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Impact of structural features of very thin stents implanted in unprotected left main or coronary bifurcations on clinical outcomes

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Impact of metal to artery ratio on clinical outcomes in LM and non-LM bifurcation: insights the RAIN-CARDIOGROUP VII study (veRy thin stents for patients with left mAIn or bifurcationN in real life)

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Word Count

Table n. 4

Figure n. 2

Key words

ABSTRACT.

Introduction. The impact on clinical outcomes of the metal coverage on the coronary surface (namely metal-to-artery ratio) of currently used Drug Eluting Stents (DESs) has not been defined.

Methods. All patients with a LM (Left Main) or bifurcation stenosis treated with PCI using ultrathin stents (struts thinner than 81 μm) were enrolled. The rate of DOE (Device oriented endpoint, defined as a composite of target lesion revascularization and stent thrombosis) was the primary endpoint, while its single components the secondary ones, evaluated according to metal-to-artery ratio.

Results. 62 (7.5%) of 830 patients undergoing PCI on LM experienced a DOE without differences in metal-to-artery ratio (14.5 ± 2.1 vs 14.4 ± 1.9 , $p=0.51$). 50 (2.4%) of 2082 patients treated with PCI on a coronary bifurcation other than LM experienced a DOE, with a higher mean metal-to-artery ratio (15.3 ± 2.1 vs 14.6 ± 2 , $p=0.01$). At multivariate analysis, together with hypertension and diabetes, metal-to-artery ratio was an independent predictor of DOE (HR1.7:1.02-1.34, $p=0.02$). When analysed for diameter, we found a significant correlation with DOE when diameter was between 3.0 and 3.25 mm (HR 1.24:1.03-1.48, $p=0.02$) or inferior to 3.0 mm (HR 1.21: 1.06-1.38, $p<0.01$, all CI 95%). Finally, a metal-to-artery ratio >15 predicted TLR in non ULM patients.

Conclusion. Metal-to-artery ratio does not impact on outcomes in LM PCI and when a drug eluting stent > 3.5 mm is implanted. Regarding non-LM PCI, it is independently related to DOE and TLR; especially for DES with a diameter ≤ 3.25 mm.

INTRODUCTION.

PCI (Percutaneous Coronary Intervention) in the last years has been largely exploited to treat high risk patients and coronary anatomies, due to satisfactory results at mid term follow up largely related to technological improvement (1-3).

From a general point of view, evolution of the stent platform, including thinner stent struts and new metal compounds associated with the utilization of drug-eluting stents (DESs) coated with anti-proliferative agents and polymers reduced the restenosis and thrombosis rates (4-6). However, when analyzing each single component of DESs (Drug Eluting Stents), only few features have been related to improved clinical outcomes. Regarding antiproliferative drugs, the recent Bioresort trial (7) did not show significant differences between everolimus and sirolimus. Regarding biodegradable (BP) vs. permanent polymer (PP), contrasting evidence has been provided: the Bioresort trial did not show differences between BP and PP, while the recent Bioflow showed a reduction of TLR with BP (8). Finally, a reduced thickness of struts has been demonstrated to reduce TLR (Target Lesion Revascularization) and ST (Stent Thrombosis) irrespectively from kind of polymer (9).

Another geometrical parameter is represented by metal to artery ratio (that is the ratio between the endoluminal vessel surface and the stent struts surface) (10). In first generation stents a lower ratio was associated with higher rates of radial and longitudinal recoil and a reduced radial expansion at the extremities of the stent with respect to the mid-section of the stent. From the other side, elevated values may increase shear stress with a close relationship with restenosis and thrombosis (11). However, to the best of our knowledge, no data have been provided about the impact of

metal coverage on the coronary surface on clinical outcomes according to different vessels diameters treated with ultrathin stents.

METHODS.

This is a prospective multicenter study (see **Appendix for enrolling sites**, NCT03622203) including patients from June 2015 to January 2017.

Inclusion criteria

All consecutive patients presenting with a critical ULM lesion of a critical stenosis of a coronary bifurcation in our Centers treated with any of the following stents, were included:

- Platinum-chromium coated with a durable polymer loading everolimus with strut thickness of 81 μm for diameters 2.25-3.5 mm (Promus Element, Boston Scientific);
- Cobalt-chromium coated with a durable polymer loading everolimus with a strut thickness of 80 μm (Xience Alpine, Abbot);
- Cobalt-chromium coated with a biodegradable polymer loading sirolimus with strut thickness of 80 μm ; (Ultimaster, Terumo Corporation);
- Platinum-chromium coated with a biodegradable polymer loading everolimus with strut thickness of 74 μm for diameters 2.25-2.75 mm, 79 μm for diameters 3.00-3.50 mm, and 81 μm for the diameter of 4.0-4.5 mm; (Synergy, Boston Scientific);
- Platinum-chromium coated with a durable polymer loading zotarolimus with a strut thickness of 74 μm for diameters ≤ 2.5 mm, 79 μm for diameters 3.0-3.50 mm, and 81 μm for diameter equal to 4.0-4.5 mm (Resolute Onyx, Medtronic).

Baseline and procedural data.

Data were derived from electronic patient records at each center and recorded online (<http://www.cardiogroup.org/RAIN/index.php?cat=home>). Cardiovascular risk factors, clinical presentation, angiographic features, use of IntraVascular UltraSound (IVUS), Optical Coherence Tomography (OCT) and Fractional Flow Reserve (FFR) was recorded, along with the characteristics of the implanted stents. IVUS or OCT was used prior to stent implantation to assess the severity of the stenosis and side branch involvement, and post stent implantation to evaluate dissection and the requirement for stent optimisation. The decision to use post-dilatation, FKB, intracoronary imaging and choice of stent technique (provisional versus 2-stent), was at the discretion of the treating physician.

“Metal-to-Artery Ratio” was defined as the ratio between the endoluminal vessel surface and the stent struts surface. Data were derived according the final stent diameter after the post dilatation, the ratio for different stent kind were provided by the Boston Scientific, Abbot, Terumo and Medtronic and resulted from bench test (see Web Appendix Table).

Follow up data was obtained from clinical assessment, telephonic consultations and/or via primary care physicians.

Endpoints.

The rate of DOE (Device oriented endpoint, defined as a composite of target lesion revascularization and stent thrombosis) was the primary endpoint. The analysis was performed according to LM and non-LM PCI.

Statistical Analysis

Categorical variables are reported as count and percentages, whereas continuous variables as mean and standard deviations or interquartile range (IQR). Gaussian or not Gaussian distribution was evaluated by Kolmogorov-Smirnoff test. The t-test has been used to assess differences between parametric continuous variables, Man-Whitney U test for non-parametric variables, the chi-square test for categorical variables and Fisher exact test for 2x2 tables. Analysis was done for all baseline features that differed between patients with DOE and without DOE in LM and non-LM groups. Further, multiple logistic regression analysis was performed the independent predictors of DOE and of TLR, along with survival analysis. All statistical analyses were performed with SPSS 21 and differences were considered significant at $\alpha=0.05$.

RESULTS.

LM PCI group.

830 patients underwent LM PCI and among them after XXXX 62 (7.5%) experienced DOE. No differences were reported about mean age (70.8 ± 10.7 vs 70.8 ± 9.1 years old $p=0.99$) and cardiovascular risk factors, except for an higher prevalence of current smokers in DOE patients (24.6% vs 13.6%, $p=0.03$, **see Table n. 1**). Regarding procedural features, these patients were treated more often with a 2 stent strategy for bifurcations (44.6% vs 21.8%, $p<0.01$), without differences for implanted stents (permanent vs. reabsorbable polymer 29% vs 28.2%, $p=0.88$): Values of metal-to-artery ratio (14.5 ± 2.1 vs 14.4 ± 1.9 , $p=0.51$, **see Table n. 2**) did not differ between patients experiencing a device oriented event.

non-LM PCI group.

2082 patients underwent non-LM PCI and after XXX months 50 (2.4%) experienced DOE. Baseline features were similar between patients with and without events regarding mean age (65.8 ± 9.1 vs 67.8 ± 11.3 years old $p=0.2$), gender (female gender 24% vs 24.6%, $p=1$) and clinical presentation. However, patients with DOE were more frequently hypertensive (92% vs 73.9%, $p<0.01$) and with non-ID diabetes mellitus (42% vs 25.6%, $p=0.01$, **see Table n. 3**).

Among procedural features, a 2 stent strategy was chosen more often for DOE patients (25.5% vs 13.4%, $p=0.05$). While there were no differences in terms of polymer (permanent vs. re-absorbable: 28% vs 31%, $p=0.64$), patients with DOE had a higher mean metal-to-artery ratio (15.3 ± 2.1 vs 14.6 ± 2 , $p=0.01$, **see Table n. 2**).

This result was confirmed at multivariate analysis, in which, together with hypertension and diabetes, metal-to-artery ratio was an independent predictor of DOE (HR1.7, CI95% 1.02-1.34, p 0.02, **see Figure n. 1**). Further, metal-to-artery ratio when analysed according the stent diameter was found to correlate significantly with DOE when DES diameter was between 3.0 and 3.25 mm (HR 1.24, CI95% 1.03-1.48, p=0.02) or inferior to 3.0 mm (HR 1.21, CI95% 1.06-1.38, p<0.01, **see Figure n. 2**). Moreover, risk of TLR was increased for patients treated on ULM with stents with a metal-to-artery-ratio>15, as confirmed at survival analysis (**see figures number 2,4 and appendix, web only tables 1,2**)

DISCUSSION.

Our main findings may be summarised as follows:

- Metal-to-artery ratio does not impact on outcomes in LM PCI, and generally when a drug eluting stent > 3.5 mm is implanted;
- On the other side, it is an independent predictor of restenosis in in non-LM PCI, especially when drug eluting stent \leq 3.25 mm was used.

The narrowing in the lumen of an expanded stent (which can be clinically translate into restenosis or stent thrombosis) is one of the major complication associated with endovascular stent implantation (12,13). It is believed to be caused by inadequate metallic surface area, together with clinical and procedural features. Recently, Palmerini et al. demonstrated that the thickness and the geometry of the stents are crucial elements for the modulation of thrombogenicity: clinically this translated into a reduction of thrombosis rate in the second generation DES due to their structural features. (14). Stent structure and configuration appear to play a crucial role in determining its short and long-term outcomes. The greater the amount of metal in relation to the vessel, the greater the risk of thrombosis and restenosis. On the other hand, an amount of metal platform may lead to mechanical problems. In particular vascular injury and foreign body reaction are important mechanisms by which stent implantation can provoke neointimal hyperplasia and impose focal, deep vascular trauma (15;16)

Indeed 30-35% of all percutaneous coronary interventions involve small-diameter vessels of less than 3 mm (17). Stents deployed in small arteries have a higher metal-to-artery ratio; this may increase the risk of sub-acute thrombosis or restenosis. Various

studies have shown that stent design, stent coating, and stent strut thickness may all influence event-free survival (18,19).

In our real life multicenter study, strut thickness appears to be an independent predictor of restenosis after stent implantation in vessels with a reference diameter < 3.0 mm (20). probably due to a relative high metal/vessel ratio when a stent is implanted in a small vessel. A low minimum lumen diameter immediately after percutaneous transluminal angioplasty and a high metal density are proposed mechanisms of unfavorable outcome after stent implantation. (21,22) In a recent meta-analysis Bangalore et al. demonstrate how thinner struts were associated with a 16% reduction in target lesion failure explain by a minor turbulence and areas of low shear, reduced arterial injury and a faster endothelization. Moreover thinner struts afford greater flexibility and deliverability (23)

Despite this knowledge, little is known about the impact of the metal-to-artery ratio in the bifurcation vessels. The impact of the amount of metal in relation to vessel size in a complex condition such as bifurcation lesions is not yet fully understood.

In the group with large diameter (> 3.5mm) and LMCA the metal to artery ratio does not seem to impact on DOE. Patients with DOE underwent more often to 2 stent strategy for LM bifurcations and there were not differences in metal-to-artery ratio probably because the impact of one or more foreign bodies in a large-caliber vessel like the LMCA is less relevant and maybe the complexity of the lesion mask and override the differences generated by a higher metal-to artery ratio.

Further, this could probably be explained by the generally lower ratio due to the deployment in bigger vessel and the more aggressive post-dilatations. Several studies evaluated the impact of stent over expansion capacity and some doubt are raised about the safety when the device is oversized, due to the structure distortion and the reduction of

radial force (24). However, by our data this does not translate in worse clinical outcome, despite a reduced vessel coverage a good stent apposition maintains a key role also in big vessel PCI.

On the other side, in our study the favourable effect of low metal to artery ratio was clinically apparent only in non LM-PCI, in particular in vessels with a reference diameter inferior to 3,25 mm. Several reason could be found, contrary to LM-PCI, smaller vessels determine necessary higher metal coverage with higher inflammatory response, a less accurate vessel sizing due to lower use rate of imaging. Indeed, as for LM PCI, strategies with multiple balloon inflation were related to reduced risk of acute stent recoil, the number of stent delivery balloon inflations has been associated with the reduction of acute stent recoil (25). Other explanation for this result is that patients with DOE underwent more often to 2 stent strategy and had a higher mean metal-to-artery ratio that remains a significant predictor at the multivariate analysis. Considering, how in the smaller vessels the benefit of a low metal-to-artery ratio may not override the small residual lumen. It is well known how small artery size itself is an independent risk factor for restenosis and MACE after stent implantation. (22;26)

Limitations.

There are many limitations to this study. First, it is not a randomized controlled trial, therefore the ability to differentiate between stent platforms is limited. Second, a main limit in the evaluation of the clinical impact of metal-to-artery ratio are that multiple factors appear to be implicated in DES acute thrombogenicity and long-term vascular healing. These factors include platform material and stent strut thickness as well as polymer biocompatibility, composition, distribution, and, in the case of bioresorbable polymers,

duration of bioresorption. It is difficult to assess the different contribution of all these confounding factors in a single study. Finally, although designed as an all comers study, only 23% of patients undergoing percutaneous interventions were enrolled in the study, so selection bias cannot be ruled out.

Conclusion

Metal-to-artery ratio seems not to impact of outcomes in LM PCI, and generally when a drug eluting stent > 3.5 mm is implanted. On the other side, it seems to be an independent predictor in in non-LM PCI, especially when drug eluting stent \leq 3.25 mm was used.

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