Revascularization for Unprotected Left Main Stem Coronary Artery Stenosis

Stenting or Surgery

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For coronary artery disease with unprotected left main stem (LMS) stenosis, coronary artery bypass grafting (CABG) is traditionally regarded as the “standard of care” because of its well-documented and durable survival advantage. There is now an increasing trend to use drug-eluting stents for LMS stenosis rather than CABG despite very little high-quality data to inform clinical practice. We herein: 1) evaluate the current evidence in support of the use of percutaneous revascularization for unprotected LMS; 2) assess the underlying justification for randomized controlled trials of stenting versus surgery for unprotected LMS; and 3) examine the optimum approach to informed consent. We conclude that CABG should indeed remain the preferred revascularization treatment in good surgical candidates with unprotected LMS stenosis. (J Am Coll Cardiol 2008;51:885–92) © 2008 by the American College of Cardiology Foundation
outcomes with percutaneous and surgical revascularization to examine whether there is sufficient clinical evidence to support the use of stents in the majority of elective patients with unprotected LMS (i.e., where there are no existing bypass grafts).

Pathology of LMS and Implications for Revascularization With Stents or Surgery

A significant LMS stenosis is considered to be a lesion occupying over 50% of the vessel diameter. Left main stem stenosis currently occurs in 4% to 6% of all patients undergoing coronary angiography (15) and in 30% of CABG patients (16).

Left main stem stenosis is theoretically an attractive target for PCI because it is the most proximal component of the left coronary circulation and because of its relatively large diameter. However, in reality, 3 important anatomical features carry important qualifications about the likely success of PCI and CABG in LMS stenosis:

- Left main stem stenosis occurs as an isolated lesion in only 6% to 9% of patients, whereas over 70% to 80% of patients also have multivessel CAD (17–24), thereby potentially enabling more complete coronary revascularization with CABG than with stenting.
- Most LMS stenoses (40% to 94%) occur in the distal segment of the artery and extend into the proximal coronary arteries (17–24); such bifurcated or trifurcated lesions have a high risk of restenosis (25), while acute occlusion at this site can have catastrophic consequences.
- Morphologically, around one-half of LMS lesions have significant calcification (15).

Whereas considerations about the precise anatomical location and complexity of LMS stenosis impact critically on both the short- and long-term outcomes of PCI, they have negligible influence on the success of CABG, as the distal anastomoses of the bypass grafts are to the mid or distal coronary vasculature, well beyond all diseased segments in both the LM and the proximal coronary arteries, thereby protecting entire proximal zones of vulnerable myocardium.

Rationale for CABG as the “Standard of Care” Treatment for LMS Stenosis

In 1975 Cohen and Gorlin (26) first reported that CABG resulted in a significant improvement in 10-year survival compared with medical therapy in patients with significant LMS stenosis, an observation confirmed in 3 randomized trials (7) and numerous observational studies over the next 2 decades. Although both the medical therapy and surgical techniques used in these studies are outdated by today’s standards (e.g., aspirin, statins, and internal mammary artery [IMA] grafts were not widely used), a meta-analysis of these trials demonstrated a significant relative risk reduction in mortality with CABG of about 66% at 5 years with the benefit extending to 10 years (7). Even so, the trials probably substantially underestimated the real survival benefit of CABG surgery because the trial patients were relatively low risk, only 10% of surgical patients received an IMA graft (which leads to superior long-term graft patency and a clear survival benefit), and analysis on an intention-to-treat basis “discounted” the survival advantage of CABG in the 40% of the medical group who crossed over to surgery (7). Indeed, in the largest prospective study of LMS stenosis, in which 1,484 patients in the CASS (Coronary Artery Surgery Study) registry were followed for up to 16 years, the overall median survival for CABG patients was 13.3 years versus 6.6 years for medical therapy (8). Since these pivotal studies, improvements in medical therapy have benefited both surgical and medical groups, but in view of the overall survival advantage of CABG in most angiographic and clinical subsets, current ACC/AHA guidelines state that “the benefit of surgery over medical treatment in patients with significant LMS stenosis (greater than 50%) is little argued” (9).

Current Results for CABG in LMS Stenosis

In the last decade, 6 groups from Europe and the U.S. have reported CABG results in cohorts of at least 300 patients with LMS stenosis (16,27–31) (Table 1). Cumulatively, these studies included almost 11,000 patients of whom around one-third (range 5% to 57%) underwent urgent surgery with an average in-hospital mortality of 2.8% and 30-day mortality of 3% to 4.2% (Table 1). In the largest individual study, the Society of Cardiothoracic Surgery in the U.K. reported a mortality of 3% for all 5,003 patients undergoing CABG for LMS stenosis in 2003 (compared with <2% in over 17,000 patients with no LMS stenosis) (31). Two recent British studies reported excellent 2-year survival rates of 94% and 95% (28,30). As for all cardiac surgical procedures, the mortality rate is strongly influenced by comorbidities; for example, Ellis et al. (27) reported that 3-year mortality for CABG in LMS stenosis varied from 4% in low-risk patients to 40% in those with significant and multiple comorbidities (27).

Left main stem stenosis may also be particularly suitable for the use of bilateral IMA grafts. The angiographic patency of both IMA placed to left-sided coronary vessels is over 95% at 1 week and at 7 years (32) and may translate into a significant survival benefit. In a systematic review of over 15,000 CABG patients matched for age, gender, diabetes, and left ventricular function, the hazard ratio for...
death was 0.81 (95% confidence interval 0.70 to 0.94) with bilateral versus single IMA grafts (number needed to treat, 13 to 16) (32). In addition, the use of bilateral IMA grafts appears safe; the ART (Arterial Revascularisation Trial) study of bilateral versus single IMA grafts reported an overall 30-day mortality of 1% in over 3,000 patients (33).

**PCI With BMS for LMS**

Initial attempts at PCI using simple balloon angioplasty in LMS stenosis were soon abandoned because of a high rate of procedural complications from elastic recoil and vessel dissection (Table 2). However, the ability of BMS to minimize these complications encouraged at least 8 studies of BMS in LMS stenosis in over 1,100 patients between 1999 to 2003 (34–41). Interpretation of outcome is, however, hampered by the absence of data regarding: 1) the actual proportion of all LMS stenosis patients undergoing PCI rather than CABG who were ineligible for CABG because of other significant comorbidity (therefore at high risk for PCI) and/or nonsurgical preference; and 2) the number of patients with significant distal LMS stenosis and multivessel CAD.

Notwithstanding these limitations, as shown in Table 2, the overall in-hospital mortality averaged 6% with further immediate revascularization in 4% (range 0% to 20%). Most worrying, however, was a 1- to 2-year mortality of 17% (range 3% to 31%) and a repeat revascularization rate of 29% (range 15% to 34%). However, several authors have also reported more favorable results in “low-risk” patients (younger patients, normal ventricular function, and predominantly ostial or midshaft lesions) with 1-year mortality rates of 3.4% (in the Ultima registry) (36) to 7% (35) and a 3-year mortality of 7.4% (39). Even in these patients, however, repeat revascularization rates were 28% to 32%. Furthermore, the results of CABG would also be excellent in such low-risk populations; for example, the 1-year mortality rate in the 504 CABG patients in the SoS (Stent or Surgery) trial was 0.8% (42).

Indeed, the overall high late mortality and revascularization rates with BMS influenced the 2001 (10) and 2005 (11) ACC/AHA guidelines to state that PCI was a class III indication for virtually all LMS stenosis in those who are otherwise eligible for CABG (11) and the European Society of Cardiology guidelines to conclude that “stenting for unprotected left main disease should only be considered in the absence of other revascularization options” (12).

**PCI With DES for LMS Stenosis**

Although, in comparison with BMS, DES do not reduce the risk of death or myocardial infarction in stable CAD (4,6), their ability to reduce restenosis has encouraged their use in LMS disease (Table 3). Although 7 different groups

### Table 1: Current Results of CABG for LMS Stenosis

<table>
<thead>
<tr>
<th>Author (Ref. #) (Year)</th>
<th>Year of Surgery</th>
<th>n</th>
<th>Hospital 30-Day Mortality (%)</th>
<th>1-Year Mortality (%)</th>
<th>2-Year Mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jonsson et al. (31) (2006)</td>
<td>1970 to 1999</td>
<td>1,888</td>
<td>2.7</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Lu et al. (30) (2006, 2005)</td>
<td>1997 to 2003</td>
<td>1,197</td>
<td>2.8</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Weighted average</td>
<td>—</td>
<td>10,788</td>
<td>2.8</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

CABG = coronary artery bypass grafting; LMS = left main stem.

### Table 2: Eight Studies of PCI Using BMS in LMS

<table>
<thead>
<tr>
<th>Author (Ref. #)</th>
<th>Sites</th>
<th>n</th>
<th>% Eligible</th>
<th>Stent</th>
<th>In-Hospital to 30-Day Mortality (%)</th>
<th>1- to 2-Year Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keeley et al. (34)</td>
<td>1</td>
<td>54</td>
<td>—</td>
<td>100%</td>
<td>5%</td>
<td>31%</td>
</tr>
<tr>
<td>Silvestri et al. (35): high risk</td>
<td>1</td>
<td>47</td>
<td>—</td>
<td>100%</td>
<td>9%</td>
<td>11%</td>
</tr>
<tr>
<td>Silvestri et al. (35): low risk</td>
<td>1</td>
<td>93</td>
<td>—</td>
<td>100%</td>
<td>0%</td>
<td>3%</td>
</tr>
<tr>
<td>Tan et al. (36): all</td>
<td>25</td>
<td>279</td>
<td>—</td>
<td>85%</td>
<td>14%</td>
<td>24%</td>
</tr>
<tr>
<td>Tan et al. (36): low risk</td>
<td>25</td>
<td>89</td>
<td>—</td>
<td>85%</td>
<td>3.4%</td>
<td>3.4%</td>
</tr>
<tr>
<td>Black et al. (37)</td>
<td>1</td>
<td>92</td>
<td>—</td>
<td>100%</td>
<td>4%</td>
<td>6.5%</td>
</tr>
<tr>
<td>Takagi et al. (38)</td>
<td>1</td>
<td>63</td>
<td>—</td>
<td>58%</td>
<td>0%</td>
<td>16%</td>
</tr>
<tr>
<td>Park et al. (39)</td>
<td>4</td>
<td>270</td>
<td>—</td>
<td>100%</td>
<td>0%</td>
<td>7%</td>
</tr>
<tr>
<td>Brueren et al. (40)</td>
<td>1</td>
<td>71</td>
<td>—</td>
<td>64%</td>
<td>1%</td>
<td>10%</td>
</tr>
<tr>
<td>Kelley et al. (41)</td>
<td>3</td>
<td>97</td>
<td>—</td>
<td>100%</td>
<td>9%</td>
<td>28%</td>
</tr>
<tr>
<td>Weighted average</td>
<td>38</td>
<td>1,155</td>
<td>6%</td>
<td>3%</td>
<td>17%</td>
<td>17%</td>
</tr>
</tbody>
</table>

BMS = bare-metal stent; LMS = left main stem; PCI = percutaneous coronary angioplasty.
have published results involving 599 patients between 2004 to 2006 (17–24), interpretation is limited by small individual patient numbers (50 to 130 per study), incomplete angiographic assessment of restenosis (only 1 study re-assesses all patients [20]), short duration of follow-up (mean of 11 months), and lack of a control group in 4 studies (thereby inviting interpretive biases). Furthermore, with the exception of the Bologna registry (24), for studies of BMS there is little data regarding what proportions of all LMS stenosis patients underwent PCI rather than CABG or were ineligible for CABG because of other comorbidity and/or nonsurgical preference (and were, therefore, also at high risk for PCI).

As shown in Table 3, considering that 42% to 94% of patients had significant distal or bifurcation LMS stenosis and 37% to 100% also had significant CAD, the immediate results are encouraging. The in-hospital mortality rate averaged 2.4% (range 0% to 11%), the immediate repeat revascularization rate was 2% (range 0% to 6%), and biochemical evidence of myocardial infarction was 6% (range 0% to 9%). However, at a mean follow-up of 11 months (range 6 to 18 months), mortality had increased to 7% (range 0% to 14%) and repeat revascularization to 13% (range from 2% to 38%).

One group has reported no deaths in 116 LMS patients at 18 months of follow-up but restenosis in 13% of the 85% of patients who underwent angiography at 6 months (18,22). In contrast, in the only study with complete angiographic follow-up, the rate of restenosis increased from 34% at 3 months to 44% at 9 months (20). This disparity in restenosis rates may not only reflect differences in patient selection, interventional techniques, and completeness and timing of angiographic follow-up but, most importantly, differences in the incidence of distal/bifurcation LMS stenosis. The crucial importance of distal LMS stenosis as a predictor of adverse outcomes has recently been re-emphasized by Valgimigli et al. (25) who, at a median of 18 months, reported a 3-fold increase in major adverse coronary events (MACE) in distal LMS stenosis (30%) compared with those without (11%). And both Price et al. (20) and Palmerini et al. (24) warned that as restenosis was frequently asymptomatic, it mandated serial angiographic follow-up, a view reiterated by Baim et al. (14) who cautioned, “Without that safety net, one would expect an up-tick in late mortality events resulting from unrecognized restenosis in this critical location” (14). Clearly, such a strategy not only has significant cost implications but also still begs the question: in view of potential late failure of DES, how long should such surveillance angiography be continued?

In contrast, the use of DES in nonbifurcation (an infrequent anatomical subset), unprotected LMS appears to be safe and effective based on a recent multicenter retrospective registry of 147 patients that reported a restenosis rate of <1% at 6-month angiographic follow-up, a major adverse clinical event rate of 7.4%, and a cumulative cardiac mortality of 2.7% at a median follow-up of 886 days (43).
Current Comparisons of PCI and CABG for LMS Stenosis

To date only 1 randomized trial of PCI versus CABG has been reported (44). The LEMANS (Study of Unprotected Left Main Stenting Versus Bypass Surgery) trial was a randomized trial of 52 PCI (35% with DES) and 53 CABG patients of whom approximately 60% had distal LMS stenosis, and of whom 75% of the CABG group and 60% of the PCI group had 3-vessel coronary artery disease ($p = 0.08$). Although, as expected, the CABG group had more short-term complications within the first month after surgery, the primary outcome of MACE at 1 year was similar in the 2 groups, as 15% of the PCI group required further PCI or CABG. Furthermore, the fact that only 72% of the CABG group received an internal mammary artery graft despite its well established survival benefit raises questions about the quality of the surgery in the LEMANS trial, as use of this graft should approach 100% in contemporary practice. Currently a larger randomized trial of DES versus CABG for LMS stenosis (the SYNTAX [Synergy between PCI and Taxus and Cardiac Surgery] trial) has now completed enrollment.

Only 2 groups have reported registry data in patients with LMS stenosis undergoing CABG or PCI with DES (21,24) with at least 1-year follow-up. In the Bologna registry of 311 patients with LMS stenosis, 68% were deemed suitable for either PCI or CABG, 19% for CABG only, and 13% for PCI only (24). At a median follow-up of 14 months, the mortality was 12% in 154 CABG and 13% in 157 PCI patients (but 3%, respectively, in low-risk patients). The repeat revascularization rate was, respectively, 3% for CABG and 26% for PCI. In an Italian registry of 249 LMS patients, there was no difference in 1-year mortality after adjustment for baseline characteristics in the 107 PCI and 142 CABG patients, who were significantly older (68 vs. 64 years) with a higher proportion of renal failure (8% vs. 2%) (21). Again, however, repeat revascularization was 20% in PCI versus 4% of CABG patients, probably reflecting the fact that 87% of patients had bifurcation disease (21).

The lack of long term follow-up is a fundamental limitation of all of these studies. The benefits of CABG surgery compared with medical therapy emerges beyond 1 year, as perioperative mortality and morbidity in the CABG group becomes offset by mortality from CAD in the medical group. Hence, the apparent lack of difference at 1 year is not reassuring and does not contradict the longer-term benefits of CABG.

Stent Thrombosis With DES

If restenosis is the Achilles heel of BMS, then stent thrombosis is a potentially important limitation of DES, with impaired endothelialization and healing the most important of several possible mechanisms (45). However, whereas restenosis usually has a relatively benign clinical outcome (except possibly in the LMS), stent thrombosis is associated with a 65% to 70% increased risk of myocardial infarction and a mortality of 25% to 45% (6). This persistent potentially prothrombotic substrate necessitates prolonged dual antiplatelet medication with aspirin and clopidogrel for at least a year (46), compared with 1 month with BMS.

The precise incidence of DES thrombosis is unknown. It was initially reported to be around 0.5%, similar to BMS, in the pre-approval pivotal trials of BMS versus DES (in low-risk patient and lesion cohorts, which involved limited follow-up of 9 to 12 months). A recent Food and Drug Administration Circulatory Devices Panel concluded that DES now account for around 80% of all stent use and that nearly 60% of their use is in “off-label” situations where, depending on the complexity of the patient and the lesion, they were “associated with increased risks of both early and late stent thrombosis, as well as death or myocardial infarction” with an annual thrombosis risk estimated at between 1% to 5% (3).

The ACC/AHA now recommend that a longer duration of dual antiplatelet therapy with aspirin and clopidogrel (perhaps indefinitely) is warranted to mitigate the increased risk of late stent thrombosis despite the significant long-term bleeding complications (47) and high costs (46).

Cautions Regarding Trials of Stents or Surgery in LMS Stenosis

The randomized controlled trial (RCT), considered the most robust form of evidence-based medicine, is predicated on the prerequisite of equipoise, defined as substantial uncertainty regarding the relative benefits and risks of competing treatment options. As the stakes for LMS stenosis are much higher than for other forms of CAD, there are 2 schools of thought regarding how justifiable are the ongoing or proposed RCT of PCI versus CABG given current knowledge.

Proponents argue that PCI already offers tangible short-term advantages over CABG as it is less invasive, reduces hospitalization duration, avoids the disability of surgical recovery, and allows patients to subsequently have CABG if necessary. As nearly one-third of LMS patients in Europe and one-fifth in the U.S. may have already been treated with DES (13) based only on underpowered, nonrandomized, and potentially biased studies, they advocate RCT to settle which is the better treatment, rather than allow the current highly variable and potentially dangerous clinical practice. They maintain that PCI should be prudently constrained within the strictly controlled and monitored environment of the RCT and argue that such RCT are essential if innovation is not to be stifled, thereby denying individual patients and society as a whole potentially better therapies.

In contrast, opponents of such RCT for LMS stenosis question if there is sufficient evidence of equipoise to warrant these trials. They maintain that the fundamental flaw of such trials is the lack of equipoise between the
treatments because CABG has a well-documented survival benefit of many years (7–9), and as stenting has no survival advantage over medical therapy in stable CAD (48,49), it is counterintuitive to believe or expect that it will do so in LMS stenosis. They emphasize that BMS in LMS stenosis were, after promising early results, abandoned because of excess late mortality and high intervention rates and that as DES do not improve clinical outcome over BMS in stable CAD (4), it is unlikely they will do so in LMS stenosis. Furthermore, they argue that the notion that “CABG can always be performed later” is a false premise with inherent risks. First, timely crossover to surgery may be precluded because restenosis in this critical lesion is often symptomatic and can be abrupt (20,24). Second, observational studies of tens of thousands of patients with multivessel CAD have consistently shown that PCI with stents, followed by crossover to CABG when necessary, resulted in inferior survival compared with an initial strategy of CABG (2). The opponents of RCT in LMS stenosis believe that patients should be offered the documented survival benefit of CABG (because in no other area of medicine would it be considered ethically justifiable to conduct an RCT that involved withholding a therapy with proven and substantial benefits) and that many appropriately informed patients would be unlikely to trade off substantial and long-term benefits of CABG (especially in an era when the procedural mortality and morbidity are relatively low) for a much less certain outcome with PCI.

Although there are no easy answers to resolve this dilemma at the current time, the results of the ongoing SYNTAX study should help inform clinical practice and guide the design of future trials. Ideally, such trials should:

• Be vetted through ethics committees and institutional review boards that are fully informed about the totality of evidence, including the clear benefits of CABG on mortality in LMS stenosis and the lack of efficacy of PCI in any situation in patients with stable CAD;
• Be powered adequately to evaluate the clinically relevant hard end point of mortality and clinically important differences to avoid a spurious conclusion that the 2 procedures are equivalent;
• Appreciate that early mortality and MACE initially “disadvantage” surgery, as most of these outcome measurements occur in the perioperative period;
• Include long-term follow-up (at least 5 years), as benefits of surgery accrue with time; and
• Maintain a registry of potentially eligible patients not entered in the trials.

Finally, for the results to be generalizable, a broad category of at-risk patients, typical of those encountered in routine clinical practice, must be included if feasible or completely described and studied in registries if excluded from randomization. It is vital that registry analysis includes risk adjustment, is published with the primary trial report, and includes sufficient patient descriptors to permit extrapolation of the results in formulating clinical judgment.

The Need for a Standardized Multidisciplinary Team Approach

As for any condition where several therapeutic approaches are possible, a multidisciplinary team is essential to ensure the highest likelihood that the most balanced advice and best treatment option are offered to patients with LMS disease. A multidisciplinary team can ensure that the patient understands that whereas short-term outcomes with PCI may appear satisfactory, the results by 1 year are less favorable and that significant uncertainties about its long-term reliability and durability mandate surveillance angiography, which should be weighed against the proven survival benefits of surgery. However, this ideal standard of care may be at risk of gradually being eroded by an increasing tendency of partisan interests to solely decide and instigate treatment, with the patient often being influenced into making a preordained “choice.” Framing information in the simplistic format—“we can fix your blockage with this stent or we can have the surgeon crack your chest”—while implying that the 2 treatments are otherwise equally efficacious may ensure patient compliance but undermines the concept of informed consent and indeed misinforms patients.

Conclusions

The fact that most patients with LMS stenosis have bifurcation disease and simultaneous multivessel CAD predates against likely long-term success with PCI. Consequently, in the absence of contraindications to surgery, CABG should remain the standard of care for most patients with LMS stenosis because of its substantial survival advantage and freedom from repeat intervention. Percutaneous coronary intervention may be a reasonable alternative in those with isolated LMS stenosis not involving the bifurcation or those ineligible for CABG. However, PCI (with or without stents of any type) has been shown not to confer any survival advantage compared with medical therapy in any category of patients with stable CAD, and concerns remain over the risk of stent thrombosis with DES, particularly when used in “off-label” situations. Despite their inherent limitations, the results of ongoing trials with randomized and registry cohorts evaluating DES with CABG should provide evidence-based guidance in selecting the preferred form of treatment for LMS stenosis in the future. Until then, consistent with ACC/AHA (10,11) and European Society of Cardiology guidelines (12) and as stated by Serruys et al. (19), “CABG should remain the preferred revascularization treatment in good surgical candidates with left main coronary artery disease.”
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