In our clinical practice we come across patients with all shades of angina: some who respond to treatment and at times others with intractable symptoms with minimal response to anti-anginal therapy. These patients continue to experience effort-limiting angina in spite of the cocktail of anti-anginals. Once blockages are taken care of with angioplasty, patients enjoy enhanced effort tolerance with relief from angina. Many patients after PCI remain symptom free during their subsequent course of life. Any instant restenosis or denovo blockages result in recurrence of angina, which again, usually does not respond to combination of anti-anginals and requires reintervention. In some patients a particular segment keeps on restenosing and resulting in angina with rapid, sustained and almost complete relief of angina after intervention. Our clinical experience encourages and guides us to offer PCI as a one of first line treatments in patients with stable angina who have presenting complaints of angina, suboptimal response to anti-anginals and have objective evidence of ischeamia as documented by exercise ECG or nuclear test. Lately any patient presenting with angina or ischemia was considered for angiography and all significant lesions were treated with angioplasty. Should angiography followed by PCI be offered to all patients with all shades of angina? What is the role of anti anginal treatment? More importantly at what stage in symptomatology and chronology intervention should be offered?

Two randomized control trials have questioned the current concept of offering angiography followed by PCI, while offering new evidence. The COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial is a randomized trial involving 2287 patients with objective evidence of myocardial ischemia and significant coronary artery disease (CAD). A total of 1149 patients were assigned to undergo PCI with optimal medical therapy (PCI group) and 1138 to receive optimal medical therapy alone (medical-therapy group) between 1999 and 2004. In the follow-up period of 2.5 to 7.0 years (median, 4.6), there were 211 primary events (death from any cause and nonfatal myocardial infarction) in PCI group and 202 events in medical-therapy group. The 4.6-year cumulative primary-event rates were 19.0% in the PCI group and 18.5% in the medical-therapy group (hazard ratio for the PCI group, 1.05; 95% confidence interval [CI], 0.87 to 1.27; p=0.62). There were no significant differences between the PCI group and the medical-therapy group in the composite of death, myocardial infarction, and stroke (20.0% vs. 19.5%; hazard ratio, 1.05; 95% CI, 0.87 to 1.27; p=0.62); hospitalization for acute coronary syndrome (12.4% vs. 11.8%; hazard ratio, 1.07; 95% CI, 0.84 to 1.37; p=0.56);
Hence the applicability of the results to the general measure of anangina therapies conducted clinical trial testing ivabradine in patients who had exercise limiting angina on the treadmill or myocardial infarction (13.2% vs. 12.3%; hazard ratio, 1.13; 95% CI, 0.89 to 1.43; p=0.33). It was concluded that as an initial management strategy in patients with stable coronary artery disease, PCI did not reduce the risk of death, myocardial infarction, or other major cardiovascular events when added to optimal medical therapy.

There were certain limitations to the study as there was major dominance - 85% of male patients and only 14% of the patients were nonwhite. The operators used bare-metal stents, since drug-eluting stents were not available until late during trial. To back up their usage of BMS authors argued that there is no evidence to suggest any short-term or long-term benefit with respect to death and myocardial infarction in patients with stable CAD in patients receiving drug-eluting stents, as compared to bare-metal stents. There were serious criticism concerning the cross over which was as high as 30 percent, more so in US based non-Veteran system though a subsequent analysis did not support any mortality benefit either way. The quality of care in three cohorts was compared and questioned. The success rate of PCI was considered not at par with current international standards. The use of number of stents especially in multi vessel disease was criticized, as it did not match. Psychological effect on patients who were randomized to medicines only was highlighted.

The authors opine that their data support existing clinical practice guidelines, that PCI can be safely postponed in patients with stable CAD, even in those with extensive, multivessel involvement and inducible ischemia, provided that intensive, medical therapy is introduced and maintained. Hence it was suggested that as an initial management approach, optimal medical therapy without routine PCI can be used safely in the majority of patients with stable CAD. It must be realized that approximately thirty percent of these patients may subsequently require revascularization for symptom control or for subsequent development of an acute coronary syndrome.

ORBITA came a decade later. It is the first blinded, multicenter, placebo-controlled trial of PCI versus a placebo procedure for stable angina for angina relief. The patient population consisted of those with severe (≥70%) single-vessel stenoses. In ORBITA, PCI did not improve exercise time beyond the effect of the placebo. The trial was conducted in patients having ischaemic symptoms, severe coronary stenosis both anatomically (84-4% area reduction) and haemodynamically (ontreatment FFR 0.69 and IFR 0.76). In patients who underwent PCI there was objective relief of anatomical stenosis, invasive pressure, and non-invasive perfusion indices (FFR p<0.0001, IFR p<0.0001, stress wall motion score index p<0.0001). There was also no improvement beyond placebo in the other exercise and patient-centred endpoints, including Canadian Cardiovascular Society class and the metrics of the Seattle Angina Questionnaire and EQ-5D-5L questionnaire.

After COURAGE, the argument from interventionalists had been that it was known for years that PCI does not reduce death or MI. PCI is done to reduce angina and improve the quality of life. These results were in concordant with a meta-analysis of all previous trials involving PCI versus medical management, based on outcome data on more than 5000 patients and showed that PCI had no effect in reducing major cardiovascular events. For this reason, clinical practice guidelines endorse PCI for angina relief if medical therapy fails or is ineffective. Now, ORBITA questions this very concept of PCI benefit for angina relief and QOL improvement.

There are many similarities in response to the two landmark trials ORBITA and COURAGE. Ten years ago, the criticism of was that as drug-eluting stents were not used in COURAGE the PCI was suboptimal and it was stated that OMT used was too good and hard to achieve in the real world. In ORBITA medical therapy optimization phase was very intensive, that entailed one to three telephone consultations per week with a consultant cardiologist supported by home blood pressure and heart rate measurements. This phase ensured a high level of anti-anginal therapy within just 6 weeks and facilitated the enrolment and retention of patients with severe coronary disease. This level of intensive personalized care is not possible in the real world. Hence the applicability of the results to the general was questioned.

Cardiologists on this side of the fence did point to the limitations of small numbers - only 200 patients and that the study was underpowered to show any real difference. Some seriously objected to the potential ethical challenge of subjecting subjects with significant flow-limiting CAD to a sham procedure (or deferred PCI for clinical need). Interestingly 28%-32% of randomized subjects had either normal FFR or IFR and therefore did not have a physiologically significant, or flow-limiting stenosis that PCI could have benefitted. As against real life situation there was a low frequency of multivessel CAD. Duration of follow up to six weeks has been seriously questioned by some quarters as it was considered too brief to assess potential benefit.

The response of patients to relief of angina depends on severity of angina. A major controversy was that ORBITA enrolled low risk population and as such there was no possibility of showing an effect. The benefit of relieving ischemia that does not have a measurable effect on quality of life (QOL) in the low risk 200 CAD patient trial is difficult to assess. This supports the inability of testing anti-anginal therapy effectively in patients with a low burden of angina, regardless of their ischemic results on stress testing or their FFR results. Asymptomatic ischemia on a stress test is not angina. Pharmaceutical companies testing anti-anginal therapies conducted clinical trial testing ivabradine in patients who had exercise limiting angina on the treadmill.
accompanied by ST depression on the exercise ECG. The MARISA trial using ranolazine enrolled patients with angina limited exercise on ETT who also had ST changes.

Patients in ORBITA had longer and better baseline ETT times - more than 8 minutes at sixty plus age. Only about 25% of patients reported exercise induced ST depression at baseline. The Duke Treadmill scores at baseline were on the edge of low risk. It appears that the opportunities for a better antianginal therapy to demonstrate its superior qualities was constrained in this trial due to the lack of patients with severe anginal symptoms.

It is of interest that the choice of exercise time as the primary endpoint as against angina was strange as exercise time had never shown itself to be a very sensitive measure of QOL. Though its objectivity may seem in its favor, yet one must consider that since the study enrolled a population most of whom did not have exercise induced ST depression and relatively few had exercise limiting angina, it is ambiguous why PCI was expected to produce a big change in exercise time. Moreover ORBITA investigators powered their study to detect a 30-second incremental change in exercise time with PCI as against placebo/medical therapy. Even if one assumes that a 30 second increase in exercise time represents something clinically important, such a small average increment will be quite difficult to detect using standard statistical testing. So the ORBITA main results were for eseeable because of two main factors: a small estimated incremental effect size of PCI due to the relatively low burden of angina with little opportunity for PCI to do something measurable and a lack of precision in estimating the effect sizes as reflected in the CIs due to a small sample size.

In the world of medicine, quite often a treatment is thought to be so beneficial that a placebo-controlled trial is deemed unnecessary and perhaps unethical. However, 40 years after the first PCI, ORBITA's findings show that placebo-controlled randomised trials remain necessary. Such trials renew our interest in placebo controlled trials and at many junctions have sprung surprise findings. What may be too obvious may not necessarily be true and relevant.

It is important to understand that the findings of COURAGE and ORBITA do not imply that patients should not be studied and never undergo PCI for stable angina. Not all patients would be satisfied with taking multiple anti-anginal agents forever. Some might prefer an invasive procedure with a small procedural risk for the potential to need fewer medications. Although the participants had anatomically and physiologically severe lesions, patients with multivessel disease were not enrolled. Patients with more extensive territories of coronary disease might receive a larger physiological benefit from PCI and have no obvious reason for a larger placebo effect.

Moreover ORBITA only investigated PCI for stable angina and the results have no implications for patients undergoing PCI for acute coronary syndrome, including ST-elevation myocardial infarction for which morbidity and mortality advantages from PCI have been proven.

It may be safely concluded that both trials emphasize to treat patients as a whole and address symptoms rather than focusing only on obstructive lesions. The approach to take all patients for angiography with any suspicion of angina has been seriously questioned and proven to be incorrect. In all fairness, all patients should be given a fair trial of anti anginals and only those who do not respond or have early positive test or have large myocardial area at jeopardy may be considered for further work up and intervention. This approach should be with clear understanding that it is not to improve mortality or reduce major adverse events but to control symptoms in selected cases till we get more evidence.

REFERENCES


