

# Revascularization in Chronic Stable Angina-Does It Really Benefits as First Line Therapy

Alok Kumar Singh\*

Department of Cardiology, Interventional Cardiologist, Heritage Hospital, Varanasi, India

## ABSTRACT

Coronary artery disease (CAD) remains a major global public health problem in 21<sup>st</sup> century, and it affects as many as 54 million people globally.<sup>1</sup> The goals of CAD treatment have several objectives which include relief of symptoms, inhibition of disease progression, prevention of future cardiac events, such as myocardial infarction (MI) and improved survival.<sup>2</sup> There is always debate among medical treatment and revascularization which one is superior to each other. Here, we will discuss and try to review in a critical manner the role of revascularization (percutaneous coronary intervention [PCI] versus coronary artery bypass grafting [CABG]) in the management of chronic stable angina in comparison to modern optimal medical therapy (OMT) in the view of recent studies

**Keywords:** Angina, optimal medical therapy, revascularization

## INTRODUCTION

Coronary artery disease (CAD) remains a major global public health problem in 21<sup>st</sup> century, and it affects as many as 54 million people globally.<sup>1</sup> The goals of CAD treatment have several objectives which include relief of symptoms, inhibition or slowing of disease progression, prevention of future cardiac events, such as myocardial infarction (MI) and improved survival.<sup>2</sup> In most industrialized countries, age-standardized mortality related to CAD has decreased by more than 40% during the last two decades and almost half of this decline resulted from prevention in major risk factors, whereas the other halves have been attributed to medical treatment and revascularization.<sup>3</sup> There is always debate among medical treatment and revascularization which one is superior to each other. Here, we will discuss and try to review in a critical manner the role of revascularization (percutaneous coronary intervention [PCI] versus coronary artery bypass grafting [CABG]) in the management of chronic stable angina in comparison to modern optimal medical therapy (OMT) in the view of recent studies.

In most studies till date, when compared with medical treatment, revascularization by PCI or CABG in patients with stable angina has improved angina to a significant degree, but revascularization by either strategy has not reduced the risk of death or the risk of subsequent MI in patients with stable angina.<sup>4</sup> In addition, revascularization by CABG or PCI in patients with stable CAD, compared with medical treatment, has not improved left ventricle (LV) function as assessed by calculated LV ejection fraction (EF). Even further, revascularization results symptomatic improvement in CAD, but this beneficial effect does not translate in to better survival and better employment status. In the following section, I will briefly discuss the findings from some of the important landmarks randomized studies in this regard.

### Medicine, angioplasty, or surgery study (MASS) II study<sup>5</sup>

In the MASS II trial, all patients were placed on an optimal open-label optimal medical regimen that included the use of nitrates, aspirin, beta-blockers, calcium channel blockers, angiotensin converting enzyme inhibitor (ACEI), or a combination regimen of these drugs before randomization to the was performed. Dietary intervention and lipid lowering therapy were provided individually to each patient. Patients were subsequently randomized to continue medical treatment only or to undergo revascularization by PCI or

#### \*Corresponding address:

Dr. Alok Kumar Singh, Interventional Cardiologist,  
Heritage Hospital, Varanasi, Uttar Pradesh, India.  
E-mail: alok\_ims@rediffmail.com

DOI: 10.5530/jcdr.2014.3.3

CABGs. During the 5 years follow-up period, compared with medical treatment and PCI, only with CABGs did a significantly lower risk (43.41% vs. 55.12% vs. 14.63%, respectively,  $P = 5.0026$ ) of the primary composite end point that included all-cause mortality, MI, or need for revascularization. The whole advantage of CABG was largely due to a significantly lower proportion of patients in the CABGs group, compared with medical therapy and PCI, that required subsequent revascularization for angina (3.5% vs. 24.2% vs. 32.2%, respectively;  $P < 0.0001$ ). Furthermore, compared with medical therapy, revascularization by PCI or CABGs resulted in a significantly greater proportion of patients free of angina (54.8% vs. 77.3% vs. 74.2%, respectively, both  $P < 0.001$  vs. medical therapy). However, if we evaluate individual end points independently then it revealed that compared with medical therapy, revascularization by PCI or CABGs resulted in a similar risk of cardiac death (12.3% vs. 11.6% vs. 7.9%, respectively), of acute MI (15.3% vs. 11.2% vs. 8.3%, respectively), and of cerebrovascular accident (3.5% vs. 3.4% vs. 5.9%, respectively), of overall mortality (16.2% vs. 15.5% vs. 12.8%, respectively).

#### **Trial of invasive versus medical therapy in elderly patients (TIME) study<sup>6</sup>**

In a TIME which randomly assigned 301 elderly patients (75 years of age) to a medical or invasive strategy. In TIME study, baseline angiography was not done prior to allocation of strategy, it was done only in the invasive arm. Survival of invasive-strategy versus medical-strategy patients was 91.5% versus 95.9% after 6 months, 89.5% versus 93.9% after 1 year, and 70.6% versus 73.0% after 4.1 years, so overall long-term survival is not affected by the initial strategy of treatment.

#### **COURAGE TRIAL<sup>7</sup>**

COURAGE was a randomized multicenter trial involving 2287 patients who had objective evidence of myocardial ischemia and significant CAD. A total of 1149 patients was assigned to undergo PCI with OMT (PCI group) and 1138 to receive OMT alone. The primary outcome was death from any cause and nonfatal MI during a median follow-up of 4.6 years. 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, 0.87-1.27;  $P = 0.62$ ). Hence, COURAGE trial investigators concluded as an initial management strategy in patients with chronic stable angina; PCI did not reduce the risk of death, MI, or other major cardiovascular events when added to OMT.

#### **STITCH TRIAL<sup>8</sup>**

Stitch trial has examined the role of CABG in the treatment of patients with CAD and heart failure. A total of 1212 patients with an EF of 35% or less and CAD suitable to CABG was randomly assigned to medical therapy alone (602 patients) or medical therapy plus CABG (610 patients). The primary outcome was the rate of death from any cause. Major secondary outcomes included the rates of death from cardiovascular causes and of death from any cause or hospitalization for cardiovascular causes.

In this randomized study, there was no significant difference between medical therapy alone and medical therapy plus CABG with respect to the primary end point of death from any cause over a follow-up of study although patients assigned to CABG, as compared with those assigned to medical therapy alone, had lower rates of death from cardiovascular causes and of death from any cause or hospitalization for cardiovascular causes.

#### **THE BARI 2D STUDY<sup>9</sup>**

BARI-2D study tries to examine optimal treatment for patients with both Type 2 diabetes mellitus and stable ischemic heart disease. In this trial, a total of 2368 patients with both Type 2 diabetes and heart disease to undergo either prompt revascularization (either by PCI or CABG) with intensive medical therapy or intensive medical therapy alone and to undergo either insulin-sensitization or insulin-provision therapy was randomly assigned. During the trial follow-up of 5 years, rates of survival did not differ significantly between the medical-therapy group (87.8%) and the revascularization group (88.3%) or between the insulin-sensitization group (88.2%) and the insulin-provision group (87.9%, in the CABG group, the rate of major cardiovascular events was significantly lower in the revascularization group (22.4%) than in the medical-therapy group (30.5%,  $P = 0.01$ ;  $P = 0.002$  for interaction between stratum and study group) whereas in the PCI stratum, there was no significant difference in primary end points between the revascularization group and the medical-therapy group. Overall, there was no significant difference in the rates of death and major cardiovascular events between patients undergoing prompt revascularization and those undergoing medical therapy or between strategies of insulin sensitization and insulin provision.

#### **FAME II STUDY<sup>10</sup>**

FAME II trial enrolled 1220 stable patients with suspected CAD and examined their coronaries with fractional flow

reserve (FFR) to ascertain, whether they had any significant flow-limiting lesions, defined as an FFR <0.80. Patients with at least one such lesion ( $n = 888$ ) were randomized to either PCI or OMT. Patients with no flow-limiting lesions shown by FFR were put into the registry and treated with medical therapy ( $n = 332$ ). The primary end point of the study was a composite of death, MI, or urgent revascularization. Results of FAME II trial reveal that among the patients with flow-limiting coronary disease, the need for urgent revascularization was the only significant outcome difference between the patients randomized to OMT only, and those randomized to PCI (9.5% vs. 0.7%, heart rate 0.7,  $P < 0.001$ ). So overall, 12.7% of the medical-therapy-only group had a primary end-point event compared with 4.3% of the PCI group. Death and MI rates were similarly low for both groups. Again even FFR guided PCI in stable CAD in flow limiting lesions does not have any mortality benefit over and above OMT.

### **Why revascularization is not effective as first line strategy instable angina?**

In acute coronary syndromes (ACS with or without ST-segment elevation), a routine invasive strategy with revascularization in most patients provides the best outcome with a significant reduction in death and MI compared with an initial conservative strategy. Conversely, the benefit of revascularization among patients with chronic stable CAD has been a matter of controversy. CAD is not just a mechanical narrowing of coronary artery; it is a result of various long standing problems such as dyslipidemia, hypertension, and diabetes in the milieu of genetic predisposition and faulty lifestyle. It is clear from the result of previously discussed studies irrespective of EF and diabetic status all patients first started on OMT if angina is not controlled, then only revascularization should be offered. It ignites our mind why revascularization is not as effective as first line treatment; we should look in to some landmark studies of basic coronary pathology. Hence, we have to understand myocardial ischemia is a multi-factorial clinical syndrome other than visible coronary plaque such as coronary micro vascular dysfunction, endothelial dysfunction, and coronary vasospasm in the milieu of enhanced inflammation so focusing on visible plaque by intervention will tackle the only one part of the syndrome. However, so many advances in revascularization but still the natural history of CAD in terms of recurrent MI and death remain unchanged. If we go in depth of natural history of chronic stable angina for a visible plaque requiring an angioplasty, in the same coronary artery, several non-occlusive plaques are present. These nonocclusive plaques are responsible for recurrent events are well-stabilized by

medical therapy, whereas angioplasty takes the care for only angina producing focal lesion, so we have to understand CAD is diffuse process before producing a critical lesion in focal area it already involves the whole artery in diffuse manner, lesion may be occlusive or not. It has been demonstrated plaque rupture occurred more frequently at site <50% stenosis.<sup>11</sup> Plaque vulnerability to rupture is no matter related to a degree of severity of stenosis, in fact, it is related to macrophage content and lipid core content of the lesion. If we compared PCI versus CABG in terms of recurrent event protection, CABG scores over PCI because it offers more complete revascularization, and it protects the vessel if events occurred in proximal to the graft whereas in angioplasty if plaque rupture occurs in the proximal to stented lesion then whole artery is affected. So, as far as events and mortality are concerned angioplasty does not give enough protection without medical therapy.

Another thing which is also important to considering in revascularization how much myocardium is affected by particular stenosis. Benefit of revascularization in terms of survival is directly proportional to the amount of ischemic myocardium as assessed by single photon emission computed tomography imaging prior to revascularization.<sup>12</sup> In the same study, it was demonstrated very nicely if the ischemic myocardium is more than 10% of LV then only revascularization have impact over cardiac death otherwise not.

### **Angina after revascularization**

PCI is prominent in the treatment of patients with stable CAD. Across multiple studies, it has been seen approximately half of procedures are performed in patients with chronic stable CAD. If we look the result of randomized intervention treatment of angina-2<sup>13</sup> PCI patients were almost twice as likely not to have angina at 3 years, whereas in COURAGE trial only a small incremental relief was demonstrated with PCI in comparison to OMT alone. Most of the interventionalist feels like angina pretty uncommon following PCI because most patients in follow-up are seen by family physicians. In fact, a National Heart, Lung, and Blood Institute registry from U.S.A showed a 1-year recurrence rate of post-PCI angina of 26% among 1755 patients who initially underwent successful PCI for CAD and 79% of patients still required one or more antianginal drugs.<sup>14</sup> In another landmark trial arterial revascularization therapy study which compared clinical outcomes among 1205 patients were randomized to bare metal stent PCI versus CABG overall 81% of PCI treated patients and 62% of CABG treated patients continued to have angina or required antianginal

medicines at 1 year follow-up.<sup>15</sup> In another contemporary SYNTAX trial of recent time, 28% of PCI treated patients had recurrent angina at 1 year follow-up.<sup>16</sup> Whereas in BARI-2D study, 60% exhibited recurrent angina at 1 year of follow-up in the background of diabetes. Hence, the results of all these studies reinforce the fact in spite of adequate revascularization significant proportion of patients continue to have angina. But overall compared with medical therapy, revascularization by CABG or PCI has been consistently shown to more effectively relieve angina, reduce the use of anti-angina drugs, improve exercise capacity and quality of life.<sup>17</sup> In recent, meta-analysis of 12 randomized clinical trials by Pursnani<sup>18</sup> *et al.*, has concluded that in patients with stable CAD, PCI, as compared with OMT, did not reduce the risk of mortality, cardiovascular death, nonfatal MI, or revascularization.

The discussion should not be medical versus revascularization therapy, but rather which patients should be offered revascularization at what time. The timing of revascularization requires careful attention. Patients with mild symptoms and little ischemia (<10% of LV myocardium) confidently treated with OMT, which consists of antiplatelet, ACEI, beta blockers, statins, and nitrate and lifestyle modification. If patient symptoms are not controlled with OMT and a significant amount of myocardium is at risk as demonstrated by noninvasive testing patients should be subjected to coronary angiogram. If coronary angiogram shows single and double vessel CAD then it can be treated with PCI and if coronary angiogram shows left main and triple vessel disease then as per the appropriateness criteria of ACC/AHA<sup>19</sup> CABG will be appropriate revascularization strategy.

## REFERENCES

- Mathers C, Ma Fat D, Boerma JT. Global Burden of Disease 2004 Update. Geneva, Switzerland: World Health Organization; 2008.
- Singh AK. Percutaneous coronary intervention vs coronary artery bypass grafting in the management of chronic stable angina: A critical appraisal. *J Cardiovasc Dis Res* 2010;1:54-8.
- Simoons ML, Windecker S. Controversies in cardiovascular medicine: Chronic stable coronary artery disease: Drugs vs. revascularization. *Eur Heart J* 2010;31:530-41.
- Carbajal EV, Deedwania P. Role of medical versus interventional strategies to prevent coronary events in patients with stable coronary artery disease. *Cardiol Clin* 2011;29:157-65.
- Hueb WA, Soares PR, Almeida De Oliveira S, Ariê S, Cardoso RH, Wajsbrot DB, *et al.* Five-year follow-up of the medicine, angioplasty, or surgery study (MASS): A prospective, randomized trial of medical therapy, balloon angioplasty, or bypass surgery for single proximal left anterior descending coronary artery stenosis. *Circulation* 1999;100 19 Suppl: II107-13.
- Pfisterer M. Trial of Invasive versus Medical therapy in Elderly patients Investigators. Long-term outcome in elderly patients with chronic angina managed invasively versus by optimized medical therapy: Four-year follow-up of the randomized Trial of Invasive versus Medical therapy in Elderly patients (TIME). *Circulation* 2004;110:1213-8.
- Boden WE, O'Rourke RA, Teo KK, Hartigan PM, Maron DJ, Kostuk WJ, *et al.* Optimal medical therapy with or without PCI for stable coronary disease. *N Engl J Med* 2007; 356:1503-6.
- Jones RH, Velazquez EJ, Michler RE, Sopko G, Oh JK, O'Connor CM, *et al.* Coronary bypass surgery with or without surgical ventricular reconstruction. *N Engl J Med* 2009;360:1705-7.
- BARI 2D Study Group, Frye RL, August P, Brooks MM, Hardison RM, Kelsey SF, *et al.* A randomized trial of therapies for type 2 diabetes and coronary artery disease. *N Engl J Med* 2009;360:2503-15.
- De Bruyne B, Pijls NH, Kalesan B, Barbato E, Tonino PA, Piroth Z, *et al.* Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. *N Engl J Med* 2012;367:991-1001.
- Libby P. Atherosclerosis: Disease biology affecting the coronary vasculature. *Am J Cardiol* 2006;98:3Q-9.
- Hachamovitch R, Hayes SW, Friedman JD, Cohen I, Berman DS. Comparison of the short-term survival benefit associated with revascularization compared with medical therapy in patients with no prior coronary artery disease undergoing stress myocardial perfusion single photon emission computed tomography. *Circulation* 2003;107:2900-7.
- Henderson RA, Pocock SJ, Clayton TC, Knight R, Fox KA, Julian DG, *et al.* Seven-year outcome in the RITA-2 trial: Coronary angioplasty versus medical therapy. *J Am Coll Cardiol* 2003;42:1161-70.
- Holubkov R, Laskey WK, Haviland A, Slater JC, Bourassa MG, Vlachos HA, *et al.* Angina 1 year after percutaneous coronary intervention: A report from the NHLBI Dynamic Registry. *Am Heart J* 2002;144:826-33.
- Serruys PW, Unger F, Sousa JE, Jatene A, Bonnier HJ, Schönberger JP, *et al.* Arterial Revascularization Therapies Study Group. Comparison of coronary-artery bypass surgery and stenting for the treatment of multivessel disease. *N Engl J Med* 2001;344:1117-24.
- Serruys PW, Morice MC, Kappetein AP, Colombo A, Holmes DR, Mack MJ, *et al.* Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. *N Engl J Med* 2009;360:961-72.
- Mukherjee D, Moliterno DJ. Effectiveness of PCI for non-acute coronary artery disease. *Lancet* 2009;373:870-2.
- Pursnani S, Korley F, Gopaul R, Kanade P, Chandra N, Shaw RE, *et al.* Percutaneous coronary intervention versus optimal medical therapy in stable coronary artery disease: A systematic review and meta-analysis of randomized clinical trials. *Circ Cardiovasc Interv* 2012;5:476-90.
- Patel MR, Dehmer GJ, Hirshfeld JW, Smith PK, Spertus JA, American College of Cardiology Foundation Appropriateness Criteria Task Force, *et al.* ACCF/SCAI/STS/AATS/AHA/ASNC 2009 Appropriateness Criteria for Coronary Revascularization: A report by the American College of Cardiology Foundation Appropriateness Criteria Task Force, Society for Cardiovascular Angiography and Interventions, Society of Thoracic Surgeons, American Association for Thoracic Surgery, American Heart Association, and the American Society of Nuclear Cardiology Endorsed by the American Society of Echocardiography, the Heart Failure Society of America, and the Society of Cardiovascular Computed Tomography. *J Am Coll Cardiol* 2009;53:530-53.