

# Management of Left Main Coronary Artery Stenosis

S Satyavan

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## Abstract

The optimal treatment of left main coronary artery disease (LMD) continues to evolve and remains a topic for exciting scientific debate. As a large segment of the myocardium depends on this vessel, adequate perfusion is necessary for a proper function of the heart. The available modalities for management of LMD include pharmacotherapy, bypass surgery or nonsurgical percutaneous revascularisation. Medical therapy of patients with LMD is associated with a poor prognosis (1,2,3). However, randomized trials and large registries (4,5,6,7,8,9,10) have shown improved survival by coronary artery bypass graft surgery (CABGS) and generally this technique has remained the preferred therapeutic option. Gruntzig et al (11) reported the first percutaneous interventions of left main coronary artery (LMCA) and concluded that the technical difficulties and high early mortality made this unacceptable as a standard treatment. As a result in 1984, the National Heart Lung and Blood Institute published a consensus document that percutaneous transluminal coronary angioplasty (PTCA) was contraindicated for this subset (12).

## INTRODUCTION

Despite, these discouraging reports, PTCA of LMCA stenosis remained the sole option for patients at high risk of CABGS (e.g. patients in a highly critical haemodynamic status due to acute myocardial infarction (AMI) or patients in cardiogenic shock) or even for patients with contraindication to operation or with limited life expectancy. The pioneering early experience of O'Keefe et al (13) using balloon angioplasty for unprotected LMCA stenosis revealed satisfactory short-term success, however, followup revealed attrition rates, leading to recommendations proscribing this practice for CABG eligible patients (14). The advent of better percutaneous coronary intervention (PCI) equipment, stents, ablative devices, haemodynamic support systems, intravascular ultrasound (IVUS), and antithrombotic agents ushered a renewed interest in the practice of unprotected LMCA percutaneous revascularisation. The ULTIMA registry (15) concluded that use of stents and atherectomy devices significantly improved the short term clinical outcome of patients undergoing PCI of LMCA stenosis. Since then, a large number of reports (16,17,18,19,20,21) published their experience concerning the immediate and late outcome of PCI in LMD without contraindications to CABGS. Their conclusion was that elective percutaneous intervention to treat protected and unprotected LMCA stenosis can be a safe and effective therapeutic choice. Consequently, the most recent American Heart Association guidelines (22,23) relating

to treatment of stable and unstable angina no longer regard LMCA stenosis as an absolute contraindication to a percutaneous intervention.

## CLINICAL FEATURES

The prevalence of significant (> 50%) isolated LMCA stenosis varies from 0.25 to 1.3 percent in patients undergoing diagnostic catheterization (24). In about 80 percent of patients with LMCA stenosis there is concomitant significant atherosclerosis in other major coronary vessels. The reported prevalence of LMCA stenosis varies from 2.5 to 10 percent depending upon the cohort of patients studied in different series (25,26). The prevalence of significant LMCA stenosis has been reported to be approximately nine percent in patients undergoing bypass surgery, approximately five percent in patients with chronic angina and about seven percent in patients with AMI (27,28).

## PROTECTED VERSUS UNPROTECTED LMCA STENOSIS

Left main trunk (LMT) or LMCA is defined as "Protected" when there is atleast one patent bypass graft to the left circumflex (LCX) or left anterior descending (LAD) artery. In the absence of such a patent graft, LMCA (LMT) is said to be unprotected. The intervention for protected or unprotected LMD may be elective or in emergency. Unfortunately, in the literature there is lot of mix-up about

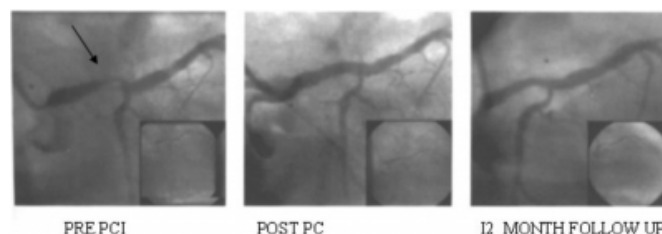
the results of these groups (<sup>29</sup>). The distinction becomes important when outcome from different studies are to be compared. The interventions performed in emergency usually are in critically ill patients presenting with haemodynamic collapse. In contrast, the elective interventions are performed in relatively stable patients. During the last few years, the number of elective interventions in unprotected LMD have increased. Initially, LMCA elective interventions were performed only in CABG ineligible patients or in those with limited life expectancy. In the post stent era, the indications of elective LMCA interventions have widened and even includes CABG eligible patients with normal or reduced left ventricular (LV) function.

### EMERGENT INTERVENTIONS IN UNPROTECTED LMCA STENOSIS

The interventional cardiologist faces the toughest challenge while dealing with patients of unprotected LMD in emergency. These patients carry the highest risk as they present with AMI, haemodynamic instability with or without cardiogenic shock. There have been small reports of LMCA interventions in this setting often with poor results. A recent study by Sperker et al (<sup>30</sup>) is of great interest when one evaluates the results of unprotected LMCA intervention in emergency. Eleven of the 18 patients in this group were in cardiogenic shock. Seven of the eleven either died as a procedural complication or while in hospital. Obviously, this represents a very high mortality rate, nonetheless, 4 of the 11 patients did survive hospitalization. In followup, two of the four patients survived without additional interventions, where as two lived to undergo CABGS. The results in this study are truly remarkable considering the fact that patients on initial presentation had systolic blood pressure of 50-60 mm of Hg and several had had or were having cardiopulmonary resuscitation. Figure 1 shows example of a patient who underwent stenting of LMCA during cardiogenic shock. The procedure resulted in clinical stabilization.

**Figure 1**

Figure 1 : PCI and stenting of unprotected LMCA stenosis in cardiogenic shock. Arrow shows tight LMCA stenosis in pre PCI angiogram. Post PCI angiogram shows fully deployed stent with clinical stabilization of patient. At 2 month follow up there is slight in stent restenosis.



### PERCUTANEOUS REPERFUSION OF LMCA STENOSIS COMPLICATED BY AMI

There is a paucity of data on outcomes of patients undergoing emergency percutaneous or surgical revascularisation of LMD complicated by AMI. Initial studies on percutaneous revascularisation in patients with AMI and LMD reported very poor in-hospital results. In a series of 6 patients reported by Chauhan et al (<sup>31</sup>), the in-hospital mortality was 83% (5/6 patients) and led the authors to conclude that there is a prohibitive risk for percutaneous revascularisation in LMD complicated by AMI. Quigley et al. (<sup>32</sup>) reported the in-hospital outcome of 34 patients with AMI and LMD. Out of these, 16 patients were in cardiogenic shock; 7 patients were treated medically, 4 were managed with PTCA, and 5 with CABGS. The overall mortality rate was 100% (4/4 patients) in the PTCA group and 100% (7/7 patients) in the medical treatment group; the surgical revascularisation group mortality rate was 89% (8/9 patients).

In contrast to poor results in earlier studies, the outcomes in ULTIMA registry (<sup>33</sup>) and in study by Neri et al (<sup>34</sup>) are more favourable. The better results in these series can be attributed to use of intracoronary stents, newer antiplatelet therapy and mechanical support. In ULTIMA (Unprotected left main trunk intervention multicenter assessment) multicentric registry from 13 countries (<sup>33</sup>), 40 patients underwent percutaneous LMCA interventions for AMI with in hospital mortality of 55% and 18% requiring CABGS. Neri et al (<sup>34</sup>) reported results of PCI in 22 patients with most (82%) of the patients presenting in cardiogenic shock. The primary success of PCI was 91% and primary stenting was performed in 17 patient (77%). The overall in-hospital mortality was 50% (11/22 patients) and all deaths were due to refractory shock. The 6-month survival rate was 41% 1%, while the event-free survival was 27% 10%. At 6-month

follow up, the mortality rate increased to 59%, the target vessel revascularisation rate was 14%. The results of ULTIMA registry and data of Neri et al (<sup>33, 34</sup>) suggest that emergency percutaneous revascularisation in patients with LMD and AMI is technically feasible. The benefit of percutaneous coronary interventions on mortality is likely. However, the small number of patients prevents any definitive conclusion.

With respect to the emergent CABGS for LMD complicated by AMI, the only reported data are those of Nakanishi et al. (<sup>35</sup>) and are based on a series of 13 patients. The mortality rate was 46% for the entire group and 53% for the patients presenting with cardiogenic shock. These results are comparable to those observed by Neri et al (<sup>34</sup>) and by ULTIMA registry experience (<sup>33</sup>). However, the paucity of data does not allow any conclusion on whether percutaneous or surgical reperfusion is preferred in patients with LMD complicated by AMI.

Adjunctive intra-aortic balloon pump (IABP) is mandatory when PCI of LMD is performed during emergency, during AMI, in cardiogenic shock and in haemodynamically unstable patients. Emergency LMCA intervention has also been performed using retrograde perfusion via the coronary sinus and retroinfusion of coronary veins by using extra corporal membrane oxygenation pump.

### ELECTIVE INTERVENTIONS

#### A) INTERVENTIONS IN PROTECTED LMCA STENOSIS

In most studies on protected LMCA stenosis, procedural success and long term outcome are favourable (<sup>36</sup>). No comparative data is available in this patient population with alternative treatment strategies like redo CABGS or medical treatment alone. A study by Lopez et al (<sup>36</sup>) included 42 patients of whom 43 percent were treated with rotational atherectomy (RA) followed by stenting and 30 percent with primary stenting. Palmaz-Schatz coronary stent was the most commonly used stent (79%), but 24 percent patients received Palmaz-Schatz biliary stent. Balloon angioplasty was performed as a single technique in seven percent, directional coronary atherectomy (DCA) in four percent, and RA in 15 percent of the total patients. In another report of 124 patients by Kornowski et al (<sup>19</sup>), 40 percent of patients received stents alone, 24 percent had RA followed by stenting and six percent had DCA followed by stenting. Balloon angioplasty was a single treatment in three percent, DCA in six percent, and RA in 16 percent of total patients. In the study by Lopez

et al (<sup>36</sup>), stenting improved post-procedural angiographic result with less residual stenosis (30.24 in non-stented compared to 3.21 in stented group); however, 100 percent technical success was achieved in the entire study population.

Similar post-procedural angiographic benefit was noted in the study by Kornowski et al (<sup>19</sup>). In the study by Lopez et al (<sup>36</sup>) subgroup analysis demonstrated that angiographic benefits of stenting were most pronounced in ostial LMT stenosis, Rotational atherectomy prior to stenting did not improve immediate angiographic outcome in all patients, but in patients with fluoroscopic calcification it yielded a somewhat lower residual stenosis (0.20 vs. 14.18%;  $p = 0.07$ ). Target vessel revascularisation was needed in 13 percent and repeat revascularisation of different sites was performed in additional nine percent patients in this study. In a multivariate analysis from the study by Kornowski et al (<sup>19</sup>), unstable angina (odds ratio = 1.42;  $p = 0.045$ ) independently predicted any cardiac events, whereas the final lumen diameter (odds ratio = 0.40;  $p = 0.021$ ) was negatively associated with cardiac events at 12 months followup. Diabetes mellitus (odds ratio = 3.2;  $p = 0.04$ ) independently predicted target lesion revascularisation and the final lumen diameter (odds ratio = 0.30;  $p = 0.017$ ) was negatively associated with target lesion revascularisation. The use of stents did not influence either of these endpoints independently. The overall survival of 98 percent and 99 percent, event-free (death MI, revascularisation) survival of 71 percent and 77 percent at one year in these studies, along with high-risk in association with repeat CABG, makes percutaneous intervention a treatment of choice.

#### B) INTERVENTIONS IN UNPROTECTED LMCA STENOSIS

With the advances in technology, the short and long term outcome following unprotected LMCA intervention has improved. This has led to widening of indications for use of PCI in management of this subset. A brief review of evolving technologies (balloon angioplasty, intracoronary stenting, debulking, IVUS guidance and haemodynamic support systems) will be presented.

#### BALLOON ANGIOPLASTY

Several studies have reported the results of balloon angioplasty (without stenting) of unprotected LMCA stenosis. O'Keefe et al (<sup>13</sup>) reported the results of 127 LMCA balloon angioplasty procedures of which 33 were elective for unprotected LMCA stenosis and 9 were

unprotected LMCA acute occlusions. In the elective subgroup the procedural mortality rate was 9.1% and late mortality reached 65% at a mean followup 20 months. Repeat revascularization procedure (PTCA or CABG) were required in 42% of patients. In nine patients who had presented with acute occlusion, five died in-hospital, of the four who survived to discharge, two subsequently died and two others underwent bypass surgery. The results of PTCA alone were not favourable in many other studies and were associated with unfavourable early and long term outcome. The high concentration of elastic fibers in the aorto-ostial lesions and subsequent marked recoil have been proposed as possible causes of the high restenosis rate after conventional balloon angioplasty. Due to these limitations of balloon angioplasty, elective percutaneous revascularisation of unprotected LMCA stenosis received temporary set back (<sup>14</sup>).

### INTRACORONARY STENTING

The widespread availability of intracoronary stents rejuvenated interest in percutaneous treatment of LMCA stenosis. Initially, the stents were used as a “last resort” in selected patients with prohibitive surgical risk, however, soon they became the device of choice. Elective stenting provides several advantages over balloon angioplasty alone : reduction of abrupt closure, greater acute gain after the procedure with a large maximum lumen diameter (MLD), and a lower restenosis rate at follow up. The risk of subacute thrombosis after stent placement is estimated at about 1% with the current technique of stent implantation utilizing high pressure and or intravascular ultrasound guidance, together with the use of combined aspirin and ticlopidine (clopidogrel) therapy. In most series, tubular design stents were selected for ostial and mid segment LMCA stenosis and coil stents for distal stenosis involving bifurcation into LAD or LCX.

During the recent years, several studies (<sup>16, 17, 18, 19, 20, 37, 38, 39</sup>) have reported promising results of elective stenting for patients with unprotected LMCA stenosis. In a recent study of LMCA stenting in a population of 42 consecutive patients with unprotected LMCA stenosis and normal left ventricular (LV) function, Park et al (<sup>16</sup>) presented excellent results with a procedural success rate of 100%, clinical recurrence at 6 months follow up of 17% and angiographic restenosis of 22%. These patients were categorized as low surgical risk cases. Black et al (<sup>38</sup>) recently reported results of unprotected LMCA stenting in 92 patients belonging to two distinctive groups. Group I comprised 39 patients in whom PTCA was considered only when surgical revascularization was

contraindicated. The remaining 53 patients (group II) also included patients in whom surgery was feasible. Compared to group I, group II patients had higher LVEF (60 12% vs. 51 16%,  $p < 0.01$ ), less severe LMCA stenosis (68 12% vs. 80 10%,  $p < 0.001$ ), lower surgical risk score (13 7 vs. 20 7,  $p < 0.001$ ) and had angioplasty more often performed from radial approach (88% vs. 23%,  $p < 0.001$ ).

The procedure success rate was 100%. The in hospital mortality was 4% (4 deaths, 3 Cardiac). During follow up (7.3 5.8 months, median 239 days; range 49 to 1,477 days) there were 6 deaths, 13 patients required repeat PTCA (4 LMCA), and two required CABGS. Estimated survival was 89 6.3% at 500 days and 85 12 % at 1,000 days post stenting. Overall mortality was 3.8 % in group II and 20.5% in group I ( $p < 0.02$ ). These results suggest that, in selected patients, stenting of unprotected LMCA stenosis could be considered as a feasible alternative to CABGS with an acceptable complication rate. Patients who are candidates for CABGS appear to have a better outcome than those where CABGS is contraindicated.

The data regarding use of drug eluting stents in LMD should become available in future and may change the practice of LMCA PCI.

### DEBULKING BEFORE STENTING AND INTRAVASCULAR ULTRASOUND GUIDANCE

Dr. Park and colleagues recently reported (<sup>39</sup>) the impact of debulking procedure and intravascular ultrasound guidance on the clinical outcome of patients with unprotected LMCA stenosis. A total of 127 consecutive patients with unprotected LMCA stenosis and normal LV function were treated by elective stenting. The long term outcomes were evaluated between two groups : IVUS guidance ( $n = 77$ ) vs. angiographic guidance ( $n = 50$ ) and debulking plus stenting ( $n = 40$ ) vs. stenting alone ( $n = 87$ ). The debulking procedure utilized was DCA. Optimal atherectomy and adjunct balloon angioplasty were performed in all 40 lesions until the residual diameter was  $< 10\%$ . Stenting with IVUS guidance was performed in 77 patients. The IVUS criteria of stent optimization were as follows : Complete stent to vessel wall apposition, adequate stent expansion (i.e., lumen cross sectional area (CSA) of the target lesion 90% of the distal reference lumen CSA) and full lesion coverage. The findings of this study indicated that IVUS guidance may help to achieve excellent initial results and debulking before stenting appears to result in lower restenosis rates. In some cases of LMD (particularly ostial), it is often difficult to

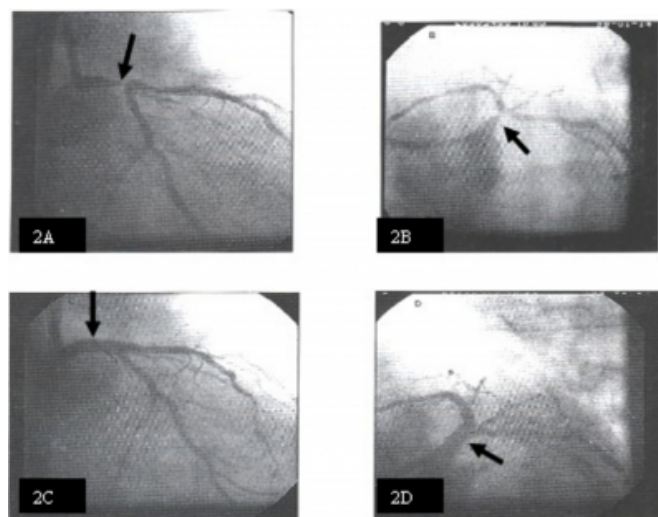
evaluate the exact size of the LMCA by angiography. IVUS before stenting provides useful anatomical information and may help in deciding the treatment strategy (debulking + stenting or stenting alone).

In this study, the post stenting MLD was significantly larger in the IVUS guided group ( $p = 0.003$ ). However, the angiographic restenosis rate at 6 months was not different between the IVUS and angiography guided procedure (18.6% vs. 19.5%). This finding may be partly explained by the fact that the reference vessel size in the current study was large (4.0 mm), and the post stenting MLD was also large (4.0 mm), even in the angiography guided group. A post stenting MLD of 4.0 mm should be large enough to maintain the final MLD, without angiographic restenosis at followup. Aggressive debulking with DCA before stenting may reduce the residual plaque burden and subsequently the restenosis, as well. On univariate analysis debulking before stenting resulted in significant reduction in restenosis (8.3% vs. 25%,  $p = 0.034$ ). However, the benefit of debulking atherectomy was not found to be significant on multivariate analysis.

The reference vessel size of the LMCA in this study varied from 2.3 to 5.8 mm and 57% of patients who had followup angiograms had large reference vessels ( $> 4.0$  mm). The most likely explanation is that the degree of debulking might be relatively insufficient in such large vessels. Regardless, it is notable that the debulking/stenting group had a lower restenosis rate, even though the reference diameter, final MLD by QCA analysis and final lumen dimensions with IVUS were similar to those in stenting alone group. This suggests that the plaque, itself may contribute to the restenosis process and supports the promise that debulking plus stenting may reduce restenosis. Figure 2 depicts example of a patient with tight distal LMCA stenosis who underwent DCA debulking followed by intracoronary stenting.

### Figure 2

Figure 2A to 2D : LMCA stenting preceded by dca debulking. Upper panel arrows show tight stenosis of distal LMCA in AP (figure 2A) and LAO caudal views (figure 2B). Figure 2C and 2D show fully expanded and deployed stents in LAD and distal LMCA. DCA debulking was performed prior to stenting.



### HAEMODYNAMIC SUPPORT

During elective intervention the need for IABP is decided by LV function. Patients with normal LV function tolerate the global ischaemia well during balloon inflation and routine insertion of IABP is not necessary. For such cases, IABP should be available in catheterization laboratory for any emergency and many operators keep left femoral arterial access available. If LV function is poor, prophylactic IABP is recommended for prevention of potentially life-threatening haemodynamic collapse.

### ANTITHROMBOTIC REGIMEN

Antithrombotic regimen includes aspirin, clopidogrel (or ticlopidine) and heparin. The duration and dose of these agents have varied from series to series. The use of glycoprotein IIB/IIIa inhibitor Abciximab has varied from 1% to 5%.

### LONG TERM CLINICAL OUTCOMES

Park SJ et al (<sup>39</sup>) in a recent study reported long term outcome of 127 consecutive cases who underwent elective stenting of unprotected LMCA. At two years the cumulative survival rate was 97.0 1.7% and the cardiac event-free survival rate was 86.9 3.3%. Similar figures have been reported by Silvestri and colleagues (<sup>17</sup>) in a low risk population. One-year mortality reported by Park and colleagues was 5.7% and the same figures have been

reported in low-risk group CABGS series (<sub>40</sub>). The mortality rate in this series over two-year followup was 3.1%, which is acceptable.

For patients with restenosis, CABG was recommended first. However, other modalities of treatment included repeat angioplasty using RA with or without radiation therapy. In this series of Park et al (<sup>39</sup>) after six months, there were no cardiac deaths or target lesion revascularizations, indicating that the long-term clinical course may be excellent after unprotected LMCA stenting in selected patients with normal left ventricular function. This result is consistent with previously published data showing that the restenotic process after stenting is time-limited and that little progression occurs beyond six months.

Tan WA et al. (<sup>37</sup>) on behalf of ULTIMA investigators reported long term clinical outcome after PCI of unprotected LMCA in 279 patients. Thirty (13.7%) patients died in hospital, and the rest were followed up for a period of 19 months. The 1-year incidence was 24.2% for all-cause mortality, 20.2% for cardiac mortality, 9.8% for myocardial infarction, and 9.4% for CABGS. Independent correlates of all-cause mortality were LVEF 30%, mitral regurgitation grade 3 or 4, presentation with myocardial infarction and shock, creatinine 2.0 mg/DL, and severe lesion calcification. For the 32% of patients (low risk group) < 65 years old with left ventricular ejection fraction > 30% and without shock, the prevalence of these adverse risk factors was low. No periprocedural deaths were observed in this low-risk subset, and the 1-year mortality was only 3.4%. On the basis of this data it becomes obvious that patients undergoing unprotected LMCA PCI are the ones with serious comorbidities and consequently have high event rates. PCI may be an alternative to CABG for a select proportion of elective patients (low risk group) and may also be appropriate for highly symptomatic inoperable patients.

Finally, on the basis of the 2% per month death rate among hospital survivors noted over the first 6 months after hospital discharge, probably partly a result of restenosis, it is strongly recommended to have surveillance coronary angiography at 2 and 4 months post PCI.

### ROLE OF CABGS IN LMCA STENOSIS

CABGS has been standard of care for LMD ever since the veterans administrations cooperative study established its superiority over medical treatment with regards to survival (<sup>41</sup>). PCI was shown in randomized clinical trials in the 1990's to be equivalent to CABGS in terms of rates of

survival and infarct free-survival in a growing number of patients with coronary artery disease. It is highly unlikely that there will be randomized clinical trials to compare results of PCI and CABGS in LMCA stenosis because of logistic considerations of prohibitive sample size and cost requirements.

From the available data, based on clinical studies and registries there is no doubt that PCI is an alternative to CABGS in selected cases. Judicious patient selection remains critical for both the interventionalist and cardiac surgeon, and further studies are needed to define which patients are truly inoperable, who among these patients still may benefit from PCI, and those in whom revascularisation attempts will be futile. Unfortunately, patients who are good candidates for surgery are typically the same ones who will do well with other invasive procedures, and poor surgical risks often mean poor global risks. It is fair to say that CABGS is still the first choice for the majority of patients with LMD, but PCI is a viable option in select circumstances : those presenting with AMI, the highly symptomatic but inoperable patient, and perhaps the low-risk patient group discussed above.

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**Author Information**

**Sharma Satyavan, M.D., D.M., M.N.A.M.S., FACC, FAMS, FSACI**  
Consultant Cardiologist, Bombay Hospital and MRC