

# Incidence, predictors and management of left main coronary artery stent restenosis: a comprehensive review in the era of drug-eluting stents

Alberto R. De Caterina, MD; Florim Cuculi, MD; Adrian P. Banning\*, MD, FRCP, FESC

*Oxford University Hospitals, Oxford, United Kingdom*

## KEYWORDS

- percutaneous coronary intervention
- restenosis
- unprotected left main

## Abstract

International guidelines recommend surgical revascularisation for unprotected left main (ULM) coronary artery disease. The introduction of drug-eluting stents (DES) as an emergency therapy has resulted in increasing numbers of patients having stents placed in ULM. As a consequence, important data on the safety and long-term outcome of PCI for ULM have progressively accumulated over recent years, derived mainly from registries rather than prospective randomised trials. These studies indicate that restenosis of the ULM still represents the main predictor of clinical events following stenting. However, the observed incidence is highly variable amongst the published studies and there is little data about the clinical management of restenosis of stents placed in the ULM. In the present paper we review the available literature regarding ULM restenosis, identify its predictors and suggest an algorithm for optimal management.

\*Corresponding author: Oxford University Hospitals, Headley Way, Oxford, OX3 9DU, United Kingdom.  
E-mail: Adrian.Banning@ouh.nhs.uk

## Introduction

Placement of a stent in an unprotected left main coronary artery stenosis (ULM) is usually well tolerated haemodynamically, and stent implantation should be considered the revascularisation option of choice when patients present with ST-elevation myocardial infarction and acute ULM occlusion. In other less extreme circumstances, concerns about long-term efficacy of stent implantation have resulted in international guidelines continuing to favour coronary artery bypass grafting (CABG) rather than percutaneous coronary intervention (PCI) for ULM<sup>1,2</sup>. These recommendations are influenced by the reports of clinical outcome of PCI for ULM in the era of bare metal stents, showing variable intermediate results and high rates of restenosis resulting in the need for repeat revascularisation. The introduction of drug-eluting stents (DES) and data from several subsequent studies have suggested increasing equivalence between DES-based PCI and CABG. These data have resulted in the initiation of the Evaluation of XIENCE PRIME™ Everolimus Eluting Stent System (EECSS) or XIENCE V® EECSS Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization (EXCEL) trial which is currently recruiting more than 2,000 patients in a randomised trial of DES-based PCI versus CABG with three-year follow-up.

Within clinical practice, increasing numbers of patients are having stents placed in ULM either as an emergency or because they

are not suitable for CABG. There is little data about management of restenosis of stents placed in the ULM. The aim of this paper is to review the available literature regarding ULM stent restenosis as well as to describe its incidence, to identify its predictors and to suggest its optimal management.

## The issue of sources: registries vs. randomised controlled trials

Several studies have reported the outcome of ULM PCI with DES since their introduction into the market in 2002. Literature in this field is difficult to interpret, as data derived from studies reflects variations in either retrospective or prospective recruitment strategies and also in different periods of clinical surveillance. We performed a systematic search on MEDLINE, Scopus and Cochrane databases from January 2003 to October 2012 using internet-based search engines. The terms used for the search included “left main”, “percutaneous coronary intervention” and “drug-eluting stent”. In the attempt to identify reliable sources of data, for this specific review we have considered only those studies: 1) enrolling at least 100 patients with ULM disease treated by PCI with the use of DES; and 2) with a follow-up of at least six months.

Most of our knowledge regarding long-term performance of ULM PCI with DES comes from registries (Table 1)<sup>3-20</sup>. Overall, data on more than 6,000 patients are currently available, deriving from both

**Table 1. Registries enrolling at least 100 patients undergoing ULM PCI with a follow-up of at least 6 months.**

Study name	N. of centres	Countries	N. patients	Type of DES	Length of follow-up (yrs)	Angio follow-up (%)	Angiographic restenosis (%)	TLR (%)	TVR (%)
Valgimigli et al <sup>3</sup>	1	The Netherlands	110	50% PES, 50% SES	1.8	66	17.8		10
Park et al <sup>4</sup>	2	Korea/USA	102	100% SES	1	84.3	5.9	2	
Kim et al <sup>5</sup>	1	Korea	116	100% SES	1.5	84.5	13.8	5.2	
Migliorini et al <sup>6</sup>	1	Italy	101	SES/PES	0.5		16		13.8
Chieffo et al <sup>7</sup>	5	Italy, Netherlands, Korea	147	73% SES, 27% PES	2.5	72.1	0.9	0.7	4.7
DELFT <sup>8</sup>	7	USA/Italy	358	55% SES, 45% PES	3.5	71.2		5.8	14.2
Gao et al <sup>9</sup>	1	China	220	SES/PES	1.3	46.4			5.9
Palmerini et al <sup>10</sup>	19	Italy	1,111	97% SES or PES	2			11.8	
MAIN COMPARE <sup>11</sup>	12	Korea	858	SES/PES	3				10.7
FAILS <sup>12</sup>	6	Italy, UK, USA	718	PES/SES/ZES	3	62.8	9.8		21.4
Tamburino et al <sup>13</sup>	19	Italy	334	SES/PES	3	69		7.9	
ASAN-MAIN <sup>14</sup>	1	Korea	176	SES PES	5			13.2	16.2
Lee et al <sup>15</sup>	1	Korea	509	97% SES or PES	3.4	80.1	17.7	10.0	
FRIEND <sup>16</sup>	23	France	151	PES	3	88		2.3	
LEMAX <sup>17</sup>	4	France	173	EES	1	47		2.9	7
PRECOMBAT-2 <sup>18</sup>	21	Korea	334	EES	1.6	60.8	9.2		6.5
MITO <sup>19</sup>	2	Italy, Japan	565	89% SES, 10% PES, 1% ZES	0.6	80.1	17.5	16.1	
French Left Main TAXUS <sup>20</sup>	4	France	291	PES	5			10.3	11.0

DES: drug-eluting stent; EES: everolimus-eluting stent; PES: paclitaxel-eluting stent; SES: sirolimus-eluting stent; TLR: target lesion revascularisation; TVR: target vessel revascularisation; ZES: zotarolimus-eluting stent

single-centre (n=1,232) and multicentre (n=5,142) registries. A major limitation of this analysis comes from the potential overlap of recruited patients. Most of the data comes from a limited number of centres, thus implying that a substantial proportion of individuals enrolled in single-centre or multicentre registries were also included in multicentre surveys. However, data coming from registries provide crucial insights to understanding the long-term outcome after ULM PCI. Ninety percent of patients have been enrolled in studies published quite recently (after the year 2008) and, since the duration of follow-up has increased progressively over time, for most of them a clinical follow-up of at least three years is available.

Conversely, to date, only four randomised controlled trials are available (Table 2)<sup>21-24</sup>. All of these studies are recent, i.e., published after the year 2009, and collectively report the outcome from almost 1,400 patients receiving DES, with a mean follow-up shorter than that of registries. The first three of them were designed for prospective comparison of PCI vs. CABG for the treatment of ULM. Specifically, one represents a subgroup analysis of the multicentre SYnergy between percutaneous coronary intervention with TAXus and cardiac surgery (SYNTAX) study<sup>22</sup>, one is a bi-centre study<sup>23</sup> and one the recently published multicentre Premier of Randomized Comparison of Bypass Surgery versus Angioplasty Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease (PRECOMBAT) trial<sup>24</sup>. The fourth study is the single-centre ISAR-LEFT MAIN which compares the angiographic and clinical outcome of paclitaxel and sirolimus-eluting stents and provides a clinical follow-up of two years<sup>21</sup>.

### Definition and incidence of ULM restenosis

Angiographic restenosis of ULM is defined as a diameter stenosis of >50% at the target site or the major side branches, such as the left anterior descending artery (LAD) or the circumflex (LCX). Despite the constant use of this definition over time and across all the published studies, the identification of the real incidence of ULM restenosis according to the available literature is challenging. To date, only 10 of 17 registries and two of four prospective trials report its occurrence, which varies widely from 0.9 to 19%.

Differentiating a benign non-functionally significant angiographic lesion from an obstructive ischaemia-inducing functionally significant one is probably more difficult in the ULM bifurcation than anywhere else in the coronary vasculature. Consequently, a simple angiographic assessment has limited relevance without additional data from either carefully performed intravascular ultrasound or

fractional flow reserve or non-invasive imaging stress tests to guide interventional decision making. Possibly as a consequence, angiographic ULM restenosis has progressively been replaced by more clinically relevant endpoints, such as target vessel revascularisation (TVR), defined as any repeat revascularisation of the treated vessel including any segments of the LAD or LCX, or target lesion revascularisation (TLR), i.e., any revascularisation performed on the treated segment. Even with these endpoints, the reported TLR and TVR in the published literature demonstrate a wide variability in incidence from 2% to 16.1% and from 4.7% to 21.4%, respectively.

### Clinical presentation of ULM restenosis

Most clinicians are anxious about the possibility that ULM stent restenosis will present without warning as sudden death. Review of the available literature does not suggest that this is likely, although there is a lack of truly comprehensive data. In the Failure in Left Main Study (FAILS) registry, approximately one third of patients with angiographic restenosis were completely asymptomatic, one third presented with stable angina and the rest with unstable angina or myocardial infarction<sup>12</sup>. Conversely, the proportion of patients with unstable presentation was more than 50% in the study of Lee et al, with the remaining patients undergoing revascularisation presenting with silent ischaemia or stable angina<sup>15</sup>. In the MITO registry, Tagaki reports 12% of patients presented with stable angina and 5% with ACS but the majority of the patients with ULM stent restenosis were detected during routine angiography (70%)<sup>19</sup>. In this registry, and following further percutaneous treatment for ULM stent restenosis, severe kidney disease and a high EuroSCORE were independent predictors of mortality. Most of the remaining studies usually report the composite incidence of cardiac death, myocardial infarction and stroke as the primary endpoint and, when reported, the rates of ULM restenosis, TLR or TVR are not linked to the modality of clinical presentation. Given these limitations, it is not possible to characterise absolutely how often ULM restenosis causes mortality *per se*.

### Clinical predictors of ULM restenosis

The identification of patients at lower risk of repeat revascularisation would potentially guide the selection of patients who would benefit most from PCI and, on the contrary, identify those for whom CABG is still the option of choice. Additionally, recognising high-risk patients will allow targeting of follow-up rather than routine surveillance for every patient.

**Table 2. Prospective trials enrolling at least 100 patients undergoing ULM PCI with a follow-up of at least 6 months.**

Study name	N. of centres	Countries	N. patients	Type of DES	Length of follow-up (yrs)	Angio follow-up (%)	Angiographic restenosis (%)	TLR (%)	TVR (%)
ISAR-LEFT MAIN <sup>21</sup>	1	Germany	607	PES/SES	2	87.1	16-19%	7.2	
SYNTAX LM <sup>22</sup>	85	Europe, US	357	PES	1				11.8
Boudriot et al <sup>23</sup>	2	Germany	100	PES	1	95	9.0		14.0
PRECOMBAT <sup>24</sup>	13	Korea	300	EES	2	75.3			6.1

DES: drug-eluting stent; EES: everolimus-eluting stent; PES: paclitaxel-eluting stent; SES: sirolimus-eluting stent; TLR: target lesion revascularisation; TVR: target vessel revascularisation

## CLINICAL AND ANGIOGRAPHIC CHARACTERISTICS

Among clinical variables, in the study from Lee et al reporting the results of a cohort of 509 patients with an angiographic follow-up of 80% at six to nine months, female gender, the presence of diabetes mellitus and renal failure were identified as independent predictors of restenosis with a univariate analysis, although only female sex remained a significant predictor using the multivariate approach<sup>15</sup>. The importance of diabetes as a major determinant of restenosis was also confirmed by the French TAXUS Left Main registry<sup>20</sup> and the DELFT study<sup>8</sup>, where the presence of insulin-dependent diabetes mellitus was found to increase the odds of TLR by almost three times at five-year follow-up. However, compared to clinical variables, the characteristics and the location of the target stenosis play an even more important role in predicting ULM restenosis. In the study of Lee et al, the involvement of ULM bifurcation and restenotic pattern were identified as major independent predictors of restenosis at multivariable analysis and patients presenting with bifurcation involvement were more likely to undergo angiographic follow-up. In FAILS, patients initially presenting with a lesion involving the bifurcation represented almost two thirds of patients with angiographic restenosis<sup>12</sup> and, similarly, in MITO, restenosis occurred in 8% of patients without bifurcation involvement and in 20% where the bifurcation was involved<sup>19</sup>. The notable impact of lesion location on angiographic restenosis or the need for revascularisation highlights the low rate of restenosis when bifurcation is not involved. In their multicentre trial including only ULM disease involving the ostium and/or the mid-shaft, therefore not requiring the treatment of the bifurcation, Chieffo et al found that restenosis occurred in less than 1% of cases at more than two-year follow-up<sup>7</sup>. Reassuring data about distal ULM come from within the SYNTAX-LE MANS study as almost 90% of patients treated with PCI to distal ULM were free of angiographic restenosis at scheduled angiographic follow-up<sup>25</sup>.

## PROCEDURAL CHARACTERISTICS

Amongst procedure-related factors, the available data are consistent in excluding a significant clinical benefit for any particular DES platform when treating ULM. Most data are derived from registries rather than from randomised prospective trials, and relate to paclitaxel (PES) versus sirolimus-eluting stents (SES). However, in the randomised ISAR-LEFT MAIN trial<sup>21</sup>, 607 patients were prospectively assigned to ULM revascularisation with PES or SES to compare the one-year composite outcome of death, myocardial infarction, and TLR. The study did not show any significant difference for angiographic restenosis in the first year (PES 16.0% vs. SES 19.4%,  $p=0.30$ ) or TLR (PES 9.2% vs. SES 10.7%,  $p=0.47$ ) at two-year follow-up. Comparative data in non-ULM lesions have suggested that second-generation everolimus-eluting stents (EES) are associated with superior clinical outcomes, including TVR, compared to non-EES<sup>26</sup>. The LEMAX (Left Main XIENCE V) study reports the clinical and angiographic efficacy of this second-

generation EES<sup>17</sup> and, despite a very high rate of involvement of the distal left main (>90%), EES was associated with an encouragingly low rate of both TLR (2.9%) and TVR (7%). The PRECOMBAT-2 study demonstrates similar outcomes in a registry comparison following either EES or a first-generation SES in ULM PCI (MACCE 8.9% vs. 10.8%, respectively)<sup>18</sup>. The prospective EXCEL trial will test whether EES has comparative outcomes to CABG surgery in patients with ULM.

Conversely, the number of implanted stents and the need for a complex procedure requiring >2 stents in a bifurcation lesion are independent predictors of ULM restenosis<sup>16</sup>. Consequently, most clinicians now favour a “provisional” single-stent approach, which can be utilised in up to 60% of cases, particularly when the LCX vessel is small and free of disease. In a cohort of 773 patients in a multicentre Italian registry, the one-stent technique was associated with a significant reduction in the incidence of two-year major adverse cardiac events<sup>27</sup>. Of note, this was mainly driven by a significant reduction in TLR, but also by a reduction in cardiac death and myocardial infarction. However, this study is not a true comparison of a single versus a two-stent strategy, as it did not report the proportion of true bifurcations (Medina class 1,1,1), which often necessitate the use of more than one stent. In these cases of “true” Medina 1,1,1<sup>28</sup> ULM bifurcation with extensive disease in both vessels, a two-stent technique is probably inevitable, and careful and complete lesion preparation, either with non-compliant/cutting balloons or rotational atherectomy, should always be considered. Optimal expansion of the stent at the LCX ostium appears to be a key determinant of clinical outcome<sup>18,29</sup>.

## Follow-up of ULM PCI: clinical or angiographic?

Careful clinical surveillance within the first six months after stent implantation is the usual recommendation with particular emphasis on antiplatelet drug compliance<sup>30</sup>. Routine coronary angiography was initially suggested by expert consensus, but this has no proven clinical benefit and consequently a clinically-driven symptom-guided management strategy has become an increasingly standard practice for most cases<sup>31</sup>. As shown in **Table 1**, most registries report angiographic surveillance in more than 50% of cases, with coronary angiography being scheduled and performed in the first year. Similarly, in prospective trials, angiographic follow-up was often scheduled by protocol, thus reaching rates >80% (**Table 2**). In the SYNTAX-LEMANS study, angiographic follow-up was mandated at 15 months to preclude the angiogram impacting on the primary endpoint of the study which included the need for repeat revascularisation at one year<sup>25</sup>.

The type of follow-up, angiographic or clinical, appears modestly to affect the reported rate of restenosis across the studies. For instance, using the same stent (PES) and with a similar proportion of patients undergoing angiographic follow-up (95% and 87%, respectively), TLR at one year varies widely from 9% in the study of Boudriot et al<sup>23</sup> to 16.0% in the ISAR-LEFT MAIN<sup>21</sup>. Similarly, the duration of surveillance can affect the rate of angiographic restenosis or clinically-driven revascularisation. For instance, the

rate of TLR in the FRIEND study was 2.3% at two-year follow-up<sup>16</sup>, while in the study of Palmerini it was 11.8% after three years<sup>10</sup>.

Coronary computed tomography (CT) has the potential to guide ULM stent follow-up. A number of technical issues, such as the relatively large calibre of stents used, the coaxiality of scan direction with ULM-proximal LAD plane, and the relative protection from motion artefact of this part of the coronary tree, support its use as a valid alternative to repeat coronary angiography. Van Mieghem et al<sup>32</sup> have demonstrated that the evaluation of stent patency in the ULM is feasible and that its diagnostic accuracy is very high (98%), including those patients with distal LM bifurcation lesions requiring stenting of only one of the major branch vessels (i.e., the LAD or the CX). However, in patients who required complex bifurcation stenting, i.e., treatment of the LM and both major side branches, the diagnostic accuracy of cardiac CT decreased significantly to 83%.

In the EXCEL trial, routine angiographic follow-up has not been recommended. Recent encouraging data from five-year follow-up of the French Left Main TAXUS registry<sup>20</sup> and our review of the existing data support this strategy. Clinicians should emphasise drug compliance, and surveillance with CT or angiography should be reserved for patients with recurrent symptoms or patients with distal bifurcation disease and clinical risk factors for restenosis such as diabetes and/or renal failure.

### Mechanisms of ULM restenosis

The left main coronary is a large vessel and is prone to calcification. These specific features mean that ULM stent restenosis can generally be summarised as the consequence of two main mechanisms, either stent underexpansion or marked proliferative neointima formation. It is likely that an element of stent underexpansion is the predominant factor in most cases. From the current literature it is not possible to compare the outcomes of the different bifurcation approaches. However, unless intravascular ultrasound (IVUS) is performed, the initial stent may be undersized and stent expansion cannot be predicted by angiographic examination alone. IVUS guidance of left main stent implantation has been shown to impact on three-year outcome<sup>33</sup>, and recently target values of minimal lumen areas to be achieved following ULM intervention have been suggested. Indeed, among a cohort of 403 patients undergoing post-stenting IVUS and nine-month angiographic follow-up, Kang et al reported that IVUS-assessed stent underexpansion in at least one segment (ostial LAD, ostial LCX, distal ULM before bifurcation and proximal ULM) was associated with an almost five times higher rate of angiographic restenosis compared to patients with appropriate stent expansion, and that post-stenting underexpansion was an independent predictor of MACE<sup>29</sup>.

Unfortunately, neointima formation is a largely unpredictable event. Cases where an optimally expanded stent in the ULM are obstructed by neointima are likely to be unusual. Importantly, IVUS will detect predisposing factors, such as stent fracture, or identify areas of incomplete lesion coverage with DES. Consequently, although there is some conflicting evidence in the setting of bifurcation

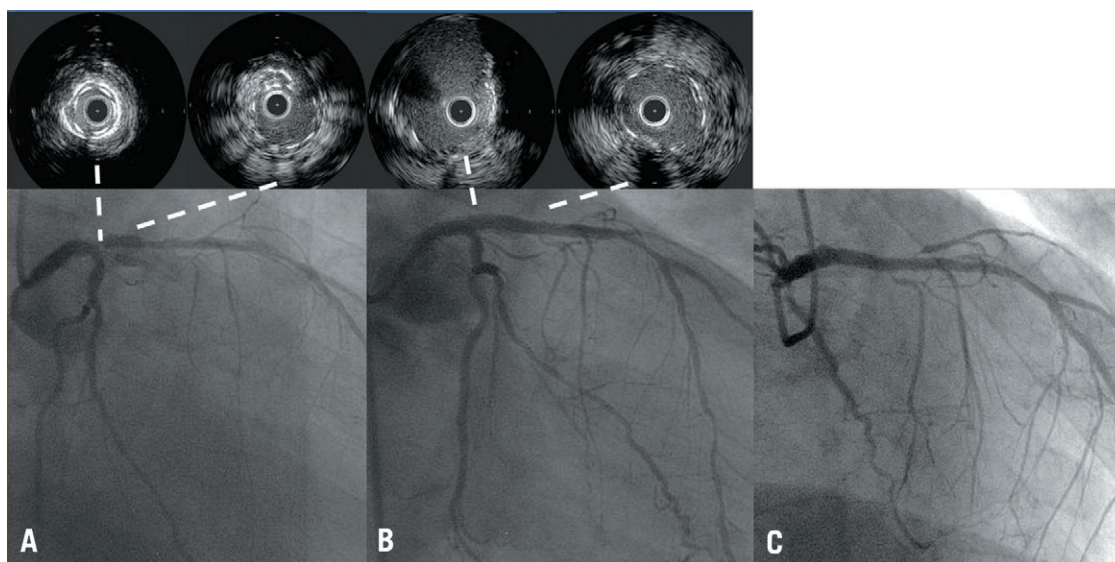
lesions generally<sup>34</sup>, we believe the use of IVUS is mandatory to define the mechanism of restenosis and guide treatment strategies in the ULM.

### Management and outcome

Optimisation of medical therapy is unlikely to be the treatment of choice for patients with ULM stent restenosis. Consequently, the choice is either repeat PCI or a switch to surgical revascularisation. Only two retrospective registries have so far reported data on clinical management of ULM restenosis. In the FAILS registry, Sheiban et al reported follow-up data of a cohort of 718 patients receiving DES in six high-volume centres<sup>12</sup>. Clinical follow-up was available in almost the totality of patients (97.5%) and included repeat angiography in 62.5%, which was clinically driven in a minority of cases (16%). Among 70 patients showing ULM restenosis (9.7%), four were treated with optimisation of medical therapy, seven with CABG and the majority (59 patients) by repeat PCI. Most of these patients presented with a stable clinical condition, thus allowing best clinical management to be discussed appropriately. Overall, the prognosis of 59 patients undergoing repeat PCI was favourable at clinical follow-up to 24 months, revealing a very low rate of cardiac death (one case) or myocardial infarction (two cases), but a rate of TLR in more than 20% of cases. In the Korean registry from Lee et al<sup>15</sup> the incidence of ULM restenosis was higher (71 cases in 509 patients, 17.6%) than in the FAILS study. Again, the majority of these patients were treated by PCI (n=40) with the rest receiving CABG (n=10) or optimal medical therapy (n=21). Importantly, MACE-free survival at more than three-year follow-up was not different among the three groups (ranging from 10% to 14.4%), thus probably reflecting the importance of clinical judgement in choosing the best management for each single case. In the MITO registry, multifocal ISR was highly predictive of the need for repeat TLR (67% vs. 35% for focal and 24% for diffuse ISR)<sup>19</sup>. Treatment with further DES implantation was much more effective in this registry than balloon dilation alone (HR 2.79; 95% CI: 1.23–6.34, p=0.014). There is currently no evidence to recommend drug-eluting balloons in cases of ULM restenosis.

In our experience IVUS should be used to guide and decide the correct management strategy. Indeed, distinguishing the two different predominant mechanisms of restenosis, i.e., neointimal hyperplasia or stent underexpansion is crucial, and the following examples provide illustrations of the clinical issues.

In the first case the patient represented with stable angina eight months after ULM stent implantation. A two-stent strategy was used but intravascular ultrasound was not performed at implant. ULM stent restenosis was evident at diagnostic angiography, and IVUS revealed focal stent underexpansion at the ostium of LAD (**Figure 1A**). This case was managed with angioplasty with a non-compliant balloon and had a good angiographic result and good stent expansion at final IVUS run with a MLA of 6.7 mm<sup>2</sup> (**Figure 1B**). Follow-up angiogram was available at three years when he represented with symptomatic ostial right coronary artery stenosis (**Figure 1C**).

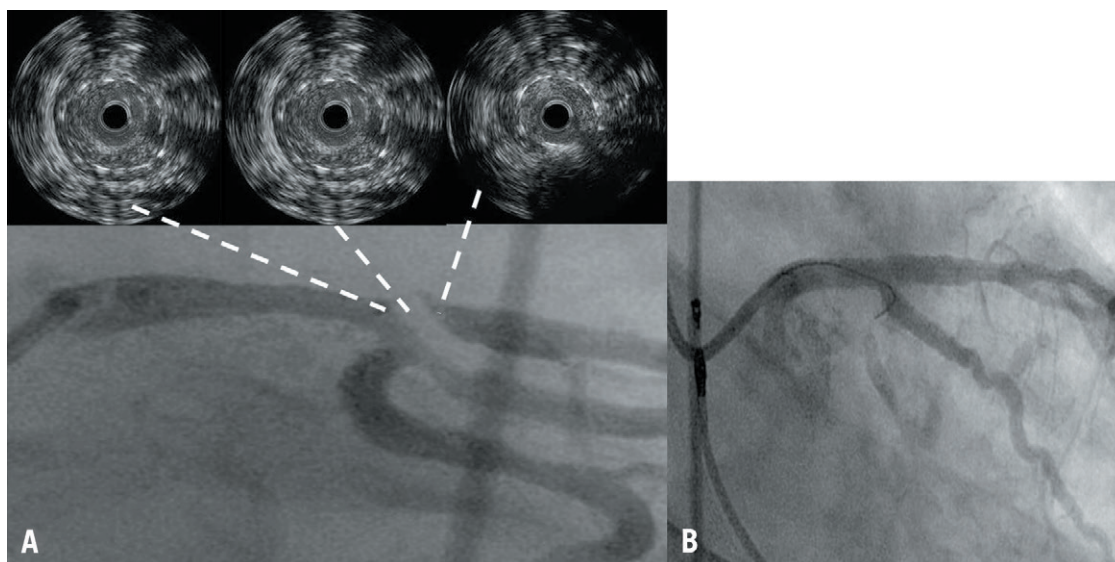


**Figure 1.** A case of ULM restenosis due to stent underexpansion. A) Diagnostic angiography reveals ULM stent restenosis, with IVUS run showing focal stent underexpansion at the ostium of LAD. B) Good angiographic and IVUS result after non-compliant balloon dilation. C) Angiographic follow-up showing good long-term result.

In a comparative illustrative case, a 61-year-old patient (with previous ULM stent using a 4.0×32 mm DES) represented to our clinical attention with non-ST-elevation myocardial infarction and severe ULM restenosis. An IVUS acquisition from proximal LAD to left main was performed after predilation with a 2.0 mm balloon. It revealed good stent expansion and diffuse in-stent restenosis from proximal LAD to ostial LM (**Figure 2A**). On the basis of the huge burden of neointima at IVUS imaging, the LCX

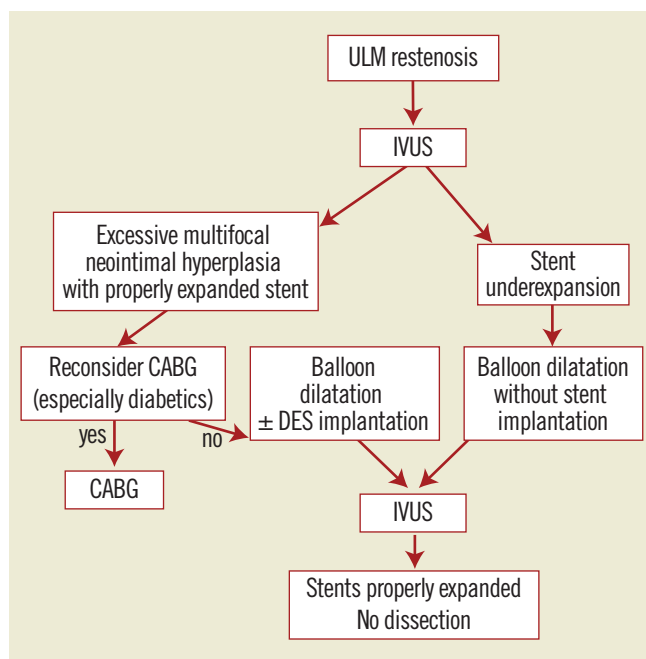
was wired before stenting and aggressive balloon dilation was undertaken. A second stent (in stent) was deployed resulting in considerable plaque shift, finally leading to the loss of the atrio-ventricular branch of the LCX (**Figure 2B**) and a moderate-sized troponin release without clinical consequence.

These cases illustrate that IVUS can identify stent underexpansion as the mechanism of restenosis and may allow management with simple balloon angioplasty. Alternatively, diffuse proliferative



**Figure 2.** A case of ULM restenosis due to neointimal proliferation. A) ULM restenosis at ostial LAD localised at the trifurcation with a large intermediate and atrioventricular branch. IVUS run after predilation reveals optimal stent expansion and diffuse in-stent restenosis from proximal LAD to ostial LM. B) Restenosis was managed with stent deployment. However, considerable plaque shift led to loss of atrioventricular branch of LCX.

neointima causing in-stent restenosis should be considered carefully, as there is potential for considerable plaque shift and branch vessel compromise. **Figure 3** shows the algorithm we propose for optimal management of ULM restenosis.



**Figure 3.** Proposed catheter-based management of ULM restenosis.

## Conclusions

PCI for ULM is already a valuable option in the emergency management of ULM stenosis. More ULM stents will be placed in patients unsuitable for surgery and further randomised studies, particularly the EXCEL trial, will determine whether elective ULM stenting is comparable with CABG. Even in the era of DES, restenosis remains the “Achilles’ heel” of PCI. Involvement of distal bifurcation, requiring two stents, and the presence of diabetes and/or renal failure are the principal risk factors for restenosis. IVUS guidance at implantation of the stent is crucial to optimise stent expansion and management of in-stent restenosis can be guided by repeat IVUS. ULM stent restenosis can usually be managed by repeat PCI when it is caused by underexpansion of the original stent. Improved implantation technique and enhanced DES technology are likely to improve results of ULM stenting in the future.

## Conflict of interest statement

A. Banning has received unrestricted research funding from Boston Scientific and speakers fees from Boston Scientific, Abbott Vascular and Medtronic. The other authors have no conflicts of interest to declare.

## References

- Kushner FG, Hand M, Smith SC Jr, King SB 3rd, Anderson JL, Antman EM, Bailey SR, Bates ER, Blankenship JC, Casey DE Jr, Green LA, Hochman JS, Jacobs AK, Krumholz HM, Morrison DA, Ornato JP, Pearle DL, Peterson ED, Sloan MA, Whitlow PL, Williams DO. 2009 Focused updates: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction (updating the 2004 guideline and 2007 focused update) and ACC/AHA/SCAI guidelines on percutaneous coronary intervention (updating the 2005 guideline and 2007 focused update): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol.* 2009;54:2205-41.
- Wijns W, Kolh P, Danchin N, Di Mario C, Falk V, Folliguet T, Garg S, Huber K, James S, Knuuti J, Lopez-Sendon J, Marco J, Menicanti L, Ostojic M, Piepoli MF, Pirlet C, Pomar JL, Reifart N, Ribichini FL, Schalij MJ, Sergeant P, Serruys PW, Silber S, Sousa Uva M, Taggart D. Guidelines on myocardial revascularization: the Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J.* 2010;31:2501-55.
- Valgimigli M, van Mieghem CA, Ong AT, Aoki J, Granillo GA, McFadden EP, Kappetein AP, de Feyter PJ, Smits PC, Regar E, Van der Giessen WJ, Sianos G, de Jaegere P, Van Domburg RT, Serruys PW. Short- and long-term clinical outcome after drug-eluting stent implantation for the percutaneous treatment of left main coronary artery disease: insights from the Rapamycin-Eluting and Taxus Stent Evaluated At Rotterdam Cardiology Hospital registries (RESEARCH and T-SEARCH). *Circulation.* 2005;111:1383-9.
- Park SJ, Kim YH, Lee BK, Lee SW, Lee CW, Hong MK, Kim JJ, Mintz GS, Park SW. Sirolimus-eluting stent implantation for unprotected left main coronary artery stenosis: comparison with bare metal stent implantation. *J Am Coll Cardiol.* 2005;45:351-6.
- Kim YH, Park SW, Hong MK, Park DW, Park KM, Lee BK, Song JM, Han KH, Lee CW, Kang DH, Song JK, Kim JJ, Park SJ. Comparison of simple and complex stenting techniques in the treatment of unprotected left main coronary artery bifurcation stenosis. *Am J Cardiol.* 2006;97:1597-601.
- Migliorini A, Moschi G, Giurlani L, Valenti R, Vergara R, Parodi G, Carrabba N, Dovellini EV, Antoniucci D. Drug-eluting stent supported percutaneous coronary intervention for unprotected left main disease. *Catheter Cardiovasc Interv.* 2006;68:225-30.
- Chieffo A, Park SJ, Valgimigli M, Kim YH, Daemen J, Sheiban I, Truffa A, Montorfano M, Airolidi F, Sangiorgi G, Carlino M, Michev I, Lee CW, Hong MK, Park SW, Moretti C, Bonizzoni E, Rogacka R, Serruys PW, Colombo A. Favorable long-term outcome after drug-eluting stent implantation in nonbifurcation lesions that involve unprotected left main coronary artery: a multicenter registry. *Circulation.* 2007;116:158-62.
- Meliga E, Garcia-Garcia HM, Valgimigli M, Chieffo A, Biondi-Zoccai G, Maree AO, Cook S, Reardon L, Moretti C, De Servi S, Palacios IF, Windecker S, Colombo A, van Domburg R, Sheiban I, Serruys PW. Longest available clinical outcomes after drug-eluting stent implantation for unprotected left main coronary artery disease: the DELFT (Drug Eluting stent for LeFT main) registry. *J Am Coll Cardiol.* 2008;51:2212-9.

9. Gao RL, Xu B, Chen JL, Yang YJ, Qiao SB, Li JJ, Qin XW, Yao M, Liu HB, Wu YJ, Yuan JQ, Chen J. Immediate and long-term outcomes of drug-eluting stent implantation for unprotected left main coronary artery disease: comparison with bare-metal stent implantation. *Am Heart J*. 2008;155:553-61.
10. Palmerini T, Marzocchi A, Tamburino C, Sheiban I, Margheri M, Vecchi G, Sangiorgi G, Santarelli A, Bartorelli A, Briguori C, Vignali L, Di Pede F, Ramondo A, Inglese L, De Carlo M, Bolognese L, Benassi A, Palmieri C, Filippone V, Sangiorgi D, De Servi S. Two-year clinical outcome with drug-eluting stents versus bare metal stents in a real world registry of unprotected left main coronary artery stenosis from the Italian Society of Invasive Cardiology. *Am J Cardiol*. 2008;102:1463-8.
11. Lee JY, Park DW, Yun SC, Lee SW, Kim YH, Lee CW, Hong MK, Park SW, Park SJ. Long-term clinical outcomes of sirolimus- versus paclitaxel-eluting stents for patients with unprotected left main coronary artery disease: analysis of the MAIN-COMPARE (revascularization for unprotected left main coronary artery stenosis: comparison of percutaneous coronary angioplasty versus surgical revascularization) registry. *J Am Coll Cardiol*. 2009;54:853-9.
12. Sheiban I, Sillano D, Biondi-Zoccai G, Chieffo A, Colombo A, Vecchio S, Margheri M, Gunn JP, Raina T, Liistro F, Bolognese L, Lee MS, Tobis J, Moretti C. Incidence and management of restenosis after treatment of unprotected left main disease with drug-eluting stents 70 restenotic cases from a cohort of 718 patients: FAILS (Failure in Left Main Study). *J Am Coll Cardiol*. 2009;54:1131-6.
13. Tamburino C, Di Salvo ME, Capodanno D, Marzocchi A, Sheiban I, Margheri M, Maresta A, Barlocco F, Sangiorgi G, Piovaccari G, Bartorelli A, Briguori C, Ardissino D, Di Pede F, Ramondo A, Inglese L, Petronio AS, Bolognese L, Benassi A, Palmieri C, Patti A, De Servi S. Are drug-eluting stents superior to bare metal stents in patients with unprotected non-bifurcational left main disease? Insights from a multicentre registry. *Eur Heart J*. 2009;30:1171-9.
14. Park DW, Kim YH, Yun SC, Lee JY, Kim WJ, Kang SJ, Lee SW, Lee CW, Kim JJ, Choo SJ, Chung CH, Lee JW, Park SW, Park SJ. Long-term outcomes after stenting versus coronary artery bypass grafting for unprotected left main coronary artery disease: 10-year results of bare-metal stents and 5-year results of drug-eluting stents from the ASAN-MAIN (ASAN Medical Center-Left MAIN Revascularization) Registry. *J Am Coll Cardiol*. 2010;56:1366-75.
15. Lee JY, Park DW, Kim YH, Yun SC, Kim WJ, Kang SJ, Lee SW, Lee CW, Park SW, Park SJ. Incidence, predictors, treatment, and long-term prognosis of patients with restenosis after drug-eluting stent implantation for unprotected left main coronary artery disease. *J Am Coll Cardiol*. 2011;57:1349-58.
16. Carrié D, Eltchaninoff H, Lefèvre T, Silvestri M, Levy G, Maupas E, Brunel P, Fajadet J, Le Breton H, Gilard M, Blanchard D, Glatt B. Twelve month clinical and angiographic outcome after stenting of unprotected left main coronary artery stenosis with paclitaxel-eluting stents: results of the multicentre FRIEND registry. *EuroIntervention*. 2009;4:449-56.
17. Salvatella N, Morice MC, Darremont O, Tafflet M, Garot P, Leymarie JL, Chevalier B, Lefèvre T, Louvard Y, Boudou N, Dumonteil N, Carrié D. Unprotected left main stenting with a second-generation drug-eluting stent: one-year outcomes of the LEMAX Pilot study. *EuroIntervention*. 2011;7:689-96.
18. Kim YH, Park DW, Ahn JM, Yun SC, Song HG, Lee JY, Kim WJ, Kang SJ, Lee SW, Lee CW, Park SW, Jang Y, Jeong MH, Kim HS, Hur SH, Rha SW, Lim DS, Her SH, Seung KB, Seong IW, Park S. Everolimus-eluting stent implantation for unprotected left main coronary artery stenosis. The PRECOMBAT-2 (Premier of Randomized Comparison of Bypass Surgery versus Angioplasty Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease) study. *JACC Cardiovasc Interv*. 2012;5:708-17.
19. Takagi K, Ielasi A, Shannon J, Latib A, Godino C, Davidavicius G, Mussardo M, Ferrarello S, Figini F, Carlino M, Montorfano M, Chieffo A, Nakamura S, Colombo A. Clinical and procedural predictors of suboptimal outcome after the treatment of drug-eluting stent restenosis in the unprotected distal left main stem: the Milan and New-Tokyo (MITO) registry. *Circ Cardiovasc Interv*. 2012;5:491-8.
20. Mylotte D, Meftout B, Moynagh A, Vaquerizo B, Darremont O, Silvestri M, Louvard Y, Leymarie JL, Morice MC, Lefèvre T, Garot P. Unprotected left main stenting in the real world: five-year outcomes of the French Left Main Taxus registry. *EuroIntervention*. 2012;8:970-81.
21. Mehilli J, Kastrati A, Byrne RA, Bruskin O, Iijima R, Schulz S, Pache J, Seyfarth M, Massberg S, Laugwitz KL, Dirschinger J, Schömig A; for the ISAR-LEFT MAIN (Intracoronary Stenting and Angiographic Results: Drug-Eluting Stents for Unprotected Coronary Left Main Lesions) Study Investigators. Paclitaxel- versus sirolimus-eluting stents for unprotected left main coronary artery disease. *J Am Coll Cardiol*. 2009;53:1760-8.
22. Morice MC, Serruys PW, Kappetein AP, Feldman TE, Stähle E, Colombo A, Mack MJ, Holmes DR, Torracca L, van Es GA, Leadley K, Dawkins KD, Mohr F. Outcomes in patients with de novo left main disease treated with either percutaneous coronary intervention using paclitaxel-eluting stents or coronary artery bypass graft treatment in the Synergy Between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery (SYNTAX) trial. *Circulation*. 2010;121:2645-53.
23. Boudriot E, Thiele H, Walther T, Liebetau C, Boeckstegers P, Pohl T, Reichart B, Mudra H, Beier F, Gansera B, Neumann FJ, Gick M, Zietak T, Desch S, Schuler G, Mohr FW. Randomized comparison of percutaneous coronary intervention with sirolimus-eluting stents versus coronary artery bypass grafting in unprotected left main stem stenosis. *J Am Coll Cardiol*. 2011;57:538-45.
24. Park SJ, Kim YH, Park DW, Yun SC, Ahn JM, Song HG, Lee JY, Kim WJ, Kang SJ, Lee SW, Lee CW, Park SW, Chung CH, Lee JW, Lim DS, Rha SW, Lee SG, Gwon HC, Kim HS, Chae IH, Jang Y, Jeong MH, Tahk SJ, Seung KB. Randomized trial of stents versus bypass surgery for left main coronary artery disease. *N Engl J Med*. 2011;364:1718-27.
25. Morice MC, Feldman TE, Mack MJ, Stähle E, Holmes DR, Colombo A, Morel MA, van den Brand M, Serruys PW, Mohr F, Carrié D, Fournial G, James S, Leadley K, Dawkins KD, Kappetein AP. Angiographic outcomes following stenting or coronary artery bypass surgery of the left main coronary artery: fifteen-month outcomes from the synergy between PCI with TAXUS



express and cardiac surgery left main angiographic substudy (SYNTAX-LE MANS). *EuroIntervention*. 2011;7:670-9.

26. Baber U, Mehran R, Sharma SK, Brar S, Yu J, Suh JW, Kim HS, Park SJ, Kastrati A, de Waha A, Krishnan P, Moreno P, Sweeny J, Kim MC, Suleman J, Pyo R, Wiley J, Kovacic J, Kini AS, Dangas GD. Impact of the everolimus-eluting stent on stent thrombosis: a meta-analysis of 13 randomized trials. *J Am Coll Cardiol*. 2011;58:1569-77.

27. Palmerini T, Marzocchi A, Tamburino C, Sheiban I, Margheri M, Vecchi G, Sangiorgi G, Santarelli A, Bartorelli A, Briguori C, Vignali L, Di Pede F, Ramondo A, Inglese L, De Carlo M, Falsini G, Benassi A, Palmieri C, Filippone V, Sangiorgi D, Barlocco F, De Servi S. Impact of bifurcation technique on 2-year clinical outcomes in 773 patients with distal unprotected left main coronary artery stenosis treated with drug-eluting stents. *Circ Cardiovasc Interv*. 2008;1:185-92.

28. Louvard Y, Medina A, Stankovic G. Definition and classification of bifurcation lesions and treatments. *EuroIntervention*. 2010;6 Suppl J:J31-5.

29. Kang SJ, Ahn JM, Song H, Kim WJ, Lee JY, Park DW, Yun SC, Lee SW, Kim YH, Lee CW, Mintz GS, Park SW, Park SJ. Comprehensive intravascular ultrasound assessment of stent area and its impact on restenosis and adverse cardiac events in 403 patients with unprotected left main disease. *Circ Cardiovasc Interv*. 2011;4:562-9.

30. Smith SC Jr, Feldman TE, Hirshfeld JW Jr, Jacobs AK, Kern MJ, King SB 3rd, Morrison DA, O'Neil WW, Schaff HV, Whitlow PL, Williams DO, Antman EM, Adams CD, Anderson JL, Faxon DP, Fuster V, Halperin JL, Hiratzka LF, Hunt SA, Nishimura R, Ornato JP, Page RL, Riegel B. ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention: a report of the

American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/SCAI Writing Committee to Update 2001 Guidelines for Percutaneous Coronary Intervention). *Circulation*. 2006;113:e166-286.

31. Biondi-Zoccai GG, Giraudi E, Moretti C, Sciuto F, Omedè P, Sillano D, Garrone P, Trevi GP, Sheiban I. Impact of routine angiographic follow-up after percutaneous coronary drug-eluting stenting for unprotected left main disease: the Turin Registry. *Clin Res Cardiol*. 2010;99:235-42.

32. Van Mieghem CA, Cademartiri F, Mollet NR, Malagutti P, Valgimigli M, Meijboom WB, Pugliese F, McFadden EP, Ligthart J, Runza G, Bruining N, Smits PC, Regar E, van der Giessen WJ, Sianos G, van Domburg R, de Jaegere P, Krestin GP, Serruys PW, de Feyter PJ. Multislice spiral computed tomography for the evaluation of stent patency after left main coronary artery stenting: a comparison with conventional coronary angiography and intravascular ultrasound. *Circulation*. 2006;114:645-53.

33. Park SJ, Kim YH, Park DW, Lee SW, Kim WJ, Suh J, Yun SC, Lee CW, Hong MK, Lee JH, Park SW. Impact of intravascular ultrasound guidance on long-term mortality in stenting for unprotected left main coronary artery stenosis. *Circ Cardiovasc Interv*. 2009;2:167-77.

34. Biondi-Zoccai G, Sheiban I, Romagnoli E, De Servi S, Tamburino C, Colombo A, Burzotta F, Presbitero P, Bolognese L, Paloscia L, Rubino P, Sardella G, Briguori C, Niccoli L, Franco G, Di Girolamo D, Piatti L, Greco C, Capodanno D, Sangiorgi G. Is intravascular ultrasound beneficial for percutaneous coronary intervention of bifurcation lesions? Evidence from a 4,314-patient registry. *Clin Res Cardiol*. 2011;100:1021-8.