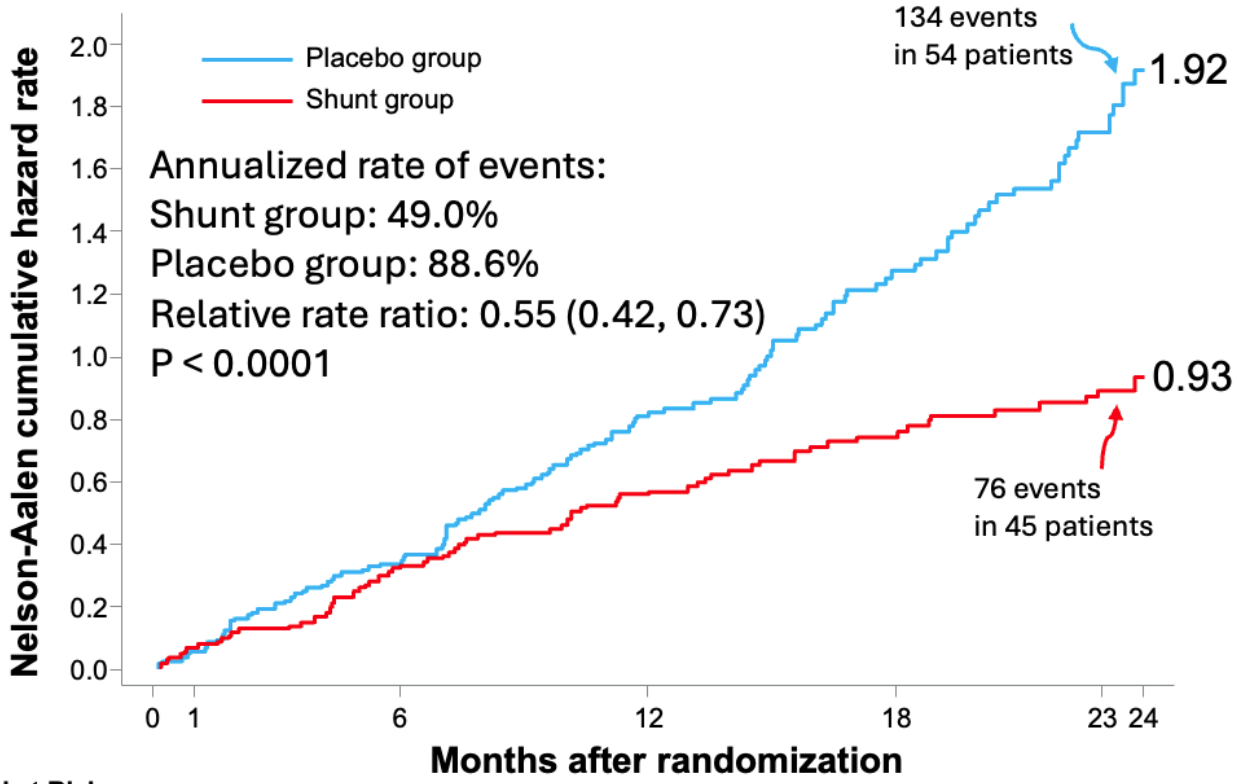
Total wins = 8809; Total losses = 12,570
Win ratio (unweighted) = 8809/12,570 = 0.70 (0.54, 0.92)
Win ratio (phase weighted for interim analysis) = 0.61 [0.39, 0.98]

$P_{interaction}$=0.0275

Risk of all Cardiovascular Events by LVEF

- All-cause death, LVAD/HT, all HFHs, and all out-patient worsening HF events -

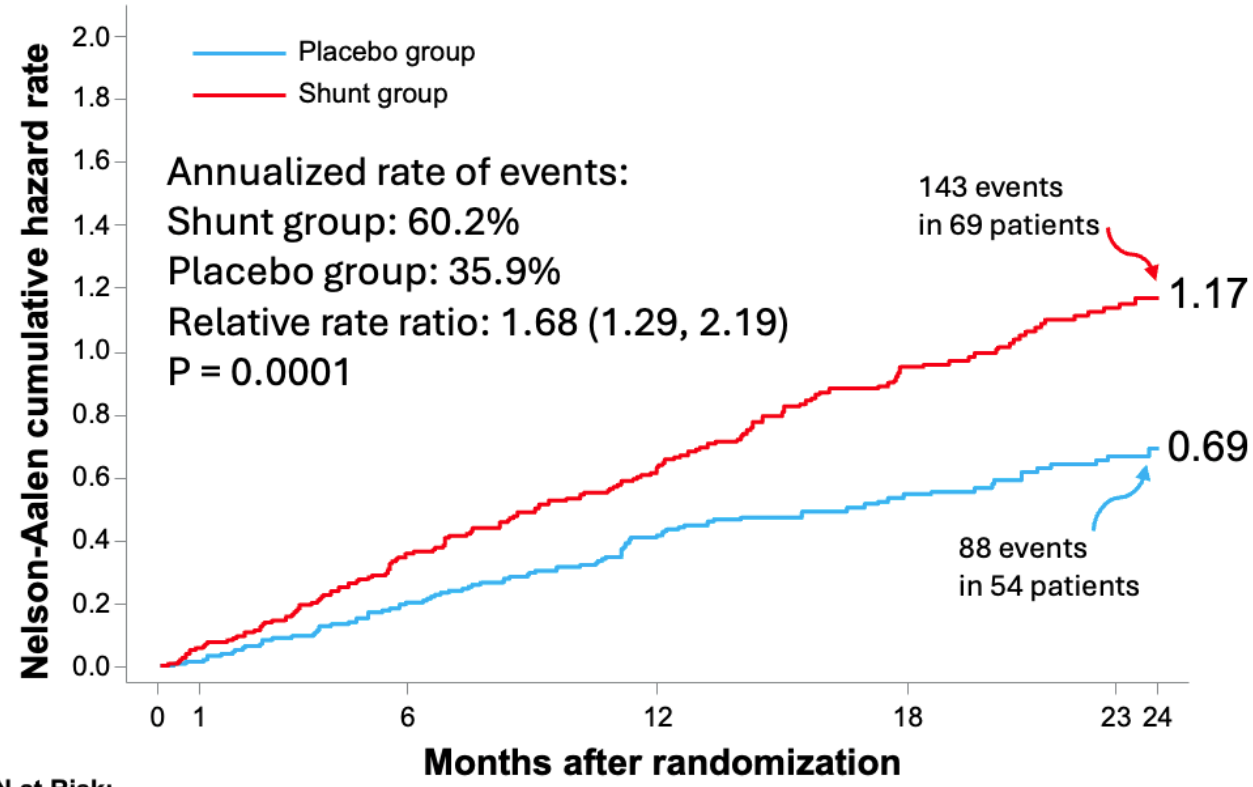
LVEF ≤40% (n=206)



N at Risk:

Placebo	105 104	101	84	51	38	19
Shunt	101 101	96	84	60	46	17

LVEF >40% (n=302)



N at Risk:

Placebo	153 153	150	138	93	72	31
Shunt	149 148	140	127	102	77	41

$P_{interaction}$<0.0001

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Risk of all Cardiovascular Events by LVEF

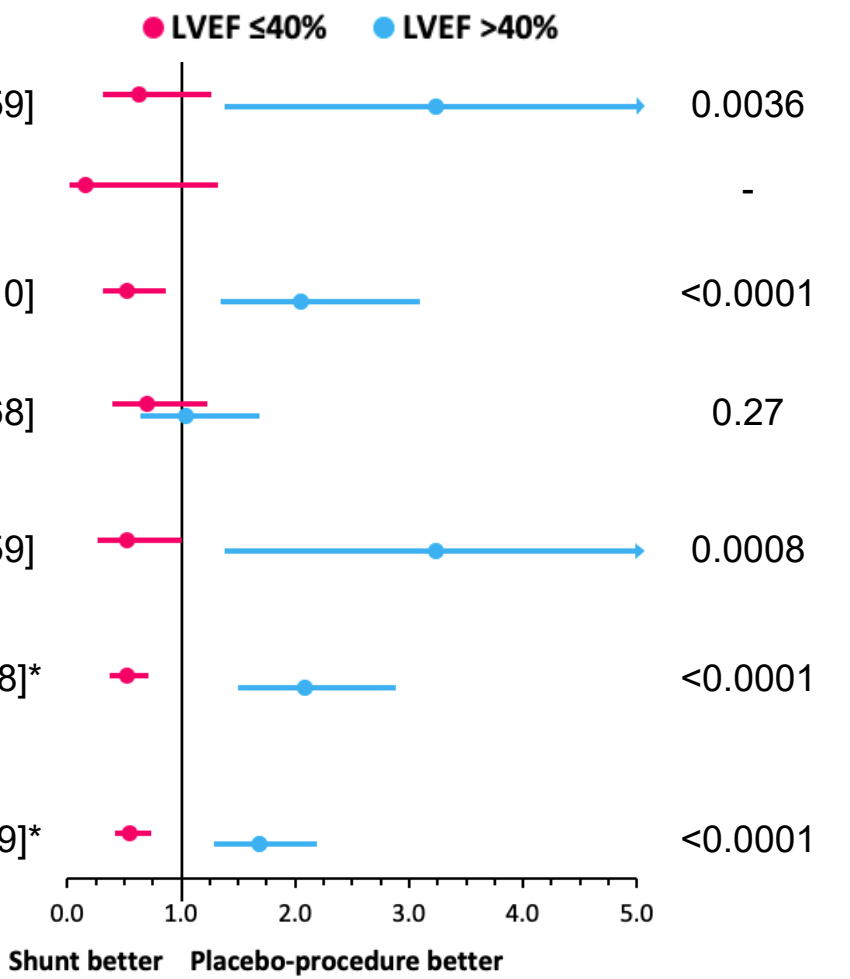
- All-cause death, LVAD/HT, all HFHs, and all out-patient worsening HF events -

	LVEF ≤40%			LVEF >40%		
2-year rates	**Shunt group (N=101)**	**Placebo group (N=108)**	**RR or HR (95% CI)**	**Shunt group (N=149)**	**Placebo group (N=153)**	**RR or HR (95% CI)**
All events[1]	76/155.2 (49.0%/year)	134/151.2 (88.6%/year)	0.55 (0.42, 0.73) **P<0.0001**	143/237.5 (60.2%/year)	88/2450 (35.9%/year)	1.68 (1.29, 2.19) **P=0.0001**
All-cause death[2]	13 (14.3%)	20 (26.8%)	0.63 [0.31, 1.26] P=0.19	22 (16.4%)	7 (5.2%)	3.24 [1.38, 7.59] **P=0.004**
LVAD/HT[2]	1 (1.5%)	6 (9.0%)	0.16 [0.02, 1.32] P=0.051	0 (0.0%)	0 (0.0%)	-
All HFHs[1,3]	41/155.2 (26.0%/year)	78/151.2 (52.0%/year)	0.52 [0.31, 0.86] **P=0.01**	87/237.5 (37.0%/year)	47/245.0 (19.0%/year)	2.05 [1.35, 3.10] **P=0.0008**
All out-pt WHFs[1,3]	21/155.2 (14.0%/year)	30/151.2 (20.0%/year)	0.70 [0.39, 1.23] P=0.21	34/237.5 (14.0%/year)	34/245.0 (14.0%/year)	1.04 [0.64, 1.68] P=0.88

[1]Total no. of events/total no. of patient-years of follow-up (annualized rate) with relative rate ratio (95% CI)
[2]Time-to-first event analysis – n events (Kaplan-Meier estimated rate) with HR (95% CI) from a Cox model
[3]HR (95% CI) from a joint frailty model accounting for the competing risk of death

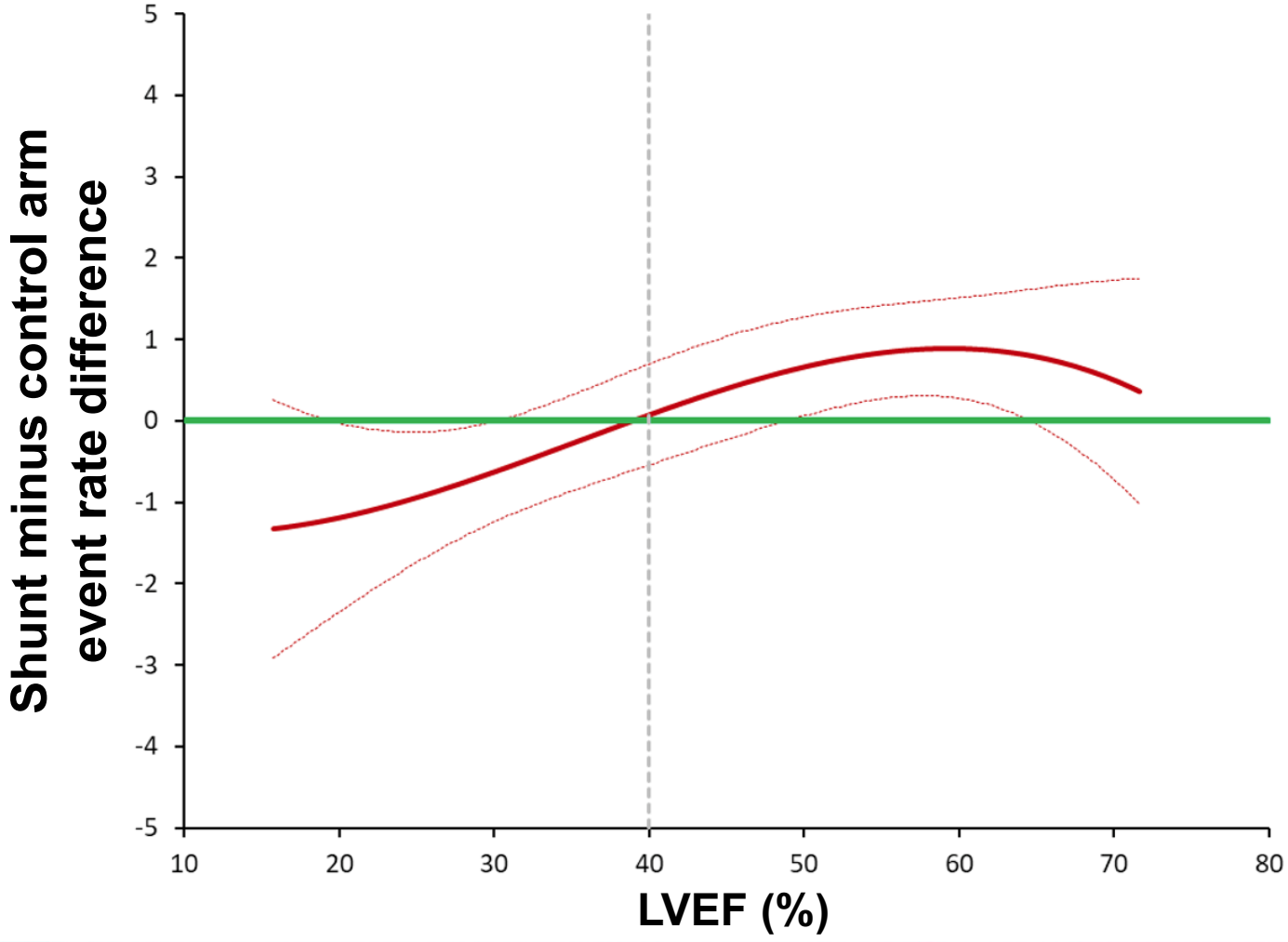
Risk of Cardiovascular Events by LVEF

	LVEF ≤40% HR or RRR [95% CI]	LVEF >40% HR or RRR [95% CI]	P-value for interaction
All-cause death through 2 years, time to first	0.63 [0.31, 1.26]	3.24 [1.38, 7.59]	0.0036
HT or LVAD implantation through 2 years, time to first	0.16 [0.02. 1.32]	-	-
Heart failure hospitalizations (HFHs), all through 2 years – no. of events/total no. of pt-yr (annualized rate), JF model	0.52 [0.31, 0.86]	2.05 [1.35, 3.10]	<0.0001
Outpatient worsening HF events, all through 2 years – no. of events/total no. of pt-yr (annualized rate), JF model	0.70 [0.39, 1.23]	1.04 [0.64, 1.68]	0.27
All-cause death or HT or LVAD implantation through 2 years, time to first	0.52 [0.27, 1.00]	3.24 [1.38, 7.59]	0.0008
All-cause death, HT or LVAD, and HFHs, all events through 2 years – no. of events/total no. of patient-yr-yr (annualized rate)	0.52 [0.37, 0.71]*	2.08 [1.50, 2.88]*	<0.0001
All-cause death, HT or LVAD, HFH and outpatient worsening HF events, all through 2 years – no. of events/total no. of patient-yr (annualized rate)	0.55 [0.42, 0.73]*	1.68 [1.29, 2.19]*	<0.0001



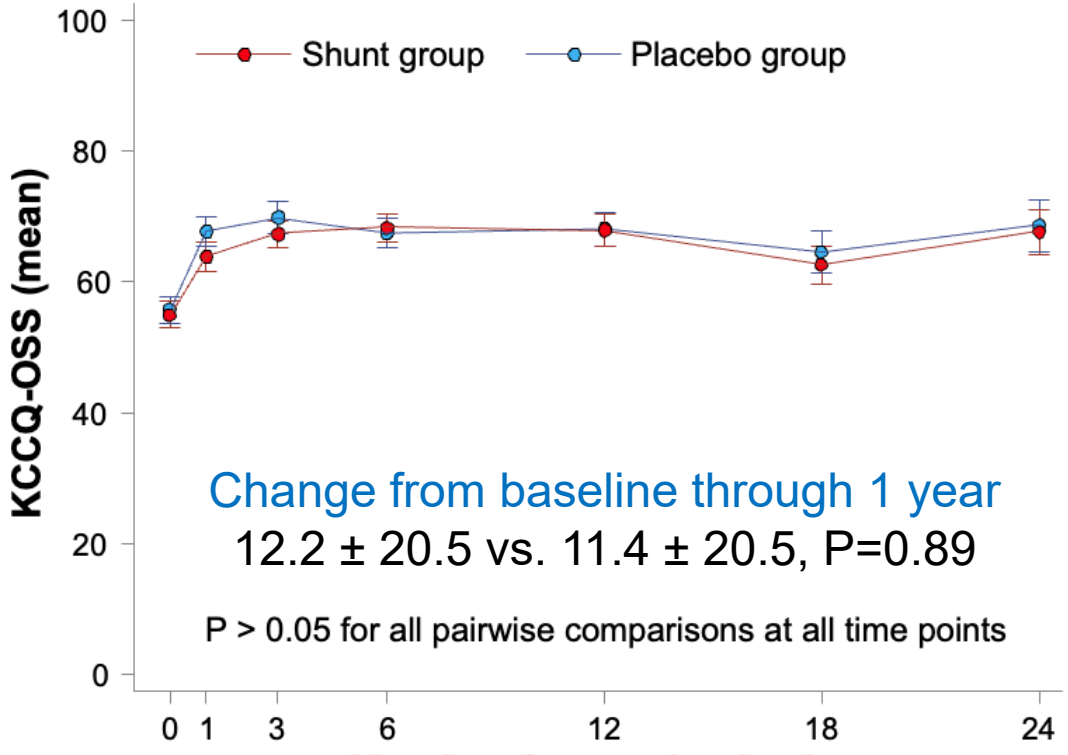
Risk of all Cardiovascular Events by LVEF

- All-cause death, LVAD/HT, all HFHs, and all out-patient worsening HF events -



Change in KCCQ-OSS Over Time by LVEF

LVEF ≤40% (n=206)



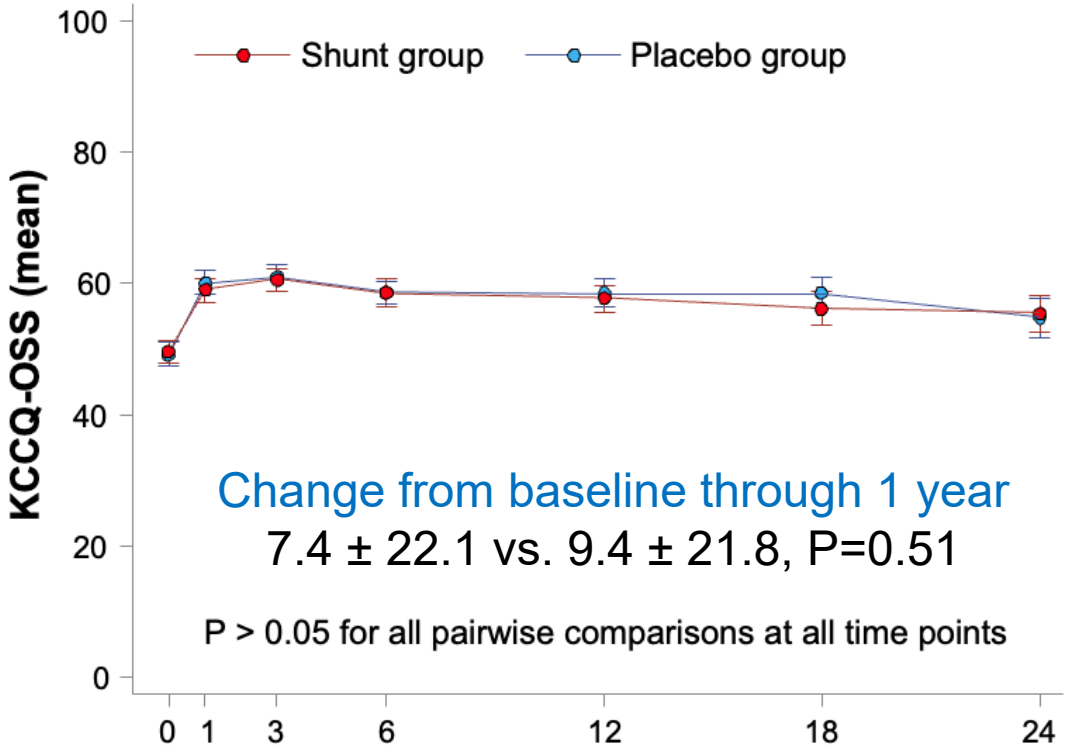
Change from baseline through 1 year

12.2 ± 20.5 vs. 11.4 ± 20.5, P=0.89

P > 0.05 for all pairwise comparisons at all time points

Number of measurements							
Placebo	105	100	96	95	86	52	35
Shunt	101	100	97	94	91	60	48

LVEF >40% (n=302)



Change from baseline through 1 year

7.4 ± 22.1 vs. 9.4 ± 21.8, P=0.51

P > 0.05 for all pairwise comparisons at all time points

Number of measurements							
Placebo	153	152	147	143	140	91	71
Shunt	149	144	139	133	130	96	73

RELIEVE-HF

Limitations

1. The present results apply only to the profile of the pts enrolled and treated with the Ventura inter-atrial shunt
2. The reduced and preserved LVEF groups, although pre-specified randomized strata, were not individually powered for effectiveness; the results within each strata must therefore be considered exploratory
   - However, the strong interaction ($P<0.0001$) and spline curve analysis for cardiovascular events suggests these findings are not due to play of chance
3. The large and similar increase in KCCQ-OSS in both the device and control groups emphasizes the relevance of the placebo effect and the necessity for blinded trials
   - Moreover, the similar magnitude of KCCQ-OSS improvement and the lack of between-group differences in this metric despite a large decrease in HFHs in shunt-treated pts with reduced LVEF and a large increase in HFHs and mortality in shunt-treated pts with preserved LVEF confounds its interpretation in blinded (and open-label) trials

RELIEVE-HF

Conclusions

- Transcatheter implantation of the Ventura inter-atrial shunt was safe but did not reduce symptoms or improve prognosis through 2 years in patients with HF across the full range of all LVEF
- The results from a pre-specified stratified analysis suggest that inter-atrial shunt implantation is beneficial in patients with reduced LVEF and harmful in patients with preserved LVEF

RELIEVE-HF

Study Leadership and Organization

- *Principal investigators:* Stefan D. Anker, JoAnn Lindenfeld, Josep Rodés-Cabau, Gregg W. Stone
- *Executive Committee:* PIs + Michael Zile, Saibal Kar, John Gorcsan, Rich Holcomb, William T. Abraham
- *Steering Committee:* EC + Maria Rosa Costanzo, Antoni Bayes-Genis, Jeroen Bax, Alan Bank, Stefan Verheye, Ariel Roguin, Gerasimos Filippatos, Stephan von Bardeleben, Raj Makkar, Tom McRae, Wayne Batchelor, Frank Ruschitzka, Berkert Pieske
- *Central Eligibility Committee:* Michael Zile (moderator), JoAnn Lindenfeld, Jeroen Bax, Alan Bank, Maria Rosa Costanzo, Gregg W. Stone, Josep Rodes-Cabau, Ariel Roguin, Stefan Verheye
- *Echocardiographic Core Laboratory:* Penn State Health-Milton S. Hershey Medical Center: Michael P. Pfeiffer (director), 1/26/21-current; Washington University: John Gorcsan (director), 2/24/18-1/26/21
- *Clinical Endpoints Committee:* Cardiovascular Research Foundation (CRF); Marrick Kukin (chair)
- *Data Safety Monitoring Board:* CRF; Bernard Gersh (chair)
- *Data management and biostatistics:* CRF; Ovidiu Dressler and Yiran Zhang
- *Site management and data monitoring:* V-Wave Ltd.
- *Sponsor and funding:* V-Wave Ltd.

RELIEVE-HF

Top 12 Randomizing Sites

PI	Hospital, City, State, Country	N randomized
Julio Núñez	Hospital Clínico Universitario, INCLIVA, University of Valencia, Valencia, Spain	32
Josep Rodés-Cabau	Institut universitaire de cardiologie et de pneumologie de Québec - Université Laval, Quebec City, Quebec, Canada	25
Elizabeth Lee	Rochester General Health System, Rochester, NY, US	23
Antoni Bayes-Genis	Hospital Universitari Germans Trias and Pujol de Badalona, Barcelona, Spain	19
Michal Laufer-Perl	Tel Aviv Sourasky Medical Center, affiliated with the Tel Aviv School of Medicine, Tel Aviv University, Tel Aviv, Israel	18
Gil Moravsky	Assaf HaRofeh Medical Center, Beer Yaakov, Israel	17
Sheldon Litwin	Medical University of South Carolina, Charleston, South Carolina, US	15
Hemal Gada	UPMC Pinnacle / Pinnacle Health Cardiovascular Institute, Harrisburg, PA, US	14
Edgard Prihadi	Antwerp Cardiovascular Center, ZNA Middelheim Hospital, Antwerpen, Belgium	13
Dimitry Schewel	Marienkrankrankenhas, Hamburg, Germany	12
Eugene Chung	Lindner Center for Research and Education at The Christ Hospital, Cincinnati, OH, US	12
Matthew Price	Scripps Clinic, La Jolla, CA, US	12

The Effect of Edetate Disodium-based Chelation on Cardiovascular Events in Patients with a Prior Myocardial Infarction and Diabetes – Results of the TACT2 Randomized Trial

Gervasio A. Lamas MD FACC, for the

TACT2 Investigators

@GLamasMD

I have no conflicts of interest

TACT2: Background

- Lead and cadmium are ubiquitous environmental pollutants and recognized risk factors for atherosclerosis
- Edetate disodium (EDTA) is an avid lead and cadmium chelator, promotes their urinary elimination
- The Trial to Assess Chelation Therapy (TACT, 2003-2012) randomized 1702 patients with a prior MI (633 with diabetes) to placebo or edetate disodium (EDTA) infusions
- Overall cardiovascular events were reduced in the edetate disodium group (HR=0.82, p=0.035)[1] with a marked effect size (HR=0.59, p=0.0002)[2] in patients with concomitant diabetes

1. Lamas G et al. JAMA 2013
2. Escolar E et al. Circ Cardiovasc Qual Outcomes 2014

TACT2: Purpose

The purpose of the Trial to Assess Chelation Therapy 2 (TACT2) was to:

- Efficiently replicate TACT in post MI patients with diabetes
- Measure the effect of repeated edetate disodium infusions on blood lead and urine cadmium

TACT2: Funding and Organization

Funded by the National Institutes of Health

National Center for Complementary and Integrative Health

National Heart Lung and Blood Institute

National Institute for Diabetes Digestive and Kidney Diseases

National Institute of Environmental Health Sciences

Coordinating Centers

Clinical Coordinating Center
Mount Sinai Medical Center
Miami Beach, FL

Data Coordinating Center- Duke Clinical Research Institute (DCRI), Durham, NC

Trace Metals Core and Biorepository Center- Mailman School of Public Health, Columbia University NY, NY

Patient management

Clinical Sites US and Canada (n=88)

DCRI Patient Reported Outcomes (PRO) Call Center

Central Pharmacy to prepare and distribute study drug

TACT2: Design

- Double blind factorial trial of
  - (i) edetate disodium-based infusions and
  - (ii) high dose oral multivitamins and minerals

vs. corresponding placebos

- Randomization was 1:1:1:1

- The present report focuses on edetate disodium vs placebo infusions only

TACT2: Methods

- 1000 post MI patients with diabetes randomly assigned to 40 weekly edetate disodium or placebo infusions and oral low-dose vitamin and mineral supplements

- Follow-up:
  - Planned minimum = 2.5 years
  - Median = 4 years

TACT2: Key Inclusion Criteria

- Age 50 or older, non-childbearing if female
- Prior MI >6 weeks
- Diabetes
- Creatinine ≤ 2.0 mg/dL
- Non-smoker

TACT2: Study Infusions

Active infusions

- edetate disodium up to 3 grams based on renal function
- 7 g of ascorbic acid
- 2 g of magnesium chloride
- Other components as detailed in the design paper *
- Total volume 500mL

Placebo infusions

- 500 mL of normal saline and 1.2% dextrose (2.5 g total).

Infusions administered through peripheral intravenous access over at least 3 hours

*Lamas G et al. Am Heart J 2022

TACT2 Endpoints

- Primary endpoint: composite of time to first occurrence of all-cause mortality, MI, stroke, coronary revascularization, or hospitalization for unstable angina

- The secondary endpoints were:
  - Recurrent events of the primary composite endpoint
  - All-cause mortality
  - Composite of cardiovascular mortality, MI, or stroke

- The metals endpoint was a decrease in body burden of blood lead and urine cadmium

TACT2: Statistical Considerations

- Time from randomization to the first occurrence of any of the primary composite event components using the Cox proportional hazards regression model
- Sample size calculations based on >85% power to detect a 30% reduction in the primary endpoint with an alpha of 0.05.
- The primary analyses are reported for the modified intention-to-treat (mITT) population, which excludes 41 of the 1000 randomized patients who never received any infusions

Selected Baseline Characteristics (mITT Population)

	Total (N=959)
Age-years (median IQR)	67 (60-72)
Female - %	26.9
Non-Hispanic White - %	61.5
Time from qualifying MI to randomization	
Median years (IQR)	5 (2 - 10)
Diabetes Medications - %	
Insulin	46.7
GLP-1a or SGLT-2i	22.2
Other Medications - %	
Aspirin, warfarin, or P2Y12 inhibitor	90.0
Beta-blocker	79.5
Statin	85.9
Hemoglobin A1c, %,Mean ± SD	7.5 ± 1.3
LDL, mg/dL, Mean ± SD	79.6 ± 35.3

Additional Characteristics (mITT Population)

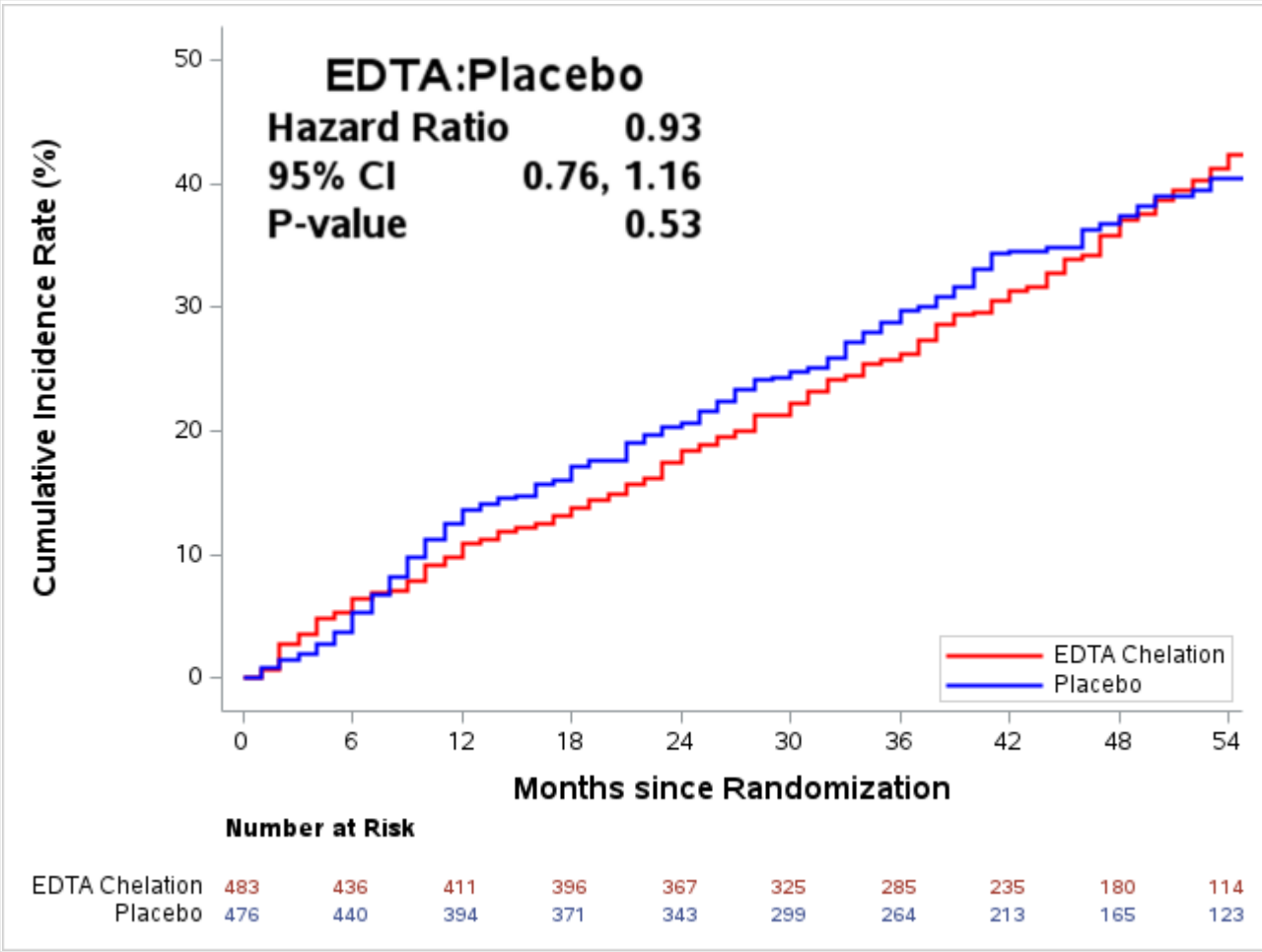
	% Detectable	Median (IQR)
Lead (blood) µg/L	100	9.22 (6.30, 14.00)
Cadmium (urine) µg metal/g Creatinine	97	0.30 (0.18, 0.52)

Compliance with Infusion Regimen

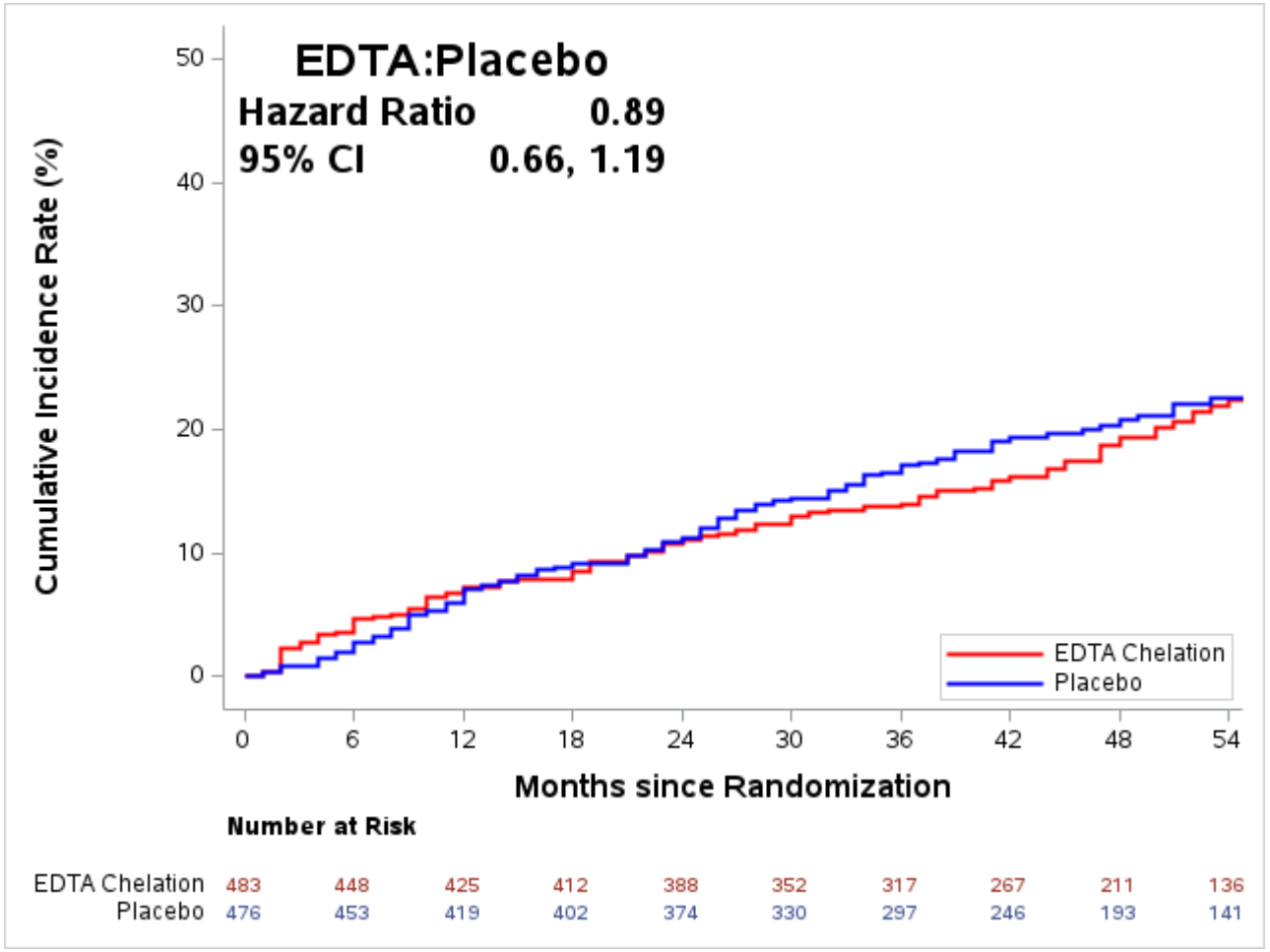
	Total # of infusions 31,615	40 Infusions	20 Infusions
Active	15,787	68%	78%
Placebo	15,828	67%	78%

Primary Outcome Results

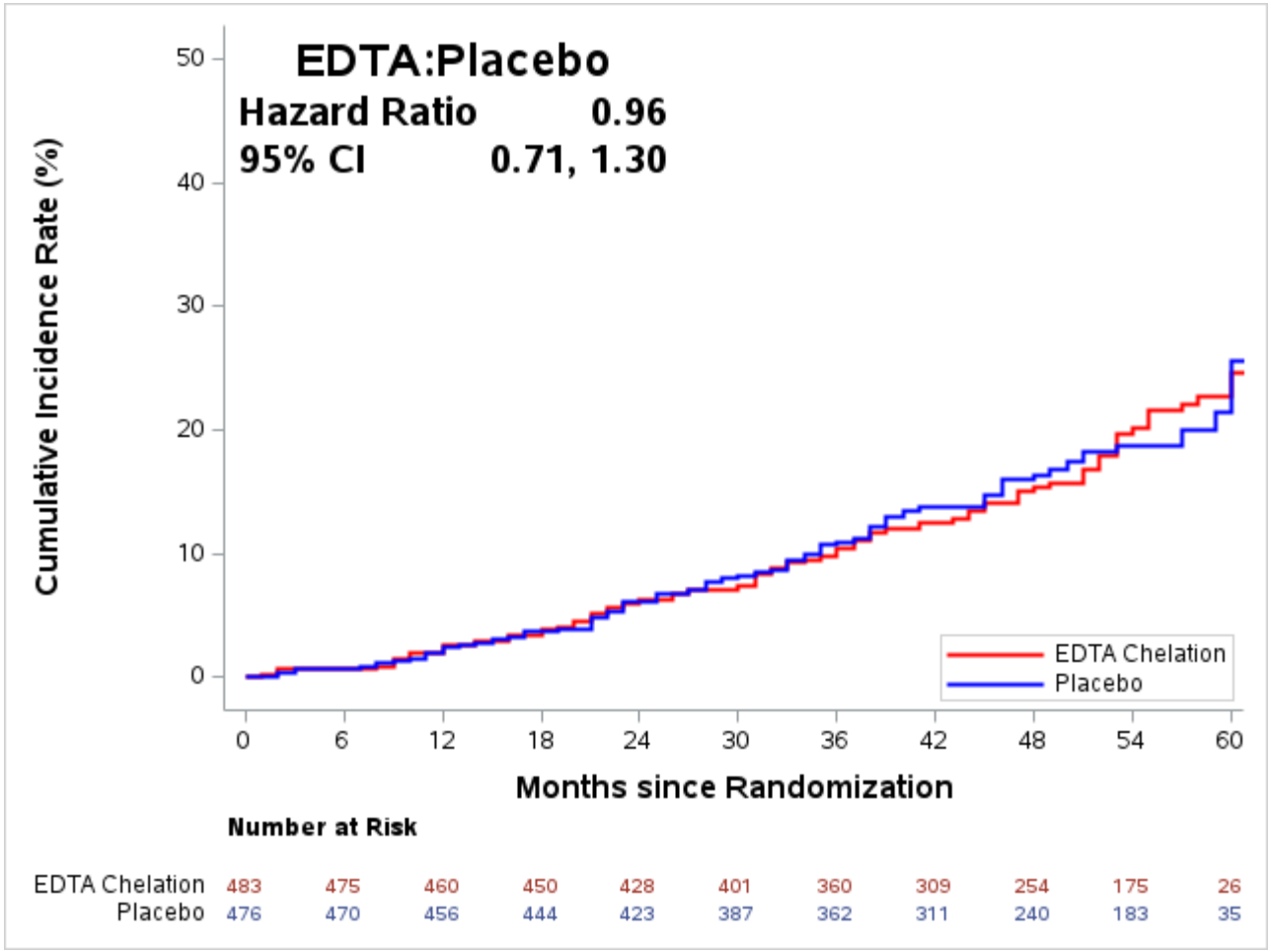
Cumulative Incidence of Time to First Event: Myocardial Infarction, Stroke, Hospitalization for Unstable Angina, Coronary Revascularization, or Death from Any Cause



Time to First Event: Myocardial Infarction, Stroke, or Cardiovascular Death

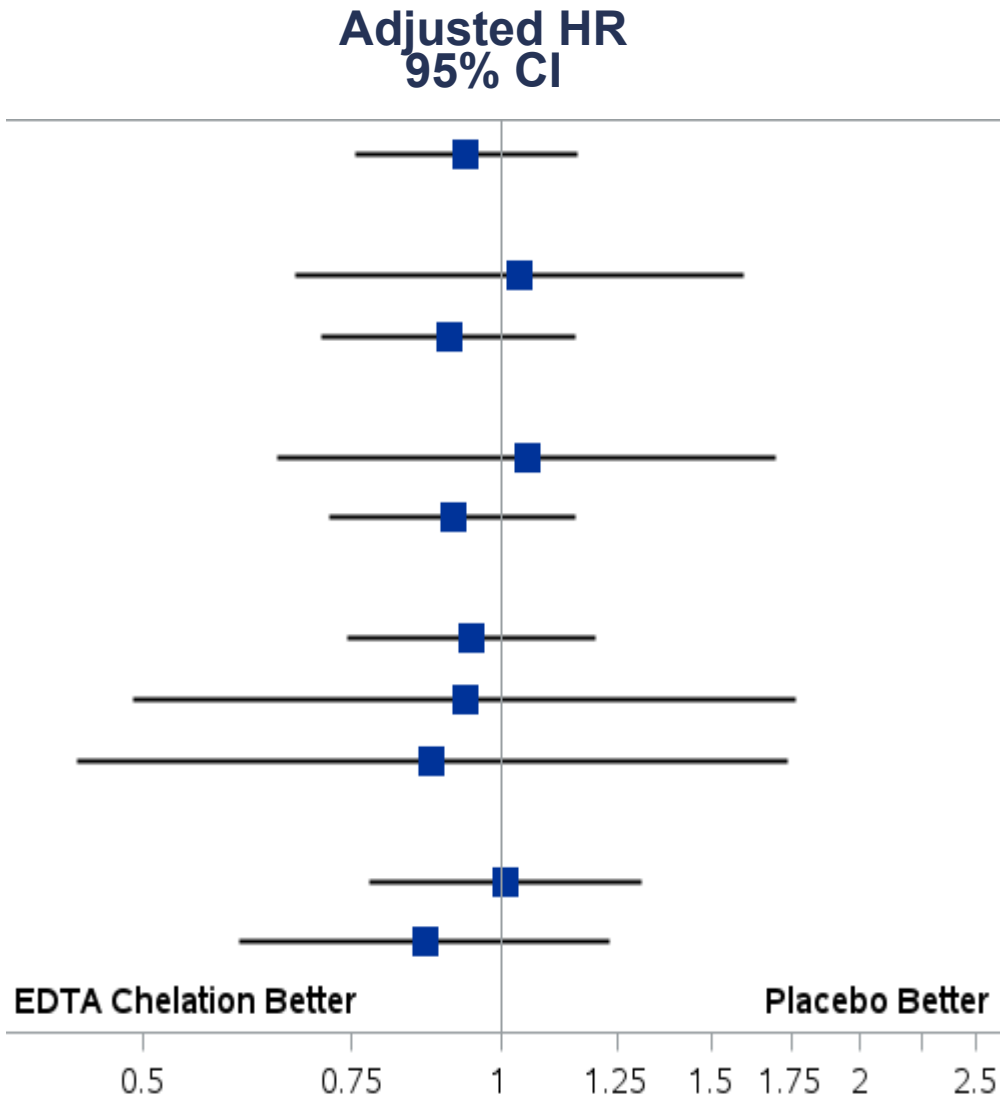


Time to All-Cause Mortality



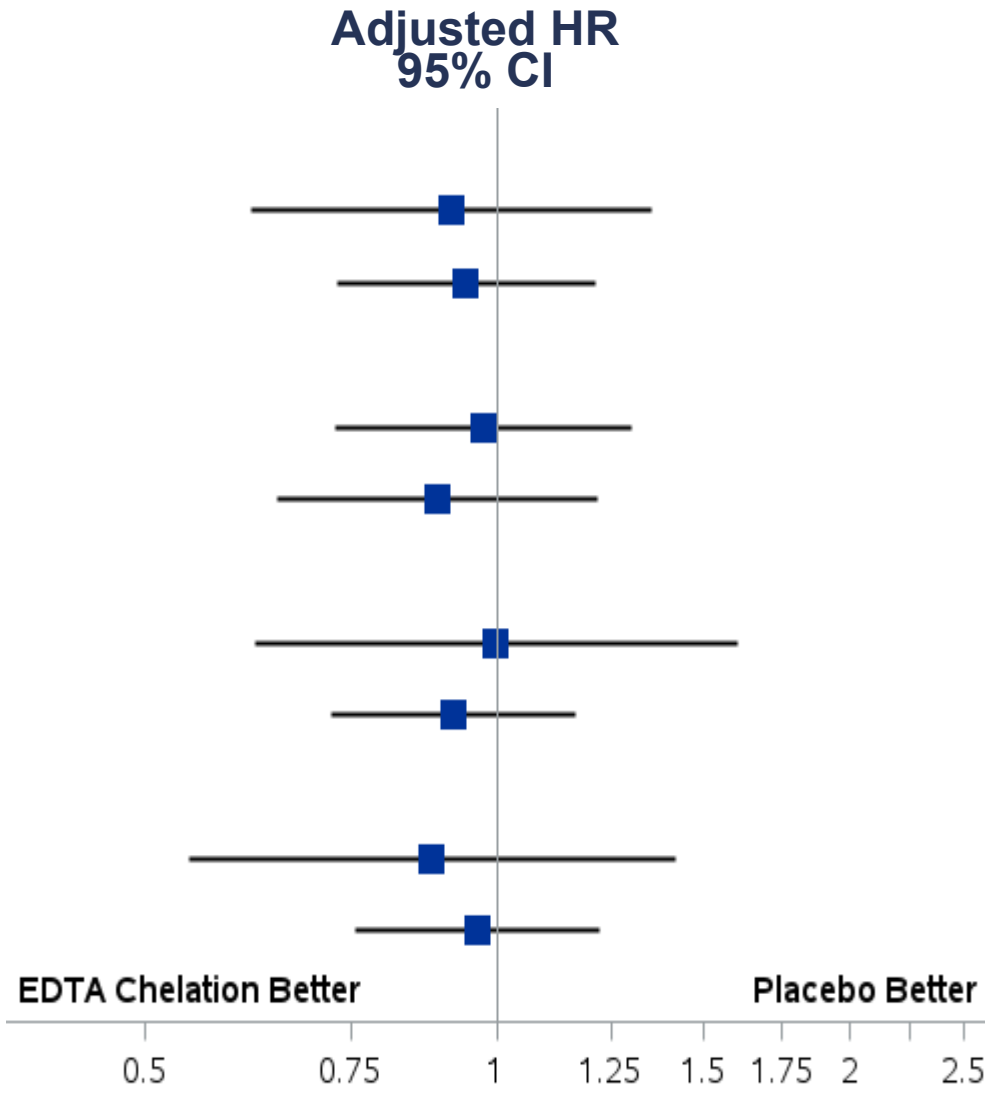
Subgroup Analysis for Primary Endpoint (mITT)

Subject Group	Adjusted Hazard Ratio	95% CI
All Participants	0.93	(0.76, 1.16)
Sex		
Female	1.03	(0.67, 1.59)
Male	0.90	(0.71, 1.16)
Ethnicity		
Hispanic/Latino	1.05	(0.65, 1.70)
Non-Hispanic/Latino	0.91	(0.72, 1.16)
Race		
White	0.94	(0.74, 1.20)
Black	0.93	(0.49, 1.76)
Other	0.88	(0.44, 1.74)
Age		
≤ 70 Years	1.01	(0.77, 1.31)
> 70 Years	0.86	(0.60, 1.23)

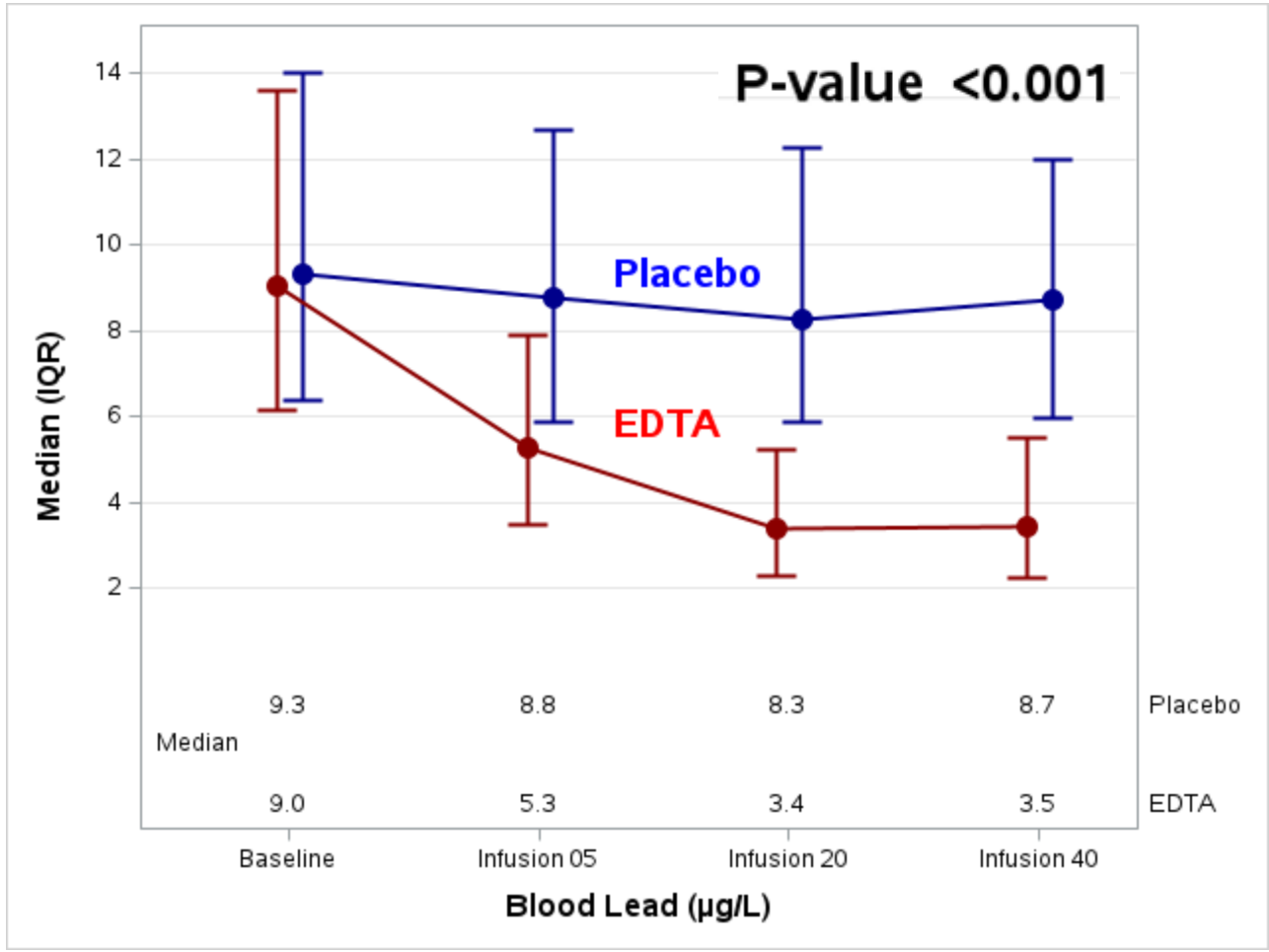


Subgroup Analysis for Primary Endpoint (mITT)

Subject Group	Adjusted Hazard Ratio	95% CI
MI Location		
Anterior MI	0.91	(0.62, 1.36)
Non-anterior MI	0.94	(0.73, 1.21)
Insulin-use at Baseline		
Yes	0.97	(0.73, 1.30)
No	0.89	(0.65, 1.22)
GLP-receptor agonist or SGLT-2 inhibitor at baseline		
Yes	1.00	(0.62, 1.60)
No	0.92	(0.72, 1.16)
Peripheral Artery Disease at baseline		
Yes	0.88	(0.55, 1.42)
No	0.96	(0.76, 1.22)

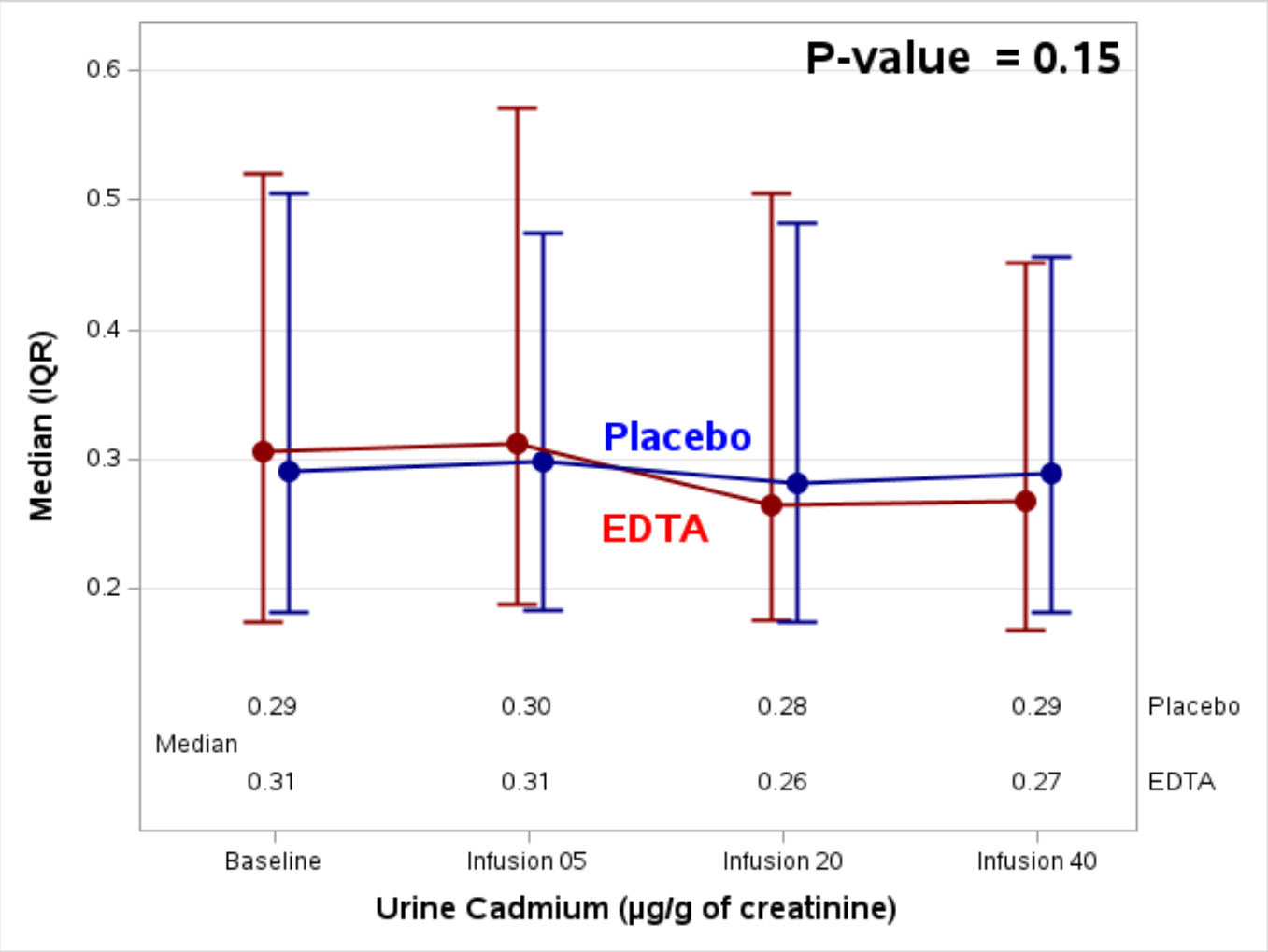


Pre-Infusion Blood Lead (µg/L) Levels at Baseline and during Study



Note: P-value tests the change from baseline to pre-infusion 40 between active and placebo using the Wilcoxon rank sums test.

Pre-Infusion Urine Cadmium (µg/g of creatinine) Levels at Baseline and during Study



Note: P-value tests the change from baseline to pre-infusion 40 between active and placebo using the Wilcoxon rank sums test.

TACT2 Summary

- EDTA chelation produced >60% reduction in blood lead levels
- No safety issues
- EDTA did not result in a significant clinical benefit on primary or secondary endpoints or on all-cause mortality

Why were the results of TACT (2003-2012) and TACT2 (2016-2023) so different?

- NHANES may shed light
  - 2003 to 2010 (TACT) blood lead levels 17 mcg/L
  - 2015 to 2020 (TACT2) blood lead levels 10 mcg/L (41% drop)
  - TACT2 blood lead levels even lower at baseline: 9 mcg/L

- Hypothesis: US blood lead levels have markedly dropped since 2003, possibly reducing the potential therapeutic impact of further lowering blood lead level

Conclusion

- TACT2 does not support the use of edetate disodium (EDTA) chelation for risk reduction in stable post MI patients with diabetes

Evaluation of a Technology Assisted Web Application to Qualify for Nonprescription Statin Administration

Steven E. Nissen MD MACC

Disclosure

Clinical Trials: AbbVie, Arrowhead, AstraZeneca, Bristol Myers Squibb, Eli Lilly, Esperion, Medtronic, New Amsterdam, Novartis, and Silence Therapeutics.

Companies are directed to pay any honoraria, speaking or consulting fees directly to charity so that neither income nor a tax deduction is received.

Co-Authors

Steven E. Nissen MD, Howard G. Hutchinson MD, Kathy Wolski MS, Karol Watson MD, Seth S. Martin MD MHS, Erin D. Michos MD, William S. Weintraub MD, Melanie Morris BS, Leslie Cho MD, Luke Laffin MD, Douglas Jacoby MD, Christie M. Ballantyne MD, Jan Ekelund MSc, Philip Birve BS, Venu Menon MD, Michelle Strzelecki RN, and Paul M. Ridker MD

Trial sponsor: AstraZeneca

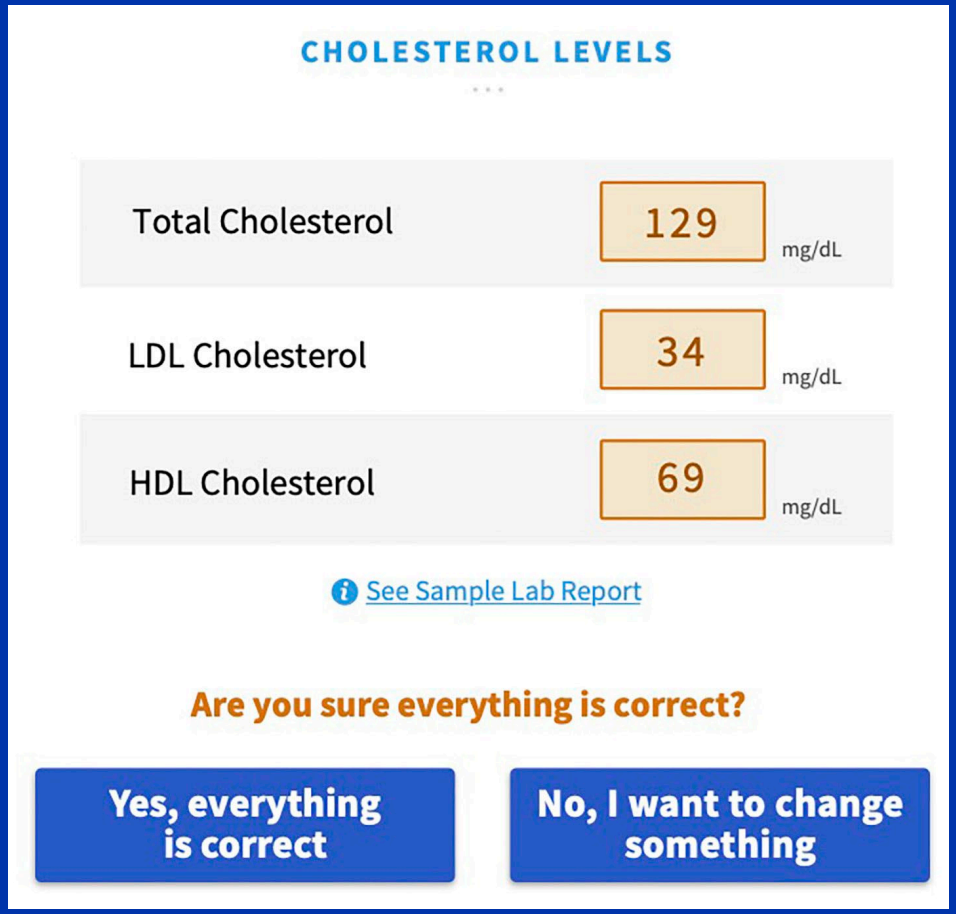
Background

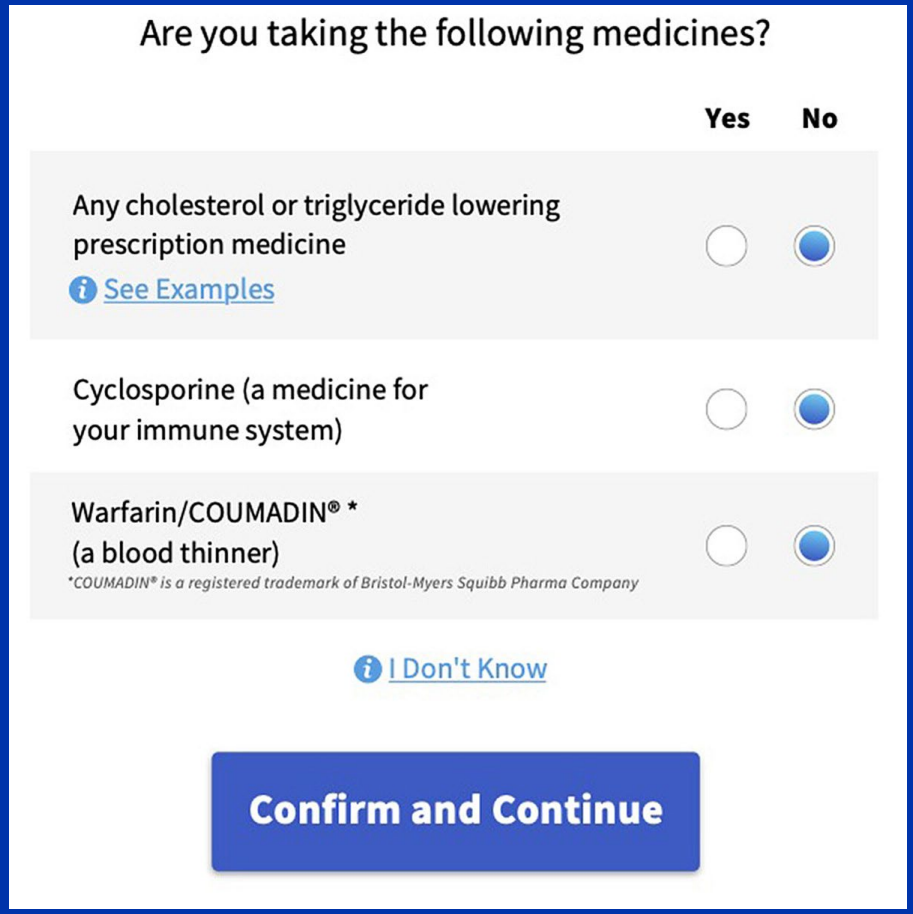
- Although statins reduce major adverse cardiovascular outcomes, less than half of eligible patients receive treatment.
- Multiple past attempts to address this problem through OTC statins were unsuccessful in achieving regulatory approval.
- There were major concerns about inappropriate use by consumers for whom statins could be unnecessary or unsafe.
- The current study sought to address this problem through a novel technology-assisted self-selection Web Application to qualify consumers for nonprescription access to rosuvastatin (5 mg).

Web App Features

- Developed as Software as a Medical Device based on FDA guidance.
- To determine eligibility, uses 10-yr ASCVD risk score (pooled cohort equations) in 2018 Cholesterol Treatment Guidelines and incorporates a proposed Drug Facts Label for rosuvastatin.
- Possible Outcomes: ‘OK to Use’, ‘Ask a Doctor’, or ‘Do Not Use.’
- Only those with ‘OK to Use’ or ‘Ask a Doctor’ outcome could qualify and enroll.

Examples of Web App Data Entry Screens





Exclusion of Participants Needing High-Intensity Statins

Have you ever had any of the following?

	Yes	No
Heart attack	●	○
Stroke	○	●
An operation or procedure on your Heart	○	●
Peripheral Artery Disease (PAD)	○	●

I Don't Know

Confirm and Continue

RESULTS

Crestor OTC is not right for you

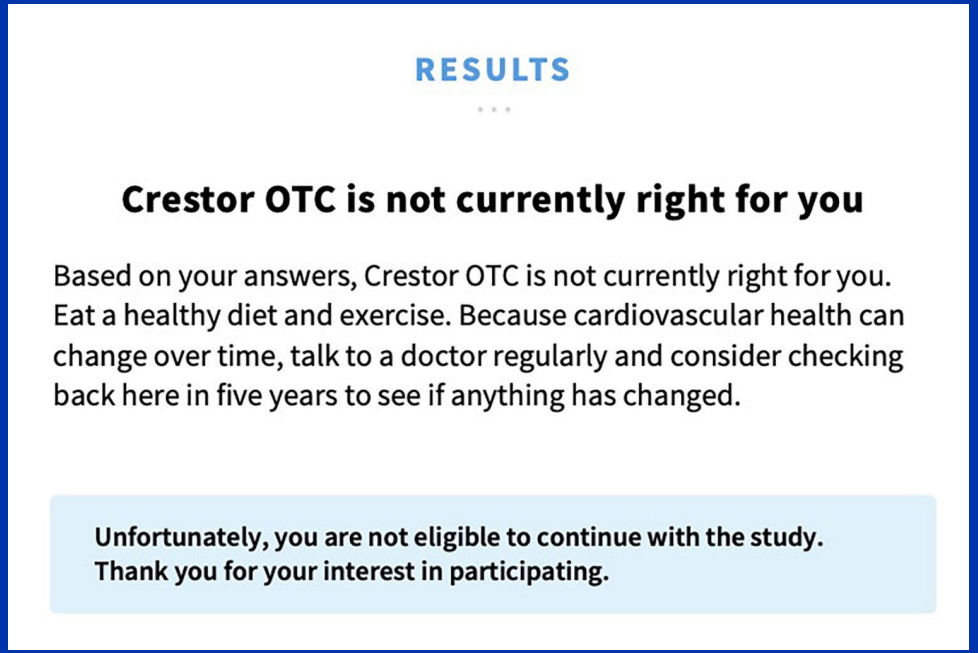
You should talk to a doctor because the following are signs that you may need a **stronger medicine** available only by prescription:

- Heart attacks
- Strokes
- Procedures of the heart
- Peripheral Artery Disease (PAD)

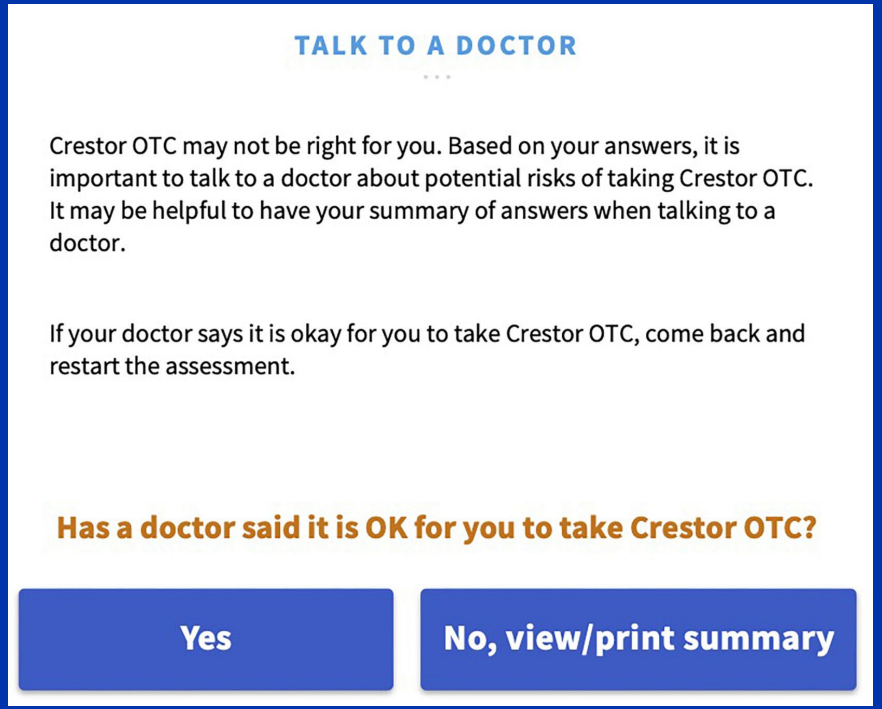
Unfortunately, you are not eligible to continue with the study. Thank you for your interest in participating.

Outcomes Reported to Non-Qualified Participants

Do Not Use



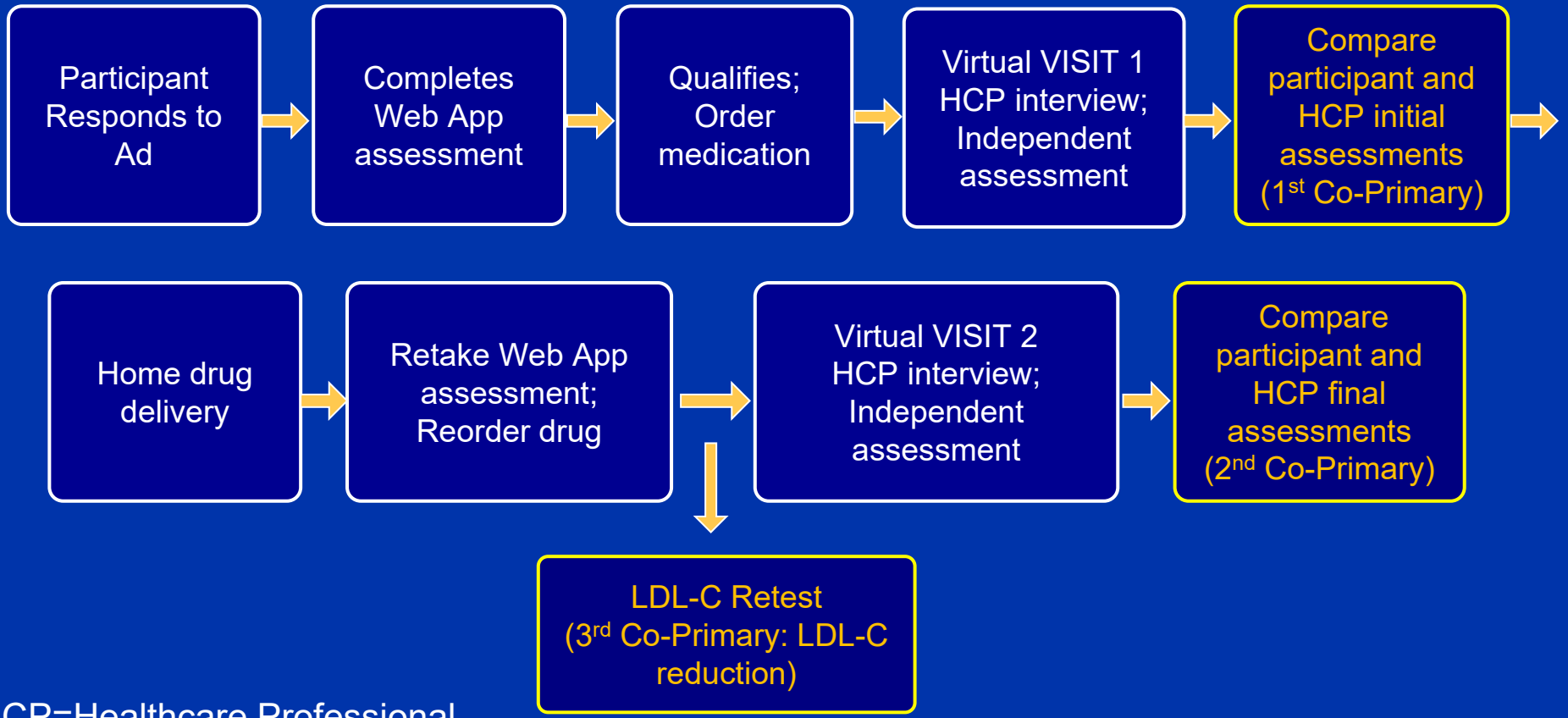
Talk to a Doctor



Selected Inclusion and Exclusion Criteria

- Inclusion:
  - Men or women 20-75 year of age
  - Ability to read and understand English
  - Access to the Internet
- Exclusion:
  - Women of childbearing potential (unless using acceptable method of birth control)
  - Any healthcare professional (physician, nurse, pharmacist, etc.) or ever employed by healthcare company

1196 Participants Enrolled: Co-Primary Endpoints



HCP=Healthcare Professional

1st and 2nd Co-Primary Endpoint Evaluation Process

- Clinicians conducted virtual visit interviews blinded to participant self-selection outcome assessments.
- Separate clinical coding team compared participant and clinician outcomes to determine if they were concordant.
- If the outcomes differed or there was disagreement within the coding team, an adjudication team at the academic coordinating center (C5Research) further assessed concordance.

Statistical Analysis of Co-primary Endpoints

1) Concordance for initial self-selection compared:
   - Success defined as a lower bound of the 95% CI >85%

2) Concordance for final use assessment compared:
   - Success defined as a lower bound of the 95% CI >85%

3) Percent change from baseline in LDL-C determined:
   - Success defined as lower bound of 95% CI < -15%

Baseline Characteristics of Participants (n=1196)

Age (years)	63 years
Male (%)	60.4%
Race	
White	79.3%
Black	11.7%
Hispanic	3.2%
Limited literacy	4.1%

Retired	42.0%
Full-Time	40.6%
Mean LDL-C	139.6 mg/dL
Median systolic BP	130.0 mmHg
Median 10-year risk	10.1%
College or technical school education grad	74%
High school or some college	25.5%

Results: Co-Primary Endpoints

1) Overall concordance between participant and clinician for initial self-selection was 90.7% (95% CI, 88.9 to 92.3).
   - Concordant for “Ok to Use” 80.3%, “Ask a Doctor” in 3.9%, and independently adjudicated as concordant in another 6.5%.

2) Final use assessment was concordant in 98.1% (95% CI, 97.1 to 98.8).
   - Concordant for “OK to Use” 72.4%, “Ask a Doctor” in 1.2%, and independently adjudicated as concordant in another 17.2%.

3) Mean change in LDL-C was -35.5% (95% CI, -36.6 to -34.3).

Secondary Outcomes

- Compliance with retesting of LDL-C was 83.8% for the full population and 92.9% for those qualified at all reassessments.
- Adherence based on pill counts was 95.1% (IQR, 84.6 to 98.9).
- Compliance with ‘Ask a Doctor’ and ‘Do Not Use’ warnings were 83% and 80%, respectively. Instances of noncompliance were not associated with a significant safety risk.
- No participants experienced a “Stop Use” warning.

Most Common Adverse Events

Any Adverse Event	**52.9%**
SARS-CoV-2 positive test	9.6%
Arthralgia	7.0%
Headache	5.4%
Pain in extremity	4.3%
Myalgia	4.1%
Adverse Event Leading to Drug Discontinuation	**7.1%**
Musculoskeletal disorders	3.1%
General disorder	1.1%
Gastrointestinal Disorders	0.8%
Serious Adverse Events (none related to study drug)	**2.3%**

Limitations

- The study was 6 months in duration. It remains uncertain whether self-selection can lead to long term adherence.
- Only participants who could read and understand English and who had internet access were enrolled.
- Other approaches to provide safe access to a nonprescription statin would be required for those who are unable to use technology.

Manuscript Now Accessible at https://www.jacc.org

Conclusions

- In an actual use study of technology assisted self-selection for access to nonprescription rosuvastatin, 90.7% of consumers correctly self-selected for statin use.
- 98.5% demonstrated correct use during the trial.
- Participants had a high level of adherence, 92.9% retesting, and achieved clinically meaningful (35.5%) reduction in LDL-C.
- There were no major safety issues.

C5Research

A Final Thought

With less than half of eligible primary prevention patients receiving statins, innovative approaches to close this treatment gap are needed.

The use of a Web App to qualify for a nonprescription statin has the potential to expand access and reduce subsequent major cardiovascular events.

ACC.24

Effect of Alcohol-mediated Renal Denervation on Blood Pressure in the Presence of Antihypertensive Drugs: 3-month Primary Results From the Target BP I Randomized Trial

David E. Kandzari, MD, FACC, MSCAI, on behalf of the TARGET BP I Investigators

Piedmont Heart Institute
Atlanta, Georgia
david.kandzari@piedmont.org
@Kandzari

AMERICAN COLLEGE of CARDIOLOGY

Disclosure

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below

Affiliation/Financial Relationship	Company
Grant/Research Support (Institutional)	Ablative Solutions, Biotronik, Medtronic Orbus Neich, Teleflex
Consulting Fees/Honoraria	Medtronic, HyperQure
Major Stock Shareholder/Equity	BioStar Ventures (none related to ASI)
Royalty Income	None
Ownership/Founder	None
Intellectual Property Rights	None
Other Financial Benefit	None

TARGET BP I
Background

- Globally, over 1/3 of adults have hypertension, yet many remain uncontrolled, leading to increased risk of cardiovascular events

  A 5-mmHg absolute reduction in office systolic blood pressure leads to a 10% reduction in major CV events[1]

- New blood pressure guidelines motivated by increasing awareness of benefit with more intensive blood pressure control, unacceptable levels of hypertension control[2,3], and increasing recognition of non-adherence to antihypertensive medications identify the need for alternative treatment options

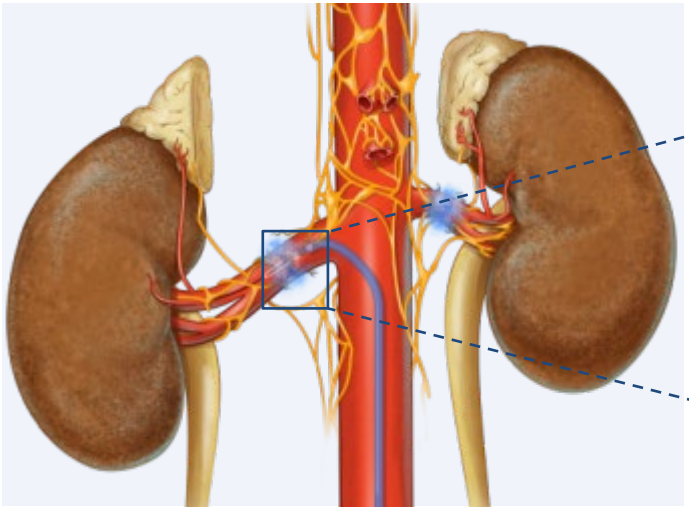
- Renal denervation (RDN) procedure targets the sympathetic nervous system to lower blood pressure

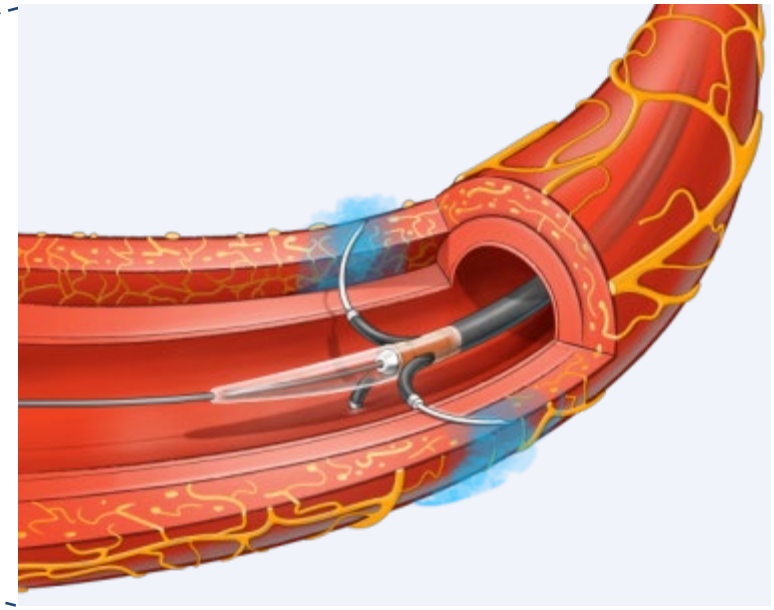
- Catheter-based perivascular delivery of dehydrated alcohol represents a novel method of neural ablation, achieving a confluent arc of ablation with single, targeted treatment within the renal artery

- To further explore outcomes with alcohol-mediated RDN in the presence of antihypertensive medications, an international sham-controlled RCT was performed

[1] Blood Pressure Lowering Treatment Trialists' Collaboration. *Lancet* 2021
[2] Muntner et al. *JAMA* 2020
[3] NHANES 2017–2020. Centers for Disease Control and Prevention. https://millionhearts.hhs.gov/data-reports/hypertension-prevalence.html. Accessed February 10, 2024.

Alcohol-Mediated Renal Denervation





Perivascular Delivery of Alcohol to Adventitial Space

Expanded View of Device Infusing Alcohol

Site-specific delivery of alcohol: Local nerve inactivation, no collateral damage

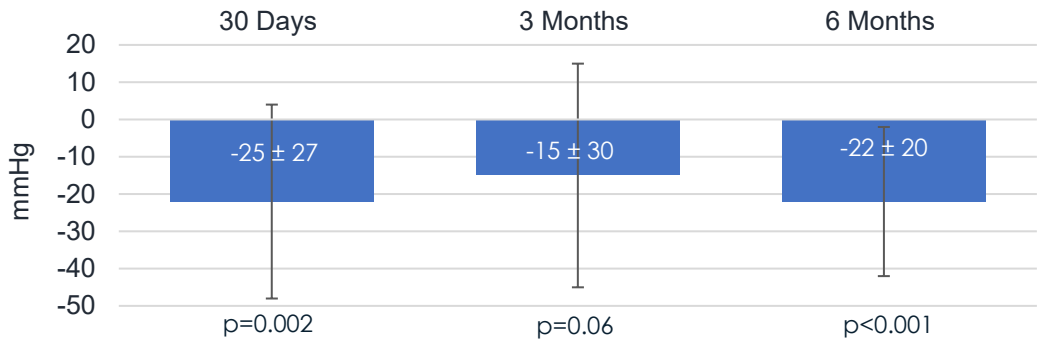
1. Micro-volume (0.6 mL) infused directly to the perivascular region
2. Extracellular fluid helps spread alcohol circumferentially in the perivascular region
3. Alcohol activity range self-limited through dilution by extracellular fluid

Fischell et al. *J Am Coll Cardiol Intv* 2016

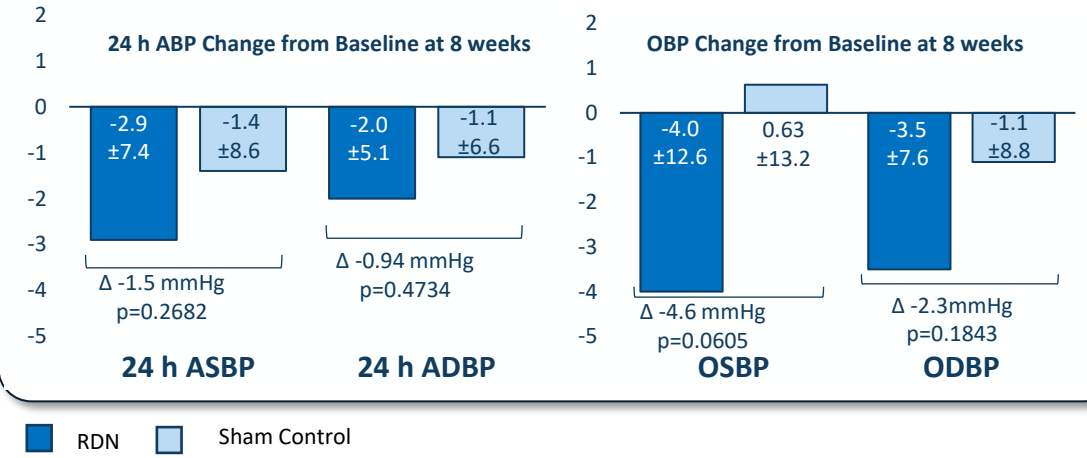
Prior Studies of Alcohol-Mediated RDN

Peregrine First In Human[1] N=17

OSBP Change From Baseline

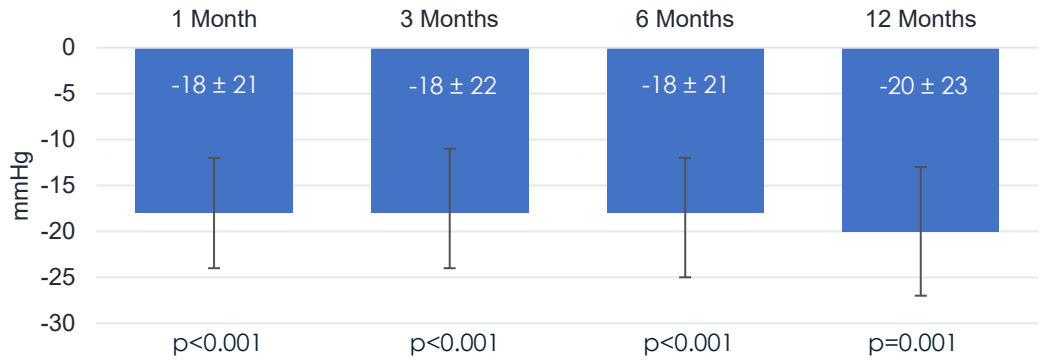


Target BP OFF MED[2] N=106

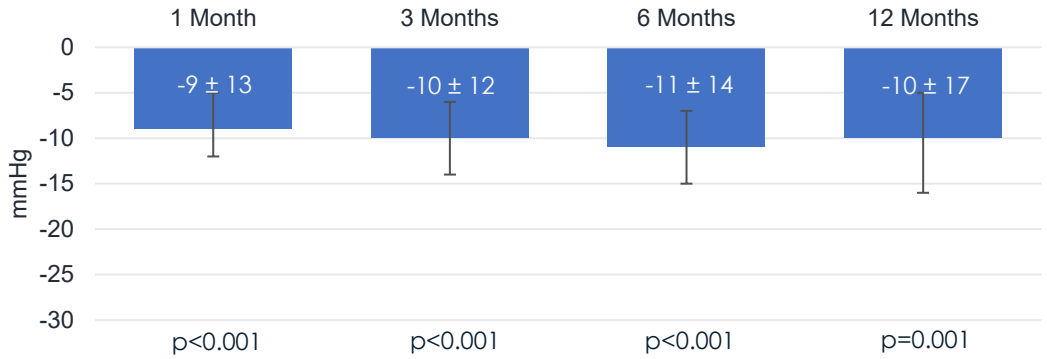


Peregrine Post-Market Study[3] N=45

OSBP Change from Baseline

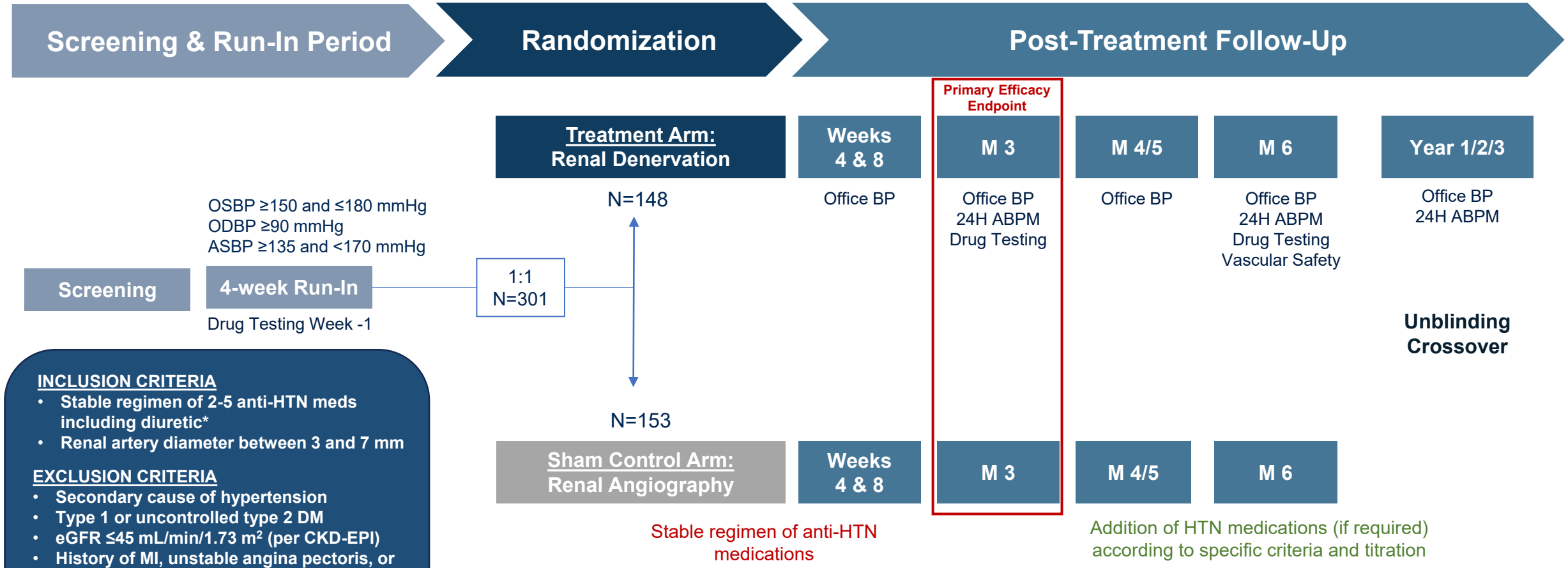


ABPM Change from Baseline



1.Fischell et al. *Cardiovasc Revasc Med* 2015
2.Pathak et al. *EuroIntervention* 2023
3.Mahfoud et al. *Circ Cardiovasc Interv* 2021

TARGET BP I
Study Design



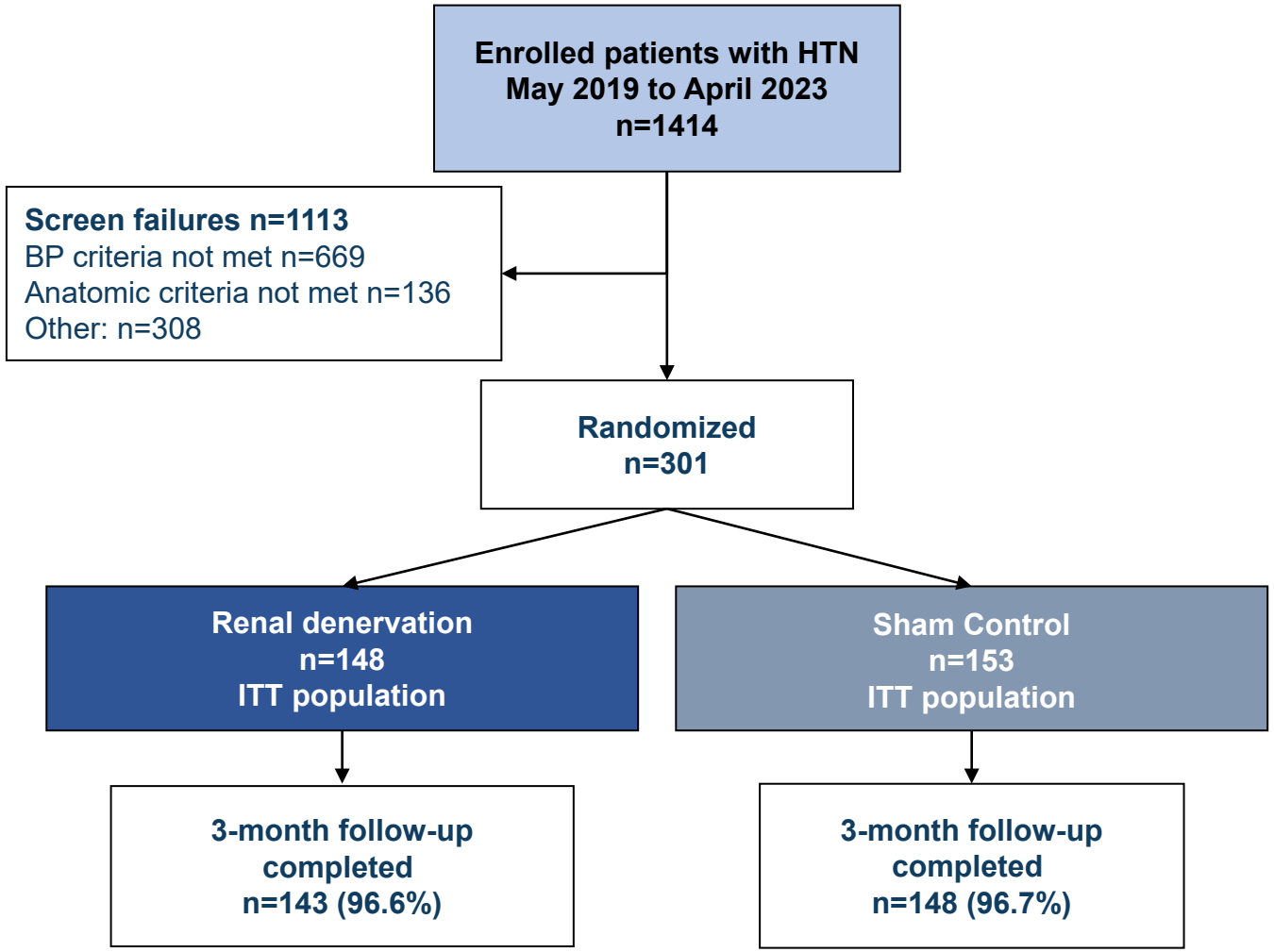
INCLUSION CRITERIA
- Stable regimen of 2-5 anti-HTN meds including diuretic*
- Renal artery diameter between 3 and 7 mm

EXCLUSION CRITERIA
- Secondary cause of hypertension
- Type 1 or uncontrolled type 2 DM
- eGFR ≤45 mL/min/1.73 m^2 (per CKD-EPI)
- History of MI, unstable angina pectoris, or stroke/TIA in prior 6 months
- Heart failure (NYHA III or IV) or EF ≤30%
- Chronic AF

*Diuretic therapy required unless documented intolerance

TARGET BP I

Patient Flow Chart



TARGET BP I

Baseline Patient Characteristics

	RDN (N=148)	Sham (N=153)
Age	56.7 ± 10.0	55.6 ± 9.1
Male	113 (76.4%)	111 (72.5%)
Body-mass index (kg/m^2)	32.6 ± 5.3	32.1 ± 5.3
Chronic kidney disease (eGFR <60 mL/min per 1.73m^2)	15 (10.1%)	20 (13.1%)
Type 2 diabetes	30 (20.3%)	40 (26.1%)
History of arrhythmia	14 (9.5%)	11 (7.2%)
History of congestive heart failure	7 (4.7%)	8 (5.2%)
Smoking (current)	14 (9.5%)	20 (13.1%)
Hyperlipidemia	57 (38.5%)	74 (48.4%)

	RDN (N=148)	Sham (N=153)
Race*		
White	45 (30.4%)	42 (27.5%)
Black/African American	23 (15.5%)	30 (19.6%)
Asian	0	2 (1.3%)
Not reported	80 (55.1%)	79 (51.6%)
Number of anti-HTN medications		
2	32 (21.6%)	35 (22.9%)
3	48 (32.4%)	40 (26.1%)
4	41 (27.7%)	43 (28.1%)
≥5	27 (18.2%)	34 (22.2%)
Aldosterone antagonist use	23 (15.5%)	35 (22.9%)

ITT population; data represented as N (%) or mean ± SD

*Information on race was not allowed to be collected by law in certain countries

TARGET BP I

Baseline Blood Pressure and Heart Rate Measures

	RDN (N=148)	Sham (N=153)
Office Measurements		
Office Systolic BP	164 ± 9	164 ± 9
Office Diastolic BP	98 ± 7	100 ± 7
24-hour Ambulatory Measurements		
Mean 24-hour Systolic BP	146 ± 9	146 ± 8
Mean 24-hour Diastolic BP	87 ± 8	88 ± 9
Heart Rate (bpm)	75 ± 12	75 + 14

Data represented as mean ± standard deviation

TARGET BP I

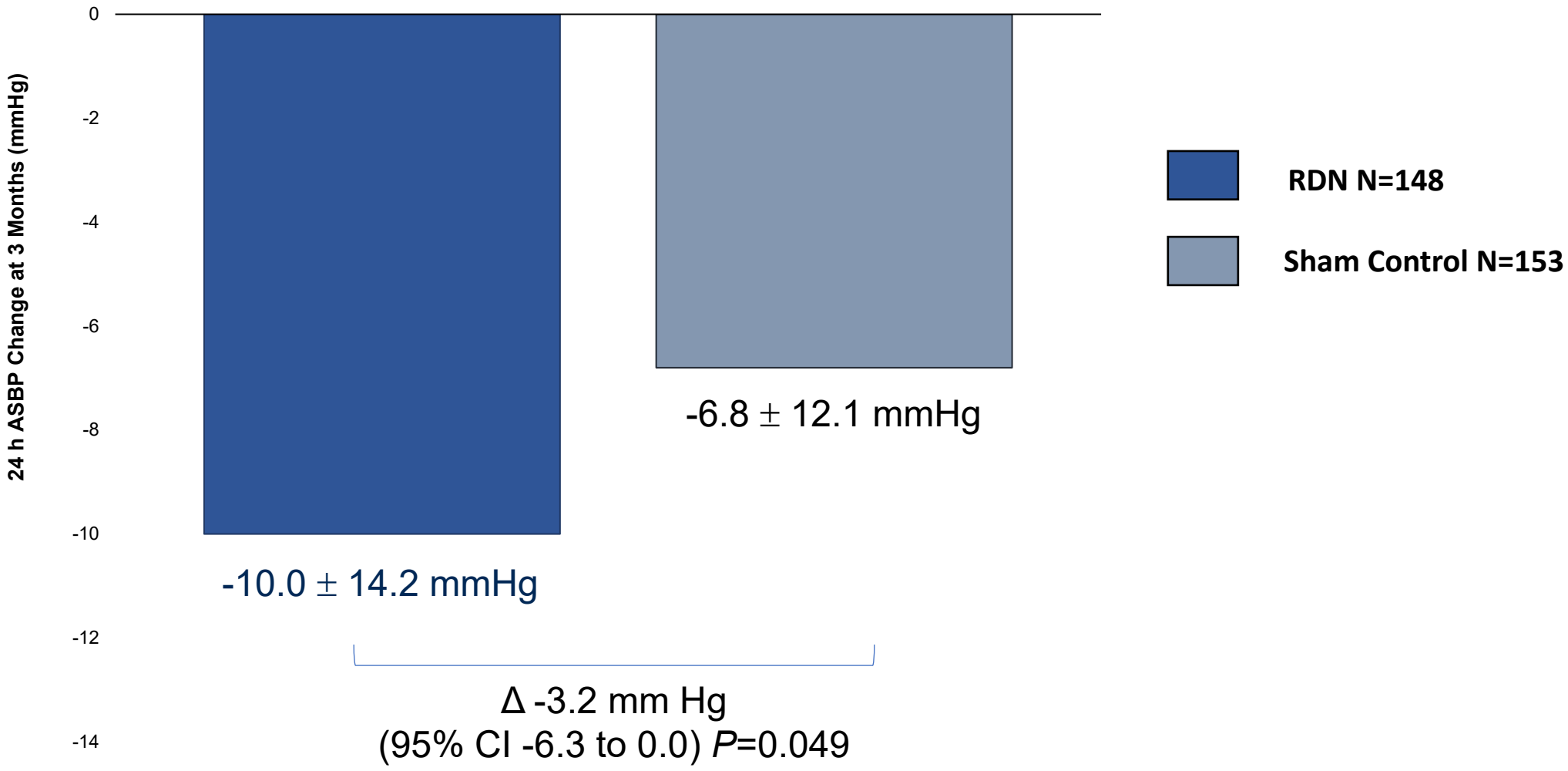
Procedural Characteristics

	RDN (N=150)	Sham (N=151)
Total procedure time (min)	55.7 ± 27.0 (150)	33.7 ± 24.1 (151)
Total volume contrast (mL)	95.7 ± 47.4 (150)	40.0 ± 22.6 (151)
Total fluoroscopy time (min)	10.8 ± 7.7 (150)	3.1 ± 2.8 (151)
Device success	143 (95.3%)	—
Procedure success	139 (92.7%)	—
Number arteries treated/patient	2.2	—

Data represented as mean ± standard deviation (N) or N (%)

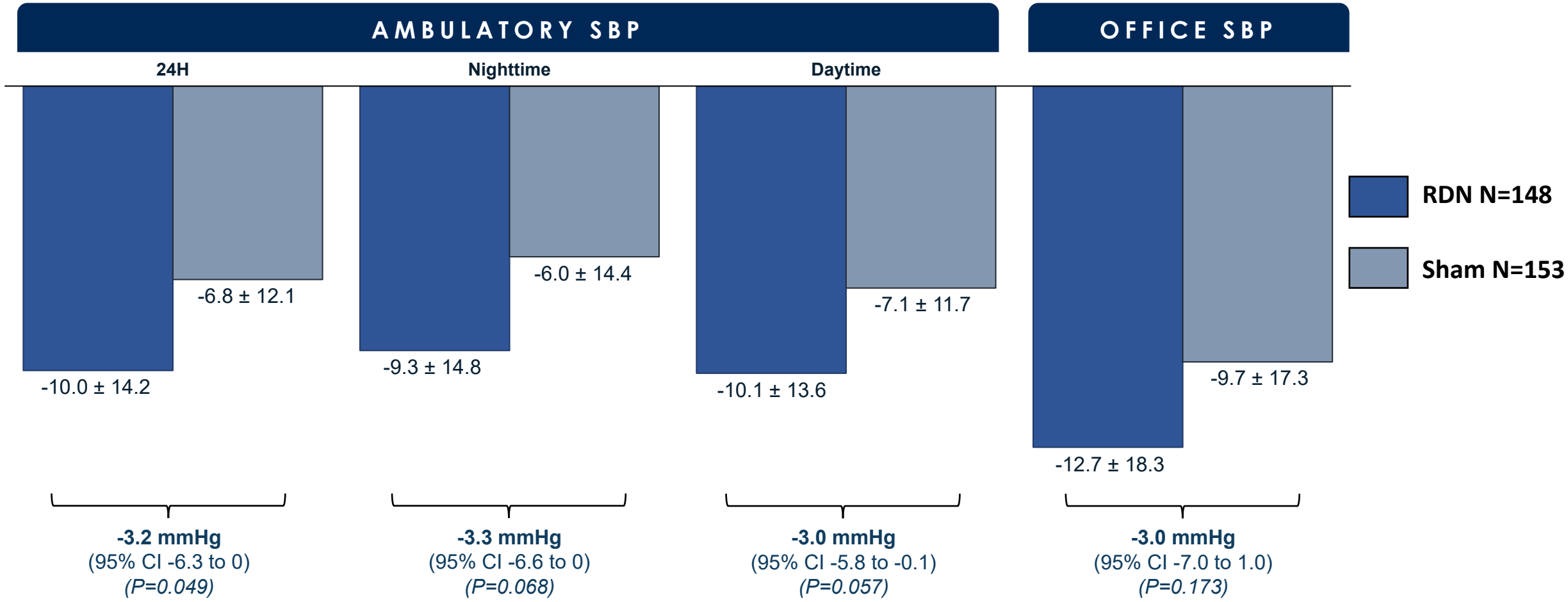
TARGET BP I

Primary Endpoint: 24-hr ASBP at 3 Months



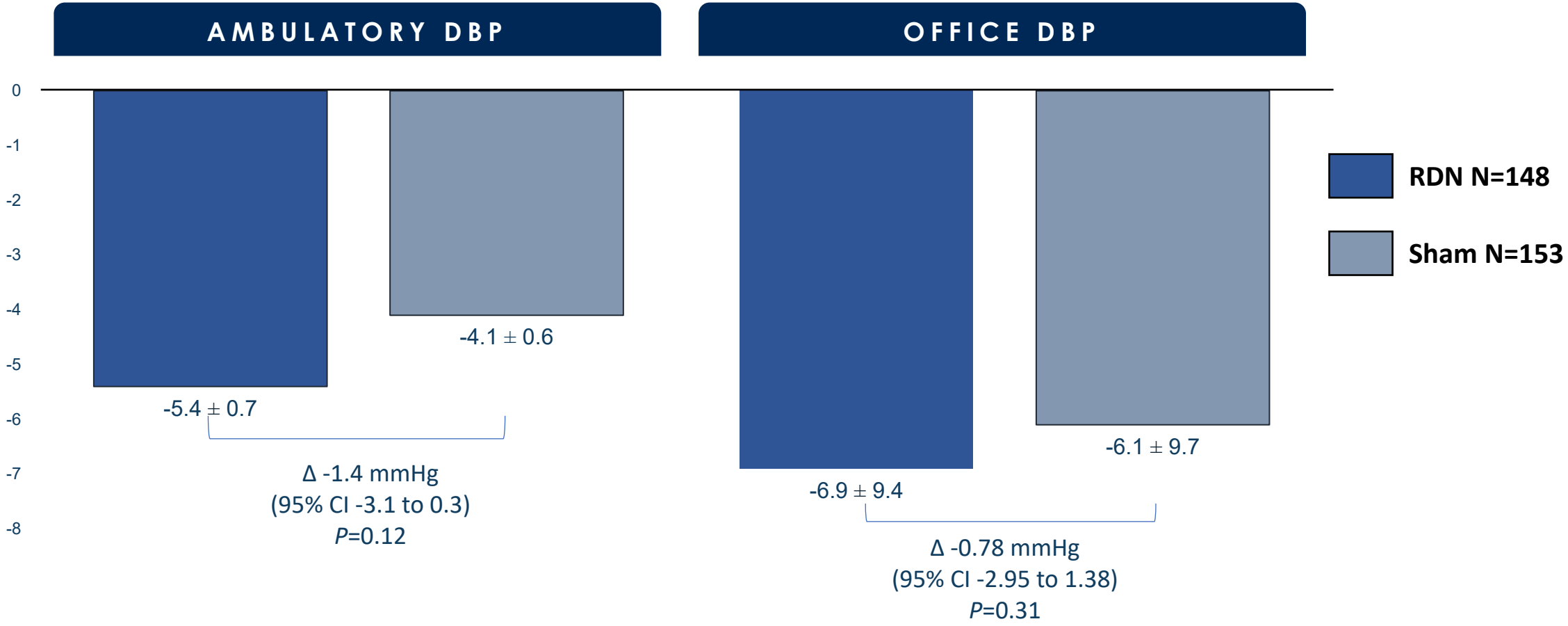
TARGET BP I

Ambulatory and Office Systolic BP at 3 Months



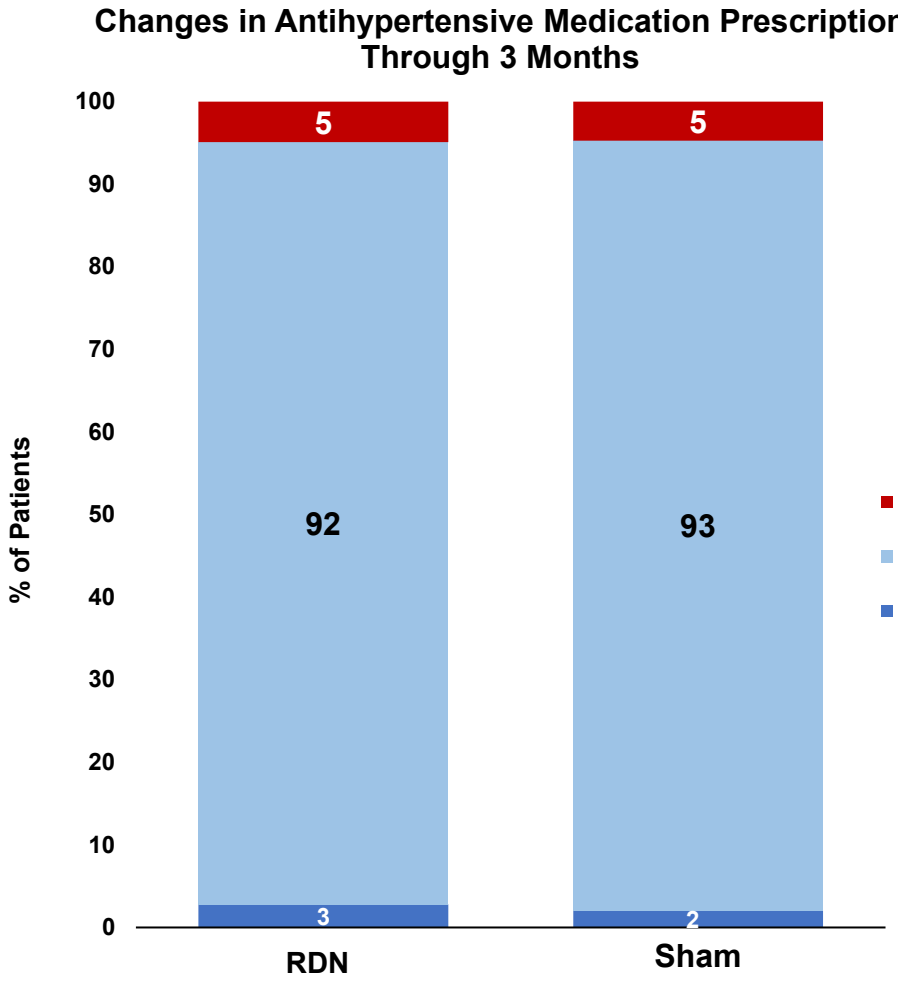
TARGET BP I

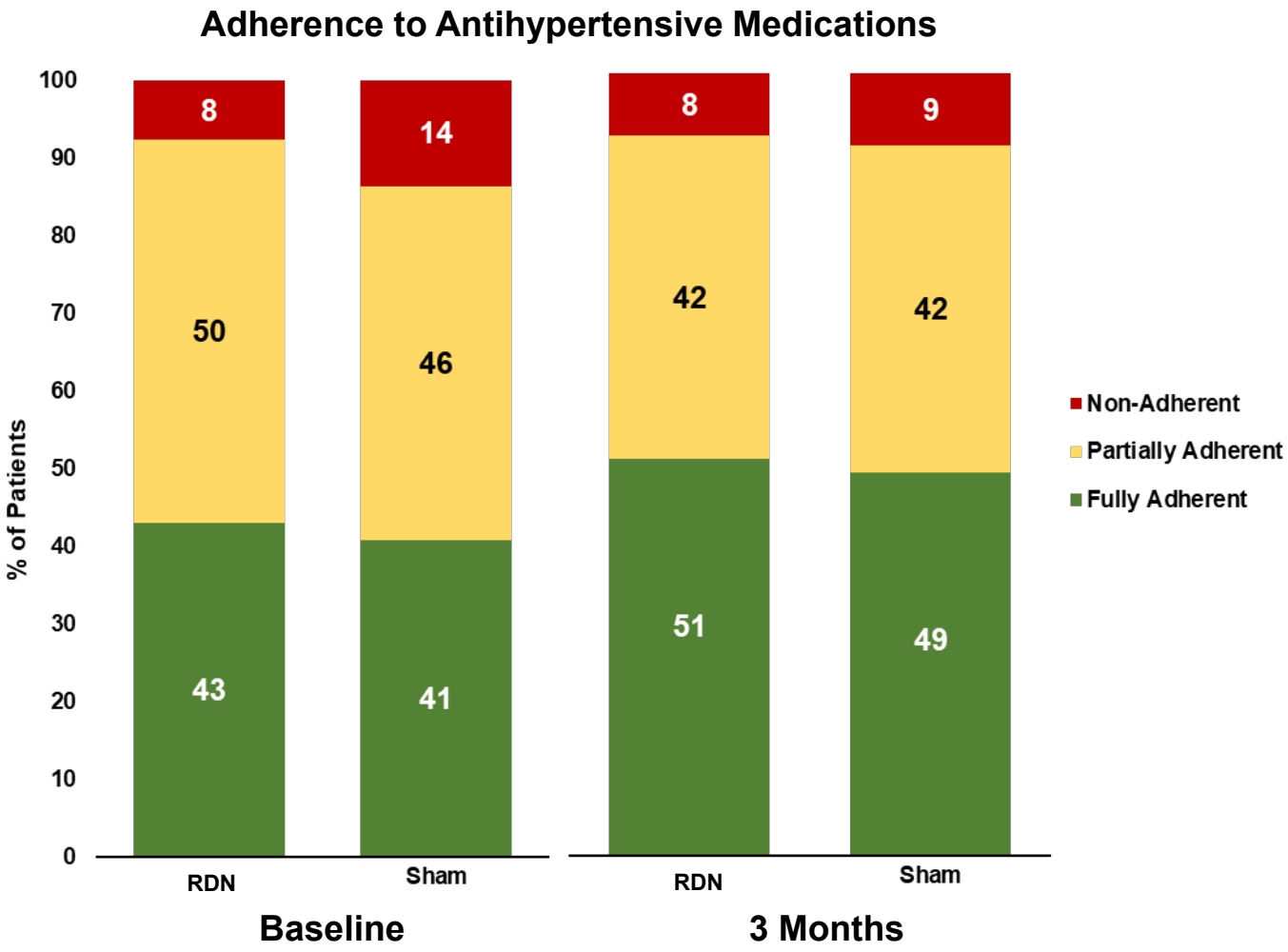
Ambulatory and Office Diastolic BP at 3 Months



TARGET BP I

Prescription Changes and Adherence Results

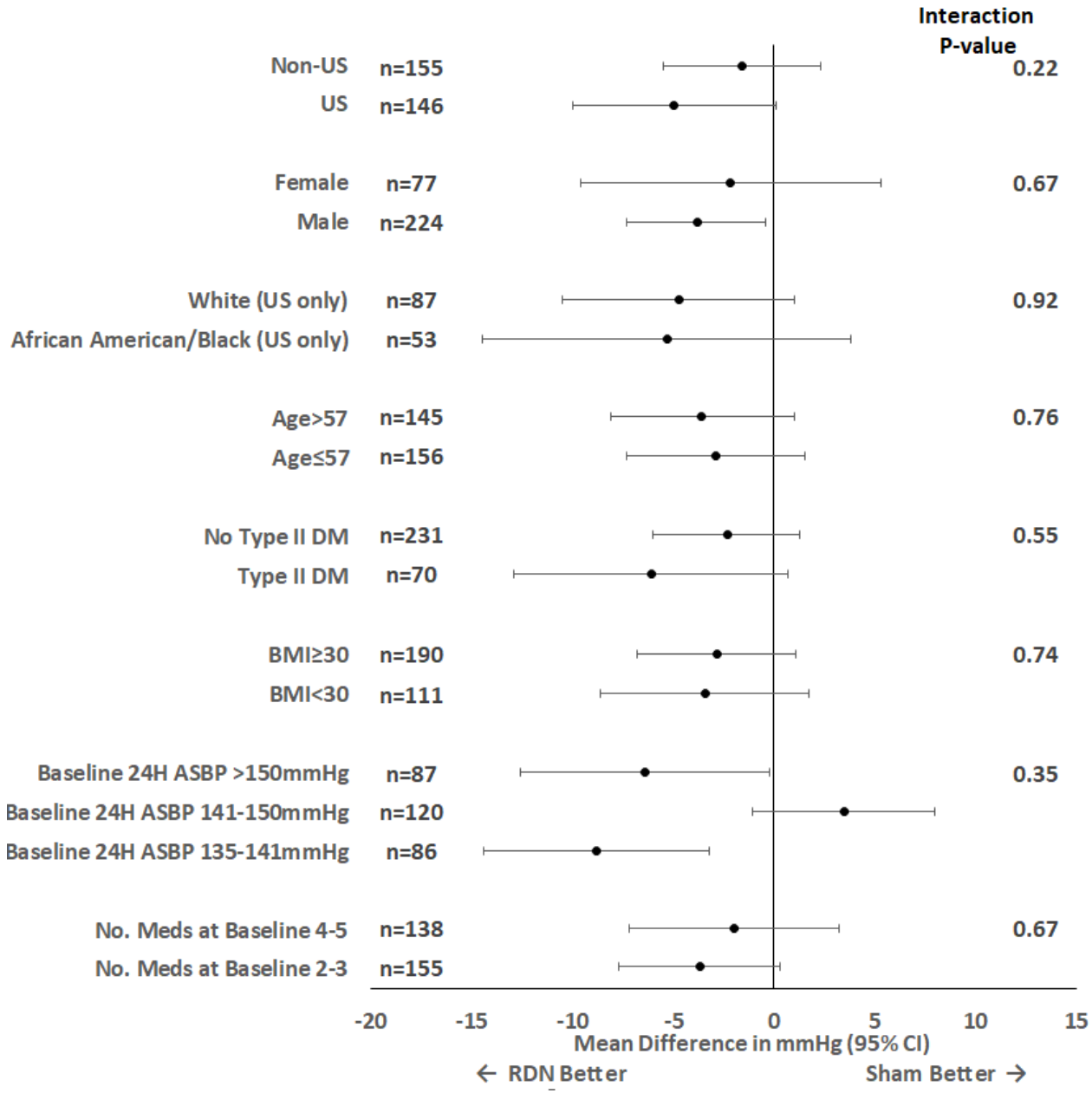




Counts are by patient visit; not individual medications or dose
Excludes subject visit compliance results that are not available

TARGET BP I

3-Month 24-hr ASBP Subgroup Analyses



TARGET BP I

Safety Outcomes

	30 Days			6 Months		
	RDN (N=149)	**Sham (N=150)**	***P* value**	**RDN (N=145)**	**Sham (N=146)**	***P* value**
Total Major Adverse Events	7 (4.7%)	0	0.007	11 (5.3%)	6 (4.0%)	0.22
All Cause Death	0	0	—	1 (0.7%)	0	0.50
Myocardial Infarction	0	0	—	1 (0.7%)	1 (0.7%)	1.00
Major Vascular Complication	1 (0.7%)	0	0.50	1 (0.7%)	0	0.50
Hypertensive Emergency	1 (0.7%)	0	0.50	2 (1.4%)	2 (1.4%)	1.00
Hypotension*	6 (4.0%)	0	0.02	7 (4.8%)	3 (2.0%)	0.22
eGFR ($mL/min/1.73m^2$) Change ± SD (N)				-1.2 ± 9.9 (138)	-0.86 ± 9.0 (146)	0.73
Vessel Safety Patency (<60% stenosis)				99.6% (280 vessels)	—	—

*Hypotension requiring intervention or medication change

TARGET BP I

Limitations

- High rates of medication nonadherence both at baseline and follow-up
  - No significant differences between groups relative to medication increase/decrease or general adherence
  - Inability of current methods to assess changes in medications within same class or timing of last administration
- Potential influence of home BP assessment uncertain
- Findings limited to 3 months follow-up, and whether progressive declines in BP occur over later follow-up uncertain
- No procedural assessment regarding completeness of denervation
- Results observed with this therapy and in this specific population may not be generalizable to alternative interventional therapies for hypertension and more varied clinical populations

TARGET BP I

Conclusions

- In this sham-controlled, randomized trial inclusive of patients with both uncontrolled and treatment resistant HTN, alcohol-mediated RDN met its primary endpoint, with a modest but significant decrease in 24-hr ambulatory SBP at 3-month follow-up
  - Results consistent across both day/night ABPM and prespecified subgroups
- No significant between group differences were observed relative to office blood pressure assessments
- RDN results observed in context of large BP reductions in sham control cohort
  - Strikingly high rates of partial and complete nonadherence
- Safety of alcohol-mediated RDN associated with favorable procedural performance and intermediate-term safety
- Ongoing, dedicated late-term follow-up will be important to inform the effectiveness as a treatment for uncontrolled HTN

TRAVERSE

Transseptal vs. Retrograde Aortic Ventricular Entry to Reduce Systemic Emboli

Gregory M. Marcus, MD, MAS, Roderick Tung, MD, Trisha F. Hue, PhD, MPH, Feng Lin, MS, J. Peter Weiss, MD, Wendy Tzou, MD, Henry Hsia, MD, Ashkan Ehdaie, MD, Daniel Cooper, MD, T. Jared Bunch, MD, Jeffrey Arkles, MD, Babak Nazer, MD, Adam Lee, MBBS, Alexios Hadjis, MD, Duy Nguyen, MD, Mihail Chelu, MD, PhD, Joshua Moss, MD, Jonathan Hsu, MD, Miguel Valderrábano, MD, Prashant Bhave, MD, Andrew Beaser, MD, Arvindh Kanagasundram, MD, Oussama Wazni, MD, Jason Bradfield, MD, Grace Wall, Kathleen Chang, Michelle Yang, Gabrielle Montenegro, Sabrina Jarrott, Joel Kramer, PsyD, Anthony Kim, MD, MS, Edward P. Gerstenfeld, MD, MS, William Dillon, MD

pcori

UCSF

University of California
San Francisco

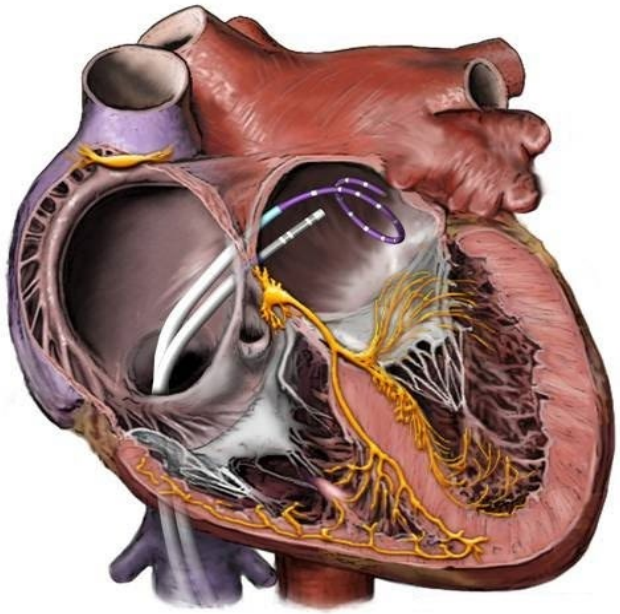
Catheter Ablation for Ventricular Arrhythmias

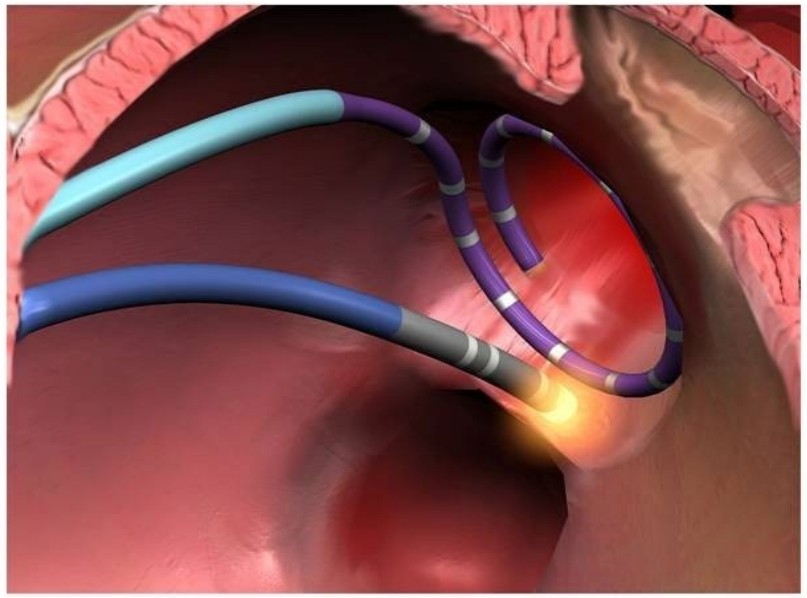
- Class 1 recommendation for recurrent VT and PVCs per AHA/ ACC/ HRS guidelines[1]
- Utilization of ablation for ventricular arrhythmias has increased 5-fold in recent years[2]

1. Al-Khatib et al. *Circulation* 2017
2. Palaniswamy et al. *Heart Rhythm* 2014

Catheter Ablation and the Brain?

- Multiple studies have demonstrated new brain emboli on MRI after ablation for atrial fibrillation in about 15%-25% of cases[1-4]





- WHY?
  - Cardioversions
  - Large number of burns
  - Long catheter dwell times
  - Low flow chamber
  - AF itself (clot in LAA)

1. Gaita et al. *Circulation* 2010
2. Schrikel *Europace* 2010
3. Herrara *J Am Coll Cardiol* 2011
4. Deneke *J Cardiovasc Electrophys* 2015

Cerebral Emboli after LV Ablation

ORIGINAL RESEARCH ARTICLE

Brain Emboli After Left Ventricular Endocardial Ablation

Circulation. 2017;135:867–877.

ORIGINAL RESEARCH ARTICLE

Editorial, see p 878

Isaac R. Whitman, MD
Rachel A. Gladstone, BA
Nitish Badhwar, MD
Henry H. Hsia, MD
Byron K. Lee, MD
S. Andrew Josephson, MD
Karl M. Meisel, MD
William P. Dillon, Jr., MD
Christopher P. Hess, MD, PhD
Edward P. Gerstenfeld, MD
Gregory M. Marcus, MD, MAS

BACKGROUND: Catheter ablation for ventricular tachycardia and premature ventricular complexes (PVCs) is common. Catheter ablation of atrial fibrillation is associated with a risk of cerebral emboli attributed to cardioversions and numerous ablation lesions in the low-flow left atrium, but cerebral embolic risk in ventricular ablation has not been evaluated.

METHODS: We enrolled 18 consecutive patients meeting study criteria scheduled for ventricular tachycardia or PVC ablation over a 9-month period. Patients undergoing left ventricular (LV) ablation were compared with a control group of those undergoing right ventricular ablation only. Patients were excluded if they had implantable cardioverter defibrillators or

Cerebral Emboli after LV Ablation

- None of those undergoing RV ablation experienced a cerebral embolism
- 7 (58% of all LV or 64% of all retrograde aortic cases) had a new brain embolism

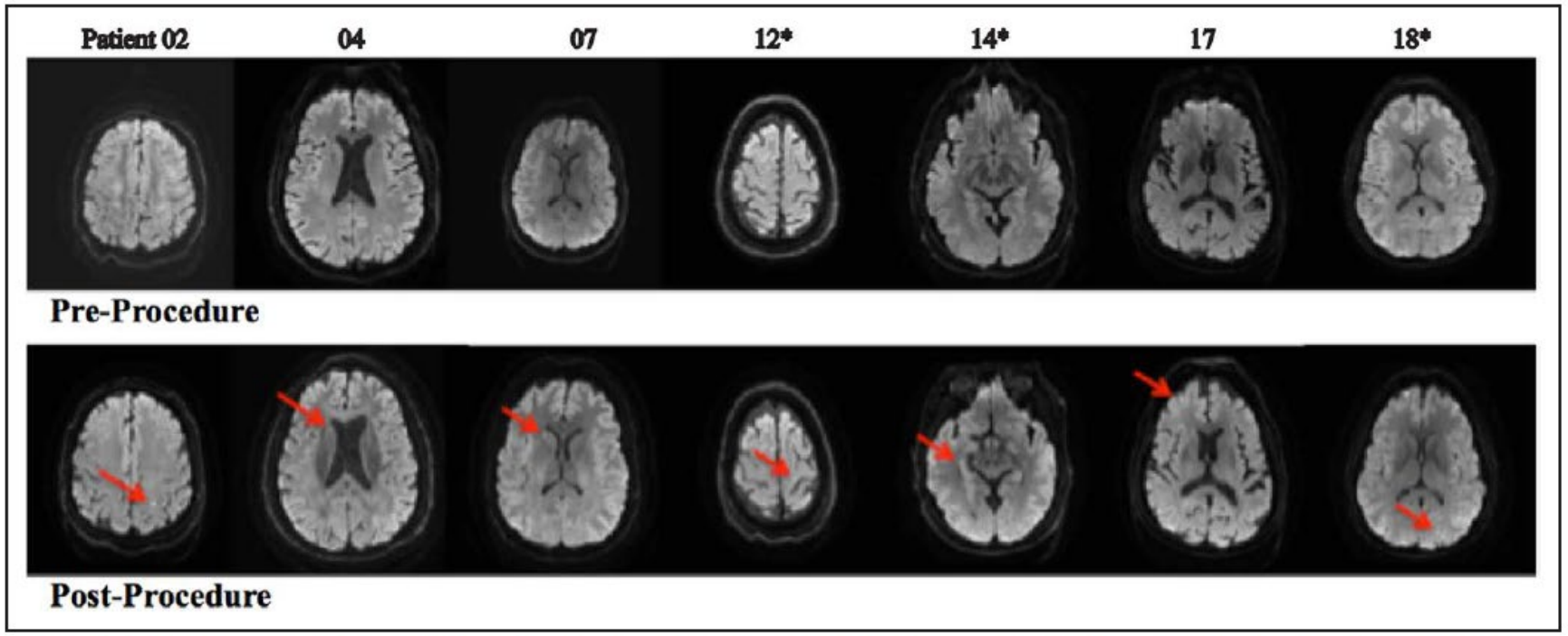


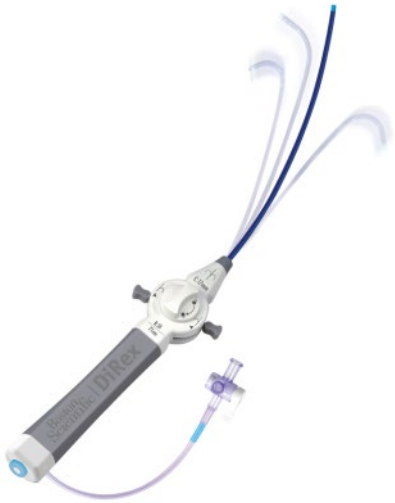
Figure 2. Diffusion-weighted MRI of the brain of each patient with representative cerebral emboli postablation. Images before left ventricular ablation (**Top**) and representative corresponding postprocedural images (**Bottom**) showing embolic lesions. *These patients were found to have multiple embolic lesions on postprocedure MRI: Patient 12 (3 lesions), patient 14 (4), and patient 18 (5).

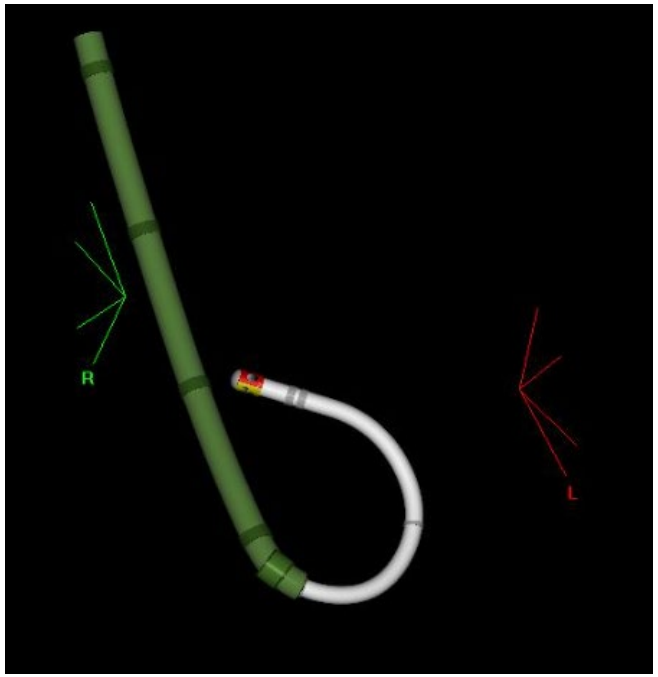
Cerebral Emboli and other LV Procedures

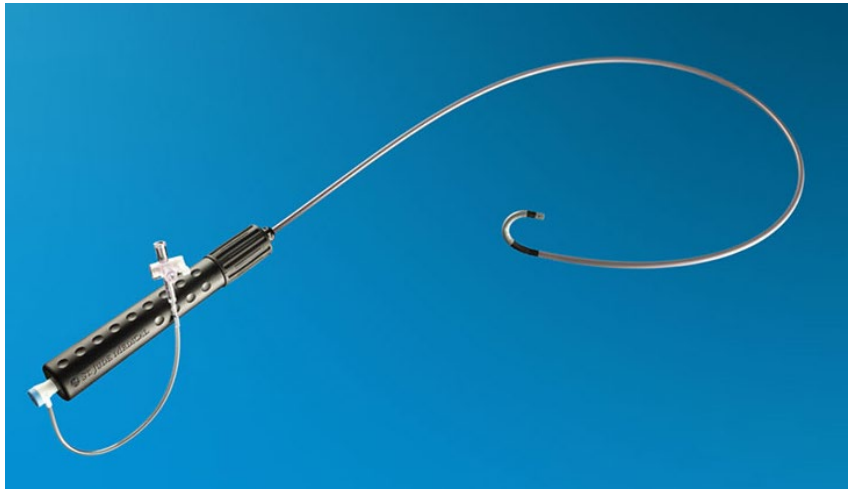
- Diagnostic aortic valve studies carry a ~20% risk of cerebral emboli[1]
- Diagnostic coronary angiography carries a ~20% risk of cerebral emboli[2]

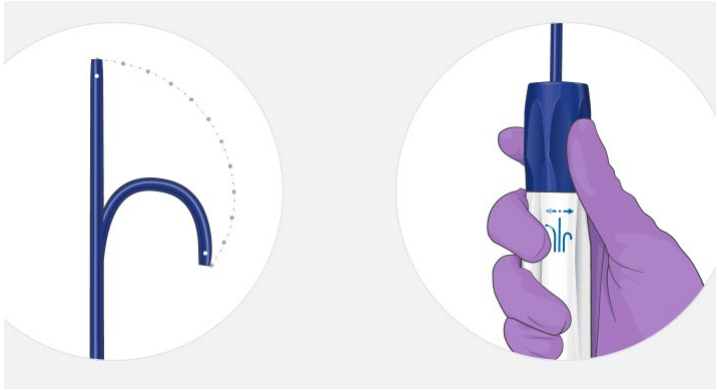
1. Omran et al. *Lancet* 2003
2. Kim et al. *int J Cardiol* 2011

Transseptal Approach Common, Easier with Deflectable Sheaths









We Sought Funding from PCORI to Conduct A Randomized Trial

- **<u>Aim 1</u>: (PRIMARY OUTCOME) To test the hypothesis that a transseptal approach to left ventricular ablation results in a substantial reduction in cerebral emboli compared to a retrograde aortic approach.**

- **<u>Aim 2</u>: To test the hypothesis that a transseptal approach to left ventricular ablation mitigates neurocognitive decline compared to a retrograde aortic approach.**

Key Inclusion Criteria

- Age ≥ 18 years
- Planned/scheduled endocardial ventricular tachycardia (VT) or premature ventricular contraction (PVC) catheter ablation procedure
- Plan is to pursue an ablation target in the left ventricular endocardium that can be accessed by either a transseptal or retrograde aortic approach

Key Exclusion Criteria

- Any contraindication to MRI (as defined by the institution performing the MRI)
- Clinical contraindication to a retrograde aortic approach as determined by the treating physician, including:
  - Severe Aortic stenosis
  - Mechanical aortic valve
- Clinical contraindication to a transseptal puncture as determined by the treating physician , including:
  - Severe Mitral valve stenosis
  - Mechanical Mitral valve
  - ASD or PFO closure device that would preclude a transseptal puncture
  - Mitralclip or Alifieri mitral valve repair that would preclude a transseptal puncture
- Planned or known need to perform either a retrograde aortic approach or transseptal approach

Study Flow

Screening

- Initial inclusion/exclusion evaluation
- Informed consent

Initial Screening Measures

- Medical history, including utilization of clinically available ECG and ambulatory ECG monitoring
- Medication inventory

Final Screening/Enrollment Measures

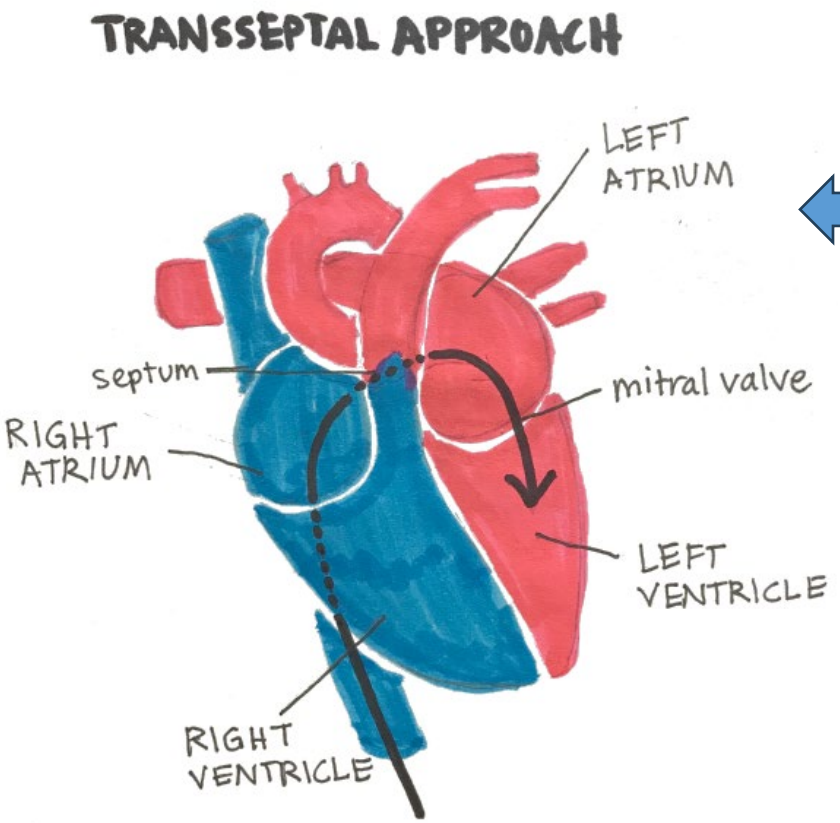
- Brain MRI [1]
- Neurocognitive function testing [1,2]
- NIH Stroke Scale evaluation [1]
- hrQOL/Physical Activity (PA) questionnaire [1]

1: must be performed within 30 days prior to study treatment
2: must be performed >24 hours free of sedating medications

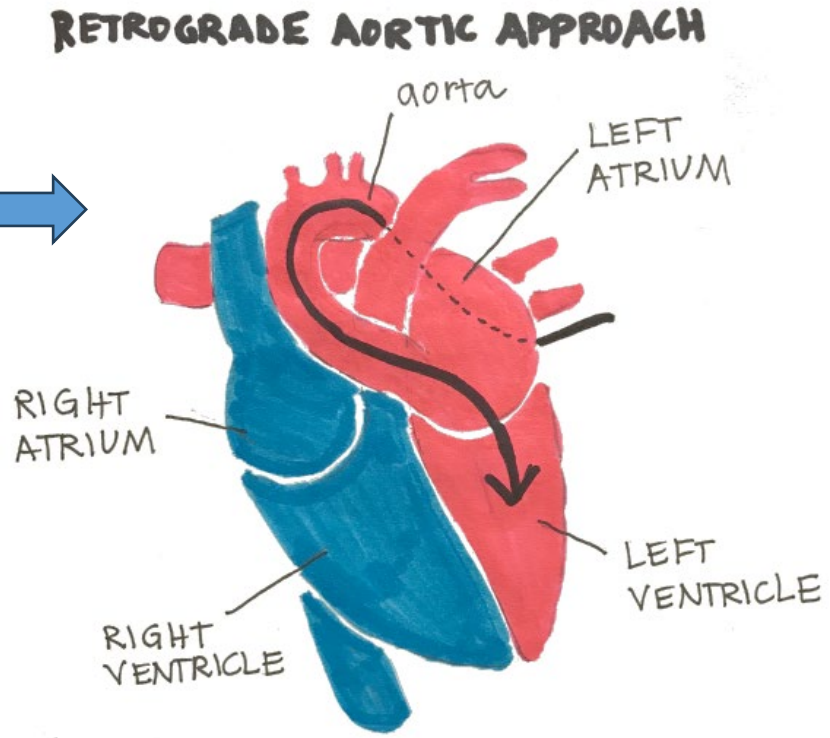
Baseline Visit (V1c)

- Anthropometry, Vital signs [3]
- Study Enrollment (Randomization)
- Study Ablation Treatment
- AE/SAE evaluation

3: may be performed within 30 days prior to study treatment



Randomized 1:1 in blocks by site



Study Flow

Day 1 Post-Ablation Visit (V2)

- Brain MRI
- NIH Stroke Scale evaluation
- Discharge summary/Medication inventory
- AE/SAE evaluation

Month 1 Visit (V3)

- Medical care utilization/Medication inventory
- Documentation of results of ECGs and any ambulatory ECG monitoring obtained for clinical purposes, if available
- hrQOL/PA questionnaire
- AE/SAE evaluation

Month 6 Visit (V4)

- Neurocognitive function testing
- Medical care utilization/Medication inventory
- Documentation of results of ECGs and any ambulatory ECG monitoring obtained for clinical purposes, if available
- hrQOL/PA questionnaire
- Vital signs, Weight
- AE/SAE evaluation

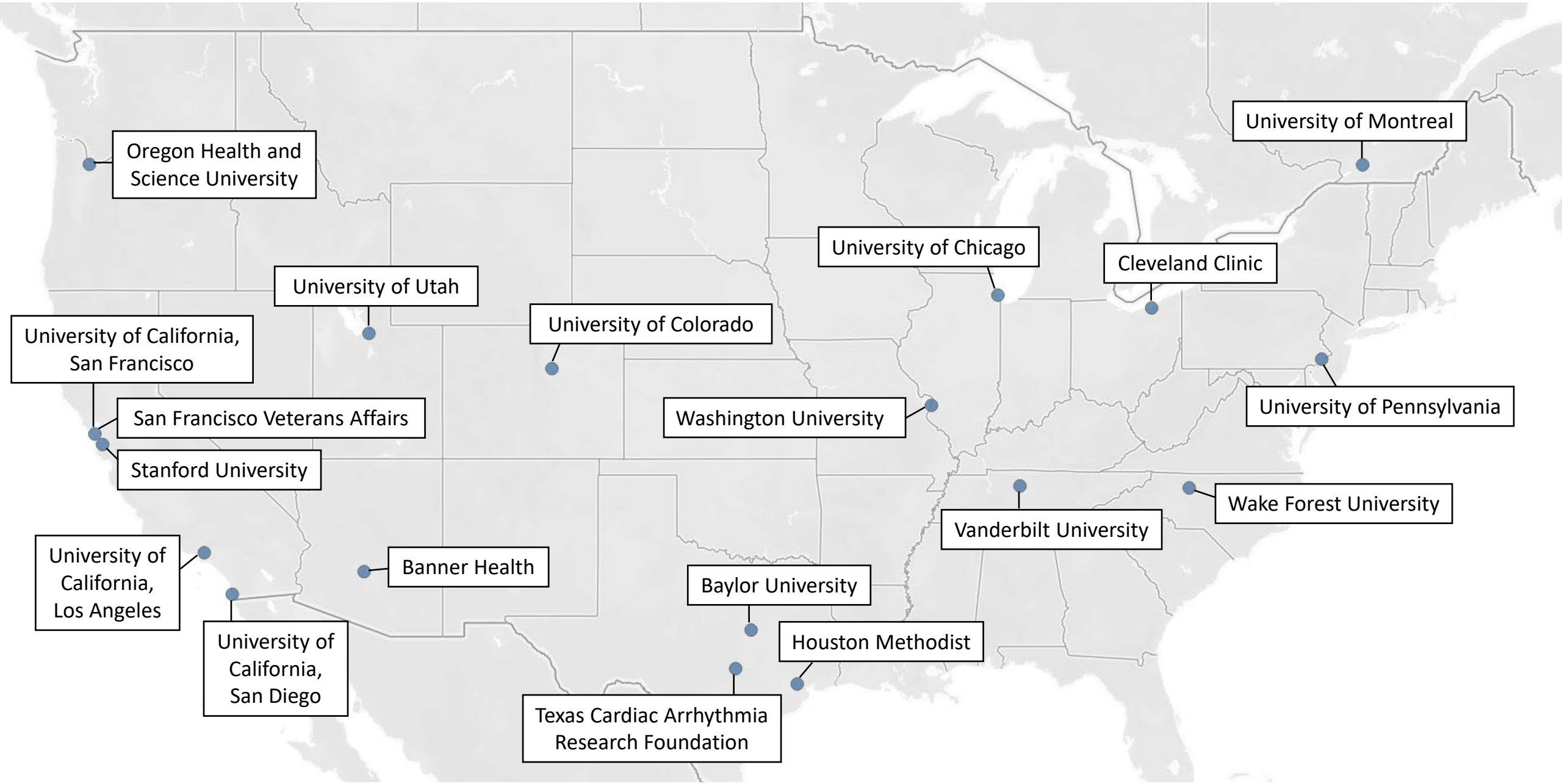
Response to COVID-19 Challenges

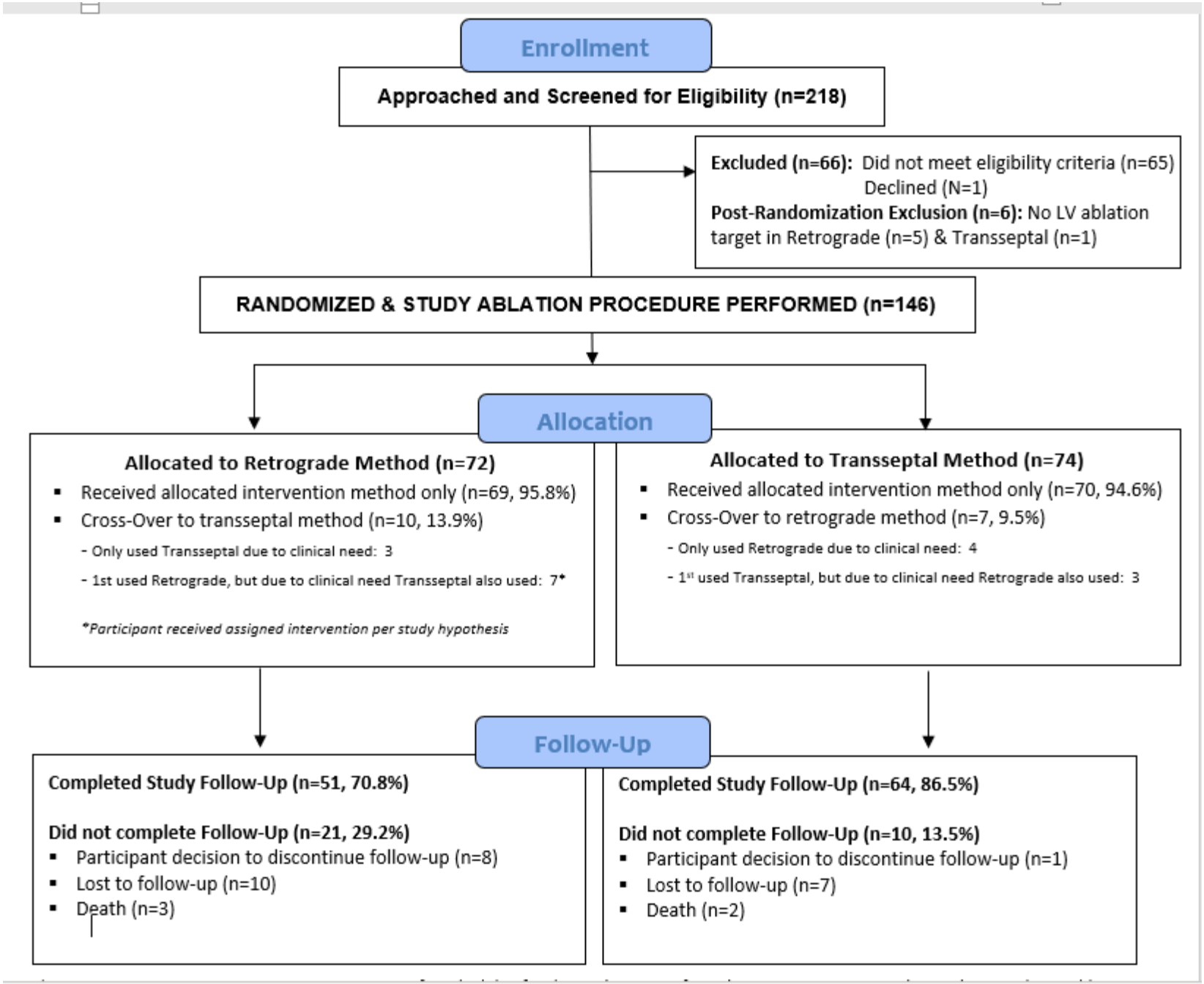
1. Abbreviated neurocognitive function exam that can be administered via Zoom
   - Includes 5/7 tests in the full exam (other 2 are dependent on reaction time)
   - Studies have shown that remote neuropsychological testing is a valid and reliable alternative to traditional face-to-face assessment (*Brearly et al., 2017; Collum et al., 2014; Wadsworth et al., 2018*)
2. Waiver for pre-ablation brain MRI so ppt will only be required to have the Day 1 post-ablation MRI
   - Post-ablation MRI will be performed using FLAIR imaging in the axial and coronal planes DWI-MRI
   - Dr. William Dillon (neuroradiologist) and Dr. Anthony Kim (neurologist) agree that DWI signal will identify the acute post-ablation lesions

Power Calculations

- Assumptions:
  - 60% incidence of cerebral emboli (we observed 64% in retrograde aortic approach) in the retrograde aortic approach
  - 20% incidence of cerebral emboli in the transseptal group (based on the AF ablation literature)
  - A 10% cross-over rate
  - A 25% loss to follow-up or post-randomization exclusion

- 150 participants will provide >95% power to detect a statistically significant difference


Oregon Health and Science University
University of Montreal
University of Chicago
Cleveland Clinic
University of Utah
University of Colorado
University of California, San Francisco
San Francisco Veterans Affairs
Washington University
University of Pennsylvania
Stanford University
Wake Forest University
Vanderbilt University
University of California, Los Angeles
Banner Health
Baylor University
University of California, San Diego
Houston Methodist
Texas Cardiac Arrhythmia Research Foundation


Enrollment
Approached and Screened for Eligibility (n=218)
Excluded (n=66): Did not meet eligibility criteria (n=65)
Declined (N=1)
Post-Randomization Exclusion (n=6): No LV ablation target in Retrograde (n=5) & Transseptal (n=1)
RANDOMIZED & STUDY ABLATION PROCEDURE PERFORMED (n=146)
Allocation
Allocated to Retrograde Method (n=72)
Received allocated intervention method only (n=69, 95.8%)
Cross-Over to transseptal method (n=10, 13.9%)
- Only used Transseptal due to clinical need: 3
- 1st used Retrograde, but due to clinical need Transseptal also used: 7*
*Participant received assigned intervention per study hypothesis
Allocated to Transseptal Method (n=74)
Received allocated intervention method only (n=70, 94.6%)
Cross-Over to retrograde method (n=7, 9.5%)
- Only used Retrograde due to clinical need: 4
- 1st used Transseptal, but due to clinical need Retrograde also used: 3
Follow-Up
Completed Study Follow-Up (n=51, 70.8%)
Did not complete Follow-Up (n=21, 29.2%)
Participant decision to discontinue follow-up (n=8)
Lost to follow-up (n=10)
Death (n=3)
Completed Study Follow-Up (n=64, 86.5%)
Did not complete Follow-Up (n=10, 13.5%)
Participant decision to discontinue follow-up (n=1)
Lost to follow-up (n=7)
Death (n=2)

Baseline Characteristics

	Retrograde Aortic (n=72)	Transseptal (n=74)
Age	63.2 ± 12.5	65.3 ±11.3
Female	12 (17%)	18 (24%)
White	60 (83%)	67 (91%)
Black	5 (7%)	2 (3%)
Asian/ Pacific Islander	5 (7%)	2 (2%)
Native American	1 (1%)	0
Other	1 (1%)	3 (4%)
Hispanic	4 (6%)	4 (5%)
BMI ($kg.m^2$)	31 ± 7	30 ± 8
Diabetes	13 (18%)	16 (22%)
Hypertension	26 (36%)	28 (38%)
Coronary Disease	40 (56%)	34 (46%)
Heart Failure	39 (54%)	32 (43%)
Stroke	2 (3%)	5 (7%)

Baseline Characteristics

	Retrograde Aortic (n=72)	Transseptal (n=74)
Aortic Vascular Disease	0	1 (1%)
Congenital Heart Disease	1 (1%)	5 (5%)
History of DVT	5 (6%)	6 (8%)
Hypercoagulable syndrome	1 (1%)	1 (%)
Pulmonary embolism	5 (7%)	5 (7%)
CABG	8 (11%)	9 (12%)
Median Pack years smoked (IQR)	0 (0-13.5)	0 (0-9.25)
Atrial Fibrillation	22 (31%)	30 (40%)
Sustained VT	31 (43%)	34 (46%)
Polymorphic VT	0 (0%)	3 (4%)
VF	1 (1%)	2 (3%)
PVCs	49 (68%)	46 (62%)
Creatinine	1.08 ± 0.32	1.12 ± 0.45

Procedural Characteristics

	Retrograde Aortic (n=72)	Transseptal (n=74)	P value
Underwent retrograde aortic approach only	62 (86%)	4 (5%)	
Transseptal only	3 (4%)	67 (91%)	
Both, started with retrograde aortic	7 (10%)	0 (0%)	
Both, started with transseptal	0 (0%)	3 (4%)	
Maximum BP	154 ± 32	160 ± 34	0.31
Minimum BP	83 ± 25	86 ± 29	0.43
Electrical cardioversion/ defibrillation	17 (24%)	19 (27%)	0.85
Mean ACT	296 ± 42	298 ± 64	0.86
Target location			0.42
Near mitral annulus	9 (15%)	5 (9%)	
Near conduction system	8 (13%)	5 (9%)	
Papillary muscles	12 (20%)	19 (35%)	
Other	20 (33%)	18 (33%)	

Procedural Characteristics

	Retrograde Aortic (n=72)	Transseptal (n=74)	P value
Median ablation time (minutes)	18 (7-32)	15 (7-32)	0.07
Average power (watts)	42 ± 16	42 ± 14	0.88
Maximum power (watts)	44 ± 7	44 ± 11	0.68
Left heart time (minutes)	154 ± 86	140 ± 79	0.29
Median fluoroscopy time (minutes)	6.6 (0.4-12.1)	9.5 (2.4-21.7)	0.014
Procedure time (minutes)	238 ± 116	237 ± 104	0.98
Total fluids in (ml)	1,406 ± 938	1,702 ± 1,545	0.17
Net fluids in versus out	881 ± 802	932 ± 783	0.71

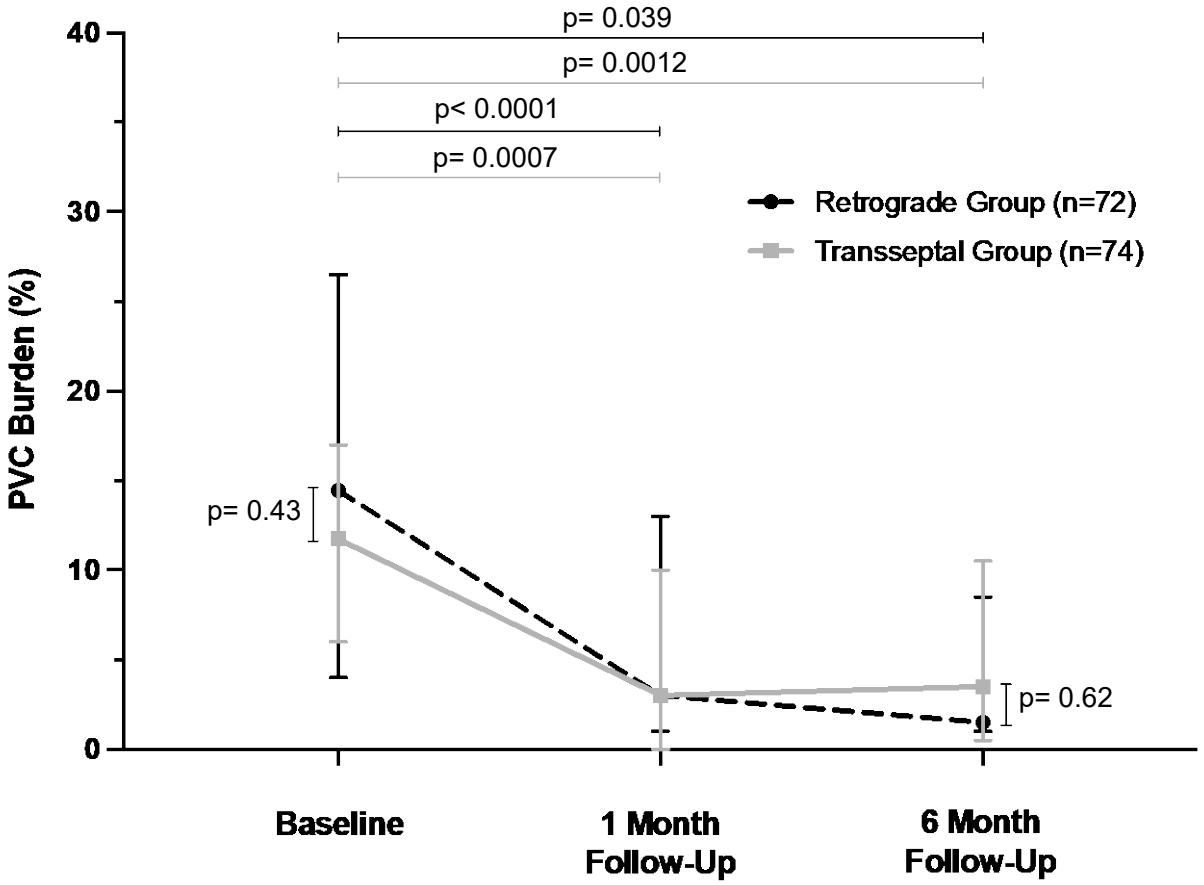
Complications within 30 days

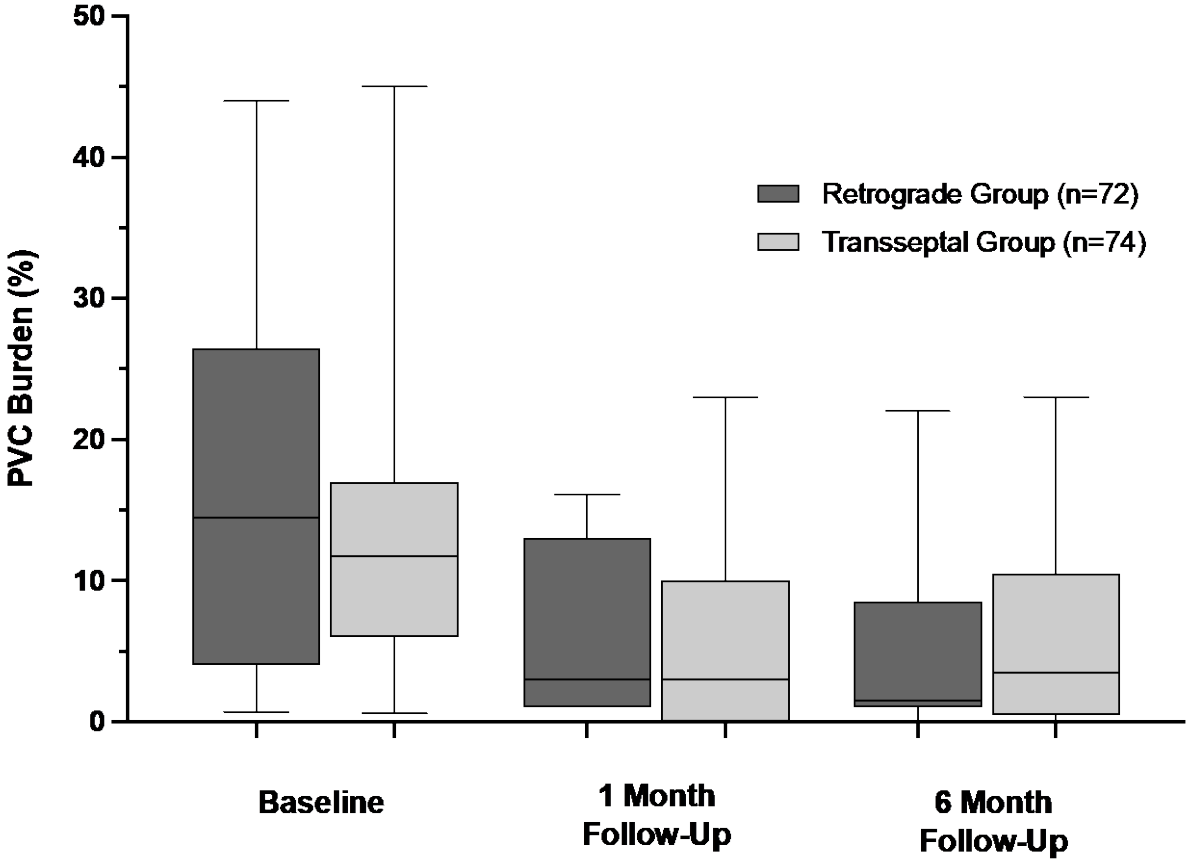
	Retrograde Aortic (n=72)	Transseptal (n=74)	P value
Total hospital days (median, IQR)	1 (1-2)	1 (1-3)	0.44
Total ICU days (median, IQR)	0 (0-0)	0 (0-0)	0.39
Pericardial effusion	0	4	0.12
Vascular injury (AV fistula, pseudoaneurysm)	2 (3%)	0	0.24
Myocardial infarction	0	0	
Stroke/ TIA			
Pneumothorax/ hemothorax	0	0	
Bleeding requiring surgical intervention or transfusion	0	4	0.12
Peripheral infarct	0	0	
Other cardiovascular disease-related complication	5 (7%)	3 (4%)	0.72
Death	0	0	

Efficacy

	Retrograde Aortic (n=72)	Transseptal (n=74)	P value
Intra-procedural success			0.66
Unable to ablate	3 (5%)	4 (6%)	
Reduced burden/ inducibility	17 (26%)	22 (33%)	
Complete success	46 (70%)	41 (61%)	
1 month visit (median 39 days)			
Eradication of target	35 (58%)	40 (64%)	0.29
Sustained VT observed	1 (2%)	2 (3%)	1.0
Appropriate ICD shocks	2 (3%)	1 (1%)	1.0
Improved symptoms	45 (63%)	53 (72%)	0.61
6 month visit (median 198 days)			
Eradication of target	31 (59%)	40 (64%)	0.94
Sustained VT observed	4 (7%)	2 (3%)	0.41
Appropriate ICD shocks	3 (4%)	1 (1%)	0.30
Improved symptoms	41 (55%)	55 (74%)	0.66

PVC Burden Pre and Post Ablation



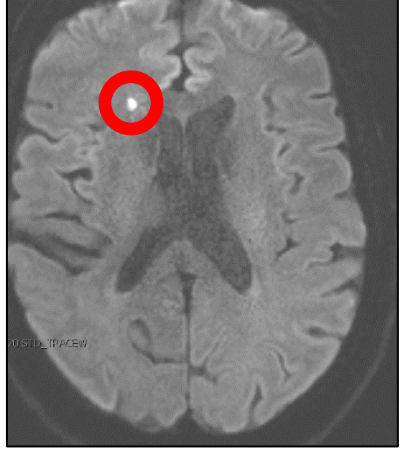


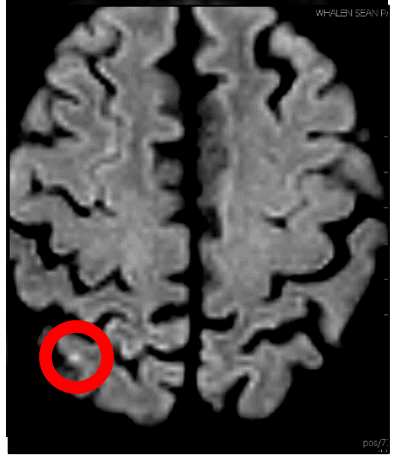
Pre-procedure MRIs

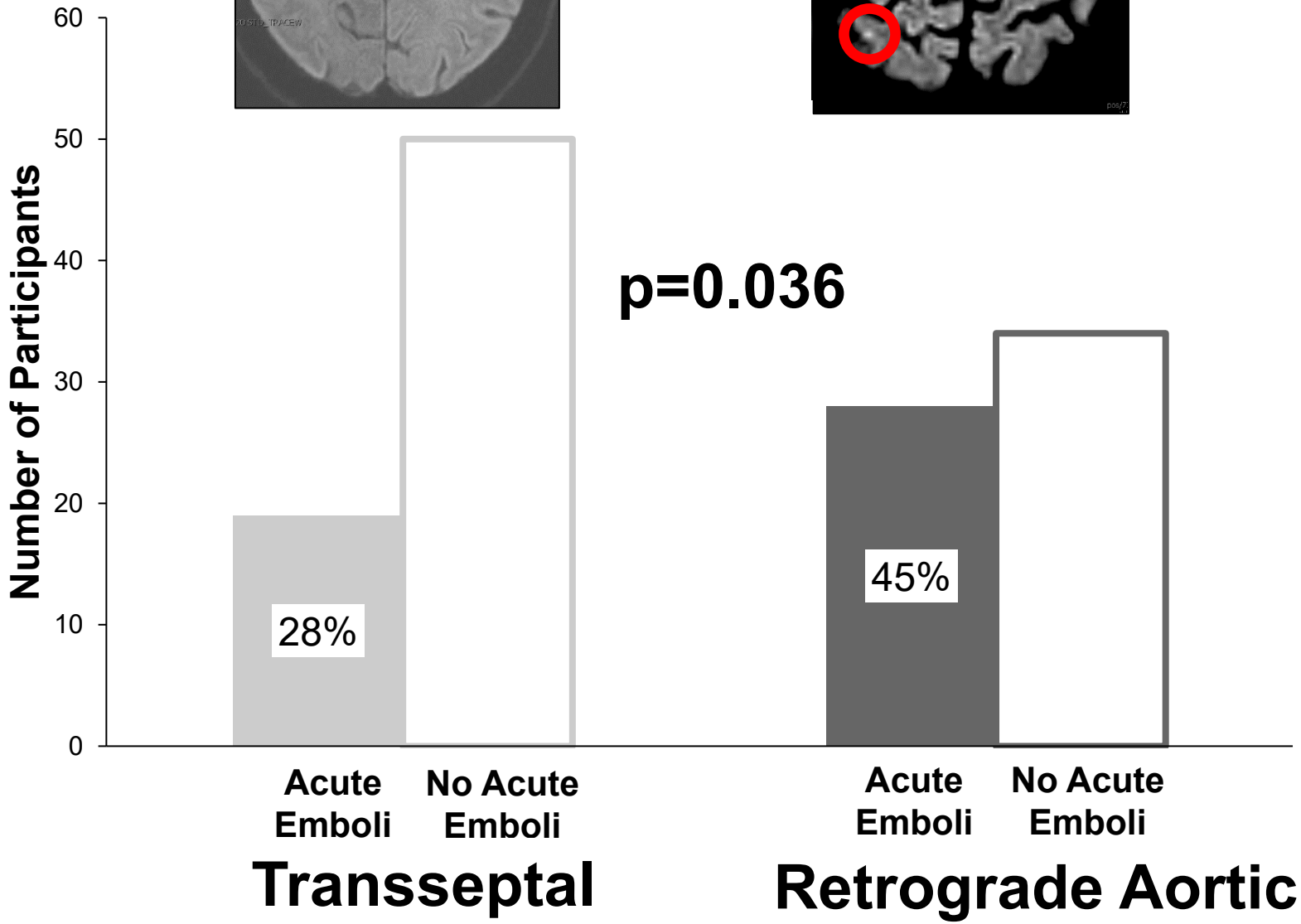
- Seventy participants (35 in each initial randomization group; among the modified intention to treat group, 34 in the transseptal group and 31 in the retrograde aortic group)
- None had an acute diffusion abnormality indicative of an acute brain embolism
- 131 (90%) of all participants had a post-operative day #1 MRI
  - 62 (86%) in the retrograde aortic group and 69 (92%) in the transseptal group

Primary Outcome

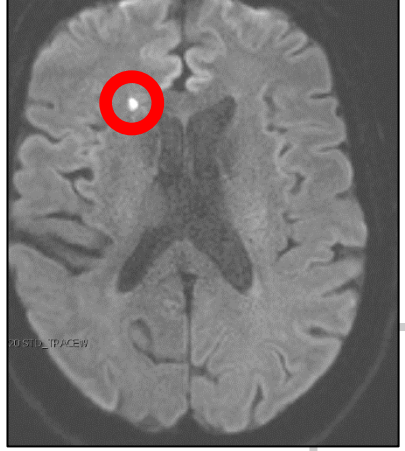
Intention-to-Treat

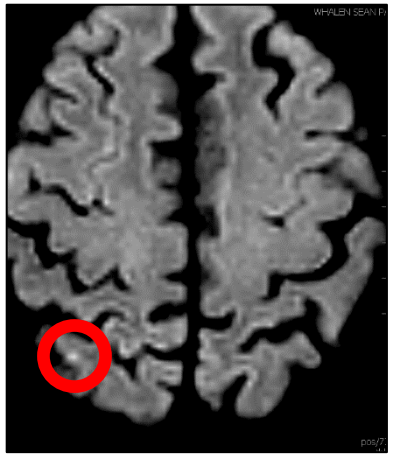




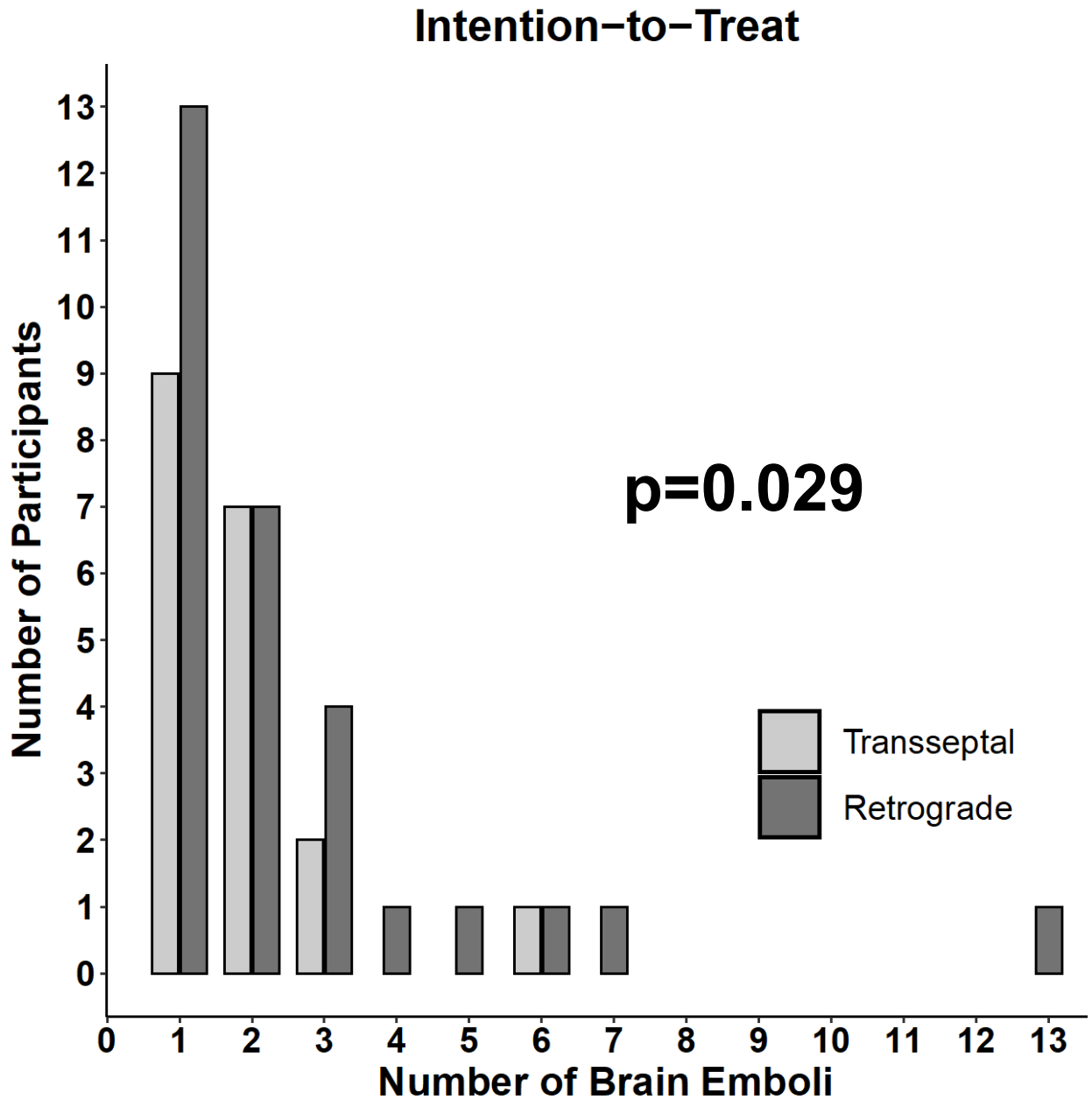


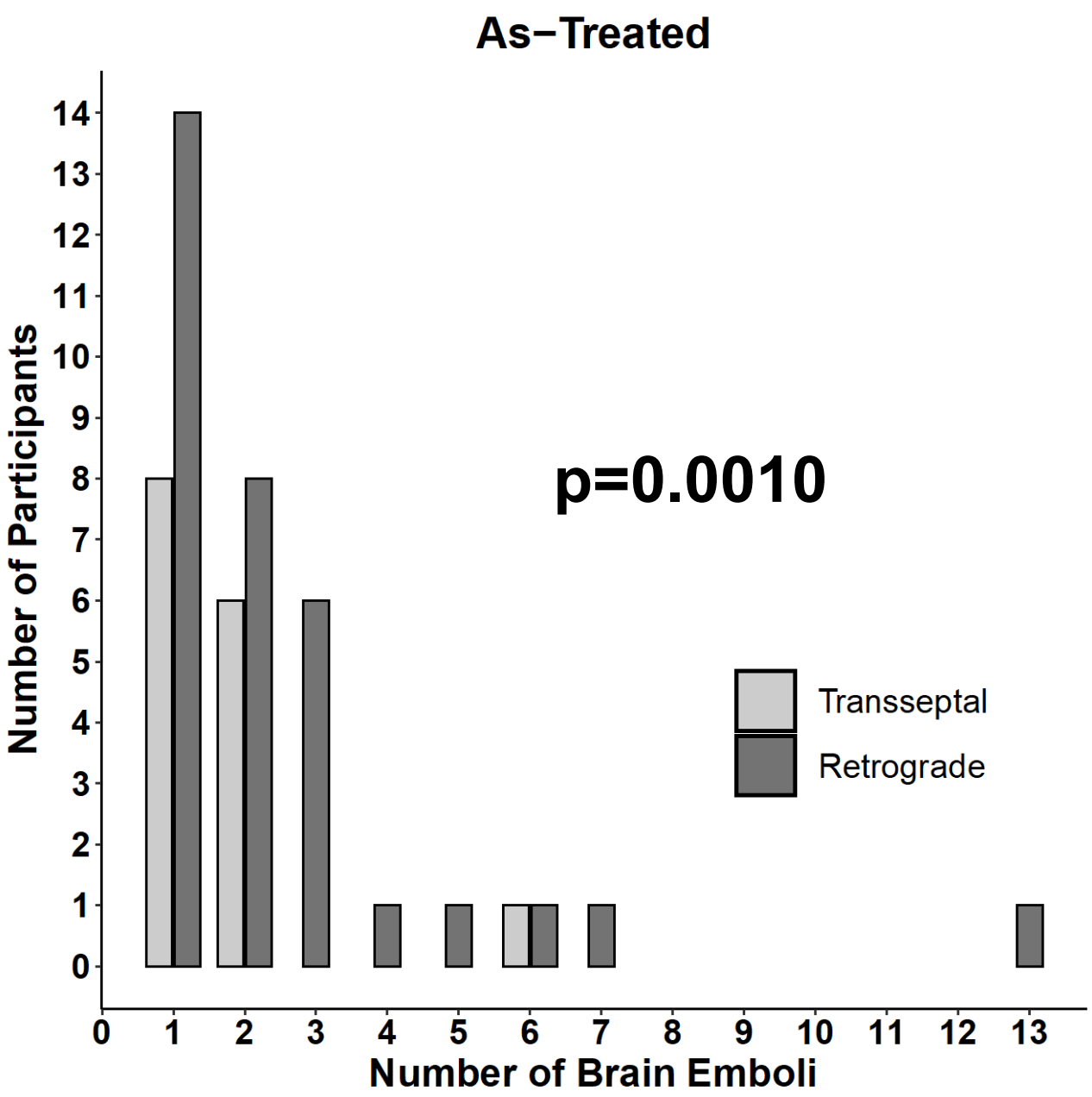
As-treated





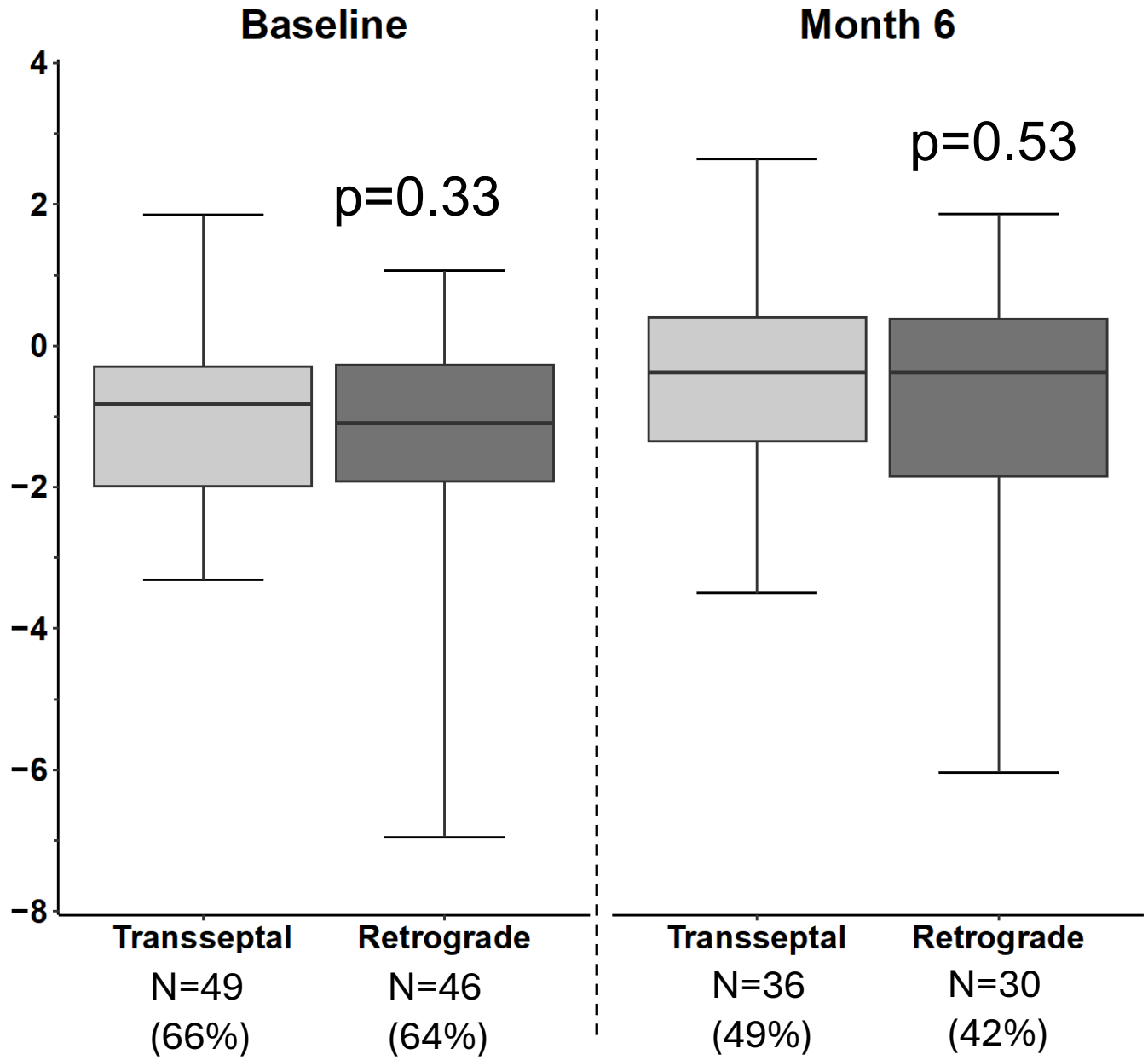
Number of Participants
60
50
40
30
20
10
0
23%
49%
p=0.0016
Acute Emboli
No Acute Emboli
Acute Emboli
No Acute Emboli
Only Transseptal
Any Retrograde Aortic


Intention−to−Treat
Number of Participants
Number of Brain Emboli
p=0.029
Transseptal
Retrograde


As−Treated
Number of Participants
Number of Brain Emboli
p=0.0010
Transseptal
Retrograde

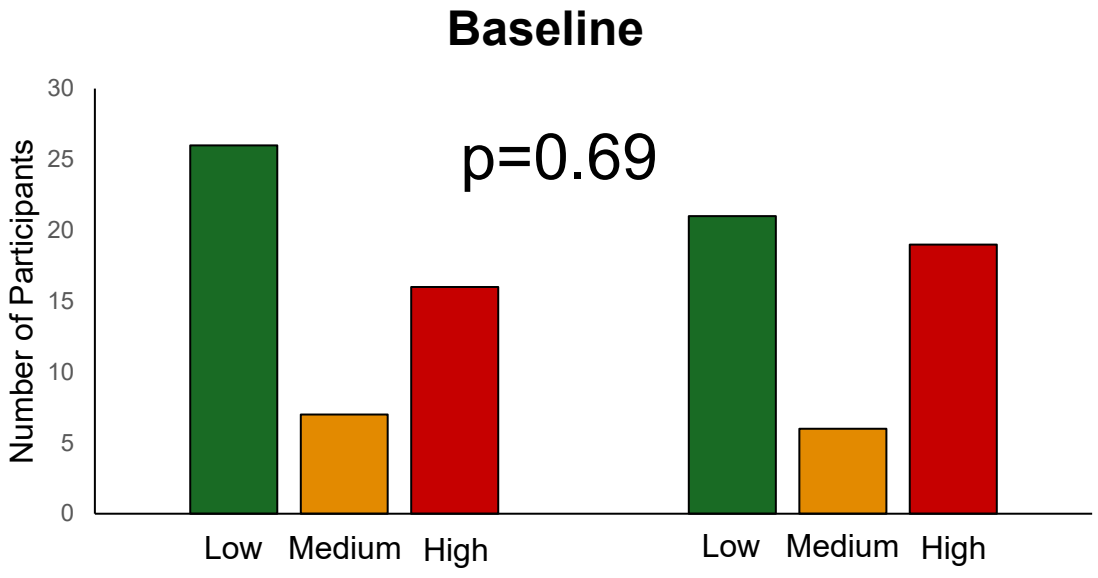
Cognitive Composite Score

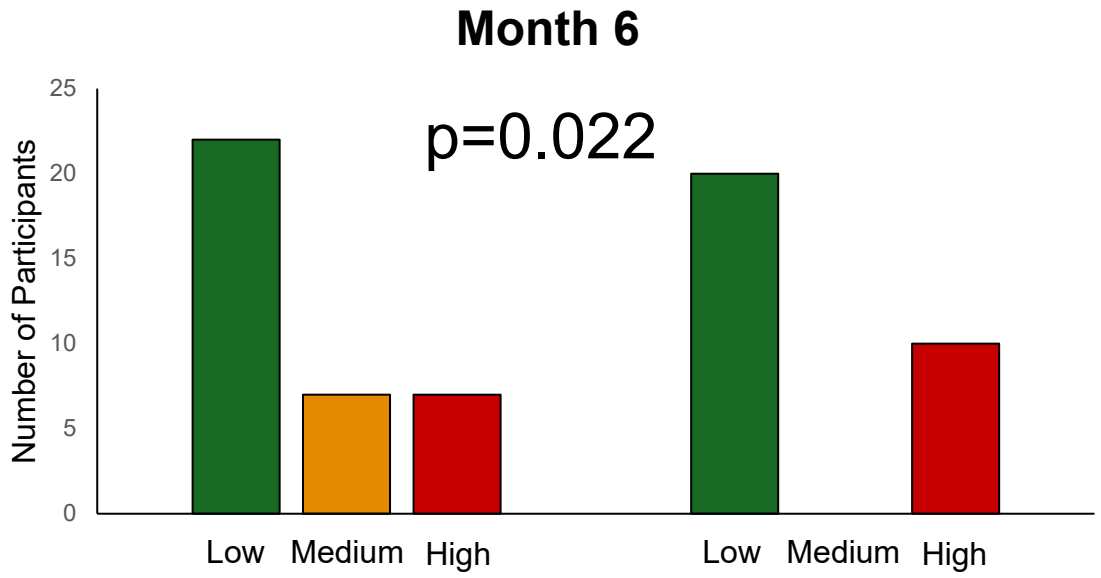
Intention-to-Treat Analysis



Likelihood of Cognitive Impairment

Intention-to-Treat Analysis





Limitations

- The study may have been insufficiently powered to detect differences in efficacy and complications
- There was substantial loss of follow-up for the 6 month neurocognitive assessment
- The brain emboli may be the “canary in the coalmine” that we can see
  - We did not assess potential impacts of emboli to other organs that may have occurred
- The presence of these infarcts does not necessarily detract from the overall benefit of the procedure, but rather may point to the optimal approach

Conclusions

- A transseptal approach to endocardial left ventricular catheter ablation results in significantly less frequent acute brain emboli compared to a retrograde aortic approach
- The transseptal approach may mitigate against neurocognitive decline after these procedures, although missing data at 6 months precludes confident conclusions
- These data suggest that a transseptal approach to other transcutaneous left ventricular (or perhaps aortic root) procedures may be beneficial
- These data may also suggest that emboli affecting other organs may more often occur with retrograde aortic access

Thank You

ACC.24

One-month Ticagrelor Monotherapy After PCI in Acute Coronary Syndromes: Principal Results From the Double-blind, Placebo-controlled ULTIMATE-DAPT Trial

Gregg W Stone MD

Icahn School of Medicine at Mount Sinai

on behalf of Shao-Liang Chen and the ULTIMATE-DAPT Investigators

@GreggWStone

ClinicalTrials.gov number: NCT03971500

AMERICAN COLLEGE of CARDIOLOGY

Background

- International guidelines currently recommend DAPT with aspirin plus a potent $P2Y_{12}$ receptor inhibitor for 12 months in most patients presenting with an ACS treated with PCI to prevent MI and stent thrombosis

- Limited data exist regarding the use of single antiplatelet therapy with a potent $P2Y_{12}$ inhibitor starting 1 month after PCI in ACS, and no such trials have been placebo-controlled

Objectives

- We therefore performed a large-scale, international, multicenter, placebo-controlled, double-blind randomized trial to determine whether the use of ticagrelor alone beginning 30 days after PCI in pts with ACS could reduce clinically-relevant bleeding without an accompanying increase in major adverse cardiovascular or cerebrovascular events (MACCE) compared with ticagrelor plus aspirin

Inclusion Criteria

Patients presenting with ACS within 30 days before randomization

- ≥18 years of age
- With either:
  - Biomarker pos NSTEMI or STEMI, or
  - Biomarker neg unstable angina → 1) DS ≥90%, *or* 2) Ruptured plaque, *or* 3) Thrombotic lesion
- Had been randomized in the IVUS-ACS trial of IVUS-guided vs. angio-guided PCI
- Remained event-free after PCI with contemporary drug-eluting stents (DES) for one month on ticagrelor (90 mg bid) plus aspirin (100 mg qd)

Key Exclusion Criteria

- ✓ Stroke within 3 months or any permanent neurologic deficit
- ✓ Previous CABG
- ✓ Any planned surgery within 12 months
- ✓ eGFR <20 ml/min/1.73 m^2
- ✓ Need for chronic oral anticoagulation
- ✓ Life expectancy <1 year
- ✓ Any condition likely to interfere with study processes

Primary Endpoints

- Assessed between 1- and 12-months post-PCI -

1. **Effectiveness:** Clinically-relevant bleeding (BARC types 2, 3, or 5), powered for superiority testing

2. **Safety:** Composite MACCE, including cardiac death, MI, ischemic stroke, definite stent thrombosis, or clinically-driven TVR, powered for non-inferiority testing

Assumptions and Sample Size Calculations

1. **Effectiveness:** Assuming a 3.0% rate of clinically-relevant bleeding between 1 and 12 months on ticagrelor plus aspirin, randomizing 3400 patients provided 80% power to detect a 50% reduction with ticagrelor monotherapy with 2-sided alpha 0.05

2. **Safety:** Assuming a 6.2% rate of MACCE between 1 and 12 months on ticagrelor plus aspirin, randomizing 3068 patients provided 80% power to demonstrate noninferiority of ticagrelor monotherapy with an absolute margin of 2.5% with 1-sided alpha 0.025

Tested hierarchically to preserve alpha: Effectiveness had to pass for safety to be tested

Sponsorship, Funding and Study Leadership

Investigator-sponsored study

Shao-Liang Chen, MD, Nanjing First Hospital, China

Executive Committee

Shao-Liang Chen, MD (Study chair and PI)

Gregg W Stone, MD (Study co-chair and co-PI)

Jing Kan, MD (Chair of Clinical Data Coordinating Center)

Jun-Jie Zhang, MD, PhD

Afsar Razar, MD

Imad Sheiban, MD

Fei Ye, MD

Ping Xie, MD

Steering Committee

Shao-Liang Chen, MD
Gregg W Stone, MD
Imad Sheiban, MD
Afsar Raza, MD
Muhammad Anjum, MD

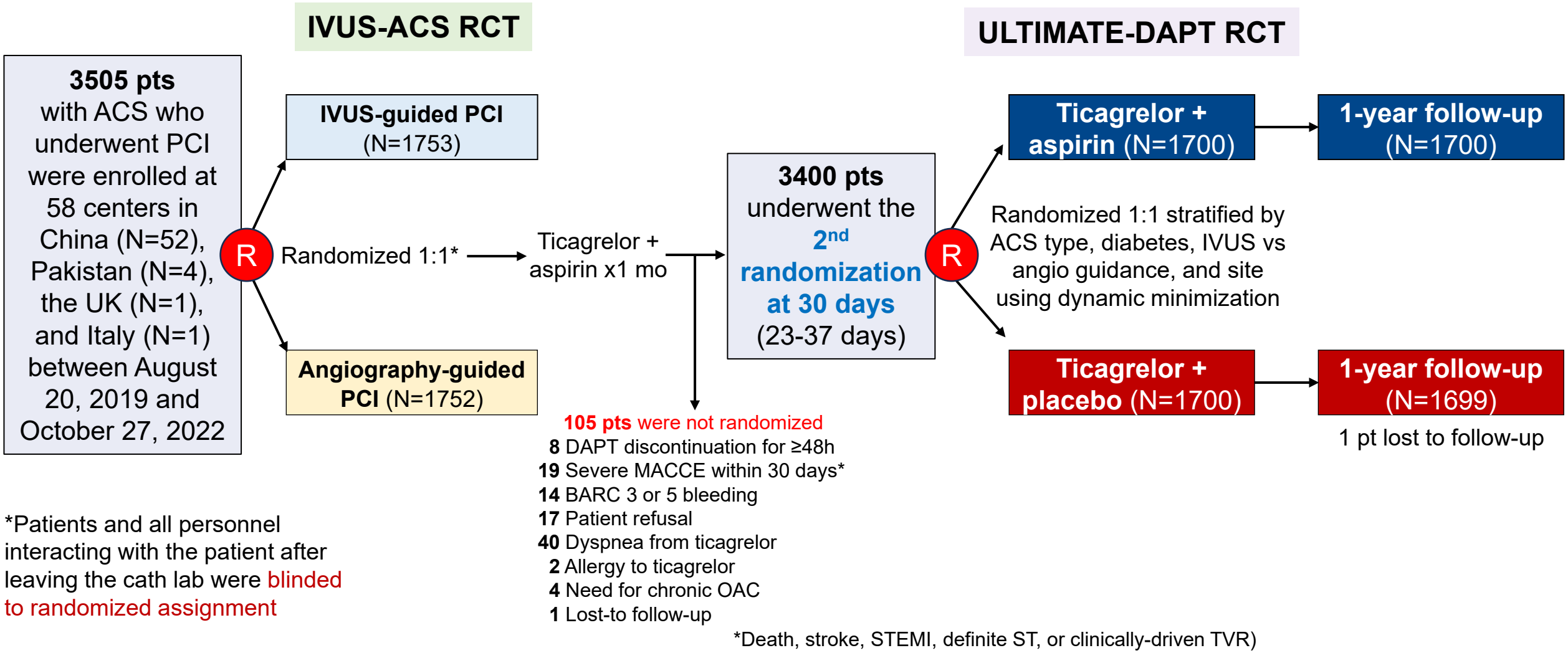
Country Leaders

Imad Sheiban, MD (Italy)
Afsar Raza, MD (United Kingdom)
Muhammad Anjum, MD (Pakistan)
Zhiming Wu, MD (China)

Funding

Chinese Society of Cardiology [CSCF 2019-A0003], the National Natural Scientific Foundation of China [NSFC, grant number: 91639303, 81770441, and 82121001] and Jiangsu Provincial & Nanjing Municipal Clinical Trial Project [BE 2019615]. Study medications were supplied by Yung Shin Pharmaceutical Industrial Co. (Kunshan, China) and Shenzhen Salubris Pharmaceuticals Co., Ltd (Shenzhen, China).

2x2 Randomization and Study Flowchart



*Patients and all personnel interacting with the patient after leaving the cath lab were blinded to randomized assignment

*Death, stroke, STEMI, definite ST, or clinically-driven TVR)

Top 10 Enrolling Sites

Principal investigator		Center	City, country	N pts enrolled
1	Shao-Liang Chen	Nanjing First Hospital	Nanjing, China	842
2	Muhammad Anjum	Punjab Institute of Cardiology	Lahore, Pakistan	175
3	Ping Xie	Gansu Provincial People's Hospital	Lanzhou, China	126
4	Guangping Li	2nd hospital of Tianjin Medical University	Tianjin, China	96
5	Yong Xia	Hospital of Xuzhou Medical University	Xuzhou, China	92
6	Yuquan He	Sino-Japan Friendship Hospital	Jilin, China	89
7	Yan Wang	Xiamen Heart Center, Xiamen University	Xiamen, China	82
8	Lin Tao	Xijing Hospital	Xi'an, China	80
9	Yibin Shao, MD	Qingdao People's Hospital	Qingdao, China	71
10	Hamid Sharif Khan	Rawalpindi Institute of Cardiology	Rawalpindi, Pakistan	70

Baseline Characteristics

	Ticagrelor plus placebo (N = 1700)	Ticagrelor plus aspirin (N = 1700)
Age, years, median (IQR)	62 (54, 70)	63 (54, 69)
Male sex	1264 (74.4%)	1257 (73.9%)
Race, Chinese	1476 (86.8%)	1519 (89.4%)
Hypertension	1058 (62.2%)	1063 (62.5%)
Diabetes mellitus	540 (31.8%)	535 (31.5%)
Dyslipidemia	1178 (69.3%)	1157 (68.1%)
Current smoking	486 (28.6%)	482 (28.4%)
CKD (eGFR <60 mL/min/1.73m^2)	119 (7.0%)	129 (7.6%)
Previous PCI	171 (10.1%)	174 (10.2%)
Previous CABG	2 (0.1%)	4 (0.2%)
Previous MI	143 (8.4%)	156 (9.2%)
Previous stroke	154 (9.1%)	147 (8.7%)
Initial clinical presentation		
Unstable angina	668 (39.3%)	708 (41.7%)
With ischemic ECG changes	650/668 (97.3%)	685/708 (96.8%)
Non-STEMI	545 (32.1%)	531 (31.2%)
STEMI	487 (28.7%)	461 (27.1%)
LVEF (TTE), %	62 (55, 65)	63 (56, 65)

Culprit Lesion Characteristics (site-assessed)

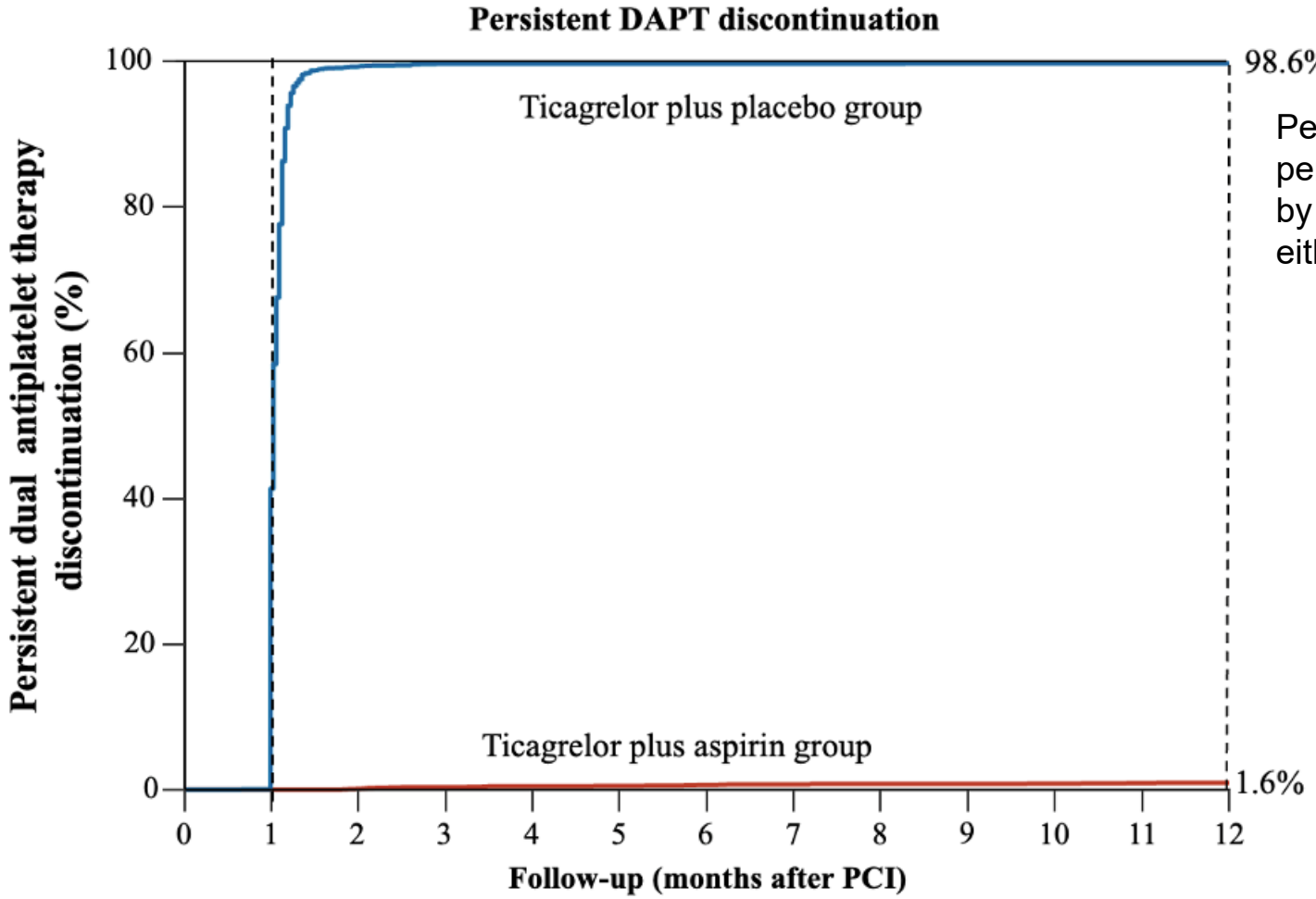
	Ticagrelor plus placebo (N = 1700)	Ticagrelor plus aspirin (N = 1700)
Number of diseased vessels		
One	1199 (70.5%)	1171 (68.9%)
Two	397 (23.4%)	393 (23.1%)
Three	104 (6.1%)	136 (8.0%)
Total number of lesions treated	1.3 ± 0.6	1.3 ± 0.6
Culprit lesion location		
Unprotected left main	86 (5.1%)	60 (3.5%)
Left anterior descending	956 (56.2%)	956 (56.2%)
Left circumflex	237 (13.9%)	258 (15.2%)
Right	421 (24.8%)	426 (25.1%)
Culprit lesion types		
True bifurcation (Medina 1,1,1 or 0,1,1)	265 (15.6%)	255 (15.0%)
Long or diffuse (≥30 mm)	1256 (73.9%)	1205 (70.9%)
Moderate or severe calcification (encircling)	120 (7.1%)	133 (7.8%)
Thrombus (filling defect in multiple views)	158 (9·3%)	147 (8·7%)
TIMI flow at baseline		
0/1	333 (19.6%)	326 (19.2%)
2	88 (5.2%)	88 (5.2%)
3	1279 (75.2%)	1286 (75.6%)

Procedural Characteristics

	Ticagrelor plus placebo (N = 1700)	Ticagrelor plus aspirin (N = 1700)
Transradial access	1645 (96.8%)	1630 (95.9%)
Intravascular imaging guidance	854 (50.2%)	857 (50.4%)
Aspiration thrombectomy used	23 (1.4%)	24 (1.4%)
Rotational atherectomy used	3 (0.2%)	10 (0.6%)
Number of stents implanted	1.5 ± 0.7	1.4 ± 0.7
Type of DES implanted		
Firehawk family	874 (51.4%)	888 (52.2%)
Resolute family	717 (42.2%)	706 (41.5%)
Mixed	103 (6.1%)	98 (5.8%)
Maximum stent diameter, mm	3.17 ± 0.43	3.16 ± 0.46
Total stent length, mm	33 (23 - 51)	32 (23 - 48)
Post-dilation performed	1625 (95.6%)	1608 (94.6%)
Maximum balloon pressure, atm	17.3 ± 3.1	17.2 ± 2.9
Contrast media used, mL	150 (120 - 180)	150 (120 - 180)
Procedural time, min	40 (25 - 60)	40 (27 - 60)
Complete revascularization	1493 (87.8%)	1496 (88.0%)
Procedural success*	1688 (99.3%)	1686 (99.2%)

*TIMI 3 flow, residual DS <20%, absence of ≥type B dissection, no intra-procedural complications

DAPT Adherence During Follow-up

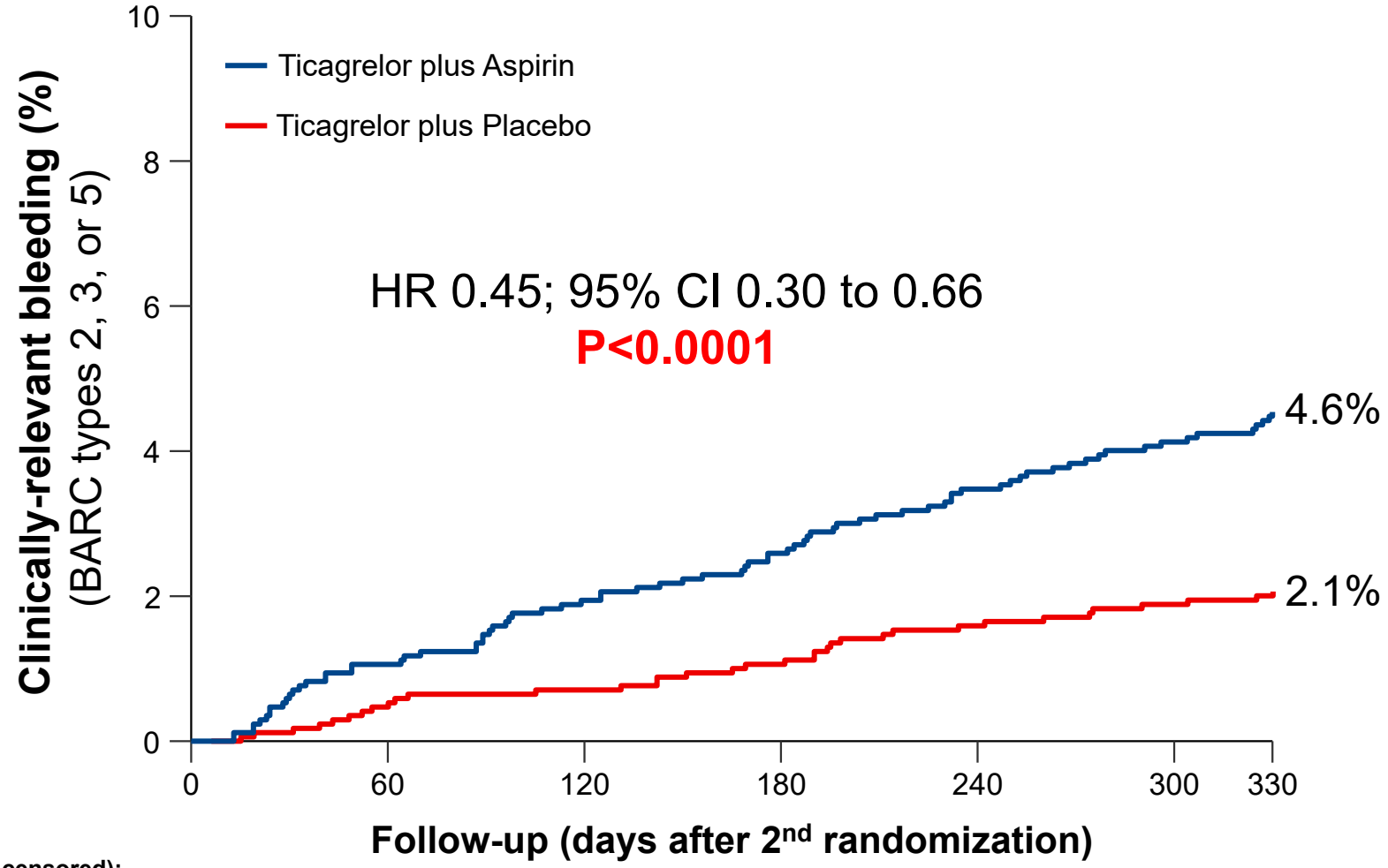


No. at risk													
Ticagrelor plus placebo	1700	1002	13	6	6	6	6	6	6	6	6	6	6
Ticagrelor plus aspirin	1700	1700	1697	1692	1688	1686	1683	1679	1676	1676	1673	1672	1672

Persistent DAPT discontinuation was defined as permanent discontinuation of either aspirin as dictated by the study protocol or non-directed discontinuation of either aspirin or ticagrelor for >60 days.

During FU a reduction in ticagrelor from 90 mg to 60 mg bid was required in 12 pts (0.7%) treated with ticagrelor plus placebo and 16 pts (0.9%) treated with ticagrelor plus aspirin. Conversion from ticagrelor to clopidogrel was required in 22 (1.3%) and 19 (1.1%) pts respectively. Unblinding was required during follow-up in 39 pts (1.1%) who had a BARC 3 or 5 bleed (11 in the ticagrelor alone group and 28 in the ticagrelor plus aspirin group) and in 8 pts (0.2%) who had a stent thrombosis (3 in the ticagrelor alone group and 5 in the ticagrelor plus aspirin group).

Primary Effectiveness Endpoint: BARC types 2, 3 or 5 bleeding



Number at risk (number censored):

Ticagrelor plus Aspirin	1700 (0)	1681 (1)	1664 (2)	1652 (1)	1634 (3)	1622 (2)	1615 (2)
Ticagrelor plus Placebo	1700 (0)	1688 (2)	1684 (2)	1676 (2)	1665 (2)	1657 (3)	1654 (3)

Bleeding Endpoints

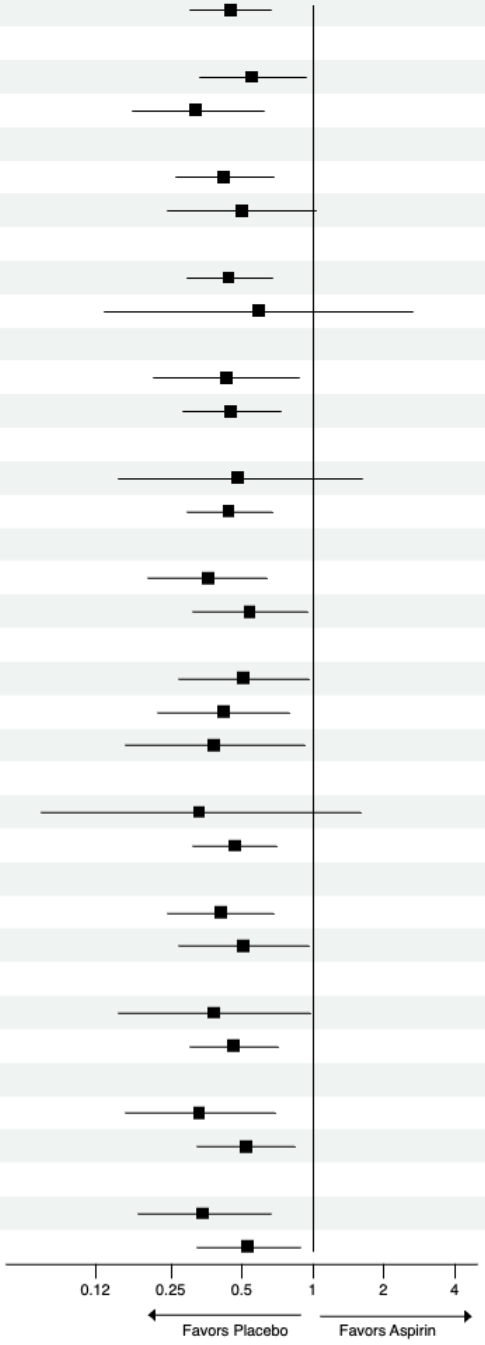
Between 1- and 12-months post-PCI	Ticagrelor plus placebo (N = 1700)	Ticagrelor plus aspirin (N = 1700)	Hazard ratio (95% CI)	P-value
Primary endpoint: Clinically-relevant bleeding (BARC types 2, 3, or 5)	35 (2.1%)	78 (4.6%)	0.45 (0.30 – 0.66)	**<0.0001**
Major bleeding				
BARC types 3 or 5	11 (0.7%)	28 (1.7%)	0.39 (0.19 – 0.79)	**0.009**
TIMI major or minor	11 (0.7%)	27 (1.6%)	0.41 (0.20 – 0.82)	**0.01**
Major	8 (0.5%)	19 (1.1%)	0.42 (0.18 – 0.96)	**0.04**
Minor	3 (0.2%)	8 (0.5%)	0.39 (0.10 – 1.46)	0.16
GUSTO moderate, severe or life-threatening	8 (0.5%)	19 (1.1%)	0.42 (0.18 – 0.96)	**0.04**
Moderate	3 (0.2%)	10 (0.6%)	0.30 (0.08 – 1.10)	0.07
Severe or life-threatening	5 (0.3%)	9 (0.5%)	0.56 (0.19 – 1.66)	0.29
ISTH major bleeding	8 (0.5%)	21 (1.2%)	0.38 (0.17 – 0.86)	**0.02**
BARC types 1-5				
1	8 (0.5%)	12 (0.7%)	0.67 (0.27 – 1.63)	0.37
2	24 (1.4%)	50 (2.9%)	0.48 (0.29 – 0.78)	**0.003**
3	10 (0.6%)	24 (1.4%)	0.42 (0.20 – 0.88)	**0.02**
5	1 (0.1%)	4 (0.2%)	0.25 (0.03 – 1.98)	0.20

Clinically-Relevant Bleeding (BARC types 2, 3, 5)

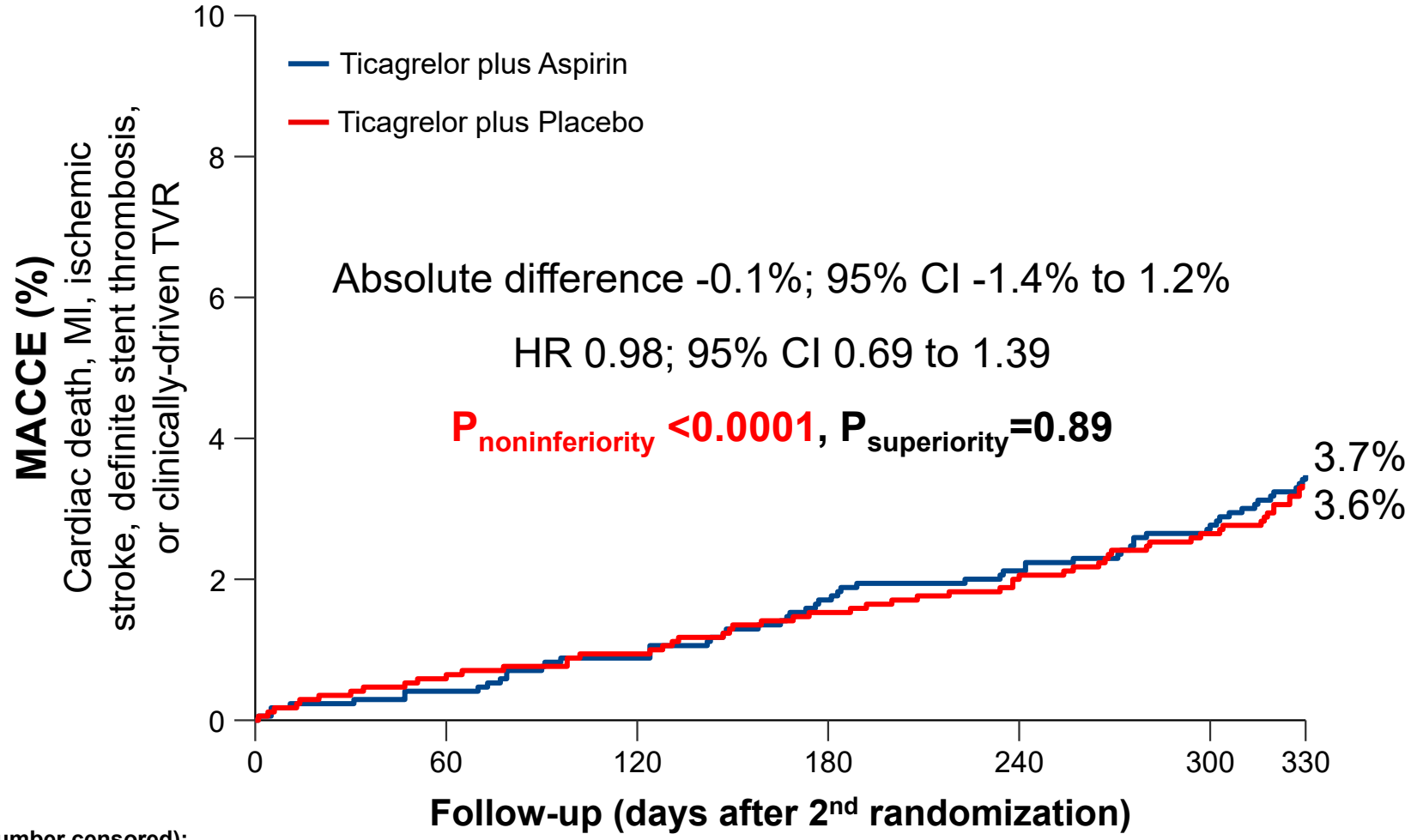
- Subgroup analysis -

No significant interactions were present in 12 pre-specified subgroups

	Clinically-relevant bleeding, n/N (%)				
	Ticagrelor Plus Placebo	Ticagrelor Plus Aspirin	Hazard ratio (95%CI)	Hazard ratio (95%CI)	$P_{interaction}$
Overall	35/1700 (2.1%)	78/1700 (4.6%)		0.45 (0.30-0.66)	
Age, years					0.30
≥65	23/729 (3.2%)	40/703 (5.7%)		0.55 (0.33-0.93)	
<65	12/971 (1.2%)	38/997 (3.8%)		0.32 (0.17-0.62)	
Sex					0.73
Male	24/1264 (1.9%)	56/1257 (4.5%)		0.42 (0.26-0.68)	
Female	11/436 (2.5%)	22/443 (5.0%)		0.50 (0.24-1.03)	
Race					0.69
Chinese	32/1476 (2.2%)	74/1519 (4.9%)		0.44 (0.29-0.67)	
Non-Chinese	3/224 (1.3%)	4/181 (2.2%)		0.59 (0.13-2.64)	
Diabetes mellitus					0.92
Yes	11/540 (2.0%)	25/535 (4.7%)		0.43 (0.21-0.87)	
No	24/1160 (2.1%)	53/1165 (4.6%)		0.45 (0.28-0.73)	
Renal dysfunction					0.82
Yes	4/119 (3.4%)	8/129 (6.2%)		0.48 (0.15-1.61)	
No	31/1581 (2.0%)	70/1571 (4.5%)		0.44 (0.29-0.67)	
BMI, Kg/m²					0.28
≤25	16/845 (1.9%)	43/842 (5.1%)		0.36 (0.20-0.64)	
>25	19/855 (2.2%)	35/858 (4.1%)		0.54 (0.31-0.95)	
Initial presentation					0.59
Unstable angina	14/668 (2.1%)	29/708 (4.1%)		0.51 (0.27-0.96)	
Non-STEMI	14/545 (2.6%)	32/531 (6.0%)		0.42 (0.22-0.79)	
STEMI	7/487 (1.4%)	17/461 (3.7%)		0.38 (0.16-0.92)	
History of prior MI					0.85
Yes	2/143 (1.4%)	8/156 (5.1%)		0.33 (0.07-1.59)	
No	33/1557 (2.1%)	70/1544 (4.5%)		0.47 (0.31-0.70)	
Biomarker positive					0.60
Yes	21/1032 (2.0%)	49/992 (4.9%)		0.41 (0.24-0.68)	
No	14/668 (2.1%)	29/708 (4.1%)		0.51 (0.27-0.96)	
Stent length (mm)					0.69
≥60	6/258 (2.3%)	15/245 (6.1%)		0.38 (0.15-0.98)	
<60	29/1441 (2.0%)	63/1454 (4.3%)		0.46 (0.30-0.71)	
Multivessel disease					0.32
Yes	10/534 (1.9%)	30/545 (5.5%)		0.33 (0.16-0.69)	
No	25/1166 (2.1%)	48/1155 (4.2%)		0.52 (0.32-0.84)	
IVUS-guided PCI					0.27
Yes	12/856 (1.4%)	35/857 (4.1%)		0.34 (0.18-0.66)	
No	23/844 (2.7%)	43/843 (4.2%)		0.53 (0.32-0.88)	



Primary Safety Endpoint: MACCE



Number at risk (number censored):

Ticagrelor plus Aspirin	1700 (0)	1693 (0)	1684 (1)	1669 (2)	1659 (2)	1648 (2)	1636 (2)
Ticagrelor plus Placebo	1700 (0)	1690 (0)	1684 (0)	1673 (1)	1664 (1)	1652 (2)	1640 (2)

MACCE and NACE Endpoints

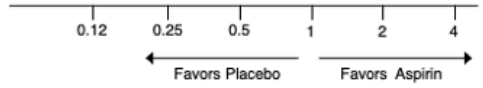
Between 1- and 12-months post-PCI	Ticagrelor plus placebo (N = 1700)	Ticagrelor plus aspirin (N = 1700)	Hazard ratio (95% CI)	P-value
Primary endpoint: MACCE	61 (3.6%)	63 (3.7%)	0.98 (0.69 – 1.39)	0.89
Secondary endpoints				
All-cause death	12 (0.7%)	13 (0.8%)	0.93 (0.42 – 2.03)	0.84
Cardiac death	8 (0.5%)	7 (0.4%)	1.15 (0.42 – 3.18)	0.46
Stroke	20 (1.2%)	24 (1.4%)	0.83 (0.46 – 1.50)	0.54
Myocardial infarction	17 (1.0%)	11 (0.7%)	1.45 (0.67 – 3.23)	0.27
Procedural MI	1 (0.05%)	1 (0.05%)	-	0.88
Non-procedural MI	16 (0.9%)	11 (0.7%)	1.42 (0.66 – 3.03)	0.29
Repeat revascularization	40 (2.4%)	41 (2.4%)	0.99 (0.64 – 1.53)	0.95
TVR	33 (2.0%)	36 (2.1%)	0.93 (0.58 – 1.49)	0.75
TLR	27 (1.6%)	28 (1.7%)	0.97 (0.57 – 1.65)	0.92
Stent thrombosis, definite or probable	5 (0.3%)	5 (0.3%)	0.97 (0.28 – 3.40)	0.96
Definite	3 (0.2%)	5 (0.3%)	0.59 (0.14 – 2.51)	0.47
Probable	2 (0.1%)	0 (0.0%)	-	-
Net adverse clinical events (NACE): MACCE or BARC types 1-5 bleeding	97 (5.7%)	140 (8.2%)	0.68 (0.53 – 0.88)	**0.007**

MACCE

- Subgroup analysis -

No significant interactions were present in 12 pre-specified subgroups, except possibly for age

	MACCE , n/N (%)		Hazard ratio (95%CI)	$P_{interaction}$
	Ticagrelor Plus Placebo	Ticagrelor Plus Aspirin		
Overall	61/1700 (3.6%)	63/1700 (3.7%)	0.98 (0.69-1.39)	
Age, years				0.02
≥65	39/729 (5%)	26/703 (4%)	1.48 (0.90-2.43)	
<65	22/971 (2%)	37/997 (4%)	0.61 (0.36-1.03)	
Sex				0.48
Male	48/1264 (4%)	46/1257 (4%)	1.05 (0.70-1.57)	
Female	13/436 (3%)	17/443 (4%)	0.77 (0.37-1.58)	
Race				0.28
Chinese	59/1476 (4%)	59/1519 (4%)	1.03 (0.72-1.48)	
Non-Chinese	2/224 (1%)	4/181 (2%)	0.38 (0.07-2.06)	
Diabetes mellitus				0.09
Yes	28/540 (5%)	20/535 (4%)	1.43 (0.80-2.53)	
No	33/1160 (3%)	43/1165 (4%)	0.77 (0.49-1.21)	
Renal dysfunction				0.43
Yes	6/119 (5%)	4/129 (3%)	1.64 (0.45-5.95)	
No	55/1581 (4%)	59/1571 (4%)	0.93 (0.65-1.35)	
BMI, Kg/m²				0.07
≤25	32/845 (4%)	23/842 (3%)	1.42 (0.83-2.43)	
>25	29/855 (3%)	40/858 (5%)	0.73 (0.45-1.18)	
Initial presentation				0.39
Unstable angina	28/668 (4%)	29/708 (4%)	1.03 (0.61-1.74)	
Non-STEMI	12/545 (2%)	23/531 (4%)	0.51 (0.25-1.03)	
STEMI	21/487 (4%)	11/461 (3%)	1.76 (0.85-3.68)	
History of prior MI				0.16
Yes	9/143 (6%)	5/156 (3%)	2.11 (0.70-6.34)	
No	52/1557 (3%)	58/1544 (4%)	0.89 (0.61-1.30)	
Biomarker positive				0.78
Yes	33/1032 (3%)	34/992 (3%)	0.93 (0.58-1.50)	
No	28/668 (4%)	29/708 (4%)	1.03 (0.61-1.74)	
Stent length, mm				0.61
≥60	12/258 (5%)	10/245 (4%)	1.21 (0.52-2.81)	
<60	49/1441 (3%)	53/1454 (4%)	0.94 (0.64-1.39)	
Multivessel disease				0.50
Yes	25/534 (5%)	30/545 (6%)	0.84 (0.49-1.42)	
No	36/1166 (3%)	33/1155 (3%)	1.09 (0.68-1.74)	
IVUS-guided PCI (first randomization)				0.10
Yes	16/856 (2%)	25/857 (3%)	0.65 (0.35-1.22)	
No	45/844 (5%)	38/843 (5%)	1.20 (0.78-1.85)	



Limitations

1. The primary efficacy endpoint included minor bleeding (BARC type 2)
   - However, major bleeding was also significantly reduced with ticagrelor monotherapy (BARC types 3 or 5, TIMI major or minor, GUSTO and ISTH)
2. Non-inferiority for MACCE was tested with an absolute margin of 2.5%. Given the lower observed ischemic event rate in the control group than anticipated (3.7% vs. 6.2%), this relative margin is wide
   - Given the 95% CI of the observed difference, it is likely that the absolute MACCE rate with ticagrelor monotherapy is <1.2% greater than with ticagrelor + aspirin
3. ~40% of pts had biomarker-negative unstable angina
   - hs-troponin assays were not widely available in China and Pakistan during the enrollment period, and it is likely that many of these pts had NSTEMI
4. 88.1% of pts were from China, possibly affecting the generalizability of the results

Conclusions and Clinical Implications

- The present results demonstrate that in pts with ACS treated with PCI with contemporary DES who are free from major adverse ischemic and bleeding events after 1 month on DAPT, treatment with ticagrelor alone between 1 and 12 months will decrease clinically-relevant and major bleeding while providing similar protection from MACCE compared with ticagrelor plus aspirin

- These results, in concert with prior trials, warrant updating the guidelines and change in practice to treat most pts with ACS after PCI with 1-month DAPT only followed by conversion to SAPT with a potent $P2Y_{12}$ inhibitor (with the strongest evidence supporting ticagrelor)

The ULTIMATE-DAPT trial is now published in *The Lancet*

April 7, 2024

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