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Additional data supporting the safety and effectiveness of unprotected left main interventions

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The development of unprotected left main intervention (ULMI) actually paralled that of percutaneous coronary intervention (PCI). One of the earliest balloon angioplasties performed by Andreas Gruentzig was, in fact, on a patient with left main (LM) stenosis. Of course, the major challenge during the early years, irrespective of the anatomical location of a stenosis, was achieving acute success. Given that the greatest technical challenge was accessing and crossing a lesion, the LM seemed the most natural target of all. It was not until a decade later that Geoffrey Hartzler reported that, despite its feasibility, balloon angioplasty of the ULM was associated with poor outcomes in the mid-and longer- term, and as such, the procedure was abandoned[1]. The availability of stents gave renewed courage to interventionists, and long-term outcomes from the ULTIMA (Unprotected Left Main Trunk Intervention Multicentre Assessment) registry provided clinical and ethical support to perform ULMI in selected patients[2]. It was the high-risk nature of the patients in this registry which led to the legitimisation of a percutaneous approach. However, its main weakness was the high rate of death or myocardial infarction (MI) (16.4% at one year), most probably due to bare metal stent (BMS) restenosis, with the result that ULMI was contraindicated unless bypass surgery (CABG) was of unacceptable risk.

More recently, the availability of drug-eluting stents (DES) offering much lower restenosis rates gave new impetus to evaluate ULMI in patients with suitable anatomy who were also candidates for CABG. ULMI were formally evaluated in the SYNTAX (Synergy between PCI with Taxus and Cardiac Surgery) trial, with favourable results prompting further evaluation in patients considered good surgical candidates[3].

The three studies presented in this issue of EuroIntervention support this line of action. As a matter of fact, the emergence of these data provide a number of important messages over and above the recommendations from SYNTAX:[4-6]

– A conservative approach to the treatment of the distal LM bifurcation by using a 1-stent strategy is not penalising the patient or the operator.
– When needed, two stents can be implanted, and the long-term outcome remains favourable.
– A negative outcome from ULMI follow-up does not necessarily result from left main disease itself, but very often from stenoses or occlusions in other vessels.
– The utilisation of newer generation DES such as those with thin struts, thin fluorinated polymers and eluting low dose everolimus, together with the added benefit of improved techniques, can result in very respectable mid- and long-term outcomes following ULMI.
– Maximising acute gain is particularly important at the distal LM bifurcation and should be achieved by more aggressive post-dilatation, kissing balloon optimisation and increased use of intravascular ultrasound (IVUS).

As one of the first randomised trials of PCI versus CABG for ULM disease, the LE MANS (Late Left Main Angiographic Substudy) substudy of the SYNTAX trial has generated a lot of interest, and despite being underpowered to detect significant differences between PCI and CABG, ongoing follow-up is eagerly awaited.[4] In this edition, Morice et al report the midterm (15-month) angiographic and clinical outcomes in the 271 patient cohort, two-thirds of which had concomitant 2- or 3- vessel disease. Interestingly, they found that as many as 15.5% of grafts were significantly

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stenosed or occluded, and that more than one-quarter (27.2%) of patients had ≥1 obstructed/occluded graft, with a surprisingly higher rate of arterial than vein graft failure (17% vs. 13%). These outcomes differ from the literature, where internal mammary patency has been consistently good (≥92%) at 6-18 months, while vein graft patency varies widely (47-97%)[7,8]. Moreover, the fact that graft obstruction/occlusion was not associated with major adverse cardiac and cerebrovascular events (MACCE) portrays a very important message. In performing CABG there is a trend to "over-grafting", as the surgeon might feel that, even where disease is moderate angiographically, it is "better to graft than not to graft", with the result that competitive flow precipitates early thrombotic graft occlusion. Although not clinically detrimental, additional grafting corresponds to additional and unnecessary cross-clamp time, and may even constitute "wastage" of arterial conduit, which may be required in the future. Better liaison between surgeons and interventional cardiologists, along with better functional and anatomical assessment of individual lesions using fractional flow reserve (FFR) and IVUS, may reduce the tendency for inappropriate grafting with its inherent risk of acute to midterm graft failure.

The authors report very positive results in the PCI arm, with 92.4% of patients having patent stents at 15 months, including an impressive 89.7% who had undergone stenting of the distal LM bifurcation. Of the three studies presented in this edition, the LE MANS enrolled the highest risk patients with SYNTAX scores of 29.9±13.6, and comparisons must be made in this context. It is noteworthy that whilst almost two-thirds of patients underwent provisional T stenting at the LM bifurcation, side branch stenting was performed in half of all patients, suggesting a fairly high crossover rate. The fact that kissing balloon dilatation (KBD) was only performed in 70% of cases may explain the numerical difference in both acute gain and late loss between distal and non-distal lesions. Furthermore, and not unexpectedly, MACCE were more common following PCI than CABG (12.8% vs. 8.8%; $p<0.001$), with rates driven primarily by repeat intervention (9%). Unlike graft failure, stent closure was significantly associated with MACCE, again stressing the importance of meticulous technique, with IVUS and FFR guidance where appropriate to ensure optimal stent expansion.

In contrast to LE MANS, the FRIEND (French Multicentre Registry for Stenting of Unprotected LMCA Stenosis) registry[5] and LEMAX (Left Main Xience) pilot study provide prospective French data supporting the use of first and second generation DES for ULMI.[6] The FRIEND registry explored the long-term safety and efficacy of the paclitaxel-eluting (PES) TAXUS Express-2 Stent System (Boston Scientific, Natick, MA, USA) in 151 low risk patients (mean SYNTAX score 17.45±7.1) across 23 centres. With 3-year clinical follow-up and the added bonus of angiographic follow-up at nine months, the authors should be commended on a robust and meaningful dataset. LEMAX, on the other hand, is the first pilot study to evaluate the mid-term (1-year) safety and efficacy of the second-generation everolimus-eluting stent (EES) in the treatment of ULM disease in intermediate risk patients (mean SYNTAX score 25.0±9.5). While the COMPARE and SPIRIT studies have provided robust evidence for the safety and efficacy of EES over PES, they did not include patients with ULM disease[9-12]. Moreover, most of the existing data for ULMI report experience with first generation sirolimus and PES, and thus far little data exist on the use of second generation DES in this lesion subset[13,14]. The results in 173 patients included in four French centres are impressive, with extremely low rates of target vessel (TVR) (7%) and target lesion revascularisation (TLR) (2.9%) at 1-year. While the stent thrombosis rate of only 0.6% at 1-year is certainly favourable, the superior longer term safety of second generation EES has yet to be established for ULMI. It is, without doubt, encouraging that these results were obtained in intermediate risk patients for whom PCI is currently not recommended by the guidelines.

Whilst the FRIEND registry looked at a lower risk patient subset, the efficacy of first generation PES, should not be underestimated, with extremely impressive TVR rates of 2.7% out to three years. The authors report MACCE rates of 8% at one year, increasing to 21.2% by three years, and although 1-year MACCE rates are almost half those in the LEMAX study, and significantly lower than those in LE MANS, the heterogeneity of risk prevents any meaningful comparison. What can be said, however, is that the FRIEND data at least validate, if not surpass those of the ISAR-LMS (Intracoronary Stenting and Angiographic Results- Left Main Study) results at one year, where MACE rates were 13.6% in the PES cohort, and mortality 10.4% at two years, compared with only 6.7% at three years in the current registry[15]. This data is certainly encouraging, and most likely reflects increasing experience with ULMI and the current trend to limit angiographic follow-up.

Based on the mean SYNTAX score, it is not surprising to learn that the LEMAX study included more patients with involvement of the distal LM than the FRIEND registry (81% vs. 66%). As with the LE MANS substudy, both used a provisional side branch T-stenting strategy, during which the crossover rate was higher with PES than with ESS (28% vs. 20%). In addition, both studies performed final KB optimisation in ≥92% of patients, with an almost universal use (98%) in the higher risk LEMAX population. It is interesting to note that, unlike the LE MANS study where acute luminal gain was lower at the distal bifurcation following a KBD rate of only 70%, the FRIEND registry report equivalent acute gain in distal versus non-distal lesions, highlighting the importance of KB optimisation when a 1-stent strategy is used.

In summary, the three papers published in this edition of the journal report very encouraging results following ULMI using both first and second generation DES, and provide evidence for improved long-term outcomes with greater technical experience and improved DES platforms. All studies recognise that the optimal strategy for LM PCI now advocates a 1-stent technique with final KBD based on their promising outcomes.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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