Outcomes Following Percutaneous Coronary Intervention in Patients Previously Considered "Without Option": A Subgroup Analysis of the PACIFIC Trial

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Objectives: *The present study assesses clinical outcomes in patients from the Potential Angina Class Improvement From Intramyocardial Channels (PACIFIC) trial of percutaneous transmyocardial revascularization (PTMR) who had previously been considered "no-option," but who subsequently underwent percutaneous coronary intervention (PCI) for continuing symptoms.*

Background: *Patients with advanced symptomatic coronary artery disease who are not candidates for coronary artery bypass grafting (CABG) or PCI comprise an important group, for which no established treatment is currently available. These patients have been described as having "no option," and are currently targeted for various experimental therapies. One such proposed therapy, PTMR, was recently examined in the PACIFIC trial. A subgroup of patients in this trial subsequently underwent PCI, although to initially qualify for the study they had previously been considered as unsuitable for PCI and as having "no option." The therapeutic benefit of PCI for patients of this type is unknown.*

Methods: *A retrospective analysis was performed on data obtained from all subjects of the PACIFIC study who underwent PCI within the 12-month follow-up period.*

Results: *Ten subjects originally randomized to PTMR and 11 subjects from the medical treatment group underwent PCI. Most had undergone at least one prior PCI and at least one CABG, and there was a high prevalence of cardiovascular risk factors. Despite excellent immediate procedural success, PCI resulted in only modest, statistically nonsignificant increases in mean exercise duration, small improvements in angina status, and no significant improvements in quality of life.*

Conclusions: *These data suggest that PCI provides only marginal—if any—symptomatic benefit in these patients.*
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Introduction

Medical therapy, coronary artery bypass grafting, and percutaneous coronary intervention (PCI) are effective in relieving angina in the majority of patients with coronary artery disease. With advances in therapeutic approaches to coronary artery disease and acute myocardial infarction that have occurred in the past 20 years, patients are more likely to survive into advanced stages of the disease process.[1] Accordingly, it is increasingly common to encounter patients with advanced coronary artery disease and disabling symptoms refractory to medical therapy who are not optimal candidates for bypass grafting or PCI. These "no-option" patients, who may comprise up to 12% of patients referred for diagnostic cardiac catheterization, tend to have diffuse coronary disease, small distal vessels, or chronic total occlusions[1] and are currently targeted for various experimental treatments, such as angiogenic protein and gene therapies and, in the past, transmyocardial laser revascularization.

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Faced with "no-option" patients experiencing ongoing intractable symptoms, interventional cardiologists frequently attempt traditional PCI in less-than-optimal candidates. With recent developments in drug-eluting stents and distal protection devices, this tendency may increase. However, the outcome following conventional revascularization procedures in patients considered to be "no-option" is unknown.

The Potential Angina Class Improvement From Intramyocardial Channels (PACIFIC) trial was a prospective randomized study comparing percutaneous transmyocardial revascularization (PTMR) to continued medical therapy in patients considered to be "no option," with ongoing medically refractory angina.[2] However, because of continued intractable symptoms, 21 of these patients underwent "out-of-protocol" PCI. The purpose of the present study was to assess the clinical outcomes following PCI in these patients.

The PACIFIC trial randomized 221 patients to receive either PTMR with a holmium:YAG laser plus continued medical therapy (PTMR group, n = 110), or medical therapy alone (medical group, n = 111), the results of which have been previously published.[2] A retrospective analysis was performed on data obtained from 21 subjects of the PACIFIC study who underwent PCI within the 12-month follow-up period of the trial. Ten of these subjects were from the PTMR group and 11 were from the medical group. The postrandomization interventions occurred out of protocol, and were not generally performed or reviewed by the PACIFIC investigators. Continuing severe angina in this group of patients prompted their referring physicians to attempt these interventions.

Patients selected for the PACIFIC trial were considered by the study investigators to have no other conventional treatment options, either with PCI or bypass surgery. Other inclusion criteria included Canadian Cardiovascular Society Angina Scale III or IV despite maximum tolerated doses of at least two antianginal drugs, a left ventricular ejection fraction of at least 30% and reversible perfusion defects on baseline dipyridamole thallium stress testing. All patients underwent baseline assessment, which included an echocardiogram, a dipyridamole thallium stress test, exercise treadmill test, and a self-administered Seattle angina questionnaire within 3 months of randomization.[3] PTMR was performed as previously reported, and patients were evaluated at 3, 6, and 12 months with a Canadian Cardiovascular Society Angina Scale test, exercise tolerance test, and Seattle angina questionnaire; results were reviewed at a core laboratory.[2,4]

Data are presented as mean (± SD) or median (range) values as indicated in the text. Baseline characteristics were compared using Fisher's exact test for dichotomous data or Wilcoxon's test for continuous data. Exercise and angina questionnaire data were compared between time points using paired *t*-tests with Bonferroni correction for multiple comparisons. Canadian Cardiovascular Society Angina Scale data were compared between time points using Kruskall–Wallis test and between groups at each time point with Wilcoxon rank sum test. In all cases, $P < 0.05$ was considered statistically significant.

The baseline characteristics of the 10 subjects from the PTMR group and the 11 subjects from the medical treatment alone group who underwent PCI did not differ significantly (Table 1). Of these 21 subjects, all except two in the PTMR group had undergone at least one prior revascularization procedure, and most (16) had undergone at least one prior PCI and at least one bypass procedure. A greater number of the medical group subjects tended to have hyperlipidemia and were

Table 1. Baseline Demographics

Characteristics	PTMR + MEDs	MEDs
Number	10	11
Age	63.5 (42–73)	59 (42–84)
Male	8 (80%)	9 (82%)
Diabetes	5 (50%)	5 (45%)
Hypertension	7 (70%)	8 (82%)
Hyperlipidemia	5 (50%)	9 (82%)
Smoking		
None	2 (20%)	4 (36%)
Current	1 (10%)	2 (18%)
Former	7 (70%)	5 (45%)
Family history of CAD	7 (70%)	8 (72%)
Prior myocardial infarction	5 (50%)	8 (72%)
Prior interventions		
None	2 (20%)	0 (%)
CABG alone	0 (0%)	0 (0%)
PCI alone	2 (20%)	1 (9%)
CABG + PCI	2 (20%)	1 (9%)
Ejection fraction	56 (45–72)	50 (40–60)
Number of defects on Persantine thallium test		
Fixed	0 (0–11)	0 (0–10)
Reversible	3.5 (0–6)	5 (0–10)
Canadian Cardiovascular Society Angina Scale		
Class III	6 (60%)	8 (72%)
Class IV	4 (40%)	3 (27%)

CAD, coronary artery disease; CABG, coronary artery bypass grafting; PTCA, percutaneous transluminal coronary angioplasty.

Table 2. Procedural Details

Number of patients	21
Number of lesions	23
Acute procedural success	100%
Vessels treated	
Left anterior descending	6
Left circumflex	4
Right coronary artery	4
Vascular graft	6
Others	3
Restenotic lesion	3
Maximum balloon size*	
Native vessel lesions (n = 15)	3 (2–3.5)
Vascular graft lesions (n = 6)	3.5 (3–4)
Stent	14
Rotoblator	3
IIb/IIIa	2

*Mean (range) values.

either current or former smokers. Ejection fraction, ischemic burden (indexed by the number of reversible defects on Persantine thallium scans), and angina class distribution were similar between groups.

Procedural details are summarized in Table 2. Twenty-three lesions were treated in 21 patients. The vessels listed as "other" were one left anterior descending septal branch and two *ramus intermedius* vessels. Three restenotic lesions were treated with rotablation only; most of the remaining de novo lesions (14/20) were treated with stenting. Procedural success, defined by individual operators, was 100%. The time intervals between study enrollment, randomization, the last study follow-up prior to PCI, the PCI, and the post-PCI follow-up, summarized in Table 3, did not differ significantly between the groups.

Mean (±SD) Canadian Cardiovascular Society Angina Scale and exercise tolerance test data are summarized in Figure 1 at the various stages of the study (results were similar when expressed as median values). Overall, reductions in angina class were observed from baseline to the post-PCI conditions that were similar in the medical and PTMR groups (mean reduction in Canadian Cardiovascular Society Angina Scale of 1.0 ± 1.2 and 1.2 ± 1.2, respectively; $P < 0.05$ for within-group differences in each case, P = NS between groups). Essentially, all of this change in the medical group occurred following PCI (0.9 ± 1.4 class reduction pre- versus post-PCI). However, in the PTMR group subjects, a small reduction in angina occurred following each invasive procedure (0.7 ± 1.0 class reduction from baseline to pre-PCI; 0.6 ± 1.4 class reduction pre- versus post-PCI).

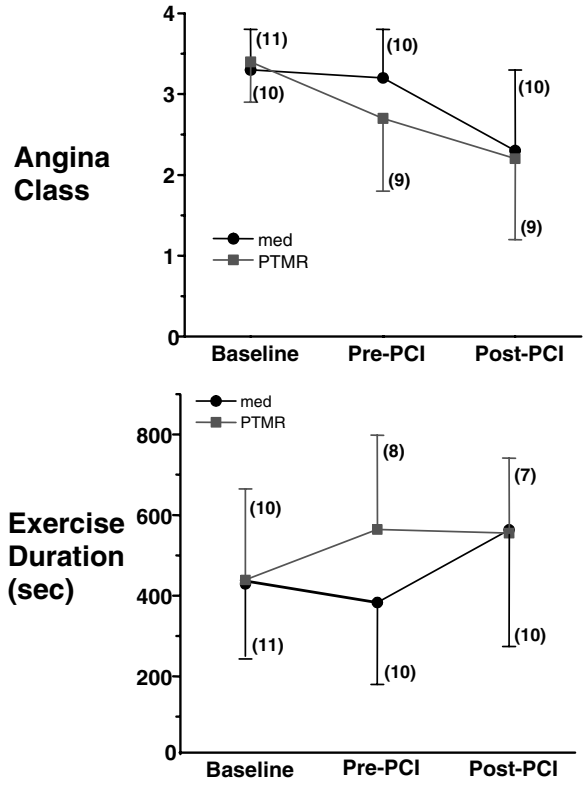

Figure 1. Outcomes following PCI. Outcomes in patients: at randomization to either PTMR or medical therapy alone (Baseline); last follow-up prior to PCI (pre-PCI); and follow-up post-PCI (post-PCI). (Timing of these events is indicated in Table 3). Brackets at each data point represent patient number. Data represented as mean (±SD). Upper panel: Angina Class. Canadian Cardiovascular Society Angina Scale (0–4). Lower panel: Exercise duration. Exercise tolerance test (seconds).

Table 3. Time (Days*) Between Follow-Up Events

Event	PTMR + MEDs	MEDs
Enrollment to randomization†	18 (7–49)	20 (6–91)
Randomization to last follow-up prior to PCI	154 (1–169)	99 (79–183)
Last follow-up prior to PCI	43 (2–167)	62 (9–192)
Randomization to PCI	146 (27–329)	161 (88–353)
PCI to last follow-up	202 (30–315)	212 (42–307)

*Median (range) values.
†Day of enrollment is the day when informed consent was signed, day of randomization is the day of PCI in PTMR + MEDs group and start date for MEDs group; PCI, percutaneous coronary intervention.

Table 4. Seattle Angina Questionnaire*

	PTMR + MEDs			MEDs		
SAQ Index	Baseline	Pre-PCI Follow-Up	Post-PCI Follow-Up	Baseline	Pre-PCI Follow-Up	Post-PCI Follow-Up
Physical limitation	30 ± 21	57 ± 23‡	54 ± 24‡	38 ± 10	37 ± 15	36 ± 16
Anginal stability	17 ± 22	64 ± 31‡	61 ± 42‡	42 ± 20†	43 ± 29	60 ± 32
Anginal frequency	31 ± 23	52 ± 29‡	52 ± 34	40 ± 23	49 ± 21	61 ± 29
Treatment satisfaction	60 ± 17	85 ± 19	84 ± 13‡	63 ± 21	76 ± 21	80 ± 21
Disease perception	16 ± 9	53 ± 26‡	52 ± 34	21 ± 13	38 ± 27	45 ± 28

*Mean ± SD values.
†$P < 0.05$ versus corresponding value in PTMR + MEDs group.
‡$P < 0.05$ versus respective baseline value.

Exercise tolerance was assessed by total duration of exercise on a modified Bruce protocol. Overall, there were similar statistically nonsignificant increases in mean exercise duration from baseline to post-PCI conditions in both medical and PTMR groups (127 ± 216 and 91 ± 143 seconds, respectively). Essentially, all of these changes in the medical group occurred following PCI (180 ± 278 seconds improvement pre-PCI versus post-PCI). In contrast, a majority of the increase occurred following PTMR in the PTMR group (140 ± 190 seconds increase, baseline versus pre-PCI) with no significant change following PCI.

Quality of life was assessed using the Seattle Angina Questionnaire[3] which indexes five disease-specific components of quality of life (mean ± SD values summarized in Table 4; results were very similar with median values). Except for an improved Anginal Stability index in the medical group, baseline scores were similar between the two groups. In the PTMR group, most indices improved following PTMR but there were no significant changes following PCI. In medical group subjects, there were no significant changes in Seattle Angina Questionnaire indices between baseline and pre-PCI nor following PCI. Thus, there were no significant improvements in quality of life following PCI as assessed by Seattle Angina Questionnaire in either group.

Major adverse events are summarized in Table 5. The most frequent adverse event was hospitalization to treat angina, which decreased slightly but was not eliminated following PCI. There were two deaths following PCI during the follow-up period, one from the medical group (age 85) and one from the PTMR group (age 78). Each death occurred ∼200 days after enrollment and ∼4 months after PCI.

The data of the present study suggest that patients with medically refractory angina initially considered to be unsuitable for PCI, who are later subjected to such a procedure, appear to derive only relatively modest—if any—benefit. In patients who previously underwent PTMR, there was essentially no reduction in angina class and no detectable improvement in exercise tolerance or quality of life beyond that observed following PTMR. In patients not previously treated with PTMR, there were modest improvements in angina, exercise tolerance, and quality of life, each of which improved to the degree initially observed following PTMR in the PTMR group.

Table 5. Adverse Events

	PTMR + MEDs				MEDs			
	Pre-PCI		Post-PCI		Pre-PCI		Post-PCI	
EVENT	Patients	Events	Patients	Events	Patients	Events	Patients	Events
Death	0	0	1	1	0	0	1	1
Hospitalizations for angina	9	10	4	12	9	16	2	2
Myocardial infarction	2	2	1	2	2	3	1	1
Bradycardia	0	0	1	2	0	0	0	0
Pulmonary edema	0	0	1	1	0	0	0	0
Increased mitral regurgitation	1	1	0	0	0	0	0	0
Thromboembolic disorders	0	0	0	0	1	2	1	1

These findings contrast with the significant clinical benefits typically observed in patients following PCI. For example, the improvement in total exercise duration on standardized testing following angioplasty in the RITA trial was greater than 3 minutes at 6 months. This was achieved by single-vessel angioplasty in patients with an average baseline exercise tolerance that was ~4 minutes longer than the patients in the present study.[5]

These observations are intriguing in view of the 100% procedural success. Although acute success does not necessarily correlate with optimal overall outcome,[6] well-preserved LV function, the high rate of stent use, the fact that patients were highly symptomatic with at least class III angina, and had evidence of reversible defects on dipyridamole thallium stress test are generally considered to be associated with improved outcomes following PCI.[7,8] These factors, however, are counteracted by the fact that the present patients tended to have a higher incidence of cardiovascular risk factors such as hypertension, diabetes, and hyperlipidemia than in previous studies.[9,10] In addition, the present study does not identify whether the subsequently treated vessel subtended an area of reversible ischemia, or if this area had been previously treated with PTMR, although patients did have a relatively high number of reversible perfusion defects (mean 3.5–5). It is also conceivable that PCI was performed to newly developed lesions, though this makes the only modest results of PCI all the more noteworthy. Perhaps most significantly, a majority of patients of the present study had undergone at least one prior revascularization procedure, and 16 had undergone at least one PCI and at least one bypass procedure. Major published trials examining outcomes following PCI and bypass have generally excluded patients with prior revascularization.[5,9,10]

Improvements in clinical status following PTMR were, by virtue of the fact that the patients had persistent symptoms, smaller than reported in the PACIFIC patient cohort as a whole.[2] Debate continues as to underlying mechanisms and the role of the placebo effect in the reported clinical effects of PTMR. One recent double blind study of PTMR with the same system used in the PACIFIC study indicated significant symptomatic improvement.[11] In contrast, another study performed with a different system showed no improvement.[12] Independent of underlying mechanisms, however, it is pertinent to note that in this patient cohort, clinical benefits or any effect attributable to placebo, were not better with PCI than with PTMR.

Although the data presented here were collected as part of a large randomized, multicenter trial, clearly the patient population of the present study is small, non-randomized, and lacks statistical power. However, these data are consistent with the hypothesis that patients with medically refractory, severe (Class III or IV) angina due to diffuse coronary artery disease, previously considered unsuitable for PCI by tertiary referral centers, do not appear to benefit significantly if PCI is subsequently performed. This patient group is commonly encountered in clinical practice: given the present lack of trials examining indices of outcomes following PCI in this important patient group, these data suggest this key question warrants further evaluation.

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