

Claudication Treatment
Comparative Effectiveness: 6
Month Outcomes from the
CLEVER Study

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Background

- Invasive stent procedures have not been shown to offer better outcomes for claudication than supervised exercise
- Stent procedures are reimbursed, supervised exercise is not
- Patients with proximal (aortoiliac) PAD are often very symptomatic, and are generally considered ideal for stent revascularization

Hypothesis and Study Design

- Stent revascularization will result in at least 30% more improvement in treadmill walking performance than supervised exercise
- Observer-blinded, multicenter randomized clinical trial with 3 treatment groups: optimal medical care (OMC), stent revascularization (ST), and supervised exercise (SE)

Population

- Moderate to severe claudication
- Hemodynamically significant aortoiliac PAD
 - If iliac, on the most symptomatic side
- No comorbid conditions that limit walking
- No rest pain, tissue loss, etc.
- SFA disease allowed, but not intervention routinely done

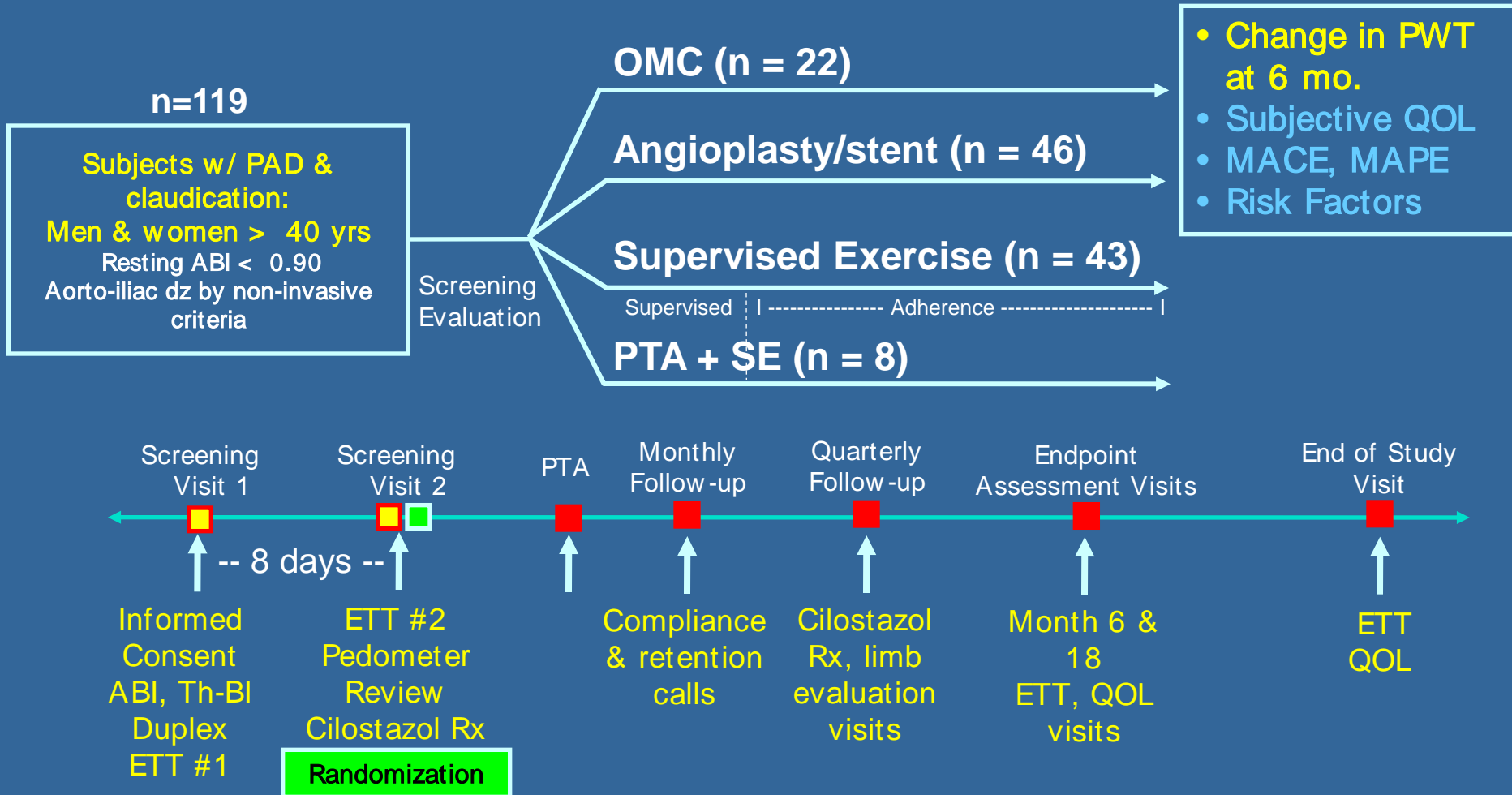
Treatments

- OMC – cilostazol 100 mg bid as tolerated, written and oral advice about exercise and diet, monthly contact
- ST – OMC plus stent revascularization of aortoiliac PAD
- SE – OMC plus 78 weeks of supervised exercise, 3X wk, 1 hr sessions

Endpoints

- Peak walking time (PWT) on a graded treadmill test (Gardner protocol)
- COT, quality of life (QOL), cardiovascular disease biomarkers
- Follow-up at 6 months
 - 18 months pending

The CLEVER Trial



CLEVER 6 MONTH ANALYSES
Total Randomized ITT Analysis Set
(N = 119)

**OPTIMAL MEDICAL CARE
(OMC)
(N = 22)**

Withdrew Consent
(N = 1)

Exited Due to "Other"
(N = 1)

**AVAILABLE FOR
6 MONTH ANALYSIS
(N = 20)**

1/20 missed visit; 19 received tx

**SUPERVISED EXERCISE
(SE) ONLY
(N = 43)**

Withdrew Consent
(N = 2)

Withdrew from Study,
Reason "Unknown"
(N = 1)

Exited Due to "Other"
(N = 1)

Lost to Follow-Up
(N = 1)

**AVAILABLE FOR
6 MONTH ANALYSIS
(N = 38)**

2/38 missed visit; 36 received tx

**STENT
(ST) ONLY
(N = 46)**

Withdrew Consent
(N = 2)

Exited Due to
"Femur Fracture"
(N = 1)

Missed 6M Visit
(N = 1)

Lost to Follow-Up
(N = 1)

**AVAILABLE FOR
6 MONTH ANALYSIS
(N = 41)**

2/41 missed visit; 37 of remaining 39 received tx

**SE + ST
(N = 8)**

Withdrew Consent
(N = 1)

**AVAILABLE FOR
6 MONTH ANALYSIS
(N = 7)**

0/7 missed visit; 7 received tx

**TOTAL AVAILABLE FOR 6 MONTH ANALYSIS
(N = 106)**

5/106 missed visit; 99 of Remaining 101 received tx; no crossovers occurred prior to the 6 month visit

Demographic and Background Characteristics

	OMC	SE + OMC	ST + OMC	P-value
	(N=22)	(N=43)	(N=46)	
Age, Mean±SD (N), years	62.4±8.0	64.1±9.5	64.9±10.2	0.56
Male (%)	72.70%	48.80%	69.60%	0.074
Diabetes	23.80%	18.60%	28.90%	0.564
Hypertension	95.50%	88.40%	76.10%	0.104
Current smoking	54.50%	58.10%	50.00%	0.751
Former smoking	40.90%	32.60%	41.30%	0.668
Hypercholesterolemia	81.80%	83.70%	76.10%	0.675
Prior TIA	4.50%	4.70%	6.50%	1
Prior stroke	0.00%	18.60%	2.20%	0.007
Prior angina	4.50%	0.00%	4.30%	0.416
Stable angina	100.00%	N/A	100.00%	N/A
Unstable angina (%)	0.00%	N/A	0.00%	N/A
Prior myocardial infarction	31.80%	14.00%	21.70%	0.485
Prior percutaneous Coronary Revascularization	22.70%	9.30%	23.90%	0.166
Prior coronary artery bypass graft surgery	18.20%	11.60%	23.90%	0.306
Prior lower extremity endovascular procedure	4.50%	2.30%	6.50%	0.84
Prior lower extremity open surgical revascularization procedure	4.50%	2.30%	4.30%	1
Prior to randomization use of cilostazol	13.60%	18.60%	19.60%	0.9

Baseline Physiologic, Biochemical and Anthropomorphic Characteristics

Blood pressure				
SBP (mmHg)	136.2±13.7	134.9±22.0	135.9±18.5	0.953
DBP (mmHg)	77.2±10.1	73.9±12.0 (43)	73.5±11.5	0.453
Lipid profile				
LDL (mg/dl)	105.1±38.6	101.2±41.8	104.1±30.1	0.903
HDL (mg/dl)	48.3±12.3	49.3±15.5	48.2±14.5	0.935
Triglycerides (mg/dl)	135.3±69.7	146.8±81.9	147.4±141.7	0.902
HbA1c (%)	6.3±1.3	6.1±1.1	6.4±1.2	0.499
C-reactive protein(mg/dl)	1.0±0.2	1.0±0.3	1.0±0.3	0.866
Fibrinogen (mg/dl)	408.4±66.1	416.4±105.1	400.3±96.3	0.737
ABI	0.7±0.2	0.7±0.2	0.66±0.2	0.381
Anthropomorphic characteristics				
BMI	28.1±5.9	27.7±5.2	29.3±6.0	0.412
Waist circumference (cm)	100.2±14.2	97.3±13.6	102.3±14.9	0.269
Baseline Performance, mean±SD (N)				
PWT (mins)	5.5±2.5	5.3±2.3	5.2±2.0	0.854
COT (mins)	1.7±0.7	1.6±0.9	1.7±0.83	0.891
7-day free-living steps	21971±16499	16803±10610	20480±1276 5	0.33
Hourly free-living steps	343±411	264±216	291±196	0.582

Primary and Secondary Endpoints

	OMC (N=22)	SE + OMC (N=43)	ST+ OMC (N=46)	OMC vs. SE	OMC vs. ST	SE vs. ST
	Mean SD (N) and	Mean SD (N) and	Mean SD (N) and	95% CI and P- Value	95% CI and P- Value	95% CI and P-Value
	Range (min, max)	Range (min, max)	Range (min, max)			
Primary Endpoint						
Change of PWT from baseline to 6 month (mins)	1.2 2.6	5.8 4.6	3.7 4.9	-4.6 [-6.5,-2.7]	-2.5 [-4.4,-0.6]	2.1 [- 0.0,4.2]
	(-4.11,8.60)	(-0.38,16.89)	(-4.65,14.60)	(p=<0.0001)	(p=0.021)	(p=0.042)
Secondary Endpoints						
Change of COT from baseline to 6 month	0.7 1.1	3.0 2.9	3.6 4.2	-2.2 [-3.3,-1.2]	-2.9 [-4.3,-1.5],	-0.7 [- 2.3,0.9],
	(-0.6,3.3)	(-0.8,10.7)	(-0.3,17.9)	(p=0.003)	(p=0.006)	(p=0.425)
Change of hourly free-living steps from Baseline to 6 month	-5.6 109.4	72.6 138.7	114.3 273.9	-78.3 [-157.2, 0.7]	-120.0 [-236.5, - 3.5]	-41.7 [- 156.8, 73.4]
	(-268.2,168.9)	(-185.2, 425.7)	(-192.6, 976.4)	(p=0.0625)	(p=0.1024)	(p=0.4661)
Change of ABI from baseline to 6 month	0.01 0.10 (19)	0.03 0.11 (36)	0.29 0.33 (40)	-0.0 [-0.1,0.0]	-0.3[-0.4,-0.2],	-0.3 [-0.4,- 0.2]
	(-0.24,0.12)	(-0.23,0.37)	(-0.12,1.59)	(p=0.578)	(p=<0.001)	(p=<0.001)

Baseline QOL Data

Measure	OMC	SE + OMC	ST + OMC	SE vs. OMC	ST vs. OCM	SE vs. ST
	(N=22)	(N=43)	(N=46)	P-value	P-value	P-value
	Mean±SD	Mean±SD	Mean±SD			
Baseline Scores						
SF-12 Physical	32.4±11.0	32.1±8.7	34.3±9.3	0.911	0.497	0.446
SF-12 Mental	52.6±8.1	54.3±9.2	53.1±11.4	0.411	0.862	0.69
WIQ Pain Severity	28.4±20.8	30.2±25.9	33.7±27.5	0.842	0.423	0.292
WIQ Walking Distance	22.9±26.8	12.7±11.6	17.9±15.5	0.023	0.359	0.061
WIQ Walking Speed	26.4±20.8	21.4±16.9	26.3±18.3	0.252	0.93	0.19
WIQ Stair Climbing	33.5±30.0	30.3±22.1	33.2±23.7	0.542	0.889	0.561
PAQ Physical Limitation	34.7±27.6	29.3±18.0	30.5±19.5	0.489	0.497	0.985
PAQ Symptoms	43.9±19.4	41.3±18.9	48.2±21.1	0.57	0.463	0.122
PAQ Symptom Stability	50.0±15.4	45.8±17.4	49.4±15.5	0.398	0.926	0.493
PAQ Social Limitation	60.4±31.7	54.7±25.9	55.0±26.5	0.547	0.449	0.793
PAQ Treatment Satisfaction	73.5±26.8	74.0±19.9	79.3±22.0	0.911	0.317	0.249
PAQ Quality of Life	43.9±25.0	43.3±18.7	46.1±19.4	0.981	0.684	0.582
PAQ Summary	46.2±23.0	42.5±16.0	45.3±18.3	0.511	0.849	0.566

Follow-up: QOL Change Scores

Measure	OMC	SE + OMC	ST + OMC	SE vs. OMC	ST vs. OCM	SE vs. ST
	(N=22)	(N=43)	(N=46)	P-value	P-value	P-value
	Mean±SD	Mean±SD	Mean±SD			
Change from Baseline to 6 Months						
SF-12 Physical	1.3±10.7	5.8±1.0	6.6±8.5	0.058	0.031	0.951
SF-12 Mental	-2.3±7.8	-2.9±12.2	-1.7±9.9	0.95	0.669	0.714
WIQ Pain Severity	16.3±34.7	26.3±36.3	40.4±43.9	0.251	<0.001	0.014
WIQ Walking Distance	-0.5±26.0	25.1±27.6	43.8±42.2	0.007	<0.001	0.029
WIQ Walking Speed	1.5±15.7	16.5±19.7	30.8±31.0	0.007	<0.001	0.007
WIQ Stair Climbing	10.2±29.3	24.0±20.9	29.3±39.1	0.071	0.051	0.539
PAQ Physical Limitation	1.6±22.3	15.0±20.4	28.1±30.9	0.028	<0.001	0.035
PAQ Symptoms	2.3±17.8	15.8±21.4	29.2±27.4	0.019	<0.001	0.001
PAQ Symptom Stability	13.1±28.1	28.7±30.9	9.8±26.2	0.076	0.646	0.008
PAQ Social Limitation	-8.9±29.9	8.5±29.7	17.6±30.2	0.03	0.001	0.131
PAQ Treatment Satisfaction	-5.9±21.5	2.6±24.0	4.0±25.9	0.098	0.01	0.229
PAQ Quality of Life	3.0±28.1	16.7±20.9	30.4±28.3	0.03	<0.001	0.005
PAQ Summary	-1.5±19.5	13.2±17.3	28.0±26.4	0.005	<0.001	0.001

Conclusions

- In patients with moderate to severe claudication and hemodynamically significant aortoiliac disease, supervised exercise offers *better* treadmill walking performance outcomes than stent revascularization
- Paradoxically, those who underwent stent revascularization reported, in general, better QOL than those treated with supervised exercise