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Mid-term outcomes after percutaneous interventions in coronary bifurcations

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ABSTRACT

Background: The optimal treatment of patients undergoing percutaneous coronary interventions (PCI) for lesions located at coronary bifurcations is still debated.
Methods: Data on 5036 consecutive patients who underwent PCI on coronary bifurcation at 17 major coronary intervention centers between January 2012 and December 2014 were collected.
Results: Follow-up at a median 18 months (IQR 11-28) was available for 4506 patients (89%). Major Adverse Cardiac Events (MACE) occurred in 395 patients (8.8%): cardiac death in 152 (3.4%), myocardial infarction, excluding periprocedural, in 156 (3.5%) and stent thrombosis in 110 cases (2.4%).
At multivariable Cox regression, left ventricular ejection fraction ≤30% ($P < 0.001$), bail-out stenting (beyond a planned strategy of either single or double stenting) ($P < 0.001$), admission for an acute coronary syndrome ($P < 0.001$), age >66 years ($P < 0.001$), multivessel disease ($P < 0.001$) and diabetes ($P < 0.001$) were independently associated with MACE. Sensitivity analysis identified premature discontinuation of dual antiplatelet therapy (DAPT) ($P < 0.001$) and side branch (SB) lesion length ≥9 mm ($P < 0.05$) as additional independent predictors of MACE.
Conclusions: Beyond traditional risk factors, multivessel disease, the length of the SB lesion, "bail-out" stenting and premature DAPT discontinuation are independent predictors of mid-term MACE after PCI of coronary bifurcations.

Abbreviations: ACS, acute coronary syndrome; BVS, bioresorbable vascular scaffold; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CI, confidence interval; DAPT, dual antiplatelet therapy; DES, drug-eluting stent; FFR, fractional flow reserve; HR, hazard ratio; IQR, interquartile range; IVUS, intravascular ultrasound; LVEF, left ventricular ejection fraction; MACE, major adverse cardiac events; MV, main vessel; OCT, optical coherence tomography; PCI, percutaneous coronary intervention; SB, side branch; SCAD, stable coronary artery disease; TVR, target vessel revascularization.

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This highlights the importance of a carefully planned PCI strategy and adequate therapy adherence to improve the clinical outcomes in these patients.
Clinical trial registration: URL: https://www.clinicaltrials.gov. Unique identifier: NCT01967615.

1. Introduction

Despite the major progress in stent technologies and adjunctive pharmacotherapies, the treatment of bifurcations is still challenging, as it is associated with worse outcomes when compared with non-bifurcation lesions [1]. Although the single stent strategy is associated with a reduced risk of untoward events [2] and is currently recommended, the double stent strategy may be required to guarantee the patency of both the main vessel (MV) and side branch (SB) [3]. In addition, it is unclear whether the clinical outcomes of PCI in bifurcations can be modulated by the choice of adjunctive $P2Y_{12}$ inhibitor, the optimal duration of dual antiplatelet therapy (DAPT), as well as the selection of the stent platform.

To investigate these important unmet clinical needs, we designed the "$P2Y_{12}$ inhibitor utilization in Bifurcation and Chronic Total Occlusion percutaneous coronary intervention with biologically active stents (P2BiTO) registry" (ClinicalTrials.gov Identifier: NCT01967615), in order to identify the major clinical, anatomic and procedural determinants of mid-term clinical outcomes in an all-comer patient population undergoing PCI in bifurcations.

2. Methods

2.1. Study population

The P2BiTO registry was a retrospective multicenter registry in which 17 major catheterization laboratories in Europe and abroad participated, with the endorsement of the EuroBifurcation Club. For the presenty study data were collected on consecutive patients who underwent PCI with drug-eluting stents (DES) on a coronary bifurcation between January 2012 and December 2014.

The "University of Chieti and Pescara Ethical Committee" approved the study, and all eligible patients signed written informed consent.

Inclusion criteria of the study were: [1] patients aged ≥18 years with a diagnosis of stable CAD (SCAD) or acute coronary syndrome (ACS); [2] PCI of a bifurcating lesion (all Medina [4] types) with single or multiple DES at participating centers; and [3] MV diameter ≥ 2.5 mm and SB diameter ≥ 2.0 mm (in order to identify bifurcations supplying a significant myocardial territory).

Exclusion criteria were: (a) patients who refused informed consent or with a life expectancy of ≤12 months; (b) pregnant or nursing mothers; women of child-bearing age will be asked if they are pregnant or think that they may be pregnant; (c) contraindication or suspected intolerance to anticoagulant (heparin, bivalirudin) or oral antiplatelet therapy (aspirin, clopidogrel, prasugrel, ticagrelor); (d) treatment of the bifurcating lesion only with balloon, either plain or drug-coated, and/or with bare metal stents; (e) absence of bifurcation lesion or unwillingness to treat with PCI any of them.

2.2. Coronary intervention technique and concomitant drugs

PCI was performed according to the current standard procedural guidelines. Bifurcations were classified according to the Medina classification [4]; a "true" bifurcation was defined as a lesion in which there was >50% diameter stenosis (DS) in both the MV and SB (Medina 1.1.1/1.0.1/0.1.1). A loading dose of clopidogrel (600 mg), prasugrel (60 mg), or ticagrelor (180 mg) was administered before or immediately after PCI, unless patients were already on chronic maintenance therapy, followed by a maintenance dose of clopidogrel (75 mg od), prasugrel (10 mg od), or ticagrelor (90 mg bid). PCI access site, as well as the choice of stent and the treatment strategy were left to the individual operator's discretion. No limitation was applied for the technique of PCI, for single or multiple DES, e.g. T-stenting (including T-and protrusion), V-stenting, culotte, crush and its modifications [5].

All the participating centers used a dedicated database for bifurcation treatment; therefore, information on the planning, with single or double stenting, and the subsequent actual treatment strategy was systematically recorded. A planned single stenting strategy was defined as the treatment of the bifurcation with one stent either on the MV or the SB, whereas a double stenting strategy was identified when planning to stent both the MV and SB. A "bail-out" stenting was defined when any stent was deployed beyond the planned strategy, after either single or double stenting.

After the procedure, aspirin was continued indefinitely, and the duration of $P2Y_{12}$ inhibitors was at the operator's discretion. Premature DAPT discontinuation was defined as DAPT cessation before 6 month in patients with SCAD, 12 months after an ACS, as recommended by current guidelines [6,7].

Patients' data were entered on a common excel data sheet, and advancement of data collection and analysis were shared among all study participant centers periodically during study progress.

2.3. Clinical follow-up and endpoints

In-hospital outcomes were recorded; all patients discharged alive were followed up with a 30-day visit. Additional information was obtained by clinical visit, further inquiry into medical records or telephone contact, according to a schedule specific for each site.

The primary endpoint of the study was the cumulative occurrence of Major Adverse Cardiac Events (MACE), defined as a composite of cardiac death, nonfatal myocardial infarction (MI) and stent thrombosis during the follow-up; the secondary endpoints were the single occurrence of death, MI, stent thrombosis and target vessel revascularization (TVR). Deaths were considered cardiac unless a definite noncardiac cause could be established. Recurrent MI was defined according to the universal definition [8]; periprocedural MI was not considered among the primary endpoint in our study. Stent thrombosis was assessed as definite/probable according to the Academic Research Consortium criteria [9].

If a patient had more than one event, only the time to first event was considered for the analysis.

Coronary angiography during follow-up was performed only when ischemia-driven; TVR was defined as revascularization with either PCI or coronary artery bypass grafting (CABG) performed on the same coronary vessel treated at the index procedure, within and beyond the target-lesion limits.

2.4. Statistical analysis

Continuous variables are presented and were analyzed according to median values (interquartile range [IQR]), unless predetermined categorical thresholds were already defined, as for Syntax score or left ventricular ejection fraction (LVEF). Results are here presented as hazard ratios (HRs) and 95% confidence intervals (CIs).

Kaplan-Meier method was used to derive the event rates at follow-up and to plot time-to-event curves and the log-rank test was used to identify event predictors by comparing survival distributions. First, the following covariates were screened in univariate models: 1) clinical variables, as age, sex, diabetes mellitus, hypertension, dyslipidemia, smoking, prior MI, CABG, PCI and stroke, LVEF and ACS at presentation; 2) angiographic variables, as left main involvement, in-stent restenosis, presence of calcifications, SB and MV lesion length, presence of Medina "true" bifurcation lesion, multivessel CAD and Syntax score; 3) procedural variables, as the use of bioresorbable vascular scaffolds (BVS), fractional flow reserve (FFR), intravascular imaging with intravascular ultrasound (IVUS) or optical coherence tomography (OCT), type and number of stents implanted, bifurcation treatment strategy with single or double stenting, bail-out stenting, total stent length, final kissing balloon inflation, use of GPIIb/IIIa inhibitors; 4) pharmacological therapy: use and duration of new $P2Y_{12}$ inhibitors - prasugrel or ticagrelor - and DAPT premature discontinuation.

Then, a multivariable Cox's proportional hazards regression analysis was performed to identify independent predictors of events and to estimate adjusted HRs and 95% CIs. Possible predictors were selected among those with $p < 0.10$ by univariate analysis. As a sensitivity analysis, additional multivariable Cox regression models were used to identify independent predictors in the subgroup of patients with quantitative coronary analysis (QCA) and among cases with detailed information on medical treatment during follow-up.

All probability values reported are two-sided, and a probability value <0.05 was considered significant. All data were processed using the Statistical Package for Social Sciences, version 20 (SPSS Inc., Chicago, IL, USA).

3. Results

Out of the 18,652 patients who underwent PCI at the participating centers in the study period, 5036 cases (27%) were treated on a coronary bifurcation; 623 (12%) in-hospital adverse events were reported: cardiac death in 53 cases (1.1%), periprocedural MI in 578 (11%) and stent thrombosis in 50 cases (1.0%).

Follow-up was available in 4506 patients (89%). At 18 months median (IQR 11-28) follow-up, the primary endpoint occurred in 395

patients (8.8%): cardiac death in 152 (3.4%), MI in 156 (3.5%) and stent thrombosis in 110 cases (2.4%). Stent thrombosis was acute in 36 cases, early in 21, late in 31 and very late in 22 patients. TVR was performed in 262 patients (5.8%): PCI in 237 (5.3%), CABG in 25 cases (0.5%).

Distribution of baseline clinical characteristics according to the occurrence of MACE is summarized in Supplement Table 1. Patients who experienced primary endpoint at follow-up were older, with a higher prevalence of diabetes, prior CABG, low (≤30%) LVEF and were more frequently admitted for an ACS (Table 1). Hypertension and prior stroke showed a trend towards an increased risk of the MACE, but were associated with an increased cardiac mortality; a prior MI was associated with a risk for subsequent MI.

Procedural variables and treatment strategies according to the occurrence of the primary endpoint are summarized in Supplement Tables 2. Patients who experienced MACE at follow-up had a higher prevalence of left main disease, more extensive CAD, as reflected by a higher prevalence of calcified lesions and multivessel CAD, longer lesions in the SB, and a higher Syntax score; they more frequently received double stenting, an additional stent in bail-out, a higher total stent length, GPIs during the procedure and more frequently discontinued DAPT prematurely (Table 2). The use of intravascular imaging - either IVUS or OCT - showed only a trend towards a reduced risk of the primary endpoint, but was significantly associated with a reduced cardiac mortality and a reduced risk of TVR. The presence of in-stent restenosis - as compared with de-novo lesions - and the use of BVS - as compared with DES - showed only a trend towards an increased risk of the primary endpoint, but were both significantly associated with an increased risk of TVR.

When analyzing the interaction between clinical presentation and angiographic morphology, ACS was associated with MACE regardless the presence of a "true" Medina lesion ($P < 0.01$, Suppl. Fig. 1A), while when taking into account the SB stenosis length, patients with SCAD and SB lesion <9 mm showed the lowest risk of MACE ($P < 0.01$, Suppl. Fig. 1B).

As for stent strategy, a single "provisional" stent was used in 4284 patients (85.1%), double stenting in 525 cases (10,4%), as planned; deploying a double stent was associated with a 47% higher risk of MACE as compared with a single stent (Suppl. Fig. 2). Beyond planning, an additional stent was deployed as "bail-out" in 227 patients (4.5%), in the setting of a provisional stent strategy in 194 (4.3%), after double stenting in 33 (5.9%, $P < 0.05$) cases. Main reasons for bail-out stenting were dissection of MV or SB in 85 (37%), plaque shift in 93 (41%), unsatisfactory result in 34 (15%) or geographical miss in 15 cases (7%). As for the mid-term outcomes, a bail-out stenting was associated with a much higher risk (2.55 HR, 95% CI 1.55–4.20) of MACE as compared with a planned strategy, regardless a single or a double stent (Fig. 1). While among patients receiving a planned strategy there was a reduced risk of the primary endpoint favoring single as compared with double stenting ($P < 0.02$), placement of an adjunctive stent in bail-out in the setting of a single provisional approach was associated with a higher incidence of MACE than double stenting without any other stent in bail-out ($P < 0.01$, Fig. 1).

The Cox proportional hazard regression analysis documented that LVEF ≤30%, bail-out stenting, ACS at admission, age > 66 and multivessel CAD were independent risk factors for MACE (Table 3). Sensitivity analysis identified as additional independent predictors of MACE side branch (SB) lesion length ≥ 9 mm ($P < 0.05$) among 1142 patients with QCA (Suppl. Table 1) and premature DAPT discontinuation ($P < 0.001$) among 2253 patients with detailed information on medical therapy at follow-up (Suppl. Table 2).

4. Discussion

To date, this is the largest registry enrolling subjects who underwent PCI for a coronary bifurcation lesion; in this series of consecutive patients treated with currently available DES, main findings were as follows:

1. Clinical variables, as age, diabetes, ACS at presentation and reduced LVEF are independent predictors of outcomes.
2. Among angiographic variables, beyond multivessel CAD, the length of SB lesion is independently associated with MACE, being more relevant than the sole SB involvement, as reflected by the Medina classification.
3. Treatment strategy must be carefully selected, as a "bail-out" placement of a stent beyond planning is an independent predictor of adverse events.
4. Adherence to medical treatment after complex PCI is of utmost relevance, as premature discontinuation of DAPT before 6 months in patients with SCAD and 12 months in patients with ACS is independently associated with MACE.

4.1. Clinical variables

Among patients with coronary bifurcation, an ACS at admission identifies a subgroup with a high atherothrombotic burden, accruing a risk for adverse events far more relevant than angiographic complexity as identified by the Medina classification [4]. COBIS II registry findings support our results, documenting that ACS was significantly associated with SB occlusion after MV stenting [10].

Low LVEF is a ubiquitous risk marker associated with death both in patients with and without CAD [11].

Diabetes is a strong predictor of recurrences after DES-PCI, mostly in complex (type B2/C) lesions [12]; a patient-level analysis of the Korean bifurcation pooled cohorts [13] recently documented that diabetes was an independent predictor of target vessel failure, mainly TVR, in the

Table 1
Clinical risk characteristics associated with primary and secondary endpoints.

	MACE HR (95% CI)	Cardiac death HR (95% CI)	MI HR (95% CI)	Stent thrombosis HR (95% CI)	TVR HR (95% CI)
Age > 66 ys	**1.69** (**1.39–2.06**)	**2.30** (**1.67–3.17**)	**1.47** (**1.07–2.02**)	1.05 (0.72–1.54)	0.98 (0.77–1.55)
Sex (M)	0.88 (0.71–1.09)	0.78 (0.55–1.11)	1.09 (0.78–1.53)	1.20 (0.80–1.80)	0.98 (0.75–1.29)
Diabetes	**1.39** (**1.126–1.72**)	**1.55** (**1.01–2.17**)	1.18 (0.84–1.65)	1.09 (0.73–1.62)	0.92 (0.76–1.19)
Hypertension	1.27 (0.98–1.62)	**1.64** (**1.11–2.42**)	1.17 (0.80–1.71)	1.89 (0.96–3.14)	1.57 (0.89–2.09)
Dyslipidemia	0.88 (0.71–1.10)	0.82 (0.58–1.17)	0.98 (0.69–1.39)	0.76 (0.53–1.11)	1.11 (0.84–1.45)
Smoker	1.12 (0.92–1.37)	0.86 (0.62–1.18)	1.20 (0.87–1.64)	1.38 (0.95–2.01)	0.89 (0.71–1.15)
Prior MI	1.22 (0.97–1.54)	1.36 (0.94–1.97)	**1.26** (**0.88–1.81**)	0.64 (0.42–1.00)	0.96 (0.74–1.28)
Prior CABG	**1.90** (**1.24–2.92**)	**2.12** (**1.06–4.23**)	1.26 (0.88–1.81)	1.36 (0.60–3.09)	**1.69** (**1.01–2.84**)
Prior PCI	0.93 (0.75–1.13)	0.73 (0.49–1.05)	0.92 (0.66–1.28)	0.79 (0.53–1.17)	1.12 (0.87–1.43)
Prior stroke	1.38 (0.90–2.11)	**2.07** (**1.02–4.21**)	1.00 (0.52–1.91)	0.99 (0.43–2.29)	0.95 (0.59–1.54)
LVEF ≤30%	**6.14** (**3.22–11.30**)	**11.9** (**4.33–32.74**)	**6.75** (**2.40–18.94**)	2.93 (0.83–10.29)	**2.20** (**1.04–5.09**)
ACS at admission	**1.88** (**1.56–2.32**)	**2.70** (**1.96–3.84**)	**2.12** (**1.53–2.94**)	**2.50** (**1.66–3.59**)	**1.33** (**1.03–1.69**)

MACE = major adverse cardiac events; M = male; MI = myocardial infarction; CABG = coronary artery bypass surgery; PCI = percutaneous coronary intervention; LVEF = left ventricular ejection fraction; ACS = acute coronary syndrome.
HR = hazard ratio; CI = confidence interval; other abbreviations as in previous table; bold characters when $p < 0.05$.

Table 2
Procedural risk variables and treatment strategies associated with primary and secondary endpoints.

	MACE HR (95% CI)	Cardiac death HR (95% CI)	MI HR (95% CI)	Stent thrombosis HR (95% CI)	TVR HR (95% CI)
Left main	**1.47 (1.04–2.07)**	**1.95 (1.12–3.39)**	1.23 (0.73–2.10)	1.28 (0.63–2.56)	**2.44 (1.64–3.63)**
In-stent restenosis (vs de-novo)	1.31 (0.83–2.07)	0.65 (0.31–1.37)	1.51 (0.74–3.07)	1.43 (0.65–3.18)	**1.35 (1.05–1.84)**
Calcifications	**1.64 (1.30–2.06)**	**1.84 (1.27–2.66)**	1.38 (0.96–2.00)	1.41 (0.91–2.20)	**1.32 (1.00–1.78)**
SB lesion length ≥ 9 mm*	**1.75 (1.16–2.73)**	**2.01 (1.05–4.76)**	1.08 (0.52–2.24)	**3.51 (1.27–9.69)**	0.70 (0.49–1.09)
MV lesion length ≥ 17 mm*	1.32 (0.83–2.33)	1.26 (0.70–2.26)	**1.88 (1.01–3.48)**	1.35 (0.65–2.81)	0.64 (0.46–1.04)
Medina "true"	1.17 (0.98–1.42)	1.16 (0.88–1.50)	1.17 (0.83–1.63)	1.14 (0.75–1.75)	0.81 (0.62–1.07)
MVD (vs. SVD)	**1.73 (1.39–2.16)**	**1.72 (1.21–2.49)**	**1.79 (1.28–2.52)**	**2.02 (1.33–3.06)**	2.03 (1.57–2.62)
SYNTAX score (vs. <22):					
22–32	0.78 (0.58–1.04)	0.87 (0.54–1.40)	0.65 (0.40–1.08)	0.72 (0.45–1.15)	0.97 (0.34–2.58)
>32	**2.16 (1.01–4.98)**	**2.38 (1.01–8.20)**	1.78 (0.48–6.62)	1.05 (0.25–4.42)	1.08 (0.77–1.08)
FFR	0.61 (0.33–1.10)	0.45 (0.21–1.08)	0.91 (0.35–2.36)	0.94 (0.24–3.72)	1.07 (0.55–2.23)
IVUS and/or OCT	0.76 (0.54–1.08)	**0.41 (0.23–0.72)**	0.87 (0.50–1.49)	0.73 (0.39–1.36)	**0.48 (0.34–0.67)**
Stent type: BVS (vs. DES)	1.54 (0.75–3.67)	0.77 (0.20–1.85)	2.51 (0.62–10.06)	2.28 (0.41–12.59)	**2.90 (1.05–8.79)**
Planned double stenting (vs. single)	**1.37 (1.02–1.86)**	1.40 (0.85–2.30)	1.03 (0.62–1.70)	1.53 (0.80–2.92)	1.36 (0.90–2.05)
Bail-out stent (vs. planned)	**2.55 (1.55–4.20)**	**2.45 (1.11–5.38)**	**3.45 (1.56–7.63)**	**2.07 (1.07–4.86)**	**1.66 (1.06–2.86)**
Total stent length ≥ 23 mm	**1.26 (1.03–1.55)**	1.36 (0.98–1.88)	1.16 (0.84–1.60)	1.33 (0.97–1.96)	0.77 (0.60–1.08)
Kissing balloon inflation	1.08 (0.87–1.34)	0.88 (0.62–1.44)	0.76 (0.54–1.07)	1.00 (0.67–1.49)	0.90 (0.70–1.26)
GPIs use	**1.70 (1.23–2.33)**	**2.45 (1.47–4.08)**	0.86 (0.53–1.41)	1.40 (0.70–2.81)	1.47(0.92–2.32)
Newer $P2Y_{12}$ inhibitors (vs. clopidogrel)	1.17 (0.88–1.55)	1.01 (0.64–1.60)	1.35 (0.86–2.12)	1.59 (0.77–3.29)	**2.38 (1.55–3.71)**
Premature DAPT discontinuation†	**2.36 (1.51–3.07)**	**4.05 (2.01–10.7)**	**2.71 (1.49–4.95)**	1.89 (0.91–3.93)	1.36 (0.90–2.95)

SB = side branch; MV = main vessel; MVD = multi-vessel disease; SVD = single-vessel disease; BVS = bioresorbable vascular scaffold; DES = drug-eluting stent; GPIs = GP IIb/IIIa inhibitors; DAPT = dual antiplatelet therapy. HR = hazard ratio; CI = confidence interval; other abbreviations as in previous table; bold characters when $p < 0.05$.
* Calculated over 1142 patients.
† Calculated over 2253 patients.

treatment of bifurcations with double stenting. The present results confirm and extend previous findings, documenting that diabetes is an independent predictors of MACE among patients undergoing PCI for coronary bifurcation.

4.2. Treatment strategy

The presence of a coronary bifurcation is one of the main causes for lacking the accomplishment of a complete coronary revascularization in patients with multivessel CAD [14]. In the past, several "adjunctive" technique has been proposed for effective treatment of ostial and bifurcating lesions [15]. The core of the controversy for the treatment of coronary bifurcations has focused mostly during the last decade on the issue whether a single or a double stenting would be the appropriate treatment. Patients who receive two stents have a higher risk of adverse events, although such treatment is often used for a more extensive disease of both branches [2]. The present results identify the length of the lesion in the SB as an independent risk related to adverse events, more than the sole involvement of both MV and SB, the feature that identifies a "true" bifurcation lesion following the Medina classification [4].

The consensus document of the EuroBifurcation Club [5] recommends the provisional single stent technique as the preferred strategy for the majority of bifurcation lesions and recommend stenting of the SB only for the presence of significant SB flow limitation or poor angiographic results in an SB supplying a significant myocardial territory; authors acknowledge that "large SBs with significant extensive disease are likely to require a two-stent strategy. Our findings confirm that double stenting is associated with an increased risk of MACE as compared with single stenting, but the true condition responsible for a heightened risk is the deployment of a stent beyond the planned strategy.

The use of newer $P2Y_{12}$ inhibitors clearly documented a risk reduction of adverse events as compared with clopidogrel among patients with ACS [16,17]. In the present registry prasugrel and ticagrelor were

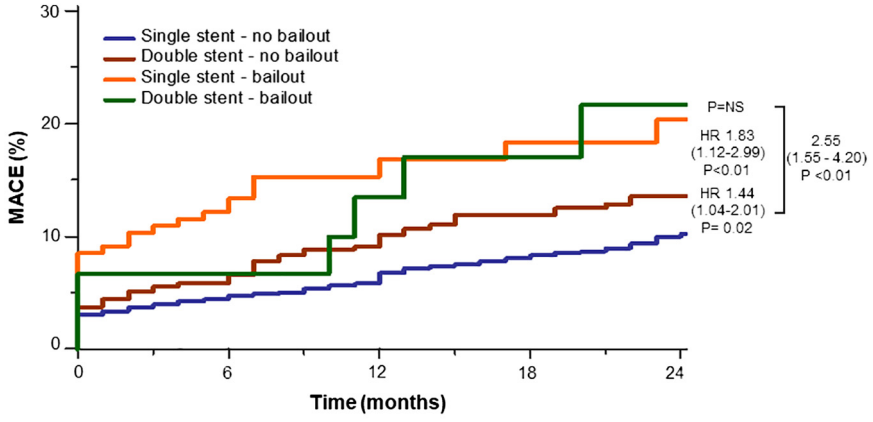

Fig. 1. Cumulative incidence proportion of major adverse cardiac events (MACE) stratified according to stent strategy.

Table 3
Cox proportional hazards regression independent risk factors for MACE.

	HR (95% CI)	*P*
LVEF ≤30%	5.18 (3.77–7.09)	<0.001
Bail-out stenting	2.21 (1.52–3.20)	<0.001
ACS at admission	1.89 (1.51–3.17)	<0.001
Age > 66	1.63 (1.29–2.08)	<0.001
Multivessel CAD	1.58 (1.21–2.04)	<0.001
Diabetes	1.46 (1.16–1.82)	<0.001

HR = hazard ratio; other abbreviations as in previous tables.

scarcely and unevenly available among the 12 countries during the study period (8.2% in 2012, 10% in 2013, 19% in 2014), and, although administered more in ACS (21%) than SCAD patients (8.4%, $P < 0.01$), their use failed to mitigate the risk associated with such clinical presentation.

Discontinuation of DAPT before the period recommended by current guidelines [6,7] was independently associated with adverse events in our real-world registry. PCI of coronary bifurcation is associated with a thrombotic propensity of the target segment; in such complex procedures, the benefit/risk ratio of an extended DAPT has already been documented as favorable, with a magnitude of benefit that is progressively greater per increase in procedural complexity [18].

5. Study limitations

The large sample size of our registry made multivariate analyses for clinical outcomes possible; however, some limitations should be considered when interpreting the results of the present study.

The main limitations of this study were the retrospective, observational design and the lack of a control cohort of patients with lesions not involving a bifurcation. As for any observational study, causal relationships between clinical and procedural features and treatment strategies with outcomes cannot be inferred. Coronary bifurcations were included based on the treating physician's judgement on relevant side branch, and this could result in a selection bias.

Being the study performed on a voluntary basis and no fee provided, no core lab was available and QCA was locally performed only in 23% of cases. Moreover, information on medication at follow-up was only available in almost half of the population (2253 patients, 50%).

Given the fact that telephone calls were only made every 6 months, recall bias leading to a reduced number of events reported cannot be excluded. Furthermore, the limited follow-up period might have prevented us from unveiling further factors associated with adverse events.

We believe that our findings apply most directly to the "real world" clinical practice setting from which they were derived. However, even with careful risk adjustment, such results cannot be easily generalized, as it is likely that therapeutic strategies applied in our unselected population reflect a complex decision process integrating multiple factors.

6. Conclusions

In patients undergoing PCI of a coronary bifurcation with currently available drug and stent technology, clinical variables, such as older age, diabetes, clinical presentation with an ACS and reduced LVEF are independent predictors of mid-term adverse events. Among procedural and treatment variables, multivessel CAD, length of the SB lesion, "bail-out" stenting beyond planning and premature discontinuation of DAPT before 6 months in patients with SCAD and 12 months in patients with ACS are independent predictors of untoward outcome.

These findings highlight the importance of a carefully planned PCI strategy in coronary bifurcations and advocate a strict adherence to medications with a close clinical follow-up.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

Disclosures

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Appendix A. Supplementary data

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