Should All Patients With Asymptomatic but Significant (>50%) Left Main Coronary Artery Stenosis Undergo Surgical Revascularization?

Gabor T. Gyenes, MD, PhD; William A. Ghali, MD, MPH

The incidental detection of asymptomatic but significant (>50%) left main coronary artery disease (LMCAD) has become more frequent with the increased use of coronary angiography for acute myocardial infarction. Most would agree that such LMCAD cannot be ignored. Yet, clarity is somewhat lacking as to the best approach to managing such patients. The long-running debate of the best revascularization method of LMCAD has flared up again. However, medical management also may be a viable option for some of these patients.

Case Presentation
A 64-year-old nondiabetic man without a history of cardiovascular disease is admitted with an acute inferior ST-elevation myocardial infarction. He undergoes successful primary angioplasty of a dominant right coronary artery. Left ventriculography reveals inferior hypokinesis with an estimated ejection fraction of 45% to 50%. However, the patient also has a smooth mid-to-distal 60% LMCAD without any significant lesions in the left anterior descending or left circumflex artery. A month later, a stress echocardiogram reveals no new wall motion abnormalities. On the basis of this presentation, should he be referred for coronary artery bypass graft (CABG) surgery?

Review of Existing Clinical Practice Guidelines
The American College of Cardiology/American Heart Association (ACC/AHA) 2002 guidelines for stable angina discuss the indications for CABG surgery separately for symptomatic and asymptomatic LMCAD, but the recommendations are the same for both: Revascularization with CABG is a class I recommendation with level of evidence B. (Class I recommendations indicate situations for which evidence or general agreement exists that a given procedure or treatment is beneficial, useful, and effective.) An abbreviated version of these same guidelines was published in 2003. The guidelines acknowledged that the evidence behind the recommendation for asymptomatic patients is weak, yet the class IB recommendation was not changed.

The ACC/AHA 2004 guidelines for use of CABG surgery also separate symptomatic and asymptomatic LMCAD recommendations and propose that CABG should be performed for both patient groups. They do not explicitly acknowledge the fact that less evidence exists to support revascularization in asymptomatic patients, and the recommendation for CABG is categorized as class IA.

Meanwhile, the ACC/AHA 2007 guidelines for non-ST-elevation myocardial infarction propose that in the absence of further evidence, prior recommendations should simply be carried over. As a result, recommendations for significant LMCAD are class IA with no differentiation between symptomatic and asymptomatic LMCAD.

In summary, these existing guidelines unequivocally suggest that the patient described above should be referred for CABG. Although it would be difficult to dispute that patients with significant and symptomatic LMCAD are very likely to benefit from revascularization, at least 6 considerations point to a need to revisit these guidelines and their underlying evidence in asymptomatic patients. Ultimately, these 6 points indicate a possible need for new contemporary studies to re-evaluate the efficacy of medical ther-
apy in situations such as the one described above.

1. The Evidence Supporting CABG for Symptomatic LMCAD Is Outdated Because Medical Therapy Has Improved Significantly

The above-mentioned guidelines are based on a meta-analysis\(^6\) that summarized the results of 4 small and 3 moderate-sized trials of stable angina and significant CAD conducted in the 1970s. Altogether, 2649 patients were randomized to CABG or to an initial strategy of medical therapy. Patients with LM disease made up only 6.6% of the study population; ie, only 150 such patients were randomized in 7 studies. The main results are summarized in the Table.

Although surgery demonstrated a significant mortality benefit over medical therapy at 5 years, the number of patients with LMCAD randomized was small, and the quality of medical management was suboptimal by today’s standards. Specifically, 66.1% of the patients in the medically treated arm were on a β-blocker, and only 18.8% were taking aspirin. Statins and angiotensin-converting enzyme inhibitors were not used.

The magnitude of benefit achieved by performance of CABG in this meta-analysis has since been paralleled by high-dose statin therapy. The Scandinavian Simvastatin Survival Study randomized patients with symptomatic CAD to simvastatin 20 to 40 mg or to placebo.\(^7\) Simvastatin-treated patients had a relative risk reduction of 30% in overall mortality (\(P=0.0003\)) mainly as a result of significantly decreased coronary mortality and morbidity. Patients in the treatment arm achieved an average low-density lipoprotein cholesterol of 3.16 mmol/L, which is still suboptimal by current standards. A recent large meta-analysis showed that a 1.09-mmol/L reduction from an average low-density lipoprotein of 3.79 mmol/L translates into a 12% reduction in all-cause mortality and a 19% reduction in mortality from coronary heart disease.\(^8\) Therefore, high-dose statin therapy alone could now result in a coronary heart disease mortality reduction similar to that found with CABG in those trials.

The significant morbidity and mortality benefits of low-dose aspirin and angiotensin-converting enzyme inhibitors in CAD also have been well established since the CABG trials. In contemporary medical care, >95% of patients would be treated with aspirin. Almost 60% of the patients in the meta-analysis had a history of myocardial infarction, 10% had diabetes mellitus, and 4% had heart failure. Therefore, in >70% of these patients, an angiotensin-converting enzyme inhibitor would be currently indicated with the expectation of a significant further improvement in outcomes.

2. Data Are Lacking on the Management of Asymptomatic LMCAD

The guidelines for the management of asymptomatic LMCAD appear to be inferred from the same meta-analysis, although the main inclusion criterion in all of the studies was mildly to moderately symptomatic CAD.

The only article referenced by the ACC/AHA guidelines that addressed asymptomatic LMCAD was a nonrandomized CASS Registry analysis in which 53 of the 1477 patients with LMCAD were identified as being asymptomatic.\(^9\) However, these patients were referred for a coronary angiogram because of either a history of myocardial infarction or a positive stress test and thus were not truly asymptomatic. Rather, they had silent ischemia.

3. Patients With Significant but Not Critical (50% to 70%) LMCAD Are a Potentially Low-Risk Subgroup

Some smaller studies suggest that 50% to 70% LMCAD may not carry such a poor prognosis. A subgroup analysis of the Veterans Affair trial included 91 patients with LMCAD of 50% to 75% who had only a trend for benefit with CABG (\(P=0.089\)), and no benefit was seen in those with normal left ventricular function.\(^10\)

Similar results have been reported from the large CASS Registry, which contained 1484 patients with ≥50% LMCAD.\(^11\) CABG did not significantly prolong survival in patient subgroups with an LM stenosis of 50% to 59%, with or without significant RCA stenosis, as long as the patients had preserved left ventricular function.

Stress imaging studies have been shown to further risk stratify LM patients. A study of 22 medically treated patients with significant LM and/or 3-vessel disease with normal left ventricular function who underwent nuclear stress testing revealed that during a follow-up period of 36±26 months, patients with normal exercise capacity or no perfusion defects had an annual event rate of only 2.8%.\(^12\)

4. Invasive Physiological Assessment Can Refine Risk Stratification

Physiological assessment of coronary fractional flow reserve by pressure

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**Table. Main Results of a Meta-Analysis of 7 Randomized Trials of CABG Versus Medical Management in Stable Angina and Significant CAD, Including LMCAD**

<table>
<thead>
<tr>
<th>Total Patients Randomized, n</th>
<th>Patients With LMCAD, n (%)</th>
<th>Overall Benefit of CABG</th>
<th>Benefit of CABG in LMCAD</th>
<th>Medical Management, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>2649</td>
<td>150 (6.0)</td>
<td>At 5 y, RRR=39% ((P=0.0001))</td>
<td>At 5 y, RRR=68% (RR=0.32; 95% CI, 0.15–0.70; (P=0.004))</td>
<td>Aspirin, 18.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>At 10 y, RRR=17% ((P=0.03))</td>
<td>At 10 y, RRR=33% (RR=0.67; 95% CI, 0.35–1.30; (P=0.24))</td>
<td>(\beta)-Blockers, 66</td>
</tr>
</tbody>
</table>

RRR indicates relative risk reduction; RR, relative risk.
wire has been shown to be helpful in differentiating high-risk lesions from low-risk LM stenosis.\textsuperscript{13,14} In a study of 54 patients with LMCAD, a fractional flow reserve of $>0.75$ appeared to identify a patient population in which revascularization could be deferred safely.

It has long been acknowledged that coronary angiography has its limitations in assessing the severity of luminal stenosis, especially in the case of LMCAD. Intravascular ultrasound is being used to assess ambiguous LM disease. Jasti et al\textsuperscript{15} compared intravascular ultrasound studies with “gold standard” fractional flow reserve values in 55 patients using 0.75 as a cutoff for determining hemodynamic significance of LMCAD. A minimal luminal diameter of 2.8 mm was found to have the highest sensitivity and specificity (93% and 98%, respectively), followed by a minimal luminal area of 5.9 mm$^2$ (93% and 95%, respectively) for determining the significance of LM stenosis. On the basis of the above-mentioned fractional flow reserve cutoff value for revascularization, no significant differences were found in the outcomes of the 2 groups during the 38-month follow-up period.

Sano et al\textsuperscript{16} compared the intravascular ultrasound study of 115 patients with quantitative coronary angiography and found that fewer than half of “real-world” patients with ambiguous LM stenosis had a minimal luminal area of $<6.0$ mm$^2$. Therefore, instead of “blindly” sending them for revascularization, routine invasive assessment of such patients was recommended to determine which LM lesions are hemodynamically significant.

5. The Risk of Plaque Rupture in the LM Coronary Artery Appears to Be Low
One of the arguments often mentioned against medical management of LMCAD is that an incidental plaque rupture might be fatal. This concern is somewhat abated, however, by findings from a prospective cardiac registry study\textsuperscript{17} that longitudinally followed up 11,855 patients with nonsignificant (<50%) LMCAD. The 7-year risk-adjusted mortality hazard ratio of patients with <50% LMCAD compared with those with no LMCAD was 0.98 (95% CI, 0.79 to 1.23). In absolute terms, the observed 7-year crude mortality of 12% to 14% in the 2 groups also was generally reassuring in indicating that mortality risk is not extraordinarily high in individuals with <50% LMCAD.

6. There Can Be Serious Adverse Consequences of Premature CABG
Two major problems exist with potentially untimely CABG surgery. First, grafts occlude more often if competitive blood flow is present in a noncritically diseased native coronary artery. Second, native CAD progression to total occlusion after CABG is common. The rate of disease progression is 3 to 6 times higher in grafted arteries than in nongrafted arteries.\textsuperscript{18} These data suggest that bypassing an artery with noncritical disease may ultimately be harmful to patients who might incur the risk of graft closure and the increased risk of accelerated obstruction of native vessels.\textsuperscript{19}

Revisiting the Care Paradigm for Asymptomatic LMCAD
All of the above points shed some question on the existing guideline recommendations suggesting that all patients with $\geq$50% LMCAD should receive CABG surgery. They are based on studies in which medical management of the comparator arm did not include aspirin, statins, and angiotensin-converting enzyme inhibitors and on trials in which the patients were, for the most part, symptomatic and thus were not representative of patients with asymptomatic LMCAD. On the other hand, the outcomes of CABG surgery have also improved significantly since the above-mentioned trials were carried out, as the internal mammary artery was a very rarely used conduit at that time.

The Need for a New Contemporary Trial
There may now be a need to conduct a randomized controlled trial to see if patients with $>50\%$ LMCAD who do not have ischemia attributable to LMCAD benefit from CABG. Achieving support from the clinical community for such a study would be a daunting task because many clinicians might question whether enough clinical equipoise is possible surrounding the questions we raise to support contemporary clinical trials addressing this question. Others may go even further to question the ethics of revisiting this question with new trials.

However, a recent history exists of such assumptions based on “clinical sense” being disproven through well-designed trials. The Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial is a case in point, having produced results that hint at a need for the medical community to similarly revisit the paradigm of the benefits of CABG over medical therapy for the patient population that we discuss here.

We emphasize that the points raised above should not lead to a change in current revascularization practice patterns or guidelines. Rather, we simply propose a reevaluation of existing evidence and international scientific dialogue around the possibility of new trials to better characterize the benefits of revascularization in patients such as the one presented in our clinical case. The ground that we stand on has shifted, and a need exists to revisit the care paradigm for patients with asymptomatic LMCAD.

Acknowledgment
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Disclosures
None.

References


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