Implications of the ISCHEMIA Trial on Patient Selection for CTO-PCI

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ISCHEMIA Trial: Summary

- 5179 patients randomized to INV vs. CON
 - Largest treatment strategy trial of SIHD
- Enrolled high-risk subset
 - 54% severe ischemia; 76% with multivessel CAD; 47% with proximal LAD disease (CCTA)
- Cath and Revascularization
 - Invasive strategy: 80% revascularized (74% PCI/26% CABG)
 - Conservative strategy: 28% cath; 23% revasc at 4-years
- Medication Therapy
 - 95% statins; 66% high intensity statin; LDL 64 mg/dl; SBP 129 mm Hg

Which Patients were Not Enrolled in ISCHEMIA?

- ACS within 2 months
- EF < 35%
- NYHA Class III-IV HF
- Unacceptable angina despite medical therapy
- PCI or CABG within 1 year
- Severe left main disease

ISCHEMIA Trial *Summary of Major Findings*

- No difference in primary or major secondary endpoint
- To improve survival
 - No improvement in survival compared with MT
 - INV-Reduction (0.3%/year) in cardiac death at long term follow-up
- To prevent other cardiovascular events
 - INV Reduces spontaneous MI, unstable angina and lowers CV stays
- To improve quality of life
 - INV results in faster and more durable relief of angina in symptomatic patients

Randomized Trials of CTO Revascularization vs. OMT *Primary Endpoint*

- EXPLORE: 304 patients with STEMI and CTO
 CMRILVEF and LVEDV at 4 months: No difference
- EURO-CTO: 396 patients with CTO (planned 600)

SAQ Angina frequency and QoL at 12 m: PCI better

- DECISION CTO: 834 patients with CTO (planned 1284)
 - Death, MI, stroke, or any repeat revascularization at 5 years: No difference
 - SAQ angina frequency and QoL: No difference

ISCHEMIA CTO Substudy Study Population



Number and Location of CTOs

- Total of 1797 CTOs in 1470 patients
- The mean number of CTO was 1.22 (SE 0.46)



ISCHEMIA CTO Substudy Baseline Characteristics

		CTO (N=1470)	No CTO (N=1643)	P-Value
	Demographics			
	Age (Q1, Q3)	62 (56, 69)	64 (57, 70)	<0.01
	Female sex	17%	21%	0.01
C	Clinical history			
	Hypertension	69%	68%	0.90
	Diabetes	41%	41%	0.72
	Prior MI	19%	13%	<0.01
	Prior Heart Failure	4%	2%	<0.01
	Angina History	89%	91%	0.03
	New onset angina within 3 months	17%	23%	<0.01

ISCHEMIA CTO Substudy *Stress Test Characteristics*

	CTO (N=1470)	No CTO (N=1643)	P-Value
Stress imaging overall			<0.01
Severe	537/1040 (52%)	522/1051 (50%)	-
Moderate	422/1040 (41%)	401/1051 (38%)	-
Mild/None	81/1040 (8%)	128/1051 (12%)	-
Exercise tolerance test			0.30
Severe	368/410 (90%)	492/567 (87%)	-
Moderate	30/410 (7%)	49/567 (9%)	-
Mild/None	12/410 (3%)	26/567 (5%)	-

ISCHEMIA CTO Substudy CCTA Characteristics

	CTO (N=1470)	No CTO (N=1643)	P-Value
Number of diseased vessels (≥50% stenosis)			<0.01
1	14.4% (181/1254)	25.1% (316/1261)	-
2	30.1% (378/1254)	33.1% (418/1261)	-
3	55.4% (695/1254)	41.8% (527/1261)	-
LAD	84.2% (1238/1470)	84.5% (1389/1643)	0.84
Proximal LAD disease	46.0% (676/1470)	46.4% (762/1643)	0.85
RCA	72.2% (1061/1470)	57.5% (944/1643)	<0.01
LCX	72.9% (1071/1470)	59.0% (969/1643)	<0.01

ISCHEMIA CTO Substudy *Medication Use by CTO Status*



ISCHEMIA CTO Substudy

Cardiac Cath/Revasc by CTO Status and Randomized Group



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ISCHEMIA CTO Substudy Aggregate Outcome based on CTO Status

			Hazard Ratio and 95% Cl	
Event	Total Events (4-year No CTO (n=1643)	Cumulative Incid CTO (n=1470)	ence)	P-value
Primary endpoint	177 (12.1%)	186 (14.1%)		0.058
CV Death/MI	160 (11.1%)	168 (12.8%)		0.077
Net benefit	193 (13.3%)	203 (15.5%)		0.047
All-cause death	69 (4.9%)	80 (6.3%)		0.063
CV death	40 (2.6%)	63 (5.2%)		0.003
MI	131 (9.1%)	126 (9.4%)		0.407
Procedural MI	32 (2.1%)	32 (2.1%)		0.645
Spontaneous MI	91 (6.4%)	87 (6.7%)		0.477
Unstable Angina	13 (0.8%)	12 (0.9%)		0.794
Heart failure	16 (0.8%)	19 (1.5%)		- 0.359
Stroke	23 (1.6%)	22 (1.8%)		0.692
Death/MI/UA/HF/RCA	203 (14.3%)	201 (15.0%)		0.139
All-cause death/MI	187 (13.3%)	183 (13.7%)		0.203
Death/MI/UA/HF/RCA/Stroke	219 (15.5%)	218 (16.4%)		0.112

Models adjusted for age, sex, treatment, eGFR, diabetes, and ejection fraction

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ISCHEMIA CTO Substudy

Outcomes by Treatment Group and CTO Status

INV (N=1567) 81 (10.2%) 90 (13.2%) 73 (9.5%) 80 (11.7%) 88 (11.2%) 100 (14.6%) 34 (4.8%)	CON (N=1546) 96 (13.5%) 96 (15.1%) 87 (12.3%) 88 (13.9%) 105 (15.0%) 103 (16.4%)			-3.4% (-6.9%, 0.2%) -1.9% (-6.0%, 2.2%) -2.8% (-6.3%, 0.6%) -2.1% (-6.0%, 1.8%)	0.590
81 (10.2%) 90 (13.2%) 73 (9.5%) 80 (11.7%) 88 (11.2%) 100 (14.6%) 34 (4.8%)	96 (13.5%) 96 (15.1%) 87 (12.3%) 88 (13.9%) 105 (15.0%) 103 (16.4%)	•		-3.4% (-6.9%, 0.2%) -1.9% (-6.0%, 2.2%) -2.8% (-6.3%, 0.6%) -2.1% (-6.0%, 1.8%)	0.590 0.787
81 (10.2%) 90 (13.2%) 73 (9.5%) 80 (11.7%) 88 (11.2%) 100 (14.6%) 34 (4.8%)	96 (13.5%) 96 (15.1%) 87 (12.3%) 88 (13.9%) 105 (15.0%) 103 (16.4%)			-3.4% (-6.9%, 0.2%) -1.9% (-6.0%, 2.2%) -2.8% (-6.3%, 0.6%) -2.1% (-6.0%, 1.8%)	0.787
73 (9.5%) 80 (11.7%) 88 (11.2%) 100 (14.6%) 34 (4.8%)	87 (12.3%) 88 (13.9%) 105 (15.0%) 103 (16.4%)			-2.8% (-6.3%, 0.6%) -2.1% (-6.0%, 1.8%)	0.787
88 (11.2%) 100 (14.6%) 34 (4.8%)	105 (15.0%) 103 (16.4%)	8			
34 (4.8%)	105 (10.470)			-3.8% (-7.5%, -0.0%)	0.497
34 (4.8%)				-1.0 /0 (-0. 1 /0. 2.0 /0)	0.503
41 (6.8%)	35 (5.0%) 39 (5.7%)	-		-0.2% (-2.8%, 2.4%) 1.2% (-1.9%, 4.2%)	
16 (1.8%) 31 (5.3%)	24 (3.4%) 32 (5.0%)			-1.6% (-3.4%, 0.2%) 0.3% (-2.5%, 3.1%)	0.259
63 (8.3%) 61 (8.6%)	68 (9.5%) 65 (10.2%)			-1.2% (-4.3%, 2.0%)	0.844
0110.0700					1.000
25 (3.1%) 24 (3.1%)	7 (1.1%) 8 (1.2%)			1.9% (0.5%, 3.4%) 1.9% (0.5%, 3.4%)	
34 (4.6%)	57 (7.8%) 55 (8.6%)			-3.1% (-5.8%, -0.4%)	0.726
					0.604
6 (0.6%) 4 (0.5%)	7 (1.0%) 8 (1.3%)			-0.4% (-1.3%, 0.6%) -0.7% (-1.8%, 0.3%)	
7 (0.6%) 15 (2.5%)	9 (0.9%) 4 (0.6%)			-0.4% (-1.3%, 0.5%) 1.9% (0.4%, 3.4%)	0.009
11 (1.3%) 14 (2.1%)	12 (1.8%)			-0.5% (-1.9%, 0.9%) 0.6% (-1.1%, 2.3%)	0.319
14 (2.170)	0 (1.570)		_	0.070 (11170, 2.070)	0.743
98 (13.0%) 99 (14.5%)	105 (15.1%) 102 (15.6%)		B	-2.0% (-6.0%, 1.9%) -1.1% (-5.3%, 3.1%)	
90 (12.3%) 89 (13.0%)	97 (13.9%) 94 (14.3%)			-1.5% (-5.4%, 2.4%) -1.3% (-5.4%, 2.8%)	0.938
105 (14.1%) 109 (15.9%)	114 (16.5%) 109 (16.9%)		• · · · · · · · · · · · · · · · · · · ·	-2.4% (-6.5%, 1.7%) -1.0% (-5.4%, 3.4%)	0.638
	-1	0 -5	0 5		
	34 (4.8%) 41 (6.8%) 16 (1.8%) 31 (5.3%) 63 (8.3%) 61 (8.6%) 25 (3.1%) 24 (3.1%) 34 (4.6%) 32 (4.8%) 6 (0.6%) 4 (0.5%) 7 (0.6%) 15 (2.5%) 11 (1.3%) 14 (2.1%) 98 (13.0%) 99 (14.5%) 90 (12.3%) 89 (13.0%) 105 (14.1%) 109 (15.9%)	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$

ISCHEMIA CTO Substudy *Quality of Life- Treatment Effect*



ISCHEMIA CTO Substudy *Quality of Life- Treatment Effect*



ISCHEMIA CTO Substudy Study Limitations

- Analysis is based on intention to treat
 - As treated (based on actual status of CTO revascularization) is in progress
 - The determination of CTO was based on coronary CTA
 - Patients who were very symptomatic, or dissatisfied with medical therapy were excluded and the results do not apply to such patients

ISCHEMIA CTO Substudy Summary

- Almost 1 in 2 randomized patients in ISCHEMIA who underwent coronary CTA had at least 1 CTO. Sample size more than EURO CTO and DECISION CTO combined together.
- Patients with CTO when compared to no-CTO in ISCHEMIA had:
 - Greater amount of ischemia
 - Worse prognosis with higher risk of cardiovascular events
 - Similar quality of life including angina-specific quality of life

Implications of the ISCHEMIA Trial on Patient Selection for CTO-PCI

- Aggressive GDMT for all patients
- Consider invasive strategy and revascularization
 - To improve angina related health status in symptomatic patients
 - Reduce spontaneous MI
 - No significant difference in death