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Prognostic Impact of New-Onset Atrial Fibrillation After Single or Double Stent Left Main Bifurcation PCI

Tek veya Çift Stent Sol Ana Bifürkasyon PCI Sonrası Yeni Başlangıçlı Atriyal Fibrilasyonun Prognostik Etkisi

ORIGINAL ARTICLE
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ABSTRACT

Objective: Incidence and prognostic value of new-onset atrial fibrillation after single versus double stent strategy in bifurcation left main disease has not been yet investigated.

Methods: We retrospectively analyzed the procedural and medical data of patients referred to our center for complex left main bifurcation disease, treated using crossover provisional stenting, T or T-and-Protrusion, Culotte, and Nano-inverted-T techniques between January 1, 2008, and May 1, 2018. Multivariate Cox-regression analysis was used to assess the role of different stent strategies, adjusted for confounders, on the risk of new-onset atrial fibrillation during the follow-up period.

Results: Five hundred two patients (316 males, mean age 70.3 ± 12.8 years, mean Syntax score 31.6 ± 6.3) were evaluated. At a mean follow-up of 37.1 ± 10.8 months (range: 22.1-39.3 months); Target lesion failure rate was 10.1%. Stent thrombosis and cardiovascular mortality were observed in 1.2% and 3.6% in of cases, respectively. New-onset atrial fibrillation occurred in 23 out of 502 patients (4.6%). Patients with new-onset atrial fibrillation resulted more frequently female, older, obese, and diabetic and more frequently experienced target lesion failure and cardiovascular death. New-onset atrial fibrillation-free survival favored single versus double stent technique and among double stent techniques nano-inverted-T techniques compared to the others. Single stent strategy had a lower risk of new-onset atrial fibrillation compared to double stent technique on multivariate analysis (Hazard Ratio (HR): 1.14, 95% CI: 1.10-1.19, $P < .001$ vs. HR: 1.28, 95% CI: 1.23-1.32, $P < .0001$).

Conclusion: New-onset atrial fibrillation in distal left main bifurcation disease treated with percutaneous coronary intervention had a low incidence but resulted more frequently after double than after single stenting technique and was associated with worse outcomes.

Keywords: Left main, bifurcation stenting, atrial fibrillation, complex bifurcation

ÖZET

Amaç: Sol Ana (LM) bifürkasyon hastalığında tekliye karşı çift stent stratejisinden sonra yeni başlangıçlı atriyal fibrilasyonun (NOAF) insidansı ve prognostik değeri henüz araştırılmamıştır.

Yöntemler: Merkezimize 1 Ocak 2008 ile 1 Mayıs 2018 arasında komplex LM bifürkasyon hastalığı ile sevk edilen, Cross-over provizyonel stentleme, T veya T-ve-Protrüzyon (TAP), Culotte ve Nano-inverted-T (NIT) teknikleri kullanılarak tedavi edilen hastaların prosedürel ve tıbbi verilerini geriye dönük olarak analiz ettik. Farklı stent stratejilerinin takip döneminde NOAF riski üzerindeki rolünü değerlendirmek için çok değişkenli Cox-regresyon analizi kullanıldı.

Bulgular: Beş yüz iki hasta (316 erkek, ortalama yaş 70,3 ± 12,8 yıl, ortalama Syntax skoru 31,6 ± 6,3) değerlendirildi. Ortalama 37,1 ± 10,8 aylık (aralık 22,1-39,3 ay) takipte hedef lezyon başarısızlık (TLF) oranı %10,1 idi. Stent trombozu ve kardiyovasküler mortalite vakaların sırasıyla %1,2 ve %3,6'sında gözlendi. 502 hastanın 23'ünde (%4,6) NOAF gelişti. NOAF'li hastalar daha sıklıkla kadın, yaşlı, obez, diyabetikti ve sıklıkla TLF ve kardiyovasküler ölüm yaşadılar. NOAF'sız sağkalım, tekliye karşı çift stent tekniği ve diğerlerine kıyasla çift stent teknikleri arasında NIT lehineydi. Çok değişkenli analizde tek stent stratejisinin çift stent tekniğine kıyasla daha düşük NOAF riski vardı (HR: 1,14, %95 GA: 1,10-1,19, $P < ,001$ vs HR: 1,28, %95 GA: 1,23-1,32, $P < ,0001$).

Sonuç: PCI ile tedavi edilen distal LM bifürkasyon hastalığında NOAF düşük bir insidansa sahipti, ancak çift stentleme tekniğinden sonra, tek stentleme tekniğine kıyasla, daha sık sonuçlandı ve daha kötü sonuçlarla ilişkiliydi.

Anahtar Kelimeler: Sol ana, bifürkasyon stentleme, atriyal fibrilasyon, karmaşık bifürkasyon

Previous randomized controlled trials (RCTs) and meta-analysis[1-4] revealed a lower incidence of stroke and increased mortality when treated with percutaneous coronary intervention (PCI) compared to coronary artery bypass surgery (CABG). As suggested by the latest recommendations of the European Bifurcation Club[5] and accordingly to recent RCT and meta-analysis results,[6] crossover provisional stenting remains the gold-standard technique for the percutaneous interventional management of left main (LM) bifurcation disease. However, over the latest years, the role of double stenting techniques in distal bifurcation LM disease has gained increasing interest.[7]

New-onset atrial fibrillation (NOAF) has been only partially investigated in patients with LM disease treated using PCI or CABG.[8] Conversely, both the incidence and prognostic value of NOAF after PCI using a single versus double stent strategy in bifurcation LM disease have not been yet investigated. Our study is aimed to evaluate the incidence and prognostic impact of NOAF after a single or double stent strategy for the treatment of LM bifurcation disease.

Methods

Population Enrolled

To evaluate the incidence of NOAF, we retrospectively analyzed the procedural and medical data of consecutive patients referred to our center for complex LM bifurcation disease, treated by crossover provisional stenting, Culotte, T-and-Protrusion (TAP), and Nano-inverted-T (NIT) stenting[9] between January 1, 2008, and May 1, 2018, due contraindications and/or refusal to surgical treatment. Traditional cardiovascular risk factors, Canadian Cardiovascular Score class, EuroSCORE II,[10] SYNTAX score,[11] MEDINA classification[12] as well as pre-and post-procedural angiographic characteristics were revised and analyzed, as mandatory inclusion criteria, by the Rovigo General Hospital heart team, which includes a clinical cardiologist, a cardiac surgeon, and an interventional cardiologist.

ABBREVIATIONS

AMI	Acute myocardial infarction
ARC	Academic Research Consortium
CABG	Coronary artery bypass surgery
DES	Drug eluting stent
DS	Diameter stenosis
FFR	Fractional flow reserve
HR	Hazard ratio
ISR	In-stent restenosis
IVUS	İntravascular ultrasound
LAD	Left anterior descending
LCx	Left circumflex
LM	Left main
MV	Main vessel
NIT	Nano-inverted-T
NOAF	New-onset atrial fibrillation
PCI	Percutaneous coronary intervention
RCTs	Randomized controlled trials
QCA	Quantitative coronary angiography
ST	Stent thrombosis
STEMI	ST-elevation myocardial infarction
TAP	T-and-Protrusion
TLF	Target lesion failure

Written informed consent to the indexed procedure was obtained from all patients before interventions. All records of the enrolled patients were reviewed by the heart team to verify the adherence to anatomical and clinical criteria as well as interventional procedures. An agreement was achieved in 98.8% of cases: any discrepancy was discussed and resolved by consensus between two interventionalists with 20-year of experience in the treatment of LM bifurcation (G.R and L. R.).

Inclusion criteria for LM PCI were: patients presenting with silent ischemia, stable or unstable angina as well as PCI intended in a true de novo distal LM bifurcation lesion (Medina 1,1,1 or 0,1,1), with >50% diameter stenosis (DS) of both the ostial left anterior descending (LAD) and left circumflex (LCx) coronary arteries by visual estimation and confirmed by fractional flow reserve (FFR) or intravascular ultrasound (IVUS), were included. Conversely, exclusion criteria were patients who developed an intraprocedural ST-elevation myocardial infarction (STEMI) with vessel occlusion as a complication of an elective procedure, those previously treated with CABG, and if they present in-stent restenosis (ISR) or any clinical condition that would interfere with medications compliance or long-term follow-up. To avoid potential bias in the assessment of NOAF, patients with a history of AF of any type, mitral valve regurgitation more than grade 1+/4+ (mild mitral valvular regurgitation) or a mitral transvalvular mean gradient more than 5 mm Hg (mild mitral valvular stenosis) on the first transthoracic echocardiography at admission, were excluded from the retrospective analysis.

Definitions

A standard 12-lead ECG recording or a single-lead ECG tracing of ≥30 seconds showing heart rhythm with no discernible repeating P waves and irregular RR intervals (when atrioventricular conduction was not impaired) was defined as AF, following the current guidelines.[13]

Target lesion failure (TLF) was defined as the composite of cardiovascular death, target vessel MI, and clinically driven target lesion revascularization. Cardiovascular mortality from cardiac causes was defined as any death without a clear non-cardiac cause. Protocol-defined periprocedural acute myocardial infarction (AMI) was defined as coronary intervention-related MI is arbitrarily defined by an elevation of cTn values more than 5 times the 99th percentile URL in patients with normal baseline values. In patients with elevated pre-procedure cTn in whom the cTn level is stable (≤20% variation) or falling, the post-procedure cTn must rise by >20%. However, the absolute post-procedural value must still be at least 5 times the 99th percentile URL. In addition, one of the following elements is required: New ischemic ECG changes; Development of new pathological Q waves; Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology; Angiographic findings consistent with a procedural flow-limiting complication such as coronary dissection, occlusion of a major epicardial artery or a side branch occlusion/thrombus, disruption of collateral flow, or distal embolization (Type 4a MI).[13] Spontaneous MI was defined as detection of a rise and/or fall of cTn values with at least 1 value above the 99th percentile URL and with at least one of the following: Symptoms of acute myocardial ischemia; New ischemic ECG changes; Development of pathological Q waves; Imaging evidence of

new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology; Identification of a coronary thrombus by angiography including intracoronary imaging or by autopsy (Type 1 MI).[13]

Stent thrombosis (ST) was classified according to the Academic Research Consortium (ARC) definitions as definite, probable, or possible and as early (0-30 days), late (31-360 days), or very late (>360 days). In-stent restenosis was evaluated by Quantitative coronary angiography (QCA) and eventually FFR if the luminal narrowing was <70% and classified as focal (<10 mm long), diffuse (>10 mm long), proliferative (>10 mm long and extending outside the stent edges), or totally occluded.[14]

Complex LM bifurcation lesion was defined according to the Definitions and Impact of Complex Bifurcation Lesions on Clinical Outcomes After Percutaneous Coronary Intervention Using Drug-Eluting Stents study,[15] with complex defined as the presence of both major criteria (ostial side branch SB- lesion length ≥10 mm and DS ≥70%) plus any 2 minor criteria (distal bifurcation angle <45° or ≥70°, Main Vessel (MV) reference vessel diameter ≤2.5 mm, MV lesion length ≥25 mm, multiple bifurcations, thrombus-containing lesion, and severe calcification).

Interventional Protocol and Techniques

A 6F right radial approach has been selected whenever possible. During PCI, patients were anticoagulated with unfractionated heparin (a bolus of 40 U/kg and additional heparin to achieve an activated clotting time of 250-300 seconds). Choice of stenting techniques was left to operator choice and included crossover provisional stenting, Culotte, TAP, and Nano-inverted-T stenting. Patients could receive the Orsiro (BiotronikInc, Bulach, Switzerland), Xience (Abbott Inc., USA) and Promus Premier (Boston Scientific Inc, Mantick, USA) or the Onyx Resolute (Medtronic Inc., Galway, Ireland) stents basing the diameter of the main vessel stent using the Finet's law[16] or preferably IVUS, which was recommended in all enrolled patients whenever possible depending on availability. Additional significant lesions in other vessels were treated with staged procedures and a routine last generation Drug Eluting Stent (DES) of the operator's choice. Twelve-month Ticagrelor or Prasugrel treatment in case of acute coronary syndrome patients or 12-month Clopidogrel 75 mg in the other cases and life-long aspirin were recommended to all patients according to our regional guidelines.

FFR and IVUS Protocol

Fractional flow reserve evaluation was conducted using PressureWire X device (Abbott Medical, Plymouth, MN, USA) and intracoronary bolus injection of adenosine with a dilution of 12 mg in 250 mL of NaCl solution (6-8 Ml/run): a mean cut off of <0.79 on at least 3 runs was considered significant. Intravascular ultrasound examination was performed routinely following current recommendations using the 3F Opticross coronary IVUS catheter (Boston Scientific, Fremont, Calif, USA) and automatic pull-back system (0.5 mm/s). An online ultrasound assessment was performed in diastole. IVUS images were recorded after administration of 100-200 mg of nitroglycerin. A segment of 0.5 mm proximally and distally the lesion/stent was analyzed using motorized transducer pull-back. IVUS images were interpreted by the treating physician and at least 1 experienced IVUS technician.

Follow-up

Per institutional protocol, follow-up was conducted by physical examination and surface 12 -lead electrocardiogram at 1, 6, and 12 months and then yearly. Twenty-four hours of electrocardiographic Holter was performed when suspicion of AF arose during follow-up at any stage. Transthoracic echocardiography was scheduled at 6 months and then yearly. Ergometric tests or nuclear stress tests have been conducted at 6 months and then yearly. Angiography with IVUS control was performed only at the time of additional vessel treatment or based on clinical symptoms or instrumental evidence of myocardial ischemia. Post-discharge survival status was obtained from the Municipal Civil Registries. Information on the occurrence of acute MI or repeated interventions at follow-up was collected by consulting our institutional electronic database and by contacting referring physicians and institutions and all living patients.

Statistical Analysis

Continuous variables were presented as mean ± standard deviation while categorical data were summarized as frequencies and relative percentages. For continuous variables, normal distribution was evaluated with the Kolmogorov–Smirnov test. Differences among groups were analyzed by Student's *t*-test or one-way analysis of variance followed by post hoc Bonferroni test. Multivariate Cox regression analysis was used to assess the role of different stent strategies, adjusted for confounders, on the risk of NOAF during the follow-up period. Covariates have been selected after performing a univariate analysis and when presenting a *P* value <.01. To represent the freedom from NOAF over the follow-up period, the Kaplan–Meier method was applied. Statistical significance was defined as $P < .05$. Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) package version 20.0 (IBM Corp., Armonk, NY, USA).

Results

Population

Five hundred two patients (316 males, mean age 70.3 ± 12.8 years, mean Syntax score 31.6 ± 6.3) out of 654 were evaluated. Two hundred fifty-two patients were excluded from the final analysis: 45 because of a mitral valve regurgitation >2/4, 111 patients for previous CABG, 36 patients because of STEMI <24 hours, and 60 patients because of a history or concurrent AF at the time of the procedure (Figure 1). The clinical characteristics

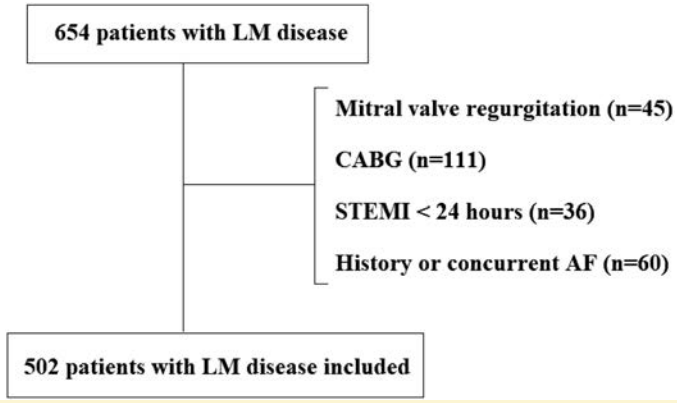

Figure 1. Flow chart: Retrospective application of inclusion and exclusion criteria of the study population.

and comorbidities of the population enrolled are shown in Table 1. Mean angles between LM and LCx were 64.8 ± 20.7 (range 17-91°). Lesion characteristics are shown in Table 2. IVUS was performed in 132/237 patients in whom NIT was performed (55.7%), in 51/171 of patients underwent crossover technique (29.8%) in 10/61 with T or TAP stenting (16.4%) and in 37/98 patients who received Culotte stenting (37.7%).

PCI Outcomes

Clinical follow-up was available for all patients. At a mean follow-up of 37.1 ± 10.8 months (range: 22.1-39.3 moths), TLF rate was 10.1% (n=51): 11/171(6.4%) in the crossover group; 10/61 (16.4%) in T/TAP group, 16/98 (16.3%) in the culotte group and finally 14/237 (5.9%) in the NIT group of patients (p). Cardiovascular mortality rate was 3.6% (n=18). While ST was 1.2% (n=6).

Clinically driven angiographic follow-up was available in 135 patients (26.8%) at a mean time from the procedure of 7.8 ± 0.7 months and showed significant restenosis in 45 patients (clinically restenosis 8.9%), predominantly located at LCx ostium or within 5 mm from the ostium in 38 patients (84.4%) or in the LAD in the rest of 8 patients (17.7%).

New-Onset AF Incidence and Prognostic Impacts

New-onset atrial fibrillation occurred in 23 out of 502 patients (4.6%) at a mean time from the indexed procedure of 4.3 months: NOAF occurred during the first month after the procedure in most patients (20/23 patients). New-onset atrial fibrillation has been detected by Holter monitoring in 13 patients and by scheduled examination and electrocardiogram in 10 patients. Patients with NOAF resulted more frequently female, older, obese, diabetic, and more frequently experienced TLF and death (Table 3). Among these latter NOAF was less frequently observed using the NIT technique. As evidenced in Figure 2, compared to NIT, both crossover [Log-rank/Mantel-Cox, $P < .0001$ (chi-square 4.6)] and Tor TAP [Log-rank/ Mantel-Cox, $P < .0001$ (chi-square 5.2)] exhibited a different temporal onset of new AF cases, while no difference, albeit at the limit of statistical significance was observed comparing NIT towards Culotte [log-rank/ Mantel-Cox, $P = .06$ (chi-square: 1.8)].

Table 1. Demographic and Clinical Characteristics of the Analyzed Cohorts of Patients

	Crossover N=171	T or TAP N=61	Culotte N=98	NIT N=172	*P*
Age (years)	68.3 ± 9.1	69.1 ± 10.3	71.9 ± 11.7	70.3 ± 12.8	.60
Male	91 (53.1)	34 (55.7)	50 (51.0)	101 (58.7)	.702
Obesity	24 (14)	11 (18.1)	16 (16.3)	27 (15.9)	.67
Arterial hypertension, n (%)	95 (55.6)	35 (57.4)	59 (60.2)	99 (57.6)	.72
Dyslipidaemia, n (%)	70 (40.9)	26 (42.6)	46 (46.9)	75 (43.6)	.25
Diabetes, n (%)	48 (28.1)	18 (29.5)	32 (32.7)	58 (33.7)	.52
Previous smokers, n (%)	54 (31.6)	22 (36.1)	35 (35.7)	57 (33.3)	.62
Active smokers, n (%)	31 (18.1)	10 (16.4)	14 (14.3)	27 (15.7)	.18
Valvular heart disease, n (%)	37 (21.6)	16 (26.2)	23 (23.5)	40 (23.2)	.72
LVEF (%)	52.5 ± 10.7	54.1 ± 8.9	52.6 ± 10.1	53.1 ± 9.7	.32
LA diameter (mm)	30.1 ± 7.3	31.6 ± 6.9	29.2 ± 7.8	30.3 ± 7.4	.78
CSS class	2.7 ± 1.1	2.4 ± 0.8	2.5 ± 0.9	2.6 ± 0.9	.59
TIA/stroke, n (%)	46 (26.9)	19 (31.1)	32 (32.7)	50 (29.1)	.61
eGFR <30 mL/min/1.73 m^2	27 (15.8)	11 (18)	16 (16.3)	42 (17.7)	.55
HF, n (%)	60 (35.1)	21 (34.4)	30 (30.6)	60 (34.8)	.68
COPD, n (%)	50 (29.2)	19 (31.1)	32 (32.7)	58 (33.7)	.72
PAD, n (%)	42 (24.6)	13 (21.3)	18 (18.4)	39 (22.6)	.25
EUROSCORE	20.3 ± 9.4	20.2 ± 9.3	23.1 ± 10.5	24.5 ± 10.1[a]	.02
Clinical presentation					
Silent ischemia	5 (2.9)	2 (3.3)	5 (5.1)	7 (4.1)	.55
N-STEMI, n (%)	78 (45.6)	26 (42.6)	40 (40.8)	73 (42.4)	.68
Unstable angina, n (%)	77 (45.0)	27 (44.3)	49 (50)	75 (43.6)	.87
Recent STEMI (>24 hours)	21 (12.3)	8 (13.1)	11 (11.2)	17 (9.8)[a]	.58

[a]$P < .05$ NIT versus crossover.

LVEF, left ventricular ejection fraction; CCS, Canadian class score; TIA, transient ischemic attack; HF, heart failure; CKF, chronic kidney failure; COPD, chronic obstructive pulmonary disease; PAD, peripheral artery disease; MI, myocardial infarction; N-STEMI, non-ST segment elevation myocardial infarction; STEMI, ST elevation myocardial infarction.

Table 2. Lesion and Procedural Characteristics of the Analyzed Cohorts of Patients

	Crossover N = 171	T or TAP N = 61	Culotte N = 98	NIT N = 172	*P*
Three-vessel disease	101 (59.6)	34 (55.7)	67 (68.4)	132 (76.8)	
LM lesion location					
Ostial, n (%)	28 (16.3)	10 (16.4)	17 (17.3)	38 (22.0)	0.01
Body shaft, n (%)	34 (19.9)	17 (27.8)[b]	37 (37.7)	69 (40.1)[a]	0.02
Distal LM, n (%)	171 (100)	61 (100)	98 (100)	172 (100.0)	0.99
Medina 1,1,1 bifurcation, n (%)	74 (43.2)	30 (49.1)	41 (41.8)	83 (48.2)	0.55
Medina 0,1,1 bifurcation, n (%)	51 (29.8)	18 (29.5)	30 (30.6)	45 (26.1)	0.65
Trifurcation, n (%)	46 (35.0)	13 (21.3)	27 (27.5)	44 (25.5)[a]	0.52
Calcification[a], n (%)					
Moderate, n (%)	18 (10.5)	11 (18.0)	17 (17.3%)	34 (19.7)[a]	0.39
Severe, n (%)	15 (8.7)	9 (14.7)	13 (13.2%)	30 (17.4)[a]	0.55
Chronic total occlusion	37 (21.6)	9 (14.7)	13 (13.2)	33 (19.8)	0.65
LM, n	1	0	0	1	-
LAD, n	13	2	8	10	-
LCx, n	19	3	0	13	-
RCA, n	4	4	5	9	-
TIMI flow grade <3					
Main vessel	15 (8.7)	6 (9.8)	7 (7.1)	12 (6.8)	0.66
Side branch	18 (10.5)	5 (8.1)	8 (8.1)	16 (9.3)	0.59
SYNTAX	28.8 ± 8.1	29.1 ± 7.6	30.3 ± 7.0	31.6 ± 6.3[a]	0.02
Stent characteristics					
Mean LM stent diameter (mm)	4.3 ± 0.8	4.3 ± 0.7	4.4 ± 0.8	4.5 ± 0.9	0.60
Mean number of stent	1.5 ± 0.5	2.2 ± 0.5	2.5 ± 0.5	2.8 ± 0.4	0.02
Global stent length (mm)	26.8 ± 10	33.8 ± 10	46.1 ± 11	46.4 ± 10	0.02

[a]Defined as moderate calcification (radiopaque densities noted only during the cardiac cycle and typically involving only 1 side of the vascular wall) or severe calcification (radiopaque densities noted without cardiac motion before contrast injection and generally involving both sides of the arterial wall).
[a]$P < .05$ NIT versus crossover.
[b]$P < .05$ NIT versus T or TAP.
LAD, left anterior descending coronary artery; LCx, left circumflex coronary artery; LM, left main; RCA, right coronary artery.

Table 3. Clinical Parameters Distribution Among Patients with and Without AF on Follow-up

	AF N = 23 (%)	Non-AF N = 479 (%)	*P*
Gender (females)	15 (65.2)	163 (34.0)	<.001
Age >80 years	18 (78.2)	220 (45.9)	<.001
Obesity	9 (39.1)	80 (16.7)	<.001
Diabetes	15 (65.2)	42 (8.7)	<.001
EF <50	14 (60.8)	182 (37.9)	<.001
LV mass Index (g/m^2)	75 ± 9.3	74 ± 9.1	ns
Crossover	5 (21.7)	166 (34.6)	<.0001
T or TAP	7 (30.4)	54 (11.2)	.001
Culotte	10 (43.4)	88 (18.3)	<.001
NIT	1 (4.3)	236 (49.2)	<.001
TLF	9 (39.1)	42 (8.7)	<.001
Stent thrombosis	1 (4.3)	5 (1.0)	.02
CV death	8 (34.7)	10 (2.1)	<.001

EF, ejection fraction; CV death, cardiovascular death; NIT, nano-inverted-T, T; T-stenting; TAP, T and protruding; TLF, target lesion failure.

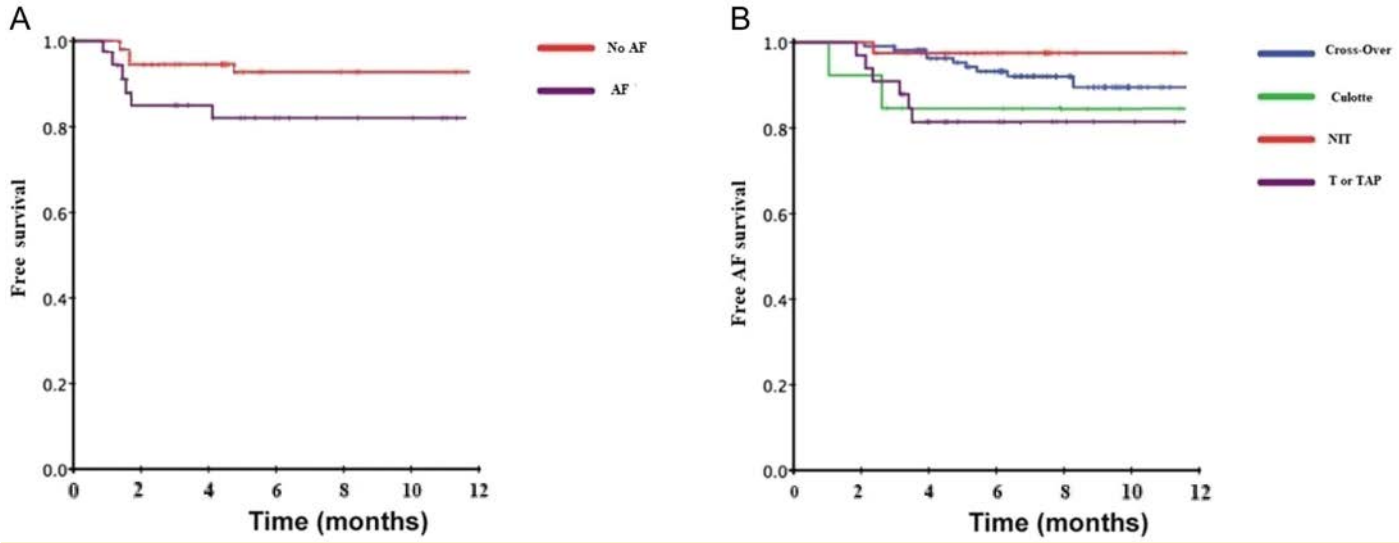

Figure 2. Kaplan–Meier of atrial fibrillation-free survival during the follow-up: Comparison of different stent techniques.

Table 4. Univariate Analysis for the Risk of New-Onset AF in Patients with LM Disease Treated with PCI

	Single Stent Strategy		Dual Stent Strategy					
	Crossover		T or TAP		Culotte		NIT	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Gender (females)	1.88 (1.72-1.64)	.001	1.25 (1.15-1.33)	.001	1.31 (1.26-1.45)	<.001	1.44 (1.38-1.56)	.001
Age>80 years	2.04 (1.88-2.25)	<.001	1.42 (1.28-1.1.58)	<.001	1.74 (1.61-1.82)	<.001	2.05 (1.88-2.15)	<.001
Obesity	1.88 (1.55-1.93)	<.001	1.39 (1.24-1.44)	.001	1.39 (1.34-1.42)	<.001	1.29 (1.24-1.44)	.001
Diabetes	2.25 (2.02-2.57)	<.0001	1.44 (1.22-1.68)	.001	1.54 (1.45-1.68)	.001	1.75 (1.52-2.03)	<.001
EF <50	1.33 (1.28-1.58)	.01	1.58 (1.33-1.79)	<.001	1.45 (1.33-1.64)	.001	1.55 (1.42-1.73)	.001
TLF	1.44 (1.33-1.68)	.001	1.32 (1.27-1.44)	.001	1.36 (1.22-1.48)	.001	1.25 (1.22-1.29)	<.001
New-onset AF	1.27 (1.15-1.43)	<.001	1.55 (1.36-1.87)	<.001	1.42 (1.34-1.52)	<.001	1.64 (1.55-1.73)	<.001

EF, ejection fraction; NIT, nano-inverted-T, T; T-stenting; TAP, T and protruding; TLF, target lesion failure.

Univariate (Table 4) and multivariate Cox-regression analysis (Table 5) demonstrated that the risk of NOAF was lower among patients receiving a treatment based on a single stent strategy compared to those treated with a double stent technique (HR: 1.14, 95% CI: 1.10-1.19, *P* < .001 vs. HR: 1.28, 95% CI: 1.23-1.32, *P* < .0001). Specifically, among double stent strategies, the lower risk of NOAF was observed using NIT [HR, 1.25, 95% 1.23-1.29], followed by T or TAP [HR: 1.31, 95% CI: 1.29-1.33] and culotte [HR: .29, 95% CI: 1.26-1.32].

Table 5. Multivariate Analysis for the Risk of New-Onset AF in Patients with LM Disease Treated with PCI

	Single stent strategy		Dual stent strategy					
	CrossOver		T or TAP		Culotte		NIT	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Gender (females)	1.23 (1.19-1.26)	.01	1.15 (1.10-1.19)	.002	1.18 (1.16-1.20)	<.001	1.20 (1.17-1.22)	.01
Age>80 years	1.55 (1.66-1.59)	<.001	1.22 (1.18-1.23)	<.001	1.23 (1.18-1.26)	<.001	1.65 (1.56-1.69	<.001
Obesity	1.12 (1.08-1.15)	.01	1.14 (1.11-1.17)	.01	1.20 (1.17-1.24)	.002	1.18 (1.16-1.20)	.01
Diabetes	1.55 (1.47-1.55)	<.0001	1.26 (1.13-1.31)	.02	1.31 (1.26-1.35)	.01	1.28 (1.26-1.31)	<.001
EF <50	1.16 (1.13-1.20)	.02	1.29 (1.22-1.34)	.001	1.33 (1.25-1.37)	.01	1.25 (1.22-1.28)	.003
TLF	1.11 (1.08-1.16)	.003	1.20 (1.17-1.23)	.01	1.22 (1.19-1.26)	.01	1.18 (1.16-1.20)	<.001
New-onset AF	1.14 (1.10-1.19)	<.001	1.31 (1.29-1.33)	.001	1.29 (1.26-1.32)	<.001	1.25 (1.23-1.29)	<.001

EF, ejection fraction; NIT, nano-inverted-T, T; T-stenting; TAP, T and protruding; TLF, target lesion failure.

The management of patients with NOAF evidenced that most patients were treated medically (65.2%) whereas 3 patients underwent drug cardioversion(13%), 3 to electrical cardioversion (13%), 2 to Transcatheter ablation (8.7%). Most patients (20; 86.9%) were put on oral anticoagulant+single antiplatelet agent.

Discussion

Our analysis evidenced that NOAF in patients treated with PCI for distal LM bifurcation disease is not a frequent complication but remains associated with higher CV mortality when compared to patients without. Single stent strategy was associated with a lower risk of NOAF compared to the use of double stenting technique (14% vs. 28%).

Patients with coronary artery disease have been associated with a higher incidence of NOAF.[16] New-onset atrial fibrillation has been evaluated in patients who underwent CABG or PCI for LM disease in a few studies. Thoren et al[17] found an incidence of NOAF of 31% in patients post-bypass surgery whereas Taha[18] found an incidence of 30% in a similar population. Kosmidou et al[19] found an incidence of NOAF occurred in 12.8% in the PCI arm and 87.2% in the CABG arm ($P < .0001$): time-updated post-discharge NOAF was an independent predictor of 3-year cardiovascular death (HR 4.91, 95% CI: 1.92-12.60, $P=.0009$), stroke (HR 4.87, 95% CI: 1.12-21.12, $P=.035$), and the composite outcome of death, stroke, or myocardial infarction (HR 3.09, 95% CI: 1.56-3.6-6.11, $P=.001$).

In our study, the incidence of NOAF is lower compared to the study of Kosmidou as 4.6% of patients underwent PCI of complex distal LM bifurcation disease with single or double stenting technique: single stent technique resulted in 50% lower incidence compared to double stenting technique but looking at the used double stenting techniques, an upfront double stenting technique with minimal wires and balloons manipulation as the NIT technique, resulted more favorable as regards as the occurrence of NOAF compared to Culotte, T or TAP. While the occurrence of NOAF after bypass surgery finds its pathogenesis in the extensive manipulation of the heart and pericardium during surgical steps, and in clamping-time, the reasons for AF after PCI are more difficult to conceptualize.

Historically, AMI and acute coronary syndrome have been associated with NOAF: Mrdovic et al[20] showed that in AMI preprocedural infarction-related artery occlusion and postprocedural thrombolysis in myocardial infarction flow less than 3 were identified as independent predictors of the occurrence of AF, suggesting that, as for bypass grafting, the ischemic time and the grade of complete flow restoring play a role in the genesis of NOAF. As matter of fact, observational studies suggest better patency of culprit vessels achieved by PCI was accompanied by improvement in signal-averaged electrocardiography indices of atrial electrophysiological properties and a higher rate of restoration of sinus rhythm during primary PCI as compared with thrombolysis.[21]

Being most patients treated in our series presenting with unstable angina or acute coronary syndrome, plausible hypothesis to explain NOAF after LM PCI might include the amount of balloon/stent occlusion time, which would depend on the number of vessels/stent to be treated/implanted, the number and inflation time of proximal optimization technique and full kissing balloon, the eventual side-branch compromise and the time needed to restore side-branch flow. Single stent technique would represent the technique with the minimal impact on balloon/stent occlusion time but has an intrinsic risk of side branch compromised flow. Otherwise, double stent techniques usually require more stent recrossing and kissing balloon steps to achieve complete revascularization. Among double stent techniques, the NIT appeared the fastest also in the emergent setting, as already suggested,[22] providing complete revascularization of the side branch with less steps than Culotte: this issue could explain the favorable effect of NIT in terms of NOAF occurrence.

Limitations

Our study has obviously several limitations. First, is the retrospective, single-center, and non-randomized fashion of the study. Second, the absence of systematic use of 24 hours Holter monitoring during the follow-up which, without the clinical and/or instrumental suspicion of AF was not performed, as generally done in clinical practice. Third, the impact of different stents used over the study period which has different geometrical and pharmacological properties which may impact the outcomes. Fourth, the different use of IVUS in the different subsets of patients which might contribute to differences in the outcomes. Finally, the retrospective nature of the study did not allow a calculation of the total ischemic time related to balloon-stent inflation, which would be interesting in understanding its relationship with NOAF. Nevertheless, we believe that the size of the patient's sample and the length of the follow-up could overcome part of these intrinsic limitations.

Conclusion

Our study for the first time in literature investigated the occurrence of NOAF in distal LM bifurcation disease treated with PCI, showing that NOAF is not frequent nor after single neither after double stent strategy, resulting in more frequent after double than after single stenting techniques but associated with worse outcomes compared to patients without NOAF occurrence. The understanding of the pathophysiological basis of these results warrants larger randomized studies.

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Informed Consent: Written informed consent was obtained from the patients who participated in this study before the interventional procedure.

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