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Percutaneous treatment of *de novo* unprotected left main stenosis in unselected consecutive patients: Experience of a high volume center

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ABSTRACT

Background: Percutaneous coronary intervention (PCI) has been increasingly employed to treat unprotected left main (ULM) stenosis, with hard endpoints similar to by-pass surgery, in patients selected by a Heart Team. Methods: From January 2008 to December 2011, 317 unselected and consecutive patients with *de novo* ULM stenosis underwent PCI with both bare metal (BMS) and drug-eluting (DES) stents. Major adverse cardiovascular events, target lesion (TLR) and vessel (TVR) revascularization were evaluated over a mean period of 590 ± 371 days. Results: Our population was characterized by a mean age 72 ± 10 years, high rate of acute coronary syndrome (ACS) (either with ST or non-ST elevation myocardial infarction, 15.5% and 35% respectively), severe comorbidity 16%, mean Euroscore 7 ± 3, mean Syntax Score 25 ± 9. In-hospital mortality was 6%. During the follow-up period, all-cause mortality was 16.7%, falling to 7% at the end of the follow-up, excluding patients presenting with ACS. TLR was observed and treated in 15% of patients. BMS utilization, age >75 years, ACS indication, Syntax Score >32 and associated peripheral artery disease were independent predictors of mortality at multivariate analysis. Conclusions: Stenting of ULM stenosis appears to be associated with a favorable mid-term outcome, even in an unselected population.

Keywords: Unprotected Left Main; Percutaneous Coronary Intervention

1. INTRODUCTION

Unprotected left main (ULM) percutaneous coronary intervention (PCI) has recently become a valid alternative to coronary artery bypass graft (CABG) showing similar mid-term results for hard endpoints (death and myocardial infarction) even if still penalized by a higher rate of repeated revascularization in the drug-eluting stent (DES) era.

Four randomized studies [1-4], 1 metanalysis [5], and several mono and multicentre registries [6-15] support these conclusions and 2010 ESC/EACT guidelines on myocardial revascularization have recognized a class IIa or IIb level of indication for ULM PCI [16] and probably they will be updated to a level of evidence A. In the metanalysis of Capodanno [5], where 1611 patients from 4 randomized clinical trials were evaluated, there were no significant differences between PCI and CABG in 1-year death (PCI 3.0% vs CABG 4.1%, $p = 0.29$) or myocardial infarction (2.8% vs 2.9%, $p = 0.95$), with increased target vessel revascularization (11.4% vs 5.4%, $p < 0.001$) and less frequent stroke (0.1% vs 1.7%, $p = 0.013$) in PCI group.

A potentially higher procedural risk due to the frequent involvement of the bifurcation with the majority of myocardium being jeopardized has been balanced by the relative easiness of ULM PCI due to the vessel shortness and big dimensions. DES development and diffusion, the experience gained by intravascular ultrasound (IVUS) use, the benefits of post-dilation and kissing techniques and the protection given by a prolonged dual antiplatelet therapy have all led to the growth and diffusion of this procedure.

The purpose of the present paper is to report the ULM PCI results of a single centre without on-site cardiac surgery, in consecutive "all comers" patients from 2008 until 2011. In all patients with *de novo* ULM lesions, PCI option was evaluated by clinical and interventional car-

diologists, and preferred over CABG, whenever a complete or at least a functionally complete revascularization was feasible or in presence of a high surgical risk determined by comorbidities.

2. METHODS

2.1. Clinical Procedure

All consecutive unselected patients treated with PCI for *de novo* lesions of ULM from 1.1.2008 to 31.12.2011 in our catheterization laboratory (CL) were collected in this registry.

Our laboratory is a province based CL in a region with almost 400.000 inhabitants and 3 hospitals (1 hub and 2 spoke centres), with a yearly volume of more than 2000 total procedures and 1300 - 1400 PCI, resulting the highest volume CL in the Emilia-Romagna Region and one of the most productive in Italy.

All clinical, angiographic and procedural data, hospital discharge and clinical follow-up data were recorded in a retrospective/prospective database. Data relative to the clinical conditions of the last available follow-up were collected by means of clinical examinations, telephone interviews or from civil registries.

All patients gave written informed consent to the procedure after full discussion of the risk/benefit profile of PCI and of the surgical alternative.

Indication and timing of the procedure (one stage or subsequent steps in case of multivessel coronary disease) were evaluated by an expert team (at least 2 expert interventional and one clinical cardiologists), while all procedural techniques (arterial access, provisional/intended two stents, type of stent, intra-aortic balloon pump (IABP), IVUS, etc.) were left to the discretion of the first operator with a strong recommendation for second generation DES utilization.

All patients were pre-treated with aspirin and clopidogrel (at least 300 mg in the previous 24 hours and 75 mg the morning of the procedure). They also received aspirin 100 mg daily indefinitely and clopidogrel 75 mg daily for at least 12 months post-procedure.

Angiographic follow-up 7 ± 1 months after PCI was strongly recommended and it was performed whenever possible.

2.2. Definitions

Cardiac death: all deaths due to cardiac causes (ischemic and non ischemic), or all deaths without a known cause.

Vascular death: all deaths due to cerebral or peripheral artery disease.

Post procedural non Q myocardial infarction (MI): CKMB elevation >3 times upper normal level (UNL), without clinical or electrocardiographic (ECG) signs of ischemia.

Spontaneous MI: every post-discharge elevation of CKMB or troponin above UNL associated with clinical or ECG signs of ischemia.

Target Lesion Revascularization (TLR): every new target lesion (left main) revascularization comprehensive of the 5 mm pre and post target (also left anterior descendent artery and circumflex artery ostia).

Target Vessel Revascularization (TVR): every new index target vessel/s revascularization also outside the target lesion.

Major vascular complications: every ischemic or hemorrhagic in-hospital complications requiring surgery or transfusions.

Euroscore: 30 days death risk was stratified according to the additive Euroscore, evaluating clinical, cardiac and surgical parameters [17].

Syntax Score: anatomic complexity of the patients was evaluated with the Syntax Score algorithm, which is available on the SYNTAX Score Website (www.syntaxscore.com) [18].

Complete revascularization: left main (LM) PCI and of every >70% stenosis of major epicardial coronary arteries.

Functionally complete revascularization: LM PCI and of every >70% stenosis of major epicardial vessels with a vital/ischemic bed.

Stent thrombosis (ST): defined on the basis of Academic Research Consortium criteria [19], as definite in case of angiographic or pathologic confirmation of ST, probable in case of any unexplained death within 30 days or target vessel myocardial infarction without angiographic confirmation, and possible ST defined as unexplained death after 30 days.

2.3. Statistical Analysis

Statistical analysis was performed with SAS statistical package. All continuous variables were expressed as mean ± SD and categorical variables as percentages.

Comparison between groups was performed using chi-square test for categorical variables and the unpaired Student's T test for continuous data. A two-side p value < 0.05 was considered statistically significant.

Logistic regression analysis was performed to identify independent predictors of mortality, adjusted for baseline confounding characteristics that were identified on the basis of univariate analysis.

The odds ratios (OR) and 95% confidence intervals (CI) were reported with two tailed probability values.

3. RESULTS

From the beginning of 2008 until the end of 2011, 383 LM PCI were performed in our CL; excluding 35 procedures of protected LM and 31 procedures for in-stent LM

restenosis, 317 were procedures on *de novo* ULM and were considered for this analysis.

3.1. Clinical Characteristics

Clinical characteristics of treated patients are described in **Table 1**.

Mean age was 72.6 years, with 49.5% of patients aged ≥75 years and 27% aged ≥80 years.

The unselected and consecutive population is composed by 201 patients with acute coronary symdrome (ACS) (63%); 49 of whom (15.5% of total) with ST elevation myocardial infarction (STEMI) and 22 (7%) presenting with cardiogenic shock.

Fifty patients (16%) presented severe comorbidity (39 neoplasia, 7 severe valvular disease, 2 dialysis, 2 severe cognitive deterioration), various degrees of associated peripheral artery disease (PAD) (cerebral or at the legs level) was seen in 56% of patients, mean left ventricle ejection fraction (LVEF) was 50% ± 11% and ≤40% in 20% of patients; mean additive Euroscore was 7 ± 3 (range 0 - 17).

3.2. Angiographic Characteristics

Angiographic characteristics of the population are summarized in **Table 2**.

LM disease was associated with multivessel coronary artery disease in more than 87% of patients, and in 28% of cases there was a chronic total occlusion (CTO), in 54 patients (17%) of the right coronary artery.

Syntax Score was calculated in 311 patients; it was ≤22 in 125, between 23 and 32 in 120, and >32 in 66 patients. LM stenosis was distal in 75% of cases, with bifurcation involvement in 227 patients (72%).

Procedural characteristics are summarized in **Table 3**. LM PCI was "ad hoc" in 54% of cases, with femoral access in 81% and with stent implantation in 99%, bare metal stents (BMS) 16%, DES 84%, first generation in 15 patients and second generation (mainly Xience and Biomatrix) in 249 patients. Isolated LM PCI was performed in 80 patients, LM and other vessel/s PCI in 237 in a unique or staged procedure; in 21 patients also an associated CTO was tempted. Mean number of implanted stents was 2.6 ± 1.5 per patient (range 0 - 10). Revascularization was complete in 177 patients (56%).

Bifurcation LM lesions were treated as follows: provisional stenting strategy was adopted in 183 patients, a two stent strategy in 41 (18%), with a minicrush technique in 20, T-stenting in 15, and V-stenting in 6 patients. Final kissing-balloon was performed in 92% of cases.

Table 1. Clinical characteristics of 317 patients treated with PCI for *de novo* unprotected left main lesions.

Males	238 (75%)
Age	72 ± 10 (39 - 92); 157 (49.5%) ≥ 75 y; 86 (27%) ≥ 80 y
Indication to PCI	STEMI 49 (15.5%)
	NSTEMI 111 (35%)
	Unstable angina 41 (14%)
	Stable ischemic heart disease 116 (37%)
Hypertension	229 (72%)
Diabetes mellitus	89 (28%)
Hypercholesterolemia	234 (74%)
Smoking	161 (51%)
Chronic obstructive pulmonary disease	31 (10%)
Peripheral artery disease	178 (56%)
Previous myocardial infarction	77 (24%)
Chronic kidney disease (creatinine >2 mg/dl)	22 (7%)
Severe comorbidity	50 (16%)
Cardiogenic shock	22 (7%)
Left ventricle ejection fraction	50 ± 11; ≤35% 42 (13%)
Euroscore	7 ± 3

NSTEMI = non-ST elevation myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST elevation myocardial infarction.

Table 2. Angiographic characteristics of the studied population.

Coronary disease	
LM alone	39 (12%)
LM + 1 vessel	83 (26%)
LM + 2 vessels	102 (32%)
LM + 3 vessels	93 (29%)
Associated CTO	89 (28%)
RCA CTO	54 (17%)
Syntax score	25 ± 9
< 22	125 (40%)
22-32	120 (38.5%)
>32	66 (21%)
Left main	
Ostial	61 (19.2%)
Body	17 (5.4%)
Distal	239 (75.4%)
Calcium	79 (25%)
Thrombus	15 (5%)

CTO = chronic total occlusion; LM = left main; RCA = right coronary artery.

Table 3. Procedural characteristics.

Ad hoc PCI	172 (54%)
Femoral vascular access	257 (81%)
Debulking	17 (5%)
IVUS	44 (14%)
IABP	61 (19%)
GP IIb/IIIa inhibitors	33 (10%)
Stent	314 (99%)
BMS	50 (16%)
DES	264 (84%)
Biforcation technic	
POBA	3
Provisional stenting	183
2 stents	41 (18%)
Final kissing	209/227 (92%)
Stent postdilatation	254 (80%)
Treated lesions	
LM alone	80 (25%)
LM + 1 vessel	120 (38%)
LM + 2 vessels	90 (28%)
LM + 3 vessels	27 (8.5%)
CTO	21
Total stents/patient	2.6 ± 1.5 (0 - 10)
Complete revascularization	177 (56%)

BMS = bare metal stent; CTO = chronic total occlusion; DES = drug eluting stent; GP = glicoprotein; IABP = intra-aortic balloon pump; IVUS = intravascular ultrasound; LM = left main; PCI = percutaneous coronary intervention; POBA = plein old balloon angioplasty.

3.3. In-Hospital Events

There were 20 in-hospital deaths (6%), of which 16 (5%) were cardiac deaths, 24 (7.5%) post-procedural non Q MI, 7 urgent repeated PCI (2.2%); 5 of these were performed for residual dissection (1 of LM, 3 of circumflex artery, and 1 of left anterior descendent artery) and 2 for sub-acute ST of left anterior descendent artery (LAD) (in a patient after urgent intestinal resection). Furthermore, 1 patient presented a hemorrhagic stroke, and 10 (3%) major ischemic or hemorrhagic vascular complications.

3.4. Follow-Up

Two hundred ninety seven patients were discharged alive; they were given statin therapy in 77%, beta-blocker in 67.5%, and ACE-inhibitor in 59% of cases; moreover 23 (7%) of them were on oral anticoagulant therapy (warfarin) together with aspirin 100 mg and clopidogrel 75 mg daily.

Mean duration of clinical follow-up was 590 ± 371 days (range 23 - 1516) median of 525 days (i.q. 25 - 75: 281 - 881 days).

One hundred and ninety patients (64%) had an angiographic follow-up, routinely performed in 138 and clinically driven in 52 patients.

Table 4 depicts clinical events at follow-up.

Total mortality was 16.7%, cardiac mortality was 10% (7.9% at 1 year); excluding patients with ACS (either with ST or non ST elevation myocardial infarction) as indication for the index procedure, total mortality falls to 3.8% at 1 year and 7% at the end of follow-up.

Among cardiac deaths, 4 were undetermined possibly due to ST: 1 at 185 days in a patient with moderate to severe mitral regurgitation, 1 at 417 days, 1 at 487 days after a red blood cells transfusion for acute anemia and 1 at 231 days for a documented ventricular fibrillation, while no cases of definite ST were documented angiographically or anatomically.

A repeated revascularization procedure for a LM lesion was necessary in 15% of cases (47/48 cases were treated with a repeated PCI and only one case with CABG), in 13 patients this was due to a LM edge restenosis, in 16 to a distal LM or LAD and circumflex artery ostial lesion, in 17 to an isolated circumflex ostial

Table 4. Clinical events at follow up.

	12 months	At follow-up (median 525 days)
Total death	41 (12.9%)	53 (16.7%)
Cardiac death	25 (7.9%)	31 (10%)
Vascular death	7 (2.2%)	8 (2.5%)
Other causes death	9 (2.8%)	14 (4.4%)
Total death excluding patients with STEMI	30/268 (11%)	40/268 (14.9%)
Total death excluding patients with STEMI/NSTEMI	6/157 (3.8%)	11/157 (7%)
Myocardial infarction (all NSTEMI)	18 (5.7%)	20 (6.3%)
LM TLR	43 (13.6%)	48 (15%)
Other vessel TVR	35 (11%)	42 (13.2%)
De novo lesion PCI	29 (9.1%)	41 (12.9%)
Stroke	2 (0.6%)	3 (0.9%)
Definite stent thrombosis	0	0
Possible stent thrombosi	2 (0.6%)	4 (1.2%)

LM = left main; NSTEMI = Non ST elevation myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST elevation myocardial infarction; TLR = target lesion revascularization; TVR = target vessel revascularization.

lesion and in 2 to an isolated LAD ostial lesion.

TLR was clinically driven only in 25 patients, with an angiographic follow-up due to symptoms or inducible ischemia. Clinically driven TLR was performed at a mean time of 208 days from the index procedure, a mean of 30 days before TLR performed during a routine angiographic follow-up (233 days).

Forty-two patients (13.2%) had a repeated procedure on an already treated vessel and 41 (12.9%) had a PCI of another vessel/*de novo* lesion.

At univariate analysis, variables correlated to total mortality were age, ACS as indication for coronary angiography, ad hoc PCI, serum creatinine, presence of chronic obstructive pulmonary disease and PAD, LVEF, Killip class 3-4, associated 1 - 3 vessel disease, Syntax Score, presence of thrombus, IABP utilization, BMS implantation, pre-PCI TIMI flow <3, an incomplete revascularization. Independent predictors of mortality at multivariate analysis were: BMS utilization (<0.001), age >75 years (p = 0.006), ACS indication (either STEMI and non ST elevation MI-NSTEMI) (p = 0.017), Syntax Score >32 (p = 0.010), and associated PAD (p = 0.042) (**Table 5**).

Comparisons between patients treated with DES or BMS and between the three Syntax Score groups are shown in **Table 6** and **7**.

4. DISCUSSION

The population studied represents a real world scenario, being composed by unselected, consecutive patients admitted to a high volume hub centre without on-site cardiac surgery. Most of the patients were admitted with an ACS, who had frequent comorbidities and a complex anatomic situation frequently associated with multivessel disease (**Tables 1** and **2**).

The peculiarity of our LM PCI experience lies in the absence of a proper "heart team" and in the presence of experienced operators leading to the preferred choice of the percutaneous revascularization option if possible (at least a functionally complete revascularization) without employing more than 4 - 5 stents, and in the absence of absolute contraindications to DES. The main intent was to avoid adverse events related to CABG, even those less known or not routinely reported (*i.e.*, sequelae of surgical wounds, psycho-intellective deterioration) that significantly impact on morbidity and on the quality of life and costs [20].

Our results show a satisfactory short-term outcome, with an acceptable in-hospital mortality considering the type of patients (15% STEMI, comorbidity, age, mean Euroscore 7 ± 3); moreover, also at 12 months, excluding patients with acute MI (STEMI and NSTEMI) total mortality results 3.8% (**Table 4**), similar to the 12-month mortality of the LM subgroup of the Syntax trial that did not enroll patients with acute MI (2). Our results also do well in comparison with the experience of the large DELTA Registry (6), with cardiac mortality of 10% versus 6.8%, if we considered that our patients were older (mean age 72 ± 10 vs 65.8 ± 1.1 years), and presented more frequently an ACS (STEMI 15% vs 2.9%, NSTEMI

Table 5. Independent predictors of total mortality at multivariate analysis.

	OR	95% CI	p value
BMS utilization	5.15	2.28 - 11.66	<0.001
Age >75 years	3.12	1.39 - 6.99	0.006
Syntax score >32	3.53	1.25 - 9.96	0.010
ACS indication (STEMI and NSTEMI)	2.69	1.19 - 6.08	0.017
Associated PAD	2.31	1.03 - 5.18	0.042

ACS = acute coronary symdrome; BMS = bare metal stent; PAD = peripheral artery disease.

Table 6. Clinical characteristics of patients treated with BMS or DES.

	BMS (n = 50)	DES (n = 264)	p value
Age	78.6 ± 10	71.5 ± 10	<0.001
STEMI inidication	15 (30%)	34 (13%)	0.001
Ad hoc PCI	36 (72%)	133 (50%)	0.005
Hypertension	37 (74%)	190 (72%)	0.768
Diabetes mellitus	14 (28%)	74 (28%)	0.996
Hypercholesterolemia	30 (60%)	203 (76%)	0.012
Creatinine, mg/dl	1.42 ± 0.6	1.17 ± 0.7	0.042
Left ventricle ejection fraction, %	43 ± 12	51 ± 11	<0.001
COPD	9 (18%)	22 (8%)	0.035
PAD	30 (60%)	145 (55%)	0.507
Previous MI	12 (24%)	64 (24%)	0.97
Severe comorbidity	18 (36%)	31 (11%)	<0.001
Atrial fibrillation	13 (26%)	20 (7.8%)	<0.001
Killip class 3-4	12 (24%)	22 (8.3%)	0.001
Syntax score	26.5 ± 10	24.5 ± 9	0.443
In-hospital death	6 (12%)	12 (4.5%)	0.048
Total death at follow up	21(42%)	30 (11.4%)	<0.001
LM TLR	8 (16%)	39 (14.8%)	0.823

BMS = bare metal stent; COPD = chronic obstructive pulmonary disease; DES = drug-eluting stent; LM = left main; MI = myocardial infarction; PAD= peripheral artery disease; PCI = percutaneous coronary intervention; TLR = target lesion revascularization; STEMI = St elevation myocardial infarction.

35% vs 11.6%) and a higher Euroscore (7 ± 3 vs 4.9 ± 3.6).

Medium term TLR rate is comparable to that reported by another study with clinical and/or angiographic follow-up [21] and seems to be linked to the routine angiographic follow-up, more often with a significant involvement of circumflex artery ostium. Almost half of (23/48) TLR were not clinically driven. Although angiographic follow-up is largely used to monitor the results of LM PCI, there are many doubts about its appropriateness [22]. All but one case of LM in-stent restenosis were treated percutaneously in our experience.

In this population of anatomically complex patients, mostly with multivessel disease, the need for a repeated revascularization of already treated segments of other vessels, or of *de novo* lesions or progression of disease has all the same importances of total TLR (13.2% of TVR and 12.9% of PCI of *de novo* lesions, **Table 4**); progression of atherosclerosis is the main cause of the PCI inferiority versus CABG as long as the long term need for new revascularizations is concerned.

Although IVUS was rarely used, a post-dilatation with

Table 7. Clinical characteristics and events in the three Syntax score groups.

	<22	22 - 33	>33	p
N° patients	125	120	66	
Age	71 ± 10	74 ± 10	73 ± 10	0.086
LVEF, %	53 ± 11	49 ± 11	47 ± 12	0.005
Creatinine, mg/dl	1.04 ± 0.4	1.4 ± 1	1.17 ± 0.46	0.001
Killip class 3-4	10 (8%)	12 (10%)	13 (19%)	0.044
Previous MI	22 (17.6%)	34 (28%)	20 (30%)	0.067
Euroscore	6.4 ± 3.6	7.4 ± 3.2	7.5 ± 3.9	0.038
Associated CTO	6 (4.8%)	35 (29%)	35 (53%)	<0.001
Other vessel treated	61 (49%)	100 (83%)	60 (91%)	<0.001
Complete revascularization	101 (81%)	55 (46%)	20 (30%)	<0.001
In-hospital death	6 (4.8%)	6 (5%)	7 (10.6%)	0.227
Total death at follow up	13 (10.4%)	20 (16.6%)	18 (27.3%)	0.011
LM TLR	19 (15%)	18 (15%)	11 (16.5%)	0.951
Other vessel TVR	14 (11%)	20 (16.5%)	8 (12%)	0.426

CTO = chronic total occlusion, LM = left main; LVEF = left ventricle ejection fraction, MI = myocardial infarction, TLR = target lesion revascularization, TVR = target vessel revascularization.

a non-compliant balloon (254/317, 80%) and final kissing-balloon in almost all bifurcation lesions were frequently performed (**Table 3**). This technical feature, derived from the results of IVUS-guided stenting studies [23], may account for the low prevalence of ST (no case of definite ST, 4 unknown cause death cases, possibly due to ST).

Multivariate analysis shows a strong correlation of BMS utilization with total mortality. This result deserves a comment because it is likely due to the presence of a higher risk profile (older age, more often STEMI presentation, severe comorbidities, necessity for oral anticoagulation, lower LVEF and compromised hemodynamic status, **Table 6**), which leads to the choice of BMS utilization in order to avoid prolonged dual antiplatelet therapy or is based on the supposedly worse cost/efficacy ratio in very compromised clinical conditions. Probably BMS utilization alone is not really an independent predictor of mortality but rather an indicator of a worse clinical setting. This hypothesis is supported by the very high acute in-hospital mortality of this subset of patients (6/50, 12% vs 13/264, 4.5% in the BMS and DES group respectively), without a concomitant higher TVR versus DES group in patients who survived the in-hospital phase (**Table 6**).

We cannot derive a difference between the first and second generations DES from our data, even if recent studies showed no significant advantage of the latter one [24].

The presence of a Syntax Score >32 is also a predictor of mortality and this result is in line with the increased major adverse event rate at 3rd and 5th years in higher Syntax Score subgroup in Syntax trial [25,26]. Notably, our patients with Syntax Score >32 had lower LVEF, higher Euroscore, more frequent Killip class 3-4 (**Table 6**). All these features made us to prefer percutaneous coronary treatment over a surgical approach.

In our experience, besides anatomical situation, clinical features (age, ACS presentation, PAD) are important determinants of prognosis. An integrated clinical judgment may be represented by the new risk scores (global and clinical Syntax Score) [27,28], and is mandatory to choose the right revascularization strategy for each individual patient in order to guarantee the best benefit-to-risk ratio and quality of life.

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