Current Indications for Percutaneous Coronary Intervention for Chronic Stable Angina: Implications of the COURAGE Trial

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We have entered an era in which it is possible to examine almost 30 years of experience with trials of treatment strategies comparing coronary revascularization with medical therapy in patients with chronic stable angina (CSA). Percutaneous coronary intervention (PCI) has now become the most common mode of revascularization for angina in most countries with the facilities for coronary bypass surgery and PCI. However, data from clinical trials have consistently demonstrated that revascularization does not offer a significant survival advantage over medical therapy for the majority of patients with CSA, unlike what has been observed in patients with acute coronary syndromes. There is evidence, however, that bypass surgery may enhance

survival in subsets of patients with multivessel disease and severe symptoms, particularly in the presence of left ventricular dysfunction. The Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial has revitalized the debate regarding the most appropriate treatment for stable disease.[1] The aim of this review is to reassess the evidence and outline the optimal treatment strategies for patients with CSA.

CABG Versus Medical Treatment in Chronic Stable Angina

Discussion

The majority of trials comparing coronary artery bypass grafting (CABG) and medical therapy for patients with CSA were conducted in the 1970s and 1980s. The Veterans Administration (VA) study,[2] the European Cooperative Surgical Study (ECSS),[3] and the Coronary Artery Surgical Study (CASS)[4] are the 3 largest randomized trials performed to compare surgical revascularization with medical treatment for CSA, and their findings form a cornerstone of current practice. They have consistently demonstrated that CABG did not improve survival in the overall study populations, but did so in subgroups of patients with a large amount of myocardium at risk or significant underlying left ventricular dysfunction. Such patients included those with significant left main disease or 3-vessel disease, particularly with abnormal left ventricular function or with more than 75% left anterior descending (LAD) artery stenosis. Patients with severe symptoms were generally excluded from the trials, but data from the CASS registry and the ECSS indicate that surgery improves survival in patients who have 3-vessel disease, regardless of left ventricular function or proximal LAD artery stenosis. In the CASS registry, a markedly positive stress test also identified a subgroup of patients with multivessel disease who experienced a survival benefit with CABG.

Although these trials are obsolete in regard to current approaches to surgical and medical management, the overall conclusions are still valid—revascularization has its major impact upon survival in "sicker" patients. In addition, the trials demonstrated that a strategy of initial CABG surgery provides greater symptomatic relief from angina, but this benefit decreases over time, probably due to a combination of crossover to surgery in the medical treatment arm, late vein graft failure, and the progression of disease in nongrafted vessels and in the distal vasculature. In addition, surgery does not reduce the rates of subsequent myocardial infarction (MI).

Conclusion

The key message of the major randomized trials of medical therapy versus CABG for CSA is that CABG is preferred for patients with multivessel disease who have a large amount of myocardium at risk, severe ischemia, or symptoms such as those seen with unprotected significant left main disease or 3-vessel disease—especially if there is diffuse atherosclerosis or impaired left ventricular function.

PCI Versus Medical Treatment in Chronic Stable Angina

Discussion

Several trials have compared PCI with medical treatment in CSA. Katritsis and Ioannidis[5] performed a meta-analysis and identified 11 eligible randomized trials incorporating 2950 patients (PCI arm, n = 1476 vs conservative arm, n = 1474) published between 1992 and 2004.[6-20] The mean age of these patients was 53 to 61 years. The vast majority of patients were symptomatic from angina, but there was considerable variability in the trials with regard to the presence of demonstrable ischemia. The authors concluded that, compared with conservative medical treatment, PCI does not decrease mortality or MI during follow-up in patients with stable disease, except in the context of a recent MI. Nonetheless, PCI did prove to be more effective in improving symptoms of angina compared with medical treatment alone. A point worth stating is that these trials were conducted prior to the advent of drug-eluting stents (DES), and represent outcomes predominantly with percutaneous transluminal coronary angioplasty (PTCA). Brophy and colleagues[21] published a comprehensive meta-analysis of the 29 randomized clinical trials from before 2002 that compared routine coronary stenting with standard PTCA. The total number of patients was 9918. The authors concluded that routine coronary stenting is safe but probably not associated with important reductions in rates of mortality, acute MI, or coronary artery bypass surgery compared with standard PTCA with provisional stenting.

The COURAGE trial published earlier this year investigated PCI with routine use of bare-metal stents with optimal medical therapy.[1] This randomized multicenter trial was conducted across North America in 50 hospitals (19 non-VA, 15 VA, and 16 Canadian) from 1999 to 2004. More than 35,000 patients were screened, but only 2287 (less than 10%) were enrolled. Randomization was performed in the cardiac catheterization laboratory following angiography. The major inclusion criteria were: 1) greater than 70% stenosis in a proximal major epicardial coronary artery, 2) Canadian Cardiovascular Society (CCS) Class I to III angina,

and 3) evidence of ischemia at baseline or inducible ischemia by whatever functional modality used. Exclusion criteria were: 1) uncontrollable angina, 2) complicated post-MI course, 3) ejection fraction less than 30%, and 4) cardiogenic shock.

The patients were randomized to PCI in addition to optimal medical therapy (n = 1149), or to optimal medical therapy alone (n = 1138). Most of the patients were white men. The mean age was 62 years, and the average number of angina episodes was 3 per week. In both groups, 11% of patients had undergone previous CABG. Approximately one-third of the patients in each group had single vessel disease, one-third had double vessel disease, and one-third had triple vessel disease. It is noteworthy that after a median follow-up of 4.6 years, PCI for symptoms was required by 21% of patients in the PCI arm compared with 32.6% in the medical arm. The repeat revascularization rates in the PCI group very likely would have been significantly less had DES been used, based on the documented reduction of restenosis.

The rates of death or nonfatal MI were no different between the PCI and optimal medical therapy groups. Freedom from angina was more common after PCI at 1 year (66% vs 58%), but at 5 years there was no difference (74% vs 72%). These findings are consistent with those of the preceding trials from the PTCA era. At the end of the trial, 25.5% of the optimal medical therapy group had crossed over to the PCI group for refractory angina or worsening ischemia on noninvasive testing.

The results of the 5-year follow-up of the Medicine, Angioplasty, or Surgery Study (MASS II) comparing CABG, PCI, and medical treatment for stable multivessel coronary artery disease have recently been published.[22] All 3 treatment regimens yielded comparable, relatively low rates of death. Medical therapy was associated with an incidence of long-term events and a rate of additional revascularization that were similar to those for PCI. CABG was superior to medical therapy in terms of the primary endpoint, with a 44% reduction. In terms of comparing medical therapy with PCI for CSA, the results of both the MASS II study and the COURAGE trial are indeed quite similar.

In contrast to the above studies, in which PCI has not been shown to reduce death or MI in CSA, there are 2 trials that have indicated otherwise. Both were conducted in patients with silent ischemia. The Asymptomatic Cardiac Ischemia Pilot (ACIP) study included 558 patients with clinically stable, angiographically documented CAD who were judged suitable for revascularization after being diagnosed with silent ischemia.[23] It found that total mortality, the combined endpoint of death or MI, and the endpoint of death, MI, or recurrent cardiac hospitalization were significantly improved in patients undergoing revascularization with either PCI or CABG.[23] The Swiss Interventional Study on Silent Ischemia Type II (SWISSI II) was a small trial of 201 patients with a recent MI who had inducible ischemia by stress testing. The results were unexpected in that cardiac death and MI were significantly lower in the group randomized to balloon angioplasty over a 10-year follow-up period.[24] These findings suggest that silent ischemia may identify a high-risk group that may benefit from revascularization, but further investigation is required. The data from the ACIP and SWISS II trials must be interpreted with the knowledge that optimal medical therapy, as defined in the COURAGE trial, was not applied, which may have resulted in a bias in favor of revascularization. Moreover, both the ACIP and SWISS II trials had a relatively small sample size.

The Trial of Invasive versus Medical therapy in Elderly patients (TIME) showed that 1-year outcomes in 282 elderly patients with CSA were similar with regard to symptoms, quality of life, and death or nonfatal infarction with invasive versus optimized medical strategies based on an intention-to-treat analysis.[25] The invasive approach carried an early intervention risk, and medical management posed an almost 50% chance of later hospitalization and revascularization.

Conclusion

The current data suggest that PCI has no benefit over optimal medical therapy for the treatment of CSA in terms of hard endpoints such as mortality and MI. However, it is certainly a highly effective modality in patients with persistent symptoms or drug intolerance. It is unknown if this paradigm will change in the light of both positive and negative developments with DES.

It is probable that the outcomes of CABG and PCI in terms of repeat revascularization may become comparable in the current era of DES.

CABG Versus PCI

Discussion

Nine randomized pre-stent clinical trials have compared balloon angioplasty with CABG (Table 1). The Bypass Angioplasty Revascularization Investigation (BARI) trial was the only one appropriately sized to assess mortality.[26] However, none of the 9 trials showed a difference in mortality, and a meta-analysis of these

Table 1
The 9 Large Randomized Trials of Balloon Angioplasty (PTCA) (Pre-Stent) Versus Bypass Surgery (CABG)

	Mortality	
Trial	CABG (%)	PTCA (%)
BARI[27]	10.2	10.0
CABRI[32]	5.7	6.7
RITA[33]	6.2	6.7
EAST[34]	18.4	13.7
GABI[35]	10.2	5.5
Toulouse[36]	7.9	7.9
MASS[14]	1.4	6.9
Lausanne[37]	3.0	8.8
ERACI[38]	10.0	12.7

PTCA, percutaneous transluminal coronary angioplasty; CABG, coronary artery bypass grafting; BARI, Bypass Angioplasty Revascularization Investigation; CABRI, Coronary Angioplasty versus Bypass Revascularisation Investigation; RITA, Randomized Intervention Treatment of Angina; EAST, Emory Angioplasty versus Surgery Trial; GABI, German Angioplasty vs Bypass Investigation; MASS, Medicine, Angioplasty or Surgery Study; ERACI, Argentine randomized trial of percutaneous transluminal coronary angioplasty versus coronary artery bypass surgery in multivessel disease.

studies showed no difference in mortality or recurrent MI, with follow-up ranging from 1 to 8 years.[27] All of the studies showed that PCI was associated with a higher rate of repeat revascularization ranging from 20% to 40% over the first year, largely due to restenosis. Both techniques were shown to be highly effective in relieving angina, and by 5 years, no differences in angina relief between the treatment strategies could be seen. The most important finding of the BARI trial was a survival benefit of CABG over coronary angioplasty (PTCA) in the predefined subgroup of treated diabetic patients. This benefit was evident, however, only in treated diabetic patients who underwent surgical revascularization with an internal mammary artery. Also, the benefit appeared to be due to reduced mortality when these patients had a subsequent MI during follow-up.[28] Subgroup analysis of diabetic patients treated with only saphenous vein grafts showed no difference in outcome as compared with those who received a balloon angioplasty. The greatest difference was seen in diabetic patients treated with insulin, whereas diabetic patients not on any drug treatment showed no difference in mortality.

Explanations for the results of the BARI trial in diabetic patients are probably multifactorial. In the BARI registry, in which patients were treated according to the preferences of their physicians, mortality rates were similar among patients treated with PCI and CABG. It would appear that in the randomized trial, diabetic patients comprised a "sicker" subgroup, which in clinical practice was more likely to be treated with CABG. In other words, the process of randomization resulted in the allocation of patients to PCI, whereas when physician and patient preference determined the choice of therapy, diabetic patients were more likely to be treated surgically.[28]

In the MASS II trial, Hueb and colleagues[13] randomized patients with CSA who were candidates for both PCI and CABG into 3 arms: medical therapy, PCI, and CABG. Eligible patients had multivessel coronary artery disease, and the LAD artery was involved in 92% of the patients. At 5-year follow-up, patients treated with PCI (72% had stents) were more likely to be free from angina compared with those treated medically (77% vs 55%), but for all other endpoints, including death, MI, and subsequent revascularization, PCI had no advantage over medical therapy. Freedom from subsequent revascularization was significantly better for the surgical group than for the medical or PCI group. The primary endpoint of the trial—death, Q-wave MI, or angina requiring revascularization—occurred significantly less often in the surgical group (21.2%) than in the medical treatment group (32.7%) or the PCI group (36%).

The results of MASS II are consistent with other studies that have compared CABG with a stent-based PCI strategy. In the Arterial Revascularization Therapies Study Part I (ARTS I) trial, the rates of death and MI were similar with both treatment strategies, but repeat revascularization was more frequent and complete revascularization was less often achieved with PCI.[29] The findings were similar in the Stent or Surgery (SoS) trial, but for reasons that are unclear as there was an unexpected higher mortality associated with PCI (5% vs 2%; $P = .01$).[30]

Data are lacking regarding PCI with DES and CABG. ARTS II is a multicenter registry that has compared outcomes with PCI using a DES with outcomes from the historical controls from the ARTS I trial.[31] The primary endpoint of all-cause death, any cerebrovascular event, nonfatal MI, or any repeat revascularization at 1-year in the DES group was similar to the CABG treatment arm of ARTS I. Repeat revascularization was 8.5% in the DES group compared with 4.1% and 21.3% in the CABG and PCI arms, respectively, of ARTS I. The findings indicate that PCI using DES may produce CABG-like results by reducing the need for repeat revascularization. However, these data must be interpreted with caution because of the use of historical controls.

Conclusion

It is probable that the outcomes of CABG and PCI in terms of repeat revascularization may become comparable in the current era of DES.

DES are being compared with CABG in ongoing large clinical trials, namely the SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery (SYNTAX) and Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM) trials of patients with more severe multivessel disease, including left main stem disease. The ongoing Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) study is a randomized clinical trial of patients with type 2 diabetes mellitus and angiographically documented stable coronary artery disease. It will compare revascularization combined with aggressive medical treatment versus aggressive medical treatment alone. The results will be eagerly awaited.

Conclusion

The current data agree with the published data of previous years insofar as patients with CSA who undergo PCI do not have decreased rates of MI or a cardiac mortality benefit when compared with patients on medical treatment. PCI does, however, confer the advantage of a greater reduction in angina over medical treatment. If PCI causes a greater improvement in angina than medical treatment, then it is conceivable to postulate that DES, by inhibiting restenosis, may provide a better way to reduce angina in the long term. Issues such as duration of combined antiplatelet medications for DES and the danger of late stent thrombosis are currently the focus of intense investigation.

Medical treatment, especially aggressive primary and secondary prevention, has an enormous role to play in patients with CSA for the future. It is likely that the landscape of treatment with PCI and medical therapy alone will be irrevocably altered by the current practice of secondary prevention. PCI for symptom reduction along with medical management will continue to play a major role for patients with symptomatic angina, but it is important that we educate patients correctly about what PCI endeavors to achieve in stable disease. ■

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