International Journal of Cardiology 254 (2018) 53–58

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Comparison of mid-term clinical outcomes after treatment of ostial right coronary artery lesions with early and new generation drug-eluting stents: Insights from an international multicenter registry

Satoru Mitomo [a,b,1], Richard J. Jabbour [a,b,c,1], Yusuke Watanabe [d], Antonio Mangieri [a,b], Marco Ancona [a,b], Damiano Regazzoli [a,b], Akihito Tanaka [a,b], Akihiro Nakajima [d], Toru Naganuma [d], Francesco Giannini [a,b], Azeem Latib [a,b], Sunao Nakamura [d], Antonio Colombo [a,b,*]

[a] Unit of Cardiovascular Interventions, IRCCS San Raffaele Scientific Institute, Milan, Italy
[b] Vita-Salute San Raffaele University, Milan, Italy
[c] Department of Cardiology, Imperial College London, United Kingdom
[d] Department of Cardiology, New Tokyo Hospital, Chiba, Japan

ARTICLE INFO

Article history:
Received 9 July 2017
Received in revised form 4 October 2017
Accepted 17 October 2017

Keywords:
Right coronary artery aosto-ostial lesion
Percutaneous coronary intervention
Drug-eluting stent

ABSTRACT

Background: There are only a limited number of studies comparing clinical outcomes after treatment of right coronary artery (RCA) aorto-ostial (AO) lesions with early (E-) and new (N-) generation drug-eluting stents (DES).
Methods: From January 2005 to December 2013, 334 de novo RCA AO lesions treated with DES (E-:142 lesions, N-:192 lesions) at 2 high-volume centers (Italy and Japan) were included in this study. The primary endpoint was target lesion failure (TLF) defined as composite of cardiac mortality, target vessel myocardial infarction, and target lesion revascularization (TLR).
Results: Baseline and lesion characteristics were well balanced between the 2 groups. The size of the stents deployed (3.35 ± 0.37 mm vs 3.39 ± 0.33 mm, p = 0.29) and non-compliant balloons used for post-dilatation (3.55 ± 0.38 mm vs 3.62 ± 0.47 mm, p = 0.21) were similar between the two groups.
The median follow-up period was 1432 (IQR: 703-2197) days in total population. The cumulative rate of TLF at 3 years was significantly higher in E-DES group when compared with N-DES group (37.7% vs 14.2%, p < 0.001), which was mainly driven by TLR (38.0% vs 11.0%, p < 0.001). Multivariable analysis revealed that N-DES [HR 0.22 (0.13–0.38), p < 0.001], stent underexpansion [HR 10.59 (6.23–17.97), p < 0.001], excessive aortic stent protrusion [HR 3.12 (1.87–5.23), p < 0.001], and proximal stent overlap [HR 1.74 (1.03–2.95), p = 0.03] were independent predictors of TLF.
Conclusion: For the treatment of RCA AO lesions, N-DES were associated with a lower incidence of TLF at 3 years when compared with E-DES. N-DES use and suboptimal implantation characteristics were independent predictors of TLF.

1. Introduction

Percutaneous coronary interventions (PCI) with drug eluting stents (DES) are now commonly performed in many types of complex lesions [1,2]. Aorto-ostial (AO) lesions remain one of the most challenging lesions for PCI. Specifically, right coronary artery (RCA) AO lesions are associated with target lesion revascularization (TLR) rates up to 10 times higher than AO lesions of the left main trunk [3], indicating that specific additional factors are responsible for poor outcomes. Histologically, rigid elastic tissue, calcifications and a specific muscle bundle make appropriate lesion preparation and stent expansion difficult while increasing the chance of stent recoil [4–6]. Anatomically, the angle between the RCA and aorta makes visualization of the precise location difficult when using angiography alone [7]. While it has been reported that 1st generation DES are associated with lower rates of TLR when compared with bare metal stent (BMS) implantation or balloon angioplasty [8–10], data regarding new generation (N-) DES are limited [11,12]. Accordingly, the aim of this study was to evaluate mid-term clinical outcomes after treatment of RCA AO lesions with early generation (E-) and N-DES from an international multicenter registry.

2. Methods

2.1. Study population and procedural details

From January 2005 to December 2013, a total of 4395 PCIs for proximal RCA were performed at 2 high-volume centers (San Raffaele Scientific Institute, Milan, Italy, and

* Corresponding author at: Unit of Cardiovascular Interventions, IRCCS San Raffaele Scientific Institute, via Olgettina 60, 20132 Milan, Italy.
E-mail address: info@emocolumbus.it (A. Colombo).
[1] Drs Mitomo and Jabbour contributed equally and are joint first authors.

https://doi.org/10.1016/j.ijcard.2017.10.066
0167-5273/

New Tokyo Hospital, Chiba, Japan). Of them, 334 patients with de novo AO lesion treated with DES were enrolled in this registry after excluding patients without AO lesion (3265 cases) or follow-up (512 cases), and those treated with balloon angioplasty alone or BMS (237 cases). Patients with incomplete AO lesion coverage with DES were also excluded (47 cases) (Supplemental fig. 1). An AO lesion was defined as a lesion located within 3 mm from the aortic orifice. Patients were divided into two groups, depending on whether E-DES or N-DES were implanted. E-DES included Cypher (Cordis/Johnson & Johnson, New Brunswick, USA), Taxus (Boston Scientific, Natick, MA, USA), and Endeavor (Medtronic CardioVascular, Santa Rosa, CA, USA). N-DES predominantly included Xience (Abbott Vascular, Redwood City, CA, USA), Promus (Boston Scientific, Natick, MA, USA), and Nobori (TERUMO Corp, Tokyo, Japan). The PCI strategy was dependent on the operator's discretion.

2.2. Definitions of angiographic findings regarding lesion and procedure

Regarding anatomical characteristics of the AO lesion, take-off angle, atypical origin location and the presence of a "funnel-shaped" ostium were evaluated. Atypical location of the origin was defined as requiring different projections from the usual left anterior oblique view to adequately visualize the AO lesion. The take-off angle was measured by quantitative coronary angiography analysis using CAAS software ver.7.2 (Pie Medical Imaging, Maastricht, the Netherlands; the methodological details are shown in Supplemental fig. 2A). Based on angiographic findings, AO lesions were classified as focal, diffuse or chronic total occlusion (CTO). Lesions were defined as focal if length <10 mm or diffuse if >10 mm. A CTO was defined as a completely occluded vessel with Thrombolysis In Myocardial Infarction flow grade 0 through the affected segment with estimated duration >3 months (Supplemental fig. 2B–D). Calcification of the AO lesion was evaluated by fluoroscopy and severity was stratified as mild, or moderate to severe. Moderate to severe calcification was defined as radiopacities noted with or without cardiac motion before contrast injection, compromising both sides of the arterial lumen, while mild was defined as cases with less calcification [13]. The presence of aortic orifice calcification was also evaluated angiographically. According to final angiography after DES implantation, implantation characteristics including stent underexpansion, excessive aortic stent protrusion, and stent overlap within 10 mm from aortic orifice were evaluated. Stent underexpansion was defined as the presence of an obvious stent indentation and excessive stent protrusion was defined as a presence of whole circumference of stent's proximal edge protruded into aorta, which could be recognized angiographically from different projections (Supplemental fig. 2E–G). Angiographic review was performed by well-experienced cardiologists who were independent from the procedure.

2.3. Study endpoints and clinical follow-up

The primary endpoint was target lesion failure (TLF) defined as composite of cardiac mortality, target vessel myocardial infarction (MI), and target lesion revascularization (TLR). Secondary endpoints including all-cause mortality and stent thrombosis (ST) were also investigated. TLR was defined as repeat revascularization for the site where DES were implanted or in the adjacent 5 mm. MI was defined as a creatinine kinase elevation >3 times the upper limit of normal accompanied by an increase in troponin level >5 times upper limit of normal at the time of follow-up [14]. ST was defined according to Academic Research Consortium definitions for definite of probable stent thrombosis [15]. Clinical follow-up was performed on all subjects by either clinic visits or telephone interview. Follow-up angiography was performed either by physician's request or due to development of cardiac symptoms or suspected ischemia warranting repeat angiography. All patients provided written informed consent regarding both the procedure and subsequent data collection and analysis. The relevant review boards in each institute approved the study protocol.

2.4. Statistical analysis

Categorical variables are presented as frequencies and analyzed using the chi-squared test or Fisher exact tests as appropriate. Continuous variables are presented as mean ± standard deviation (SD) or median with interquartile range (IQR) and compared using the Student-t or Wilcoxon rank-sum where applicable. Cumulative incidence rates during follow-up period were estimated using Kaplan-Meier method, which were compared by Log rank test. To identify the predictors for TLF, multivariable analysis using Cox-regression analysis was performed. Covariates that were clinically significant or statistically relevant after univariate analysis ($p < 0.1$) were included in the final model. To avoid overfitting, the number of variables entered into the final multivariable model was limited to a maximum of 1 for every 8 events. A p value < 0.05 was considered as statistically significant. Statistical analyses were performed using SPSS version 22.0 (IBM Inc., Chicago, IL).

3. Results

3.1. Study population and baseline characteristics

We enrolled 334 patients for the study. Of them, 142 patients (42.8%) were treated with E-DES, and 192 patients (57.2%) with N-DES. Baseline characteristics were well balanced between the 2 groups except for age, with older people receiving N-DES (67.8 ± 10.8 in E-DES vs 70.5 ± 10.1 in N-DES, $p = 0.02$) (Table 1). Regarding comorbidities known to be associated with a poor outcome, there were no statistically significant differences between the 2 groups in the prevalence of diabetes mellitus (31.7% vs 36.5%, $p = 0.42$), chronic kidney disease (estimated glomerular filtration ratio <60 ml/mg/1.72 m^2) (42.5% vs 50.5%, $p = 0.19$), or baseline left ventricular ejection fraction (56.5 ± 10.0% vs 54.6 ± 10.7%, $p = 0.11$).

3.2. Lesion characteristics

Regarding anatomical characteristics, the prevalence of funnel-shaped ostium and atypical location of the origin were similarly observed in both groups (67.6% vs 72.9%, $p = 0.24$, and 18.5% vs 15.2%, $p = 0.17$, respectively). Except for one case with high take-off, all cases were of anterior origin and there were no cases with a congenital anomaly. The take-off angle was also similar in both groups (−3.22 ± 11.1°vs −1.01 ± 10.9°, $p = 0.19$). Regarding types of lesion, there were no differences between the two groups (focal/diffuse/CTO $p = 0.42$). The presence of calcification was more likely to be detected in the N-DES group (40.1% vs 55.5%, $p < 0.01$); however, severities were similar in both groups (mild: 64.9% vs 65.4%, $p = 0.36$, moderate-severe: 35.1% vs 34.6%, $p = 0.45$) (Table 1).

3.3. Procedure characteristics

Procedural characteristics are summarized in Table 1. The rate of predilatation was similar in both groups (69.7% vs 74.3%, $p = 0.53$). Cutting/scoring balloons (2.1% vs 2.1%, $p = 1.00$), and rotational atherectomy (2.1% vs 2.6%, $p = 1.00$) were used in a small number of patients in both groups. There were no differences regarding stent diameter (3.35 ± 0.37 mm vs 3.39 ± 0.33, $p = 0.29$) and length (19.94 ± 9.36 mm vs 20.86 ± 8.99 mm, $p = 0.51$) between 2 groups. In the E-DES group, Cypher (47.9%) was used most commonly, followed by Endeavor (34.5%), Taxus (17.6%). In the N-DES group, Xience/Promus (71.3%) and Nobori (10.4%) were predominantly implanted. Postdilatation was more frequently performed in the N-DES group (69.8% vs 59.9%, $p = 0.04$), but the size of non-compliant balloons (3.55 ± 0.38 mm vs 3.62 ± 0.47 mm, $p = 0.21$) and inflation pressures (20.7 ± 5.1 atm vs 20.8 ± 4.7 atm, $p = 0.92$) were similar between the 2 groups. There were similar rates of underexpansion (34.5% vs 29.2%, $p = 0.34$), excessive aortic stent protrusion (44.4% vs 36.5%, $p = 0.18$), and proximal stent overlap (21.1% vs 21.4%, $p = 0.37$) in both groups.

3.4. Clinical outcomes

3.4.1. E-DES vs N-DES

The median follow-up period was 2205 (IQR: 1144-2878) days in the E-DES group and 1039 (IQR: 451-1654) days in the N-DES group. According to the follow-up period in the N-DES group, clinical outcomes were evaluated at 3 years. The cumulative rates of TLF at 3 years were significantly lower in the N-DES group (14.2% vs 37.7%, $p < 0.001$), which was predominantly driven by a lower rate of TLR (11.0% vs 38.0%, $p < 0.001$) (Fig. 1). The rate of cardiac mortality was low, occurring in 1 patient in the E-DES (0.9%) and 2 patients in N-DES (1.3%) group, of which, all them were due to heart failure. One target vessel MI at the distal non-stented lesion occurred 7 days after implantation in the N-DES group, which was successfully treated and the patient survived. There were no incidences of definite or probable ST (Supplemental table 1).

3.5. Multivariable analysis to identify the independent predictors of TLF

In the total population, multivariable analysis using Cox-regression analysis demonstrated that N-DES use (HR 0.22, 95% CI: 0.13–0.38; $p < 0.001$), stent underexpansion (HR 10.59, 95% CI: 6.23–17.97; $p < 0.001$), excessive aortic stent protrusion (HR 3.12, 95% CI: 1.87–5.23; $p <$