Unprotected left main coronary artery (uLMCA) disease has major prognostic implications and remains a therapeutic challenge. Current clinical practice guidelines from both sides of the Atlantic provide a Class I recommendation (Level of Evidence: A) for coronary artery bypass grafting (CABG) in these patients. Furthermore, these guidelines state that percutaneous coronary interventions (PCIs) have a Class III indication for uLMCA patients otherwise eligible for surgery. A recent consensus document also indicates that PCI is inappropriate for uLMCA (1). Although the evidence supporting the value of CABG in this setting is robust, some limitations of the available information should be acknowledged. These guidelines have been largely based upon “subgroup analyses” of 3 classical, randomized trials comparing CABG with medical treatment in stable patients back in the 1970s (2–5). Revisiting these studies, we see that only the Veteran Administration Cooperative study and the European Coronary Surgery study provided data on uLMCA patients (2,3). However, only retrospective subgroup analyses, surprisingly coming from very small cohorts of uLMCA patients (n = 91 [48 vs. 43] and n = 59 [28 vs. 31], respectively), demonstrated the survival advantage of CABG. Subsequent post-hoc analyses revealed that the benefit concentrated in patients with more severe lesions and left ventricular dysfunction (2,3). The CASS randomized study only included patients with moderate uLMCA (50% to 70% diameter stenosis) that could not be analyzed separately because they represented 1.8% of the population. However, the large CASS “registry” confirmed the clear survival benefit after CABG (4). Finally, the long-term durability of this benefit was confirmed in a landmark meta-analysis (5). In the following 3 decades, all randomized trials comparing CABG with PCI specifically excluded uLMCA patients because it was considered unethical to withhold surgery from them. During that time, extensive clinical experience and data from contemporary surgical studies corroborated the excellent long-term prognosis of CABG in uLMCA patients, especially since the widespread utilization of arterial grafts.

In this issue of the Journal, Mehilli et al. (6) report a highly provocative trial in which uLMCA patients were systematically offered PCI with drug-eluting stents (DES). Using an elegant noninferiority study design, uLMCA patients were randomized to sirolimus-eluting stents (SES) or paclitaxel-eluting stents (PES). Results were excellent and comparable in both arms. However, are stents ready for prime time in uLMCA (7)?

**From the initial steps to large observational studies.** The promising results of balloon angioplasty in this location soon became overshadowed by high restenosis rates, and the interest for this approach rapidly waned. In the bare-metal stent era, most studies included many emergency cases or patients deemed inoperable, explaining the unsatisfactory results in early series. However, since the advent of DES, uLMCA patients are being increasingly considered for PCI. Initial reports warned of the potential risk of sudden death associated with uLMCA restenosis, but currently, the emphasis has shifted to the identification of patients at risk for thrombosis. In the study of Chieffo et al. (8) with 731 uLMCA patients, however, the incidence of DES thrombosis at 2.5 years was only 0.9%. Recent observational studies have demonstrated similar rates of death and major adverse events in patients undergoing DES implantation and CABG (9,10) although the need for revascularization has been consistently lower after surgery. Again, a substantial number of patients treated with DES were poor surgical candidates. Propensity score matching is considered a more effective means of accounting for imbalances in baseline characteristics than conventional stratification or multivariate covariate adjustments. Studies using this methodology have confirmed equivalent results with both revascularization strategies (9,10). Furthermore, a systematic review of uLMCA stenting (11) (1,278 patients, median follow-up 10 months) demonstrated a mortality rate of 5.5% and a target vessel revascularization rate of 6.5% after DES. Interestingly, rates of adverse events were reduced with DES as compared with bare-metal stents or CABG.

Long-term data are also rapidly accumulating. Recently, a large multicenter study demonstrated a 3-year mortality rate of 6.2% after elective DES for uLMCA (12). The MAIN-COMPARE registry (13) analyzed an impressive number of uLMCA patients treated at 12 institutions in Korea (1,102 stenting and 1,138 CABG). Comparable subgroups were identified by propensity score matching. In contrast to previous studies, PCI was the "prefer-
ential strategy,” and 97% of patients were eligible for surgery. One-half of them had bifurcation involvement and concomitant multivessel disease. At 3 years, the primary end point (death, myocardial infarction, and stroke) was similar in both groups.

Evidence stemming from randomized studies. Erglis et al. (14) randomized 103 uLMCA patients to either bare-metal stents or DES. Lesions were pre-dilated with cutting balloons, and results were optimized with intravascular ultrasound. No hospital mortality was found, and the restenosis rate was significantly reduced in the PES arm (22% vs. 5.7%). To date, however, only a single randomized study has directly compared stenting with CABG in uLMCA patients. The LEMANS trial (15) allocated 52 patients to stenting and 53 to CABG. At 30 days, major events were significantly reduced after stenting and a similar trend was maintained at 12 months. The primary end point (improvement in left ventricular ejection fraction) favored coronary stenting. Despite the reduced sample size, these results are relevant considering that most patients had distal uLMCA and multivessel disease and that DES were only used in 35% of cases.

Recently, data from the SYNTAX randomized study (PCI with PES vs. CABG in patients with uLMCA/3-vessel disease), have been reported (16). Primary end point (equivalence in the composite of death, stroke, myocardial infarction, and repeat revascularization at 1 year) was not met, although rates of death and myocardial infarction were similar in the 2 arms. A new “score,” designed to assess coronary anatomy complexity, suggested comparable results with both strategies in patients with “simple” anatomy. Furthermore, in the large (stratified by protocol) patient cohort of uLMCA patients (705 patients: 357 PES, 348 CABG) the primary end point was similar in both arms although, again, repeat revascularization rate was higher and stroke rates were lower after PES. The authors nicely highlighted the limitations of these subgroup analyses (16).

To be fair, however, we should emphasize here how closely these analyses mirror (now with a larger number of patients) those previously performed in the pivotal trials establishing the superiority of CABG over medical therapy in this setting. Subgroup analyses should be just considered as “hypothesis generating,” but all available information—even that coming from historical surgical studies—should be critically analyzed with the same standards. Only then will we be able to identify areas for improvement in patient care and the potential benefit of emerging technologies. The limited duration of follow-up in the SYNTAX study (1 year) remains a matter of concern as the benefit of surgery might accrue with time. Despite these caveats, results of the SYNTAX study will greatly impact uLMCA revascularization decisions in the near future. Lastly, the results of the COMBAT and REVASCULARIZE trials, directly comparing DES with CABG in uLMCA, are eagerly awaited.

At this point, some major questions arise: Should current guidelines be updated to incorporate all of these relevant new pieces of evidence? Is current evidence-based information robust enough to forget about CABG and directly evaluate the best PCI strategy in uLMCA? Equipoise, defined as sufficient uncertainty regarding the potential benefits of “competing” therapeutic strategies, is required before a randomized trial is performed (7). We believe that currently, not only CABG versus DES trials are justified—and indeed needed—but also trials comparing head-to-head different coronary interventions in this critical anatomic scenario.

Present study. The ISAR-LEFT-MAIN randomized trial (6) sheds additional light on this controversial subject and provides compelling evidence supporting the value of DES in uLMCA patients. Some issues deserve consideration. First of all—and surprisingly for a randomized study—most uLMCA patients were eventually randomized, ensuring the external validity of the study to illuminate everyday clinical practice. Second, this study constitutes the largest dedicated randomized trial ever performed in uLMCA (607 patients). Therefore, the clinical evidence generated, both in terms of safety and efficacy, is sound and undisputable. Overall, 30-day mortality was only 1.3%, a striking figure considering that one-third of patients had a EuroSCORE ≥6. The combined primary end point (death, myocardial infarction, target vessel revascularization) was similar in both groups (13.6% PES vs. 15.8% SES). Third, most patients had a complex coronary anatomy, with two-thirds having multivessel disease. Surprisingly, only 12% of eligible patients underwent CABG. Nevertheless, interventions in lesions different from the uLMCA were only performed in 21% of cases, suggesting that incomplete revascularization was frequently obtained. Whether this problem would ultimately impair symptomatic status or long-term prognosis, should be investigated in an extended clinical follow-up. Furthermore, two-thirds of patients had involvement of the distal bifurcation (mostly treated with “culotte” stenting and final “kissing balloon”). This is important because restenosis was virtually always confined to this location, confirming previous observational studies with different stenting strategies (11). In this regard, data of patients with ostial/midshaft lesions would have been of interest. Fourth, additional angiographic data (late loss, loss index) would have complemented the equivalent restenosis rates (secondary end point) and might have unraveled potential mechanistic differences among DES in this setting. Last, but not least, the authors should be commended for providing the longest clinical follow-up available (2 years) together with the 1-year primary end point. No episodes of late or very late stent thrombosis occurred, and only 1% of patients required CABG for restenosis. This information is highly reassuring.

Unsettled issues. This unique site of the coronary tree, initially targeted with success by Andreas Grünentzig in his pioneering experience, is readily accessible. However, the interventional cardiology community should be proud of having adopted a largely cautious approach in the treatment of uLMCA. Although in many patients this is technically a
simple procedure (yes, we can), the burning question is: should we just do it?

“Emergency” stenting is widely used in uLMCA patients presenting with acute myocardial infarction or cardiogenic shock. Until now, “elective” uLMCA stenting has been restricted to patients at high surgical risk. In recent years, however, elective stenting is being offered to good surgical candidates. Stenting is less invasive, reduces hospitalization length and postoperative disabilities, and allows subsequent CABG if necessary. Elective stenting appears particularly attractive in octogenarians (17) and in patients with a high EuroSCORE, although results are also compromised in these patients (17). In Europe, up to one-third of all uLMCA patients are treated with stents, accounting for 3% of all PCI procedures (7,13,18). Therefore, some recommendations to address this emerging scenario should be issued. A clinical and angiographic scoring system should be devised and subsequently validated to assist decision making. Although speculative, the variables in Table 1 are proposed to help in this regard. In many centers, patients with “simple” ostial/mid shaft lesions are considered for elective stenting. After a balanced counseling that emphasizes the current lack of very long-term data after DES, many patients accept the trade-off of repeat revascularization for a lesser invasivity. In complex lesions, this enthusiasm should be tempered to avoid jeopardizing patient safety. Alternatively, “routine” PCI in uLMCA—challenging the standard of care—should be further restricted and only performed under the umbrella of controlled studies.

Many technical issues remain unsettled. An ideal mechanical solution to address uLMCA bifurcations remains elusive (8–11). Furthermore, stent underexpansion and malapposition appear particularly germane to uLMCA patients. These problems, readily detected with intravascular ultrasound, should be aggressively managed. Heavy calcification may be tackled with rotational atherectomy to guarantee full stent expansion. In patients with poor ventricular function and anticipated procedural complexity, prophylactic cardiopulmonary support might be indicated. Nevertheless, the value of all these “adjuvant” strategies remains largely speculative. Indeed, in the ISAR-LEFT-MAIN trial, despite a complex patient mix, rotational atherectomy and intra-aortic balloon pumping were only used in 1% of cases, whereas intravascular ultrasound was not used. In this regard, the meticulous care paid by the investigators to ensure an optimal antiplatelet effect might be implicated in their favorable results (6). Some final issues deserve consideration. Should surveillance late angiography be routinely scheduled? Should “indefinite” dual antiplatelet therapy be recommended? Should point-of-care assessment of platelet function be performed? Most of these questions remain undefined yet they are proposed as safety nets for patients with lesions treated at this critical site.

**Final remarks.** The study of Mehilli et al. (6) demonstrating the efficacy of DES in uLMCA patients is provocative and definitively, constitutes a major advancement in knowledge. Undoubtedly, this novel information, together with data emerging from other recent studies, will reshape the landscape of interventional cardiology. From now on, uLMCA should be perceived by surgeons and interventionists as a challenging setting where only a judicious combined clinical assessment will allow the selection of the most appropriate revascularization strategy for each individual patient. Our personal bias, however, is that interventional cardiology will eventually conquer uLMCA. In “favorable” lesions, this is already happening. In complex cases, this paradigm shift will be more gradual, but considering the superb results of the ISAR-LEFT-MAIN trial, it appears inevitable. New generation DES, together with refined techniques and improved antiplatelet regimens, will allow more effective tackling of this critical anatomic scenario with a better safety profile. Although additional information, especially regarding very late outcome, is eagerly needed, the accumulating evidence already suggests that the use of DES for uLMCA patients is no longer at the crossroads, but rather is rapidly eroding the last bastion of CABG and successfully “Crossing the Rubicon.”

### Table 1 Relevant Variables for “Elective” uLMCA Stenting in Patients Eligible for CABG

<table>
<thead>
<tr>
<th>Clinical findings</th>
<th>Anatomic features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Distal bifurcation involvement</td>
</tr>
<tr>
<td>Diabetes</td>
<td>LAD and LCX ostial disease</td>
</tr>
<tr>
<td>Left ventricular function</td>
<td>LCX size</td>
</tr>
<tr>
<td>EuroSCORE</td>
<td>Calcium</td>
</tr>
<tr>
<td></td>
<td>Additional significant stenosis in major vessels*</td>
</tr>
<tr>
<td></td>
<td>Number of lesions</td>
</tr>
<tr>
<td></td>
<td>Lesion length</td>
</tr>
<tr>
<td></td>
<td>Occluded vessel</td>
</tr>
<tr>
<td></td>
<td>Dominant RCA</td>
</tr>
</tbody>
</table>

*Vessels suitable for coronary artery bypass grafting (CABG).

LAD = left anterior descending coronary artery; LCX = left circumflex coronary artery; RCA = right coronary artery; uLMCA = unprotected left main coronary artery.

**REFERENCES**


Key Words: left main coronary artery • drug-eluting stents • paclitaxel • sirolimus • restenosis.