Effects of Acute Colchicine Administration Prior to Percutaneous Coronary Intervention: The COLCHICINE-PCI Randomized Trial

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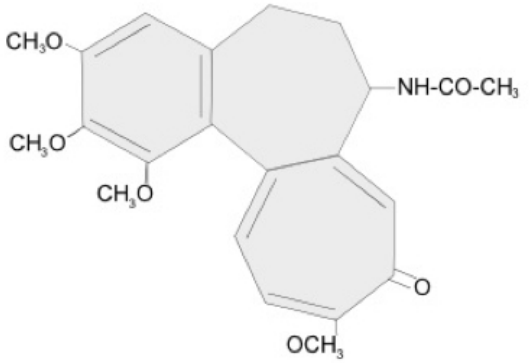
Background

- Vascular injury and inflammation during percutaneous coronary intervention (PCI):
  - Induces rapid neutrophil recruitment to the site of mechanical trauma
  - Is associated with endothelial cell and microvascular dysfunction
  - Is an independent predictor of subsequent major adverse cardiovascular events (MACE) even in the contemporary era of second-generation drug-eluting stents
- CANTOS demonstrated a reduction in recurrent MACE after myocardial infarction (MI) with anti-interleukin (IL)-1β antibody



Colchicine

- Inhibits neutrophil chemotaxis and activity in response to vascular injury
- Inhibits inflammasome signaling and reduces the production of active IL-1β
- Reduces neutrophil-platelet interaction and aggregation
- The standard regimen of colchicine used for gout flares (1.2 mg PO followed by 0.6 mg PO administered over an hour) has rapid onset of anti-inflammatory effects

Hypothesis

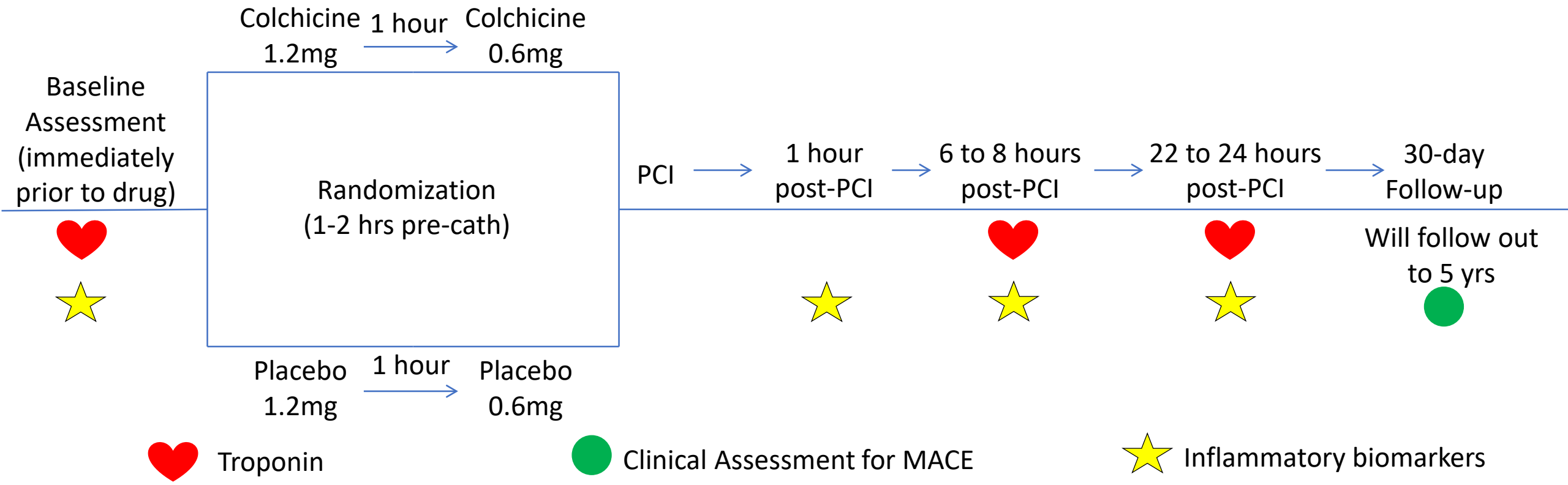
- An acute, pre-procedural oral administration of 1.8 mg of colchicine reduces biomarker evidence of PCI-related inflammation and myocardial injury when compared with placebo.

Patient Population

- Adults with suspected ischemic heart disease or acute coronary syndromes referred for clinically-indicated coronary angiography with possible PCI
- Key exclusion criteria
  - Use of oral steroids or NSAIDs
  - New high-intensity statin <24 hours prior to randomization
  - GFR <30 mL/min or on dialysis
  - Use of strong CYP3A4/P-glycoprotein inhibitor
  - Use of colchicine

Trial Design

- Investigator-initiated, randomized, double-blind, placebo-controlled, single-center trial with a nested inflammatory biomarker substudy



COLCHICINE-PCI Study Outcomes

- Primary outcome
  - PCI-related myocardial injury (Universal Definition)
    - Normal baseline cardiac biomarker: Troponin I above the upper reference limit (URL)
    - Elevated baseline cardiac biomarker but falling: Increase in Troponin I by ≥20%
- Key secondary outcomes
  - Composite of death from any cause, non-fatal myocardial infarction (MI), or target vessel revascularization at 30 days
    - Non-fatal MI was defined as type 1 or type 4a (Tn >5x URL) MI per the Universal Definition
  - PCI-related MI as defined by the Society for Cardiovascular Angiography and Interventions (Tn >70x URL)

Inflammatory Biomarker Substudy Endpoints

- Primary endpoint
  - Between group difference in the change in plasma IL-6 concentration from baseline to 1 hour post-PCI
- Secondary endpoints
  - Change in plasma IL-6 concentration from baseline to 6 and 24 hours post-PCI
  - Change in plasma IL-1β concentration from baseline to 1, 6, and 24 hours post-PCI
  - Change in hsCRP concentration from baseline to 24 hours post-PCI

Statistics

- COLCHICINE-PCI
  - Sample size of 400 subjects who undergo PCI to provide 80% power to detect 40% relative risk reduction in the primary outcome
  - Outcomes compared between groups using chi-square test
- Inflammatory biomarker substudy
  - 258 subjects to provide 80% power to detect a 35% relative reduction in the substudy primary endpoint → increased to 280 subjects *a priori* to adjust for a possible floor effect
  - Differences in the percent change in biomarkers from baseline to post-PCI were compared using the Mann-Whitney test
  - Sensitivity analysis was performed using a linear mixed model analysis
- Significance was set at a two-sided alpha level of 0.05

Enrollment

1453 patients referred for coronary angiography with possible PCI screened

549 (38%) Excluded:

129 (23%) Use of oral steroids or NSAIDs

124 (23%) High-intensity statin load <24 hrs pre-procedure

86 (16%) GFR <30mL/minute or on dialysis

37 (7%) Strong CYP3A4/P-glycoprotein inhibitors

34 (6%) Chronic colchicine use

20 (4%) Active malignancy or infection

1 (0.2%) History of myelodysplasia

66 (12%) Enrolled in a competing study

36 (7%) Unable to consent

16 (3%) Other

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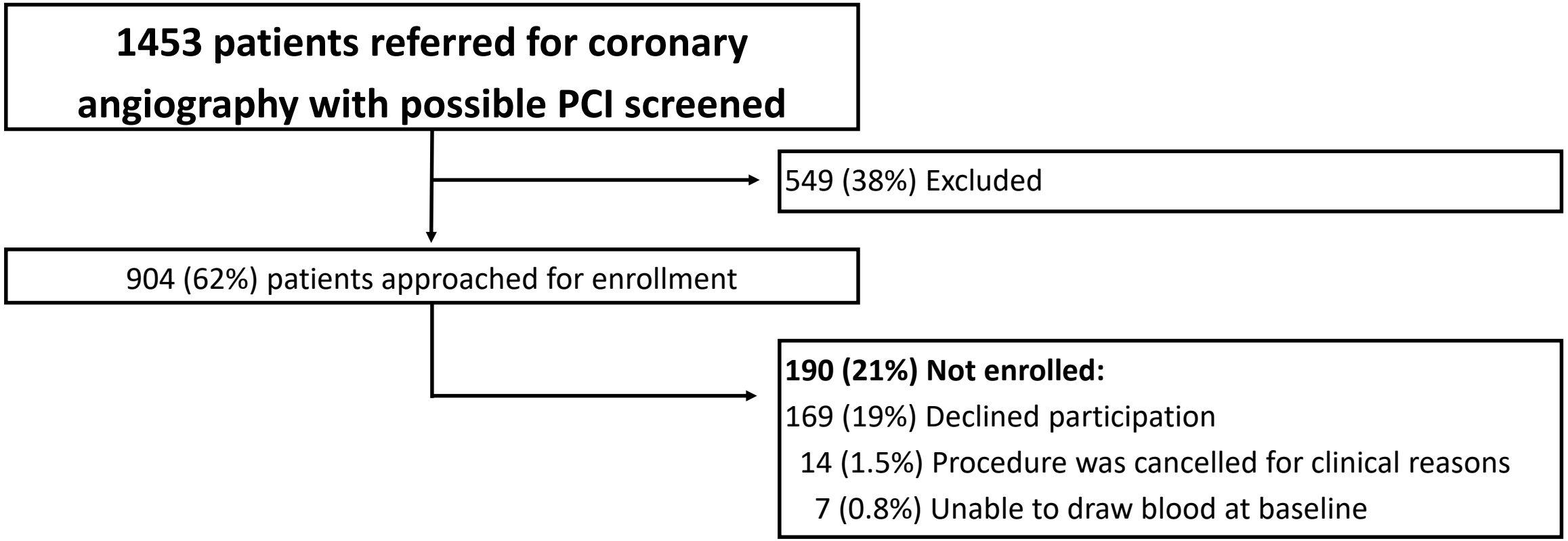
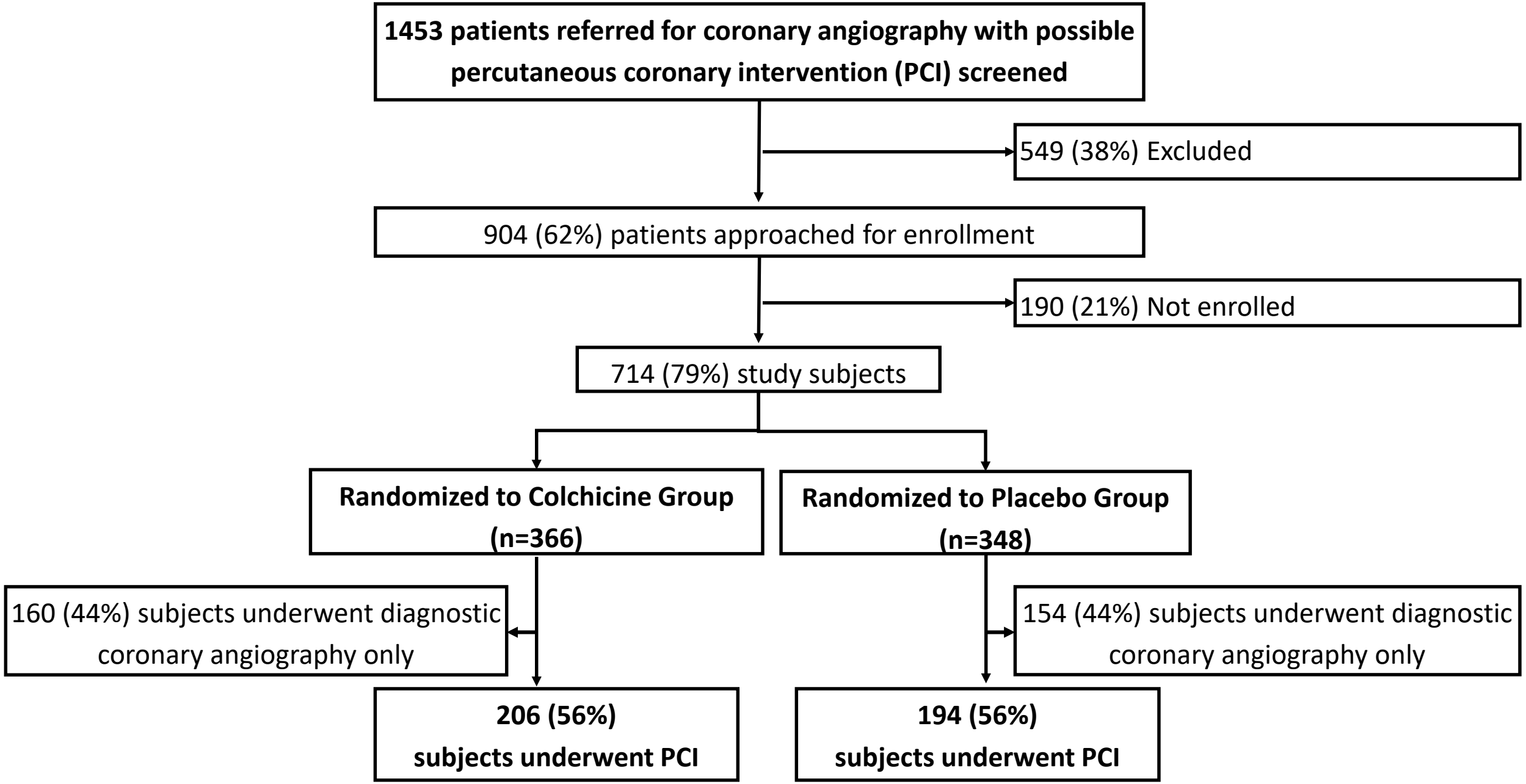
Enrollment (continued)




1453 patients referred for coronary angiography with possible percutaneous coronary intervention (PCI) screened
549 (38%) Excluded
904 (62%) patients approached for enrollment
190 (21%) Not enrolled
714 (79%) study subjects
Randomized to Colchicine Group (n=366)
Randomized to Placebo Group (n=348)
160 (44%) subjects underwent diagnostic coronary angiography only
154 (44%) subjects underwent diagnostic coronary angiography only
206 (56%) subjects underwent PCI
194 (56%) subjects underwent PCI

Baseline Characteristics

	Colchicine (n=206)	Placebo (n=194)	p-value
Age, years	65.9 ± 9.9	66.6 ± 10.2	0.54
Male sex, %	93.7	93.3	0.99
Race, %			0.28
White	77.2	74.2	
Black	19.9	19.1	
Asian	2.4	6.2	
Hispanic ethnicity, %	20.4	22.2	0.76
Hypertension, %	93.2	90.2	0.36
Dyslipidemia, %	88.3	89.2	0.92
Diabetes mellitus, %	55.3	60.3	0.37
Prior myocardial infarction, %	24.8	26.8	0.72
Renal insufficiency, %	21.8	19.6	0.67
Current tobacco use, %	20.9	23.7	0.57
Acute coronary syndrome, %	50.0	49.0	0.92
Abnormal troponin at baseline, %	31.1	27.3	0.48

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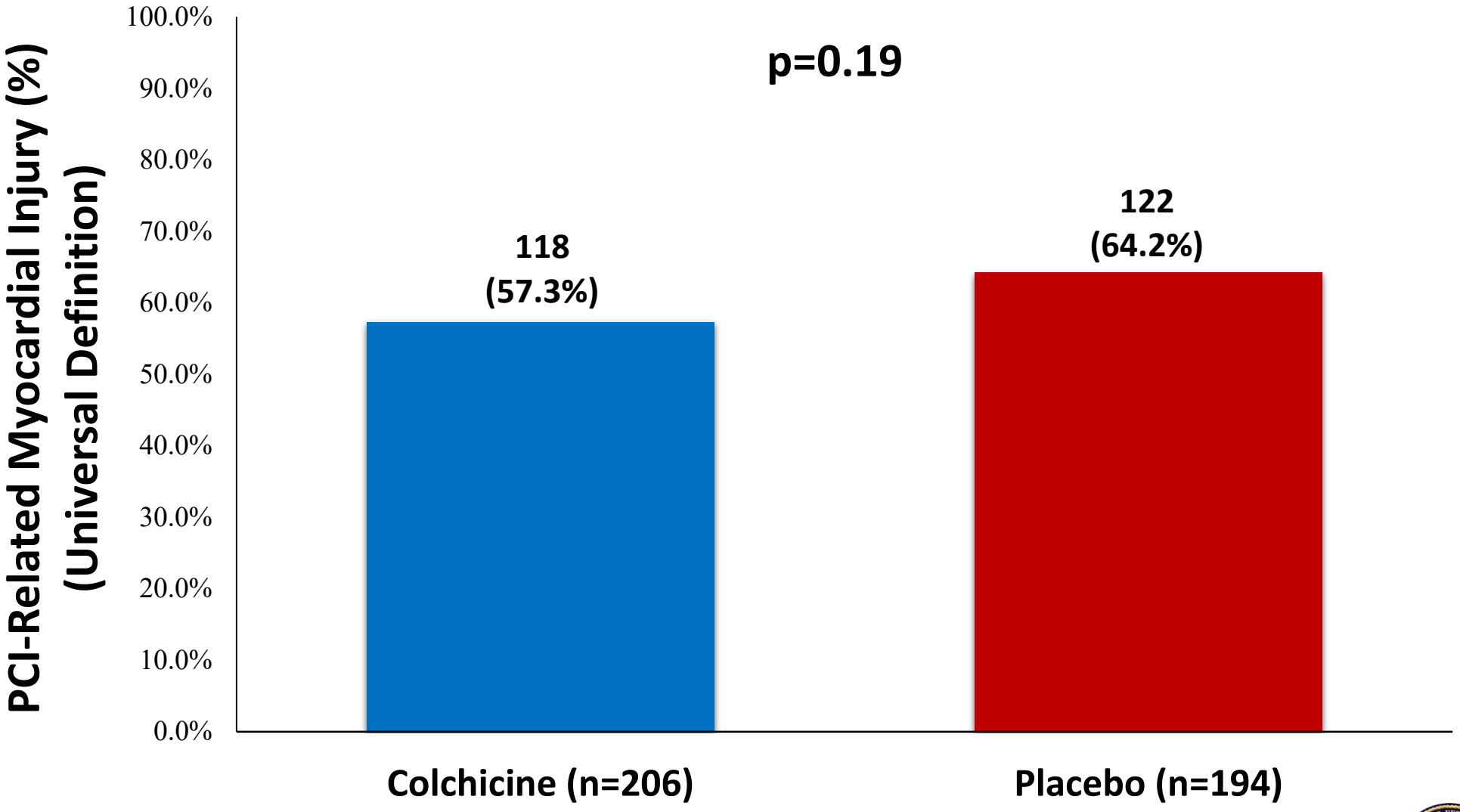
Coronary and Procedural Characteristics

	Colchicine (n=206)	Placebo (n=194)	p-value
Multivessel coronary artery disease, %	55.8	53.1	0.65
Left main disease, %	2.4	3.1	0.92
LAD artery, %	72.8	70.1	0.62
Circumflex artery disease, %	50.5	50.5	0.99
Right coronary artery disease, %	49.0	54.6	0.31
Total stent length, mm	28 [18, 38]	28 [18, 38]	0.79
Number of inflations	6 [4, 8]	6 [4, 8]	0.68
Any intra-procedural complication (e.g., abrupt closure, major dissection), %	3.9	5.2	0.71

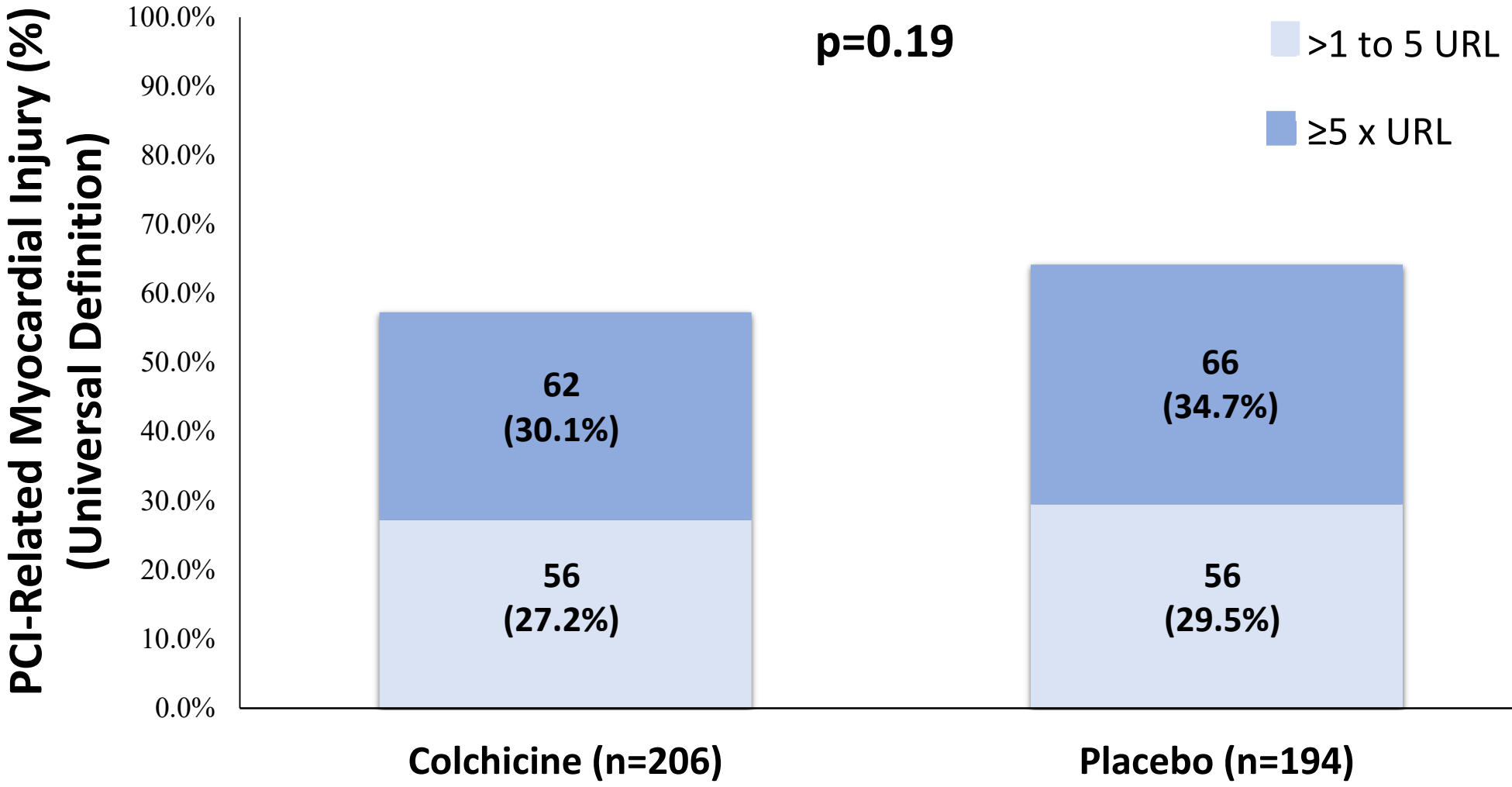
Lesion Level Characteristics

	Colchicine (n=258)	Placebo (n=242)	p-value
Pre-procedural TIMI 0/1 flow, %	5.0	7.9	0.95
Stent diameter, mm^2	3.00 [2.50, 3.00]	2.75 [2.50, 3.00]	0.59
Maximum pressure on last device, atm	20 ± 4	20 ± 5	0.65
Bifurcation, %	15.5	14.9	0.89
Heavily calcified, %	13.6	18.6	0.63
Tortuous, %	6.6	10.3	0.74
Chronic total occlusion, %	5.4	4.5	0.86
Lesion length >33 mm, %	22.1	21.5	0.77
Thrombus, %	4.7	3.7	0.91
Re-stenosis, %	6.2	4.5	0.82

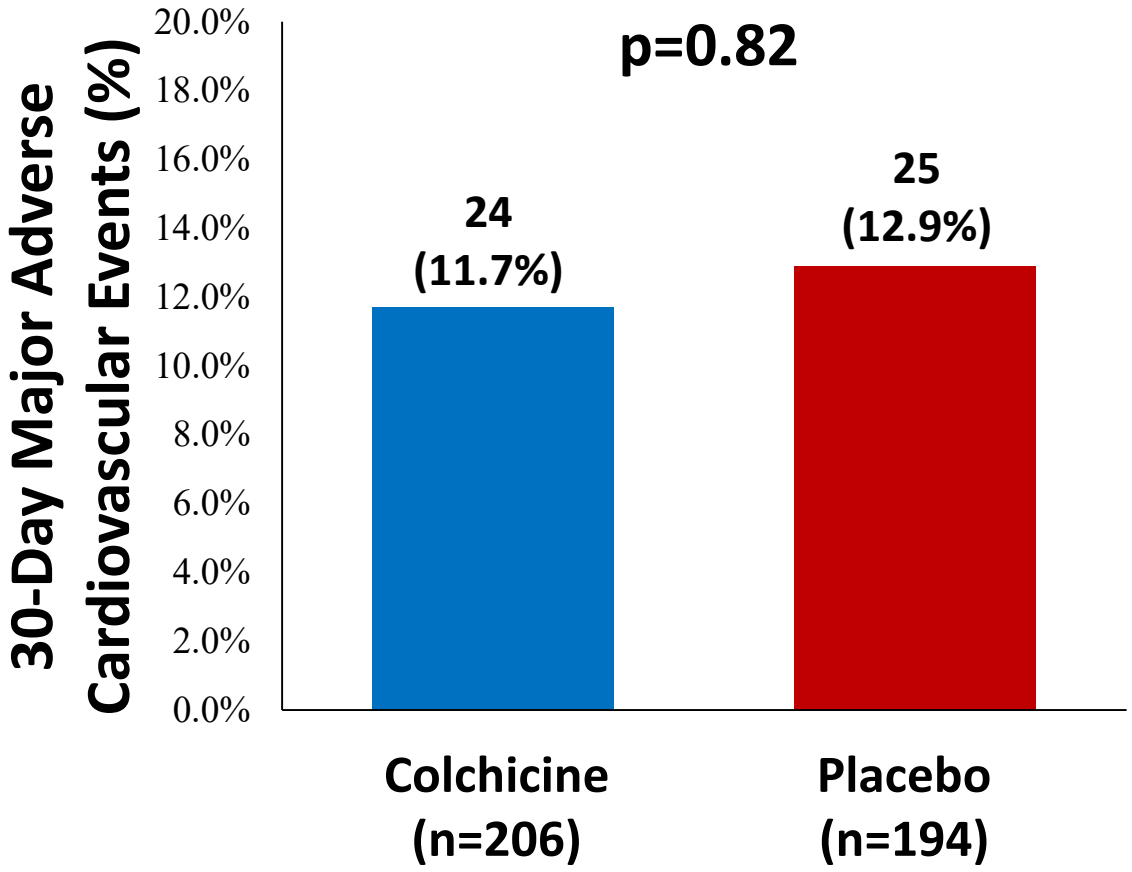
Primary Outcome



Primary Outcome



Key Secondary Outcomes



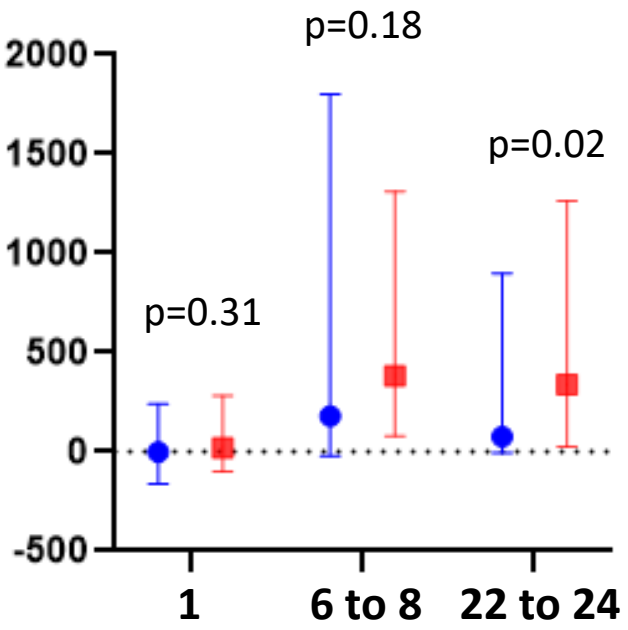
	Colchicine (n=206)	Placebo (n=194)	p-value
30-day MACE			
Type 4a MI (Universal)	23 (11.2)	23 (12.1)	0.89
Type 1 MI (Universal)	0	1 (0.5)	0.49
TVR	0	0	--
All-cause mortality	1 (0.5)	1 (0.5)	0.99

	Colchicine (n=206)	Placebo (n=194)	p-value
PCI-related MI (SCAI)	6 (2.9)	9 (4.7)	0.49

Inflammatory Biomarker Substudy Endpoints

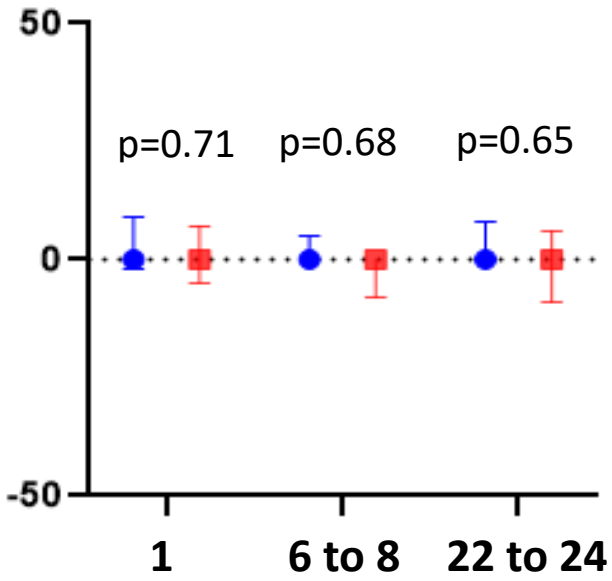
Colchicine Placebo

Percent Change in IL-6 Concentration Compared to Baseline (%)



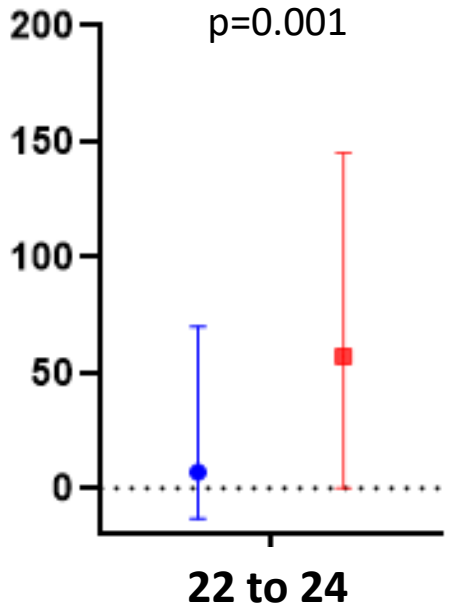
Time Post-PCI (hours)

Percent Change in IL-1β Concentration Compared to Baseline (%)



Time Post-PCI (hours)

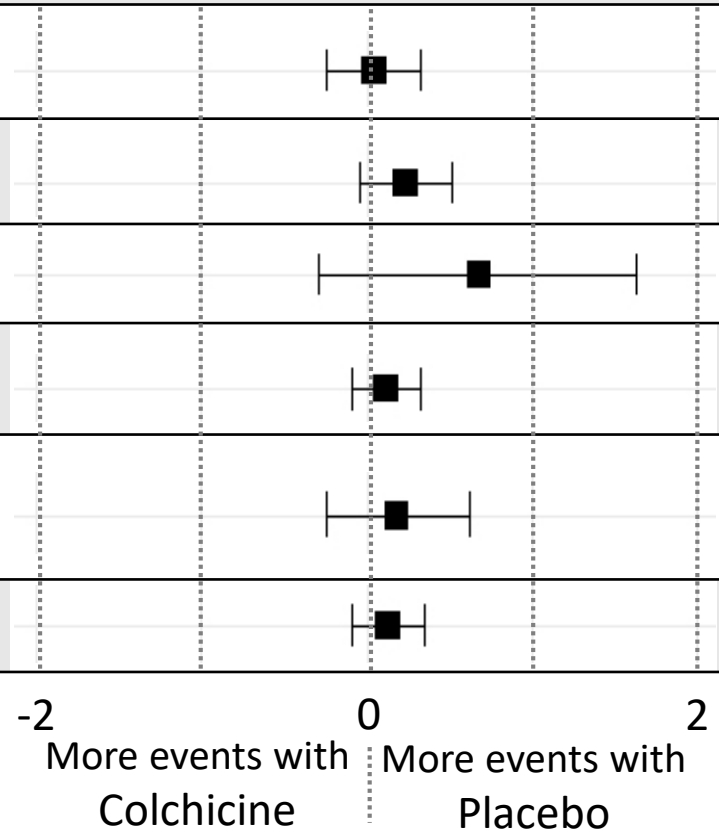
Percent Change in hsCRP Concentration Compared to Baseline (%)



Time Post-PCI (hours)

Pre-Specified Subgroups

	n		PCI-Related Myocardial Injury	
	Colchicine	Placebo	Standardized Difference	p-value
Acute coronary syndrome as indication for PCI	103	95		0.86
No acute coronary syndrome as indication for PCI	103	99		0.13
Presence of an intra-procedural complication	8	10		0.41
Absence of an intra-procedural complication	198	184		0.31
New treatment with high-intensity statin therapy 24 hours to 7 days pre-procedure	42	42		0.54
Stable statin therapy	164	152		0.30



Adverse Events

* Denotes p-value <0.05

	Colchicine (n=366)	Placebo (n=348)
Chest pain, %	9.0	7.2
Gastrointestinal symptoms, % *	9.3	3.2
Hypersensitivity reaction, %	1.1	1.1
Access site discomfort, %	1.1	1.1
Hemodynamic instability, % *	0	1.4
Fever, %	0	0.6
Elevated creatinine, %	0.3	0.6
Ischemic stroke, %	0.3	0
Fluid overload, %	0.3	0.3
Urinary retention, %	0.5	0
Bleeding, %	0.3	0.6
Palpitations, %	0	0.3
Headache, %	0.3	0
Serious adverse events total, % *	1.4	3.4

Summary

- This investigator-initiated, single-site prospective randomized double-blind study is the first to evaluate the effects of an acute pre-procedural administration of colchicine versus placebo on markers of myocardial injury and inflammation in patients undergoing PCI
- Compared with placebo, short-term pre-procedural colchicine:
  - Did not reduce PCI-related myocardial injury or MACE at 30 days
  - Did attenuate PCI-related increase in IL-6 and hsCRP concentration at 24 hours post-PCI
- This is the first study to demonstrate that an oral load of colchicine prevents a rise of inflammatory biomarkers in acute injury.

Limitations

- The majority male population enrolled within the VA system limits interpretation for women undergoing PCI.
- Observations are limited to
  - The selected acute pre-procedural dosing regimen, and
  - The short-term timepoints for biomarkers of myocardial injury and inflammation
- Genetic data were not collected in the current trial to determine predisposition to colchicine resistance.

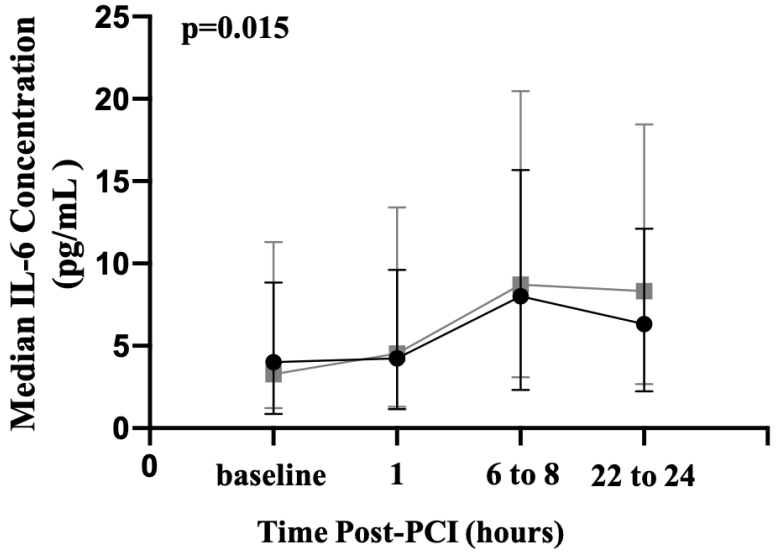
We dedicate this study to the memory of Steven Sedlis, MD, Professor of Medicine, consummate mentor, and dedicated physician who devoted his career to improving patient outcomes, educating the next generation of physicians, and advancing science. Dr. Sedlis played a pivotal role with his contributions to both the design and conduct of this trial.

Back-Up Slides

Linear Mixed Model Analysis

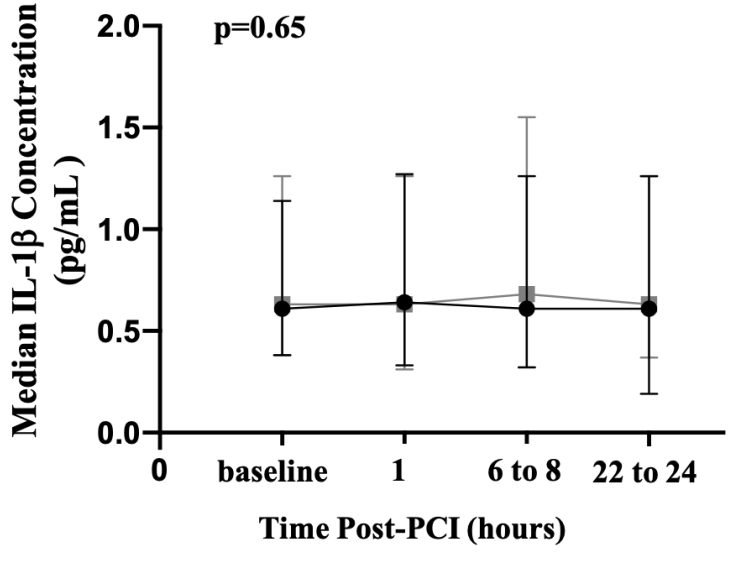
● Colchicine (n=141) ■ Placebo (n=139)

A)



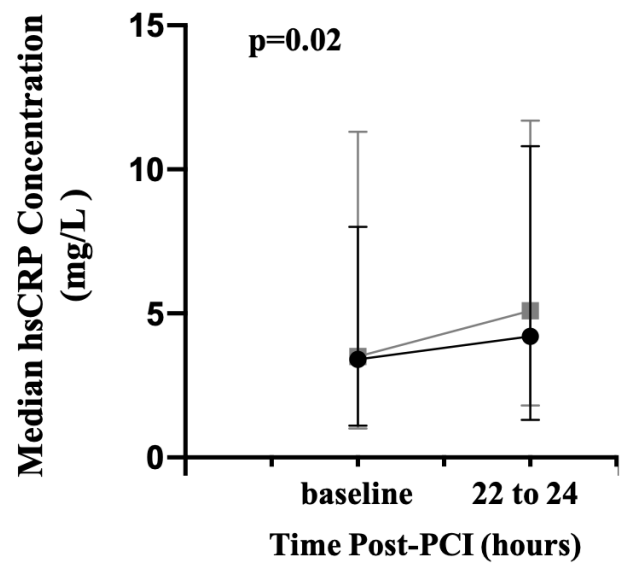
Median [IQR]	Colchicine	4.00 [0.87,8.85]	4.23 [1.16,9.61]	8.00 [2.33,15.68]	6.32 [2.24,12.12]
	Placebo	3.29 [1.22,11.31]	4.53 [1.30,13.40]	8.71 [3.10,20.46]	8.32 [2.67,18.44]

B)



Median [IQR]	Colchicine	0.61 [0.38, 1.14]	0.64 [0.33, 1.27]	0.61 [0.32, 1.26]	0.61 [0.19, 1.26]
	Placebo	3.29 [1.22,11.31]	4.53 [1.30,13.40]	8.71 [3.10,20.46]	8.32 [2.67,18.44]

C)



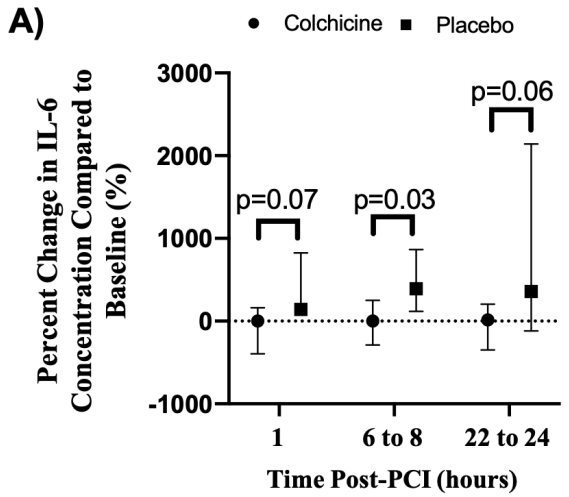
Median [IQR]	Colchicine	3.4 [1.1,8.0]	4.2 [1.3,10.8]
	Placebo	3.5 [1.0,11.3]	5.1 [1.8,11.7]

Clinical Outcomes by ACS Presentation

	Colchicine	Placebo	p-value
Subjects with acute coronary syndrome	**n=103**	**n=95**	
PCI-related myocardial injury	57 (55.3)	53 (57.6)	0.86
30-day major adverse cardiovascular events	17 (16.5)	12 (12.6)	0.57
Type 4a myocardial infarction (Universal Definition)	17 (16.5)	10 (10.9)	0.35
Type 1 myocardial infarction (Universal Definition)	0	1 (1.1)	0.48
Target vessel revascularization	0	0	0.99
All-cause mortality	0	1 (1.1)	0.48
PCI-related myocardial infarction (SCAI definition)	4 (3.9)	3 (3.3)	0.99
Subjects without acute coronary syndrome	**n=103**	**n=99**	
PCI-related myocardial injury	61 (59.2)	69 (70.4)	0.13
30-day major adverse cardiovascular events	6 (5.8)	13 (13.1)	0.12
Type 4a myocardial infarction (Universal Definition)	6 (5.8)	13 (13.3)	0.12
Type 1 myocardial infarction (Universal Definition)	0	0	0.99
Target vessel revascularization	0	0	0.99
All-cause mortality	0	0	0.99
PCI-related myocardial infarction (SCAI definition)	2 (1.9)	6 (6.1)	0.16

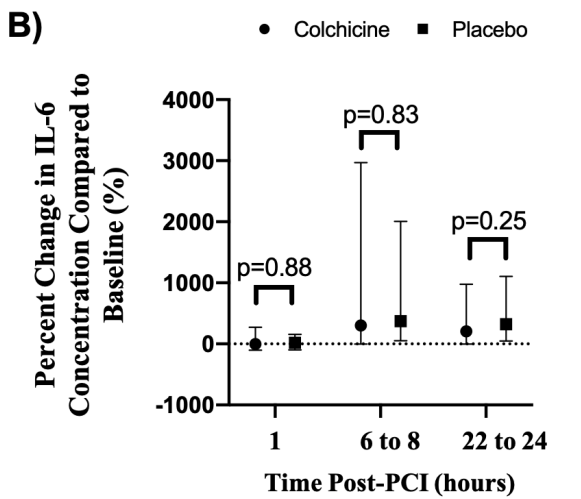
Change in Biomarkers Stratified by Abnormal or Normal Baseline Troponin

Abnormal Baseline Troponin



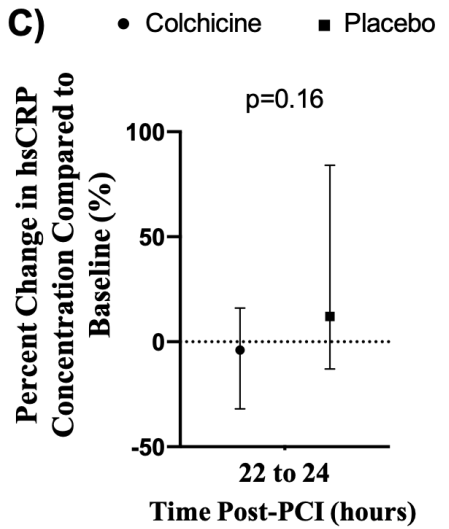
n	Colchicine	40	21	36
	Placebo	34	19	30
Median [IQR]	Colchicine	0 [-396,163]	0 [-290,253]	16 [-348, 205]
	Placebo	140 [-118,825]	393 [119,864]	359 [-117,2143]

Normal Baseline Troponin



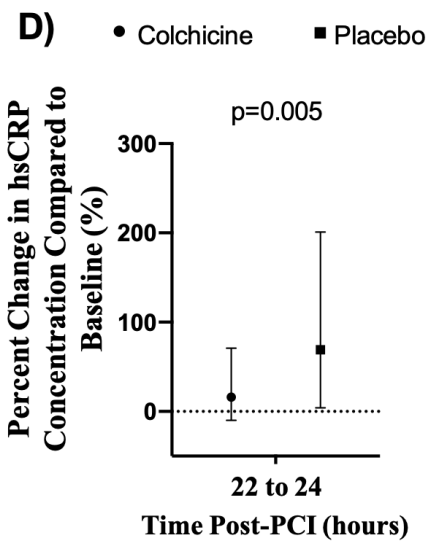
n	Colchicine	100	57	84
	Placebo	104	57	92
Median [IQR]	Colchicine	0 [-104,271]	304 [0,2968]	208 [0,977]
	Placebo	18 [-97,158]	372 [53,2007]	324 [47,1106]

Abnormal Baseline Troponin



n	Colchicine	29
	Placebo	24
Median [IQR]	Colchicine	-4 [-32,16]
	Placebo	12 [-13,84]

Normal Baseline Troponin



n	Colchicine	67
	Placebo	73
Median [IQR]	Colchicine	16 [-10,71]
	Placebo	69 [-4,201]