Randomized Comparison of XiEnce-V and Multi-link VisioN Coronary Stents in the same multivessel Patient with Chronic kidney disease (RENAL-DES) Study

Running title: Tomai et al.; RENAL-DES Study

Fabrizio Tomai, MD, FACC, FESC; Flavio Ribichini, MD; Leonardo De Luca, MD, FACC, PhD; Alessandro Petrolini, MD; Anna S. Ghini, MD, PhD; Luca Weltert, MD; Carmen Spaccarotella, MD; Igino Proietti, MD; Carlo Trani, MD; Francesco Nudi, MD; Michele Pighi, MD; Corrado Vassanelli, MD, FESC

1Dept of Cardiovascular Sciences, European Hospital, Rome; 2Division of Cardiology of the Dept of Medicine, University of Verona, Verona; 3Institute of Cardiology, University Magna Grecia, Catanzaro; 4Dept of Cardiology, Vannini Hospital, Rome; 5Institute of Cardiology, Cattolica University, Rome; 6Division of Nuclear Medicine, Madonna della Fiducia Clinic, Rome, Italy

Address for Correspondence:
Fabrizio Tomai, MD
Department of Cardiovascular Sciences, Division of Cardiology
European Hospital
Via Portuense 700
00149 Rome, Italy
Tel: +39-06-65975725
Fax: +39-06-65975724
E-mail: f.tomai@tiscali.it

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Abstract

**Background**—Percutaneous coronary interventions (PCI) in patients with chronic kidney disease (CKD) have shown suboptimal results. Drug-eluting stents (DES) might reduce the rate of target vessel revascularization compared to bare metal stent (BMS) in CKD patients. However, given the multiple concomitant individual variables present in such patients, the comparison of neointimal growth after PCI is complex and difficult to assess.

**Methods and Results**—RENAL-DES was a prospective, randomized, multicenter study to directly compare the efficacy in the prevention of clinical restenosis of everolimus-eluting stent (Xience-V) and BMS with identical design (Multi-link Vision), both implanted in the same patient with multivessel coronary artery disease and CKD (estimated glomerular filtration rate <60ml/min). The primary endpoint of the study was the ischemia-driven target vessel revascularization (ID-TVR) as detected with myocardial scintigraphy at 12 months. In 215 patients, 512 coronary vessels were successfully treated with the randomly assigned DES (n=257) or BMS (n=255). At 1 year, the rate of ID-TVR for DES and BMS groups was 2.7% [95% confidence interval (CI): 1.1-5.6%] and 11.4% (95% CI: 7.8-16%) respectively, p<0.001. For the multivariate analysis, independent predictors of the ID-TVR were BMS implantation (OR: 4.95;95% CI:2.1-11.6; p<0.001) and vessel size (OR: 0.32;95% CI:0.1-0.7; p=0.006).

**Conclusions**—This is the first randomized trial showing a reduction of clinical restenosis with a new generation DES compared to the BMS of equal design, in CKD patients with multivessel coronary artery disease.

**Clinical Trial Registration Information**—www.clinicaltrials.gov. Identifier: NCT00818792.

**Key words:** percutaneous coronary intervention, chronic kidney disease, stent, multivessel coronary artery disease
Introduction

Patients with chronic kidney disease (CKD) requiring myocardial revascularization represent a challenging group often affected by multivessel disease and complex coronary lesions.  

Percutaneous coronary intervention (PCI) in patients with CKD has shown suboptimal results compared to surgery, especially in patients without need for permanent dialysis. 2-7 Post-hoc analyses from randomized clinical trials, and large registries showed that first-generation drug-eluting stents (DES), compared with bare metal stent (BMS), reduced restenosis rate in patients with CKD. 8,9 Simsek et al 10 reported no superiority of both paclitaxel- and sirolimus-eluting stents over BMS in safety and efficacy end-points in all-comer PCI patients with CKD at long-term follow-up. The lack of dedicated randomized trials comparing new-generation DES and BMS in patients with CKD remains a well known limitation of currently available evidence.

Notably, in patients with CKD, multiple concomitant individual factors, including inflammatory and procoagulant mediators, oxydative stress, comorbidities and medical treatment, may be responsible for neointimal hyperplasia and thrombosis after coronary stenting, thus making difficult the comparison of different therapeutic strategies in different patient groups. 11-13

The RENAL-DES (Randomized comparison of XiEnce-V and Multi-link VisioN coronary stents in the sAme muLtivessel patient with chronic kiDnEy diSease) is a prospective, randomized, multicenter, spontaneous study aimed to directly compare the efficacy of everolimus-eluting stent (Xience-V™, Abbott Vascular Company, IL, USA) and its BMS counterpart with identical design, the Multi-Link Vision™ stent (Abbott Vascular Company, IL, USA), in the prevention of clinical restenosis, both implanted in the same patient with multivessel coronary artery disease and CKD. This study model allows to obviate for the multiple and unpredictable potential baseline differences of this complex population.
Methods

The rationale and study design of the RENAL-DES trial have been reported elsewhere. Briefly, the aim of the study was the comparison of the need for repeated ischemia-driven target vessel revascularization (ID-TVR) of Xience-V or Multi-Link Vision stents in consecutive patients with CKD receiving both types of stents for at least two significant coronary lesions in two major epicardial vessels, by randomizing for coronary vessel (each patient being its own comparator). This intra-individual design has been previously validated in diabetic patients with multivessel coronary artery disease undergoing multiple PCI.\textsuperscript{15}

The study protocol and related materials were approved by the Institutional Review Boards and Ethical Committees of all participating centers. The protocol was attributed the ClinicalTrials.gov ID: NCT 00818792.

Patient selection and procedure for randomization

Between January 2009 and February 2012, all consecutive patients with an estimated glomerular filtration rate (eGFR) < 60 ml/min (assessed with the Cockcroft-Gault formula)\textsuperscript{16} undergoing coronary angiography for symptoms or signs of myocardial ischemia and showing at least two significant coronary lesions amenable to PCI in at least two major epicardial vessels have been considered eligible for enrolment. In the presence of intermediate stenoses without evidence of pre-procedural inducible ischemia a fractional flow reserve (FFR) was performed as previously described\textsuperscript{17} and PCI was physiologically guided in case of FFR \leq 0.80. CKD was defined as moderate (eGFR: 30 to 59 ml/min) and severe and/or kidney failure (eGFR: < 30 ml/min), according to published guidelines.\textsuperscript{18}

The exclusion criteria to enter the study were: 1) age \textless{} 18 or \textgreater{} 85 years, 2) presence of left main coronary artery disease, or other angiographic indication to coronary artery bypass
grafting by consensus of the Heart Team, 3) in-stent restenosis, 4) saphenous vein graft disease, 5) ST-segment elevation myocardial infarction (<3 days), 6) vessel diameter <2.5 or > 4 mm, 7) contraindication to long-term dual antiplatelet therapy, 8) complete functional revascularization not achievable by PCI as defined by others 19, 9) severe valvular heart disease, and 10) childbearing potential.

For the prevention of contrast-induced nephropathy, all patients were treated according to standard protocols 14, as recommended by current guidelines 20 (see online-only Data Supplement).

Patients undergoing diagnostic coronary angiography because of stable or acute coronary syndromes and showing multi-vessel disease were jointly evaluated in each Institution by a heart team, composed by a cardiac surgeon, an interventional, and a clinical cardiologist. The final decision of patient enrolment was made after comprehensive review of all relevant factors, including a nephrology consultation, when appropriated. The informed consent was always obtained after the diagnostic catheterization and before randomization. Current recommendations for ad-hoc, or deferred PCI were applied. 20

After the guide wire had crossed the lesion, patients were randomly assigned to receive Xience-V and Multi-Link Vision with the use of sealed envelopes containing a centralized computer-generated randomization sequence for coronary vessel (left anterior descending or left circumflex or right coronary artery). The same stent (Xience-V or Multi-link Vision) was used for the treatment of multiple lesions in the same vessel (if possible, a single long DES was used, whereas a spot stenting strategy was preferred with BMS). For patients with three-vessel disease requiring implantation of other stents, the type of stent implanted in the remaining vessel was also randomized using the same computer-generated randomization sequence for coronary vessel.
Coronary Angiogram, QCA and PCI procedure

Baseline, post-procedural, and follow-up coronary angiograms were digitally recorded and assessed off-line in a quantitative coronary angiography (QCA) core laboratory (NBR Core Lab, Verona, Italy), using previously validated methodology. All measurements were performed on cineangiograms recorded after the intracoronary administration of nitroglycerin in at least two orthogonal views that demonstrate the target lesion free of foreshortening or vessel overlap.

PCI was performed via a 6F or 7F sheath in the femoral or radial artery, according to standard practice. Procedural success was defined as an angiographic residual diameter stenosis < 20% (visual estimation), without the occurrence of cardiac death, Q-wave or non Q-wave myocardial infarction (MI), or repeat revascularization of the target vessel during the hospital stay. The implantation of multiple overlapping coronary stents was allowed in case of incomplete lesion coverage, and/or endoluminal injury requiring additional stent coverage beyond the margins of the initial stent deployed. In case of stent implantation failure the patient was excluded from the study.

During the procedure, patients received IV boluses of heparin in sufficient doses to prolong the ACT (≥ 250 sec). Periprocedural antithrombotic therapy consisted of aspirin at standard dosages and clopidogrel at a loading dose of 300 mg. The use of platelet glycoprotein IIb/IIIa inhibitors was left to operator’s discretion. Following the procedure, patients continued to receive daily lifelong aspirin plus clopidogrel 75 mg a day for 12 months. In addition, patients received anti-ischemic therapy (beta-blockers, calcium antagonists, and nitrates, alone or in combination); angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers for hypertension, reduced ejection fraction, or secondary prevention; and low-density lipoprotein cholesterol–lowering therapy with statins alone or in combination with ezetimibe to achieve a
target of 60 to 85 mg/dL. After achievement of the low-density lipoprotein target, secondary targets were raising high-density lipoprotein cholesterol >40 mg/dL and lowering triglyceride levels <150 mg/dL with exercise or in combination with extended-release niacin or fibrates. Lifestyle counselling for diet, smoking cessation, glycemic control, and weight loss was also administered, according to current guidelines.23

Follow-up

Following randomization, all patients were subject to complete clinical follow-up. Telephone-based interviews and/or office-based direct visits have been performed at 30 days, and 12 months, respectively, for end-point adjudications. If any event occurred during the study period, full documentation of hospital admission (with any invasive and/or non-invasive procedure results) was provided and evaluated by an independent committee (see appendix). Stress and rest gated thallium 201 (Tl-201) myocardial single photon emission computed tomography (SPECT) was performed between 9 and 12 months after the index procedure unless recurrent ischemic symptoms required earlier repeat coronary angiography. Repeat coronary angiography was performed in case of recurrence of ischemic symptoms and/or evidence of ischemia in at least one of the treated regions at Tl-201 myocardial SPECT (see online-only Supplement Figure).

Myocardial SPECT data were stored electronically at the treatment vessel site and sent to the nuclear core laboratory (Etisan, Rome, Italy) for imaging interpretation by nuclear cardiologists blinded to the site and randomization arm. The degree of myocardial perfusion was assessed in 20 myocardial segments,24 grouped into six regions according to the anatomic distribution of the coronary vascular territories: apical, anterior and septal (left anterior descending), posterior (left circumflex), inferior (right coronary) and lateral, as extension of posterior or inferior regions (circumflex or right coronary territory, respectively). Semi-
quantitative six-region visual interpretation was performed by consensus of two experienced observers using a 5-point scoring system (0, normal; 1, equivocal; 2, moderate; 3, severe reduction in TI-201 uptake; and 4, absence of detectable tracer uptake). The summed stress and rest scores were obtained by adding the scores of the six regions of the respective images. The sum of the differences between each of the six regions from these images was defined as the summed difference score, representing the amount of ischemia. A summed difference score >1 in each region was indicative of ischemia.

Endpoints

The primary endpoint of the study was ID-TVR at 12 months defined as revascularization procedure (repeat PCI or coronary artery bypass surgery) in the target coronary vessel associated with any of the following: a) evidence of ischemia in the treated region at TI-201 myocardial SPECT, b) ischemic symptoms requiring coronary angiography and an angiographic diameter restenosis ≥50% at QCA.

Secondary endpoints of the study were the incidence of cardiac death and PCI-related vessel MI, stent thrombosis (ST), target lesion revascularization (TLR) and TVR at 30 days and 12 months. All deaths were considered cardiac unless an unequivocal non-cardiac cause could be established. Spontaneous MI after the peri-procedural period was defined as either the development of pathologic Q-waves lasting at least 0.4 s in at least two contiguous leads with an elevation of the CK-MB fraction level or, in the absence of pathologic Q waves, an elevation in CK-MB fraction levels to more than three times the URL alone. Target lesion revascularization was defined as repeated revascularization because of a coronary stenosis of at least 50% of the luminal diameter anywhere within the stent or within the 5 mm borders proximal or distal to the stent.
Statistical analysis

The size of the sample was calculated using the McNemar test for comparison of dependent proportions to achieve 80% statistical power at a significance level of 0.05. Calculations were based on previous not-randomized reports of about 20% of clinical restenosis (ID-TVR) at 12 months in patients with CKD treated with BMS implantation, with an expected reduction by DES to 10% and an occurrence of intrapatient multilesion restenosis of 2%. Assuming a 10% drop-out rate, a goal of 213 patients (426 treated vessels) was set. As 20% of the patients would require stent implantation in three vessels, we expected to analyse approximately 500 treated-vessels.

Comparisons of the continuous or discrete variables between stent groups (Xience-V and Multi-link Vision) have been performed using a paired t-test or a McNemar test, respectively. Continuous or discrete variables between patients groups (those treated on 2 or 3 coronary vessels) were compared by unpaired t test or Chi-square test, respectively. To investigate the independent predictors of ID-TVR at 12 months, a regression analysis with a random effect model (using the type of vessel as a random factor) has been performed by mixed model analysis module in the IBM SPSS 20.0 stat package and confirmed by glmer function in R open source stat package. All variables known to be relevant for the study end-point [type of stent, target vessel, lesion location, lesion type, vessel size, stent length, baseline minimal lumen diameter (MLD) and stenosis] were entered into the model. A probability value ≤0.05 (2 tailed) was considered significant. Analysis was performed with IBM SPSS 20.0 software and R open source statistical package. Results are expressed as mean ± standard deviation, unless otherwise specified.
Results

During the study period 415 consecutive patients with CKD met inclusion criteria. Of these, 126 (30.4%) underwent surgical revascularization, 31 (7.5%) were treated with pharmacologic therapy, and 43 (10.4%) presented a coronary anatomy not suitable for complete revascularization by PCI according to a joint evaluation of the Heart Team (Figure 1). The remaining 215 patients (51.8%) were enrolled in the study and randomly assigned to receive both a Xience-V and a Multi-link Vision in different coronary arteries. A total of 512 coronary vessels were successfully treated with stent implantation (2.4±0.4 vessels treated per patient): 257 assigned to Xience-V and the remaining 255 to Multi-link Vision (2.9±1.1 stents per patient).

Clinical characteristics and pharmacological therapy at the time of enrollment are summarized in Table 1. The mean age of the study population was 73 years, a high proportion of patients presented a three-vessel disease (42%), acute coronary syndromes (57%), and diabetes mellitus (44%). The mean eGFR was 46.8 ml/min (range: 7-59 ml/min) and 10% were on dialysis.

The baseline angiographic characteristics of the treated coronary vessels and procedural variables are displayed in Table 2. A total of 628 stents (318 Xience-V and 310 Multi-Link Vision) have been implanted on 607 coronary lesions (306 and 301 treated with DES or BMS, respectively). Lesion type, reference vessel diameter, pre-and post-procedural MLD and diameter stenosis percentage at angiography were similar in both groups. Stent post-dilation, total stent length and number of stents per treated vessel were higher in the DES group, while the rate of direct stenting and final stent diameter were higher in the BMS group (Table 2), according to different procedural strategies usually preferred with DES or BMS implantation. In all patients iopamidol (Iopamiro 370mg/ml, Bracco Imaging Italia s.r.l., Italy) was used as
contrast agent, at a median dose of 215 ml per patient; 5 (2.3%) patients exhibited a renal function deterioration requiring haemodialysis during hospitalization.

Twenty patients (9.3%) underwent coronary angiography before the 12-month follow-up because of symptoms recurrence. One hundred ninety-five patients (90.7%) underwent the scheduled SPECT 9-12 months after the index PCI. Among these, 16 (8.2%) underwent coronary angiography for signs of ischemia in the treated regions at TI-201 myocardial SPECT; a significant stent restenosis was detected in 14 (87.5%) patients.

**Clinical Outcomes at Follow-up**

Clinical events at 1 and 12 months in the overall population are shown in Table 3. At 1 month, 1 patient had MI attributable to sub-acute ST of a Multi-Link Vision stent that required emergency TLR, four days after the index PCI.

Clinical follow-up was obtained at 12 months (11.8±2.1 months) in all patients: 8 (3.7%) patients died, 3 of them for cardiac reasons. One additional patient required dialysis, and no case of late ST occurred. TVR was performed in 32 (14.8%) patients on 44 coronary lesions: 33 (13%) on the BMS-treated lesions, and 11 (4.3%) on the DES-treated lesions (p=0.001); accordingly, the TLR rate was 13% (28 patients), performed on 41 coronary lesions: 34 (13.4%) on the BMS-treated lesions and 7 (2.7%) on the DES-treated lesions (p=0.001) (Table 3).

The incidence of ID-TVR at 12 months (primary endpoint) was significantly higher in BMS (11.4%; 95% CI: 7.8-16%) compared with DES group (2.7%; 95% CI: 1.1-5.6%), respectively (p<0.001) (Figure 2); accordingly, ID-TLR was higher in BMS compared with DES group (11.4 versus 1.2%, p<0.001). Among the 26 patients who received an ID-TVR at follow-up, 3 (11.5%) needed CABG and the remaining 23 (88.5%) have been treated with PCI using another DES or conventional balloon angioplasty in almost all lesions. The incidence of the
primary endpoint was consistently higher in BMS compared with DES group among patients treated on two coronary vessels (9.1%; 95% CI: 4.2-13.9% versus 1.5%; 95% CI: 0.5-3.5%; p<0.001, respectively) and with diabetes mellitus (6.7%; 95% CI: 1.9-11.5% versus 1.7%; 95% CI: 0.6-4.0%; p<0.001, respectively).

In addition, the different ID-TVR rate in favor of DES compared to BMS was consistent among different grades of renal dysfunction. Indeed, among 161 patients (74.8%) with moderate CKD treated on 384 coronary vessels, the ID-TVR rate was 2.6 and 7.3%, p=0.03, respectively. Among 54 patients (25.2%) with severe CKD or patients on dialysis, treated on 126 coronary vessels, the ID-TVR rate remained significantly lower in DES compared to BMS group (3.1% versus 24.2%, p=0.005) (Figure 2).

Multivariate analysis yielded two independent predictors of ID-TVR at 1 year: BMS implantation (OR: 4.95; 95% CI: 2.1-11.6; p<0.001) and vessel size (OR: 0.32; 95% CI: 0.1-0.7; p=0.006) (Table 4).

**Discussion**

This is the first randomized trial showing a beneficial effect in terms of clinical restenosis of a new generation DES compared to its BMS counterpart, in patients with multivessel coronary artery disease and CKD with an identical biochemical milieu, as established by the specific intrapatient comparison model of this study.

The principal findings of the study could be summarized as follows: i) the performance of the Multi-Link Vision BMS is remarkable despite the known unfavourable context that CKD represents for PCI; ii) the second-generation everolimus-eluting stent Xience-V reduces significantly the recurrence of myocardial ischemia at 1 year, and the subsequent need for
reinterventions compared to BMS. This difference being strictly attributable to the fluoro-polymer coverage and the elution of everolimus, since both the metallic alloy composition, and the geometric structure of the stents are identical; iii) the efficacy of the everolimus-eluting Xience-V stent in preventing restenosis is independent of the severity of CKD, including the most unfavourable setting of permanent replacement therapy.

The good performance of BMS in our study may be related to the commitment of the investigators in respecting the best standards of practice for stenting, as reflected by the use of shorter and larger stents in the BMS group, as well as the use of new generation stents that, being those with the thinnest stent struts, cause less neointimal hyperplasia. 27 Furthermore, compliance to optimal medical therapy during follow-up is also a determinant variable of the long-term clinical success of PCI, regardless of the type of stent implanted.

As to the DES performance, our findings confirm and expand those obtained in previous investigations with first-generation DES in patients with mild to moderate CKD. 8,9,28,29 Indeed, a post-hoc analysis from the TAXUS-IV trial showed that paclitaxel-eluting stent, compared with BMS, reduces restenosis at 1 year in patients with renal dysfunction. 8 Similar results were obtained by another post-hoc analysis from the SIRIUS trial, showing a reduced 5-year restenosis rate with sirolimus-eluting stents as compared to BMS. 9 On the contrary, a recent pooled analysis from Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) and the Taxus-Stent Evaluated At Rotterdam Cardiology Hospital (T-SEARCH) registries showed no superiority of both types of DES over BMS in safety and efficacy endpoints for patients with impaired renal function at 6-year follow-up. 10 However, the retrospective nature of that study in which first-generation DESs were utilized, does not allow a direct comparison with our findings obtained at a shorter follow-up time. In addition, all these
findings refer to patients with mild to moderate renal insufficiency, as patients with severe or end-stage CKD were excluded.\textsuperscript{8-10} Arguably, these patients constitute one of the highest-risk groups in terms of efficacy of coronary revascularization procedures. Recently, Shroff et al., using the United States Renal Data System database, showed that the probability of repeat revascularization accounting for the competing risk of death was 18\% with BMS and 19\% with DES at 1 year, among more than 23,000 dialysis patients undergoing coronary revascularization.\textsuperscript{30} Accordingly, in a recent analysis from the NCDR (National Cardiovascular Data Registry) CathPCI registry among CKD and >65 years old patients, there appeared to be a differential reduction in revascularization rates for DES compared with BMS (interaction p < 0.01) in patients with normal renal function only, whereas patients with mild, moderate, or severe CKD and patients on dialysis did not show significant differences.\textsuperscript{31} It is worth noting that in our study the efficacy in terms of clinical restenosis of a new-generation DES is preserved even in patients with severe CKD. Such findings are reinforced by the utilization of an intraindividual design, previously validated in other studies on multivessel patients undergoing PCI aimed to evaluate the angiographic or clinical performance of coronary stents.\textsuperscript{15,32,33} All these studies suggested that this comparison design may allow to obviate the multiple and unpredictable baseline differences in high-risk populations, including ACS patients with thrombotic burden and non-culprit lesions. According to this particular study protocol, both Xience-V and Multi Link Vision stents were implanted in the same patient for at least two significant coronary lesions in two major epicardial vessels, by randomizing for coronary vessels. Thus, our findings also show that the superiority of Xience-V to BMS is independent of all specific biochemical and clinical features of the CKD patients. Moreover, we found that BMS was an independent predictor of clinical restenosis, which was almost 5 times higher than in DES-treated vessels. Remarkably, in
patients with CKD, coronary restenosis resulting from neointimal hyperplasia is a very complex process influenced by several pathophysiological mechanisms, including vascular inflammation, increase of calcification promoters, activation of renin-angiotensin system with consequent enhanced production of reactive oxygen species. 11-13 Indeed, CKD promotes hypertension and dyslipidemia, which together with diabetes mellitus are important risk factors for the development of endothelial dysfunction and progression of atherosclerosis. 11-13 Finally, a variety of individual features, such as creatinine and GFR control over the time, associated medical treatments and response to treatment, might contribute to the accelerated atherosclerosis observed in these patients. 11-13 The role played by all these mechanisms may also vary among different CKD patients, rising in magnitude as the severity of CKD increases. The particular design of our study permitted to adjust the obtained results for all these variables. Nevertheless, the present intraindividual design precludes any comparison between different coronary stents in terms of major clinical endpoints and it is still unknown whether it provides similar results to inter-individual studies. Indeed, the impact of lesion specific factors on outcome in our population cannot be completely assessed as a lesion characterization by intravascular devices instead of angiographic evaluation was not routinely performed. In addition, operators were not blinded to the type of randomized stent, as in the majority of stent studies.

The death rate and ST observed at 1 year in our study were lower than previously reported. 8,9,28,29 This may be explained by the relatively short duration of the follow-up and the prospective nature of our study in which each patient was systematically treated for the prevention of contrast-induced nephropathy, the optimal medical treatment achieved in almost all patients and the use of new-generation DES and BMS. Finally, our findings refer to approximately 50% of patients with CKD and multivessel coronary artery disease in whom a
complete myocardial revascularization could be achieved by PCI, therefore they cannot be applied to all CKD patients with multi-vessel coronary artery disease.

Conclusions

This is the first randomized trial showing a beneficial effect in terms of clinical restenosis of a new generation DES compared to the BMS of equal design, in patients with multivessel coronary artery disease and CKD. Long-term data will clarify whether these favorable results are maintained over time and the relative impact of plaque progression in this high-risk population.

Conflict of Interest Disclosures: None.

References:


24. Hachamovitch R, Berman DS, Kiat H, Cohen I, Cabico JA, Friedman J, Diamond GA. Exercise myocardial perfusion SPECT in patients without known coronary artery disease:


Table 1. Baseline characteristics and medical therapy at follow-up of total population, and among patients treated on 2- and 3-coronary vessels.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total population (n=215)</th>
<th>Patients treated on 2 coronary vessels (n=133)</th>
<th>Patients treated on 3 coronary vessels (n=82)</th>
<th>P value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>73.0±7.9</td>
<td>73.4±7.3</td>
<td>72.1±8.8</td>
<td>0.2</td>
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<tr>
<td>Male, n (%)</td>
<td>156 (72.6)</td>
<td>95 (71.4)</td>
<td>61 (74.4)</td>
<td>0.6</td>
</tr>
<tr>
<td>Weight (Kg)</td>
<td>72.6±11.0</td>
<td>72.5±11.4</td>
<td>72.6±10.2</td>
<td>0.9</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>142.1±21.8</td>
<td>142.1±22.1</td>
<td>142.2±21.6</td>
<td>0.9</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>71.6±11.7</td>
<td>72.2±12.5</td>
<td>70.8±10.1</td>
<td>0.4</td>
</tr>
<tr>
<td>eGRF (ml/min)</td>
<td>46.8±17.1</td>
<td>45.9±16.9</td>
<td>46.9±18.6</td>
<td>0.6</td>
</tr>
<tr>
<td>Chronic kidney disease, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>161 (74.9)</td>
<td>98 (82.3)</td>
<td>63 (85.1)</td>
<td>0.6</td>
</tr>
<tr>
<td>Severe</td>
<td>32 (14.9)</td>
<td>21 (17.6)</td>
<td>11 (14.8)</td>
<td>0.7</td>
</tr>
<tr>
<td>Dialysis</td>
<td>22 (10.2)</td>
<td>14 (10.5)</td>
<td>8 (9.8)</td>
<td>0.8</td>
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<td>Diabetes mellitus, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 1</td>
<td>16 (7.4)</td>
<td>10 (7.5)</td>
<td>6 (7.3)</td>
<td>0.9</td>
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<tr>
<td>Type 2</td>
<td>78 (36.4)</td>
<td>46 (34.6)</td>
<td>32 (39.0)</td>
<td>0.8</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>193 (89.8)</td>
<td>117 (88.0)</td>
<td>76 (92.7)</td>
<td>0.3</td>
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<tr>
<td>Current smoker, n (%)</td>
<td>61 (28.4)</td>
<td>42 (31.6)</td>
<td>19 (23.2)</td>
<td>0.2</td>
</tr>
<tr>
<td>Family history of CAD, n (%)</td>
<td>63 (29.3)</td>
<td>42 (31.6)</td>
<td>21 (25.6)</td>
<td>0.3</td>
</tr>
<tr>
<td>Obesity, n (%)</td>
<td>52 (24.2)</td>
<td>26 (19.5)</td>
<td>26 (31.7)</td>
<td>0.04</td>
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<td>Peripheral artery disease, n (%)</td>
<td>41 (19.1)</td>
<td>28 (21.1)</td>
<td>13 (15.9)</td>
<td>0.3</td>
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<tr>
<td>Dyslipidemia, n (%) **</td>
<td>117 (54.4)</td>
<td>70 (52.6)</td>
<td>47 (57.3)</td>
<td>0.5</td>
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<tr>
<td>Previous MI, n (%)</td>
<td>34 (15.8)</td>
<td>19 (14.3)</td>
<td>15 (18.3)</td>
<td>0.4</td>
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<tr>
<td>Previous CABG, n (%)</td>
<td>8 (3.7)</td>
<td>6 (4.5)</td>
<td>2 (2.4)</td>
<td>0.4</td>
</tr>
<tr>
<td>Previous PCI, n (%)</td>
<td>20 (9.3)</td>
<td>15 (11.3)</td>
<td>5 (6.1)</td>
<td>0.2</td>
</tr>
<tr>
<td>ACS, n (%)</td>
<td>123 (56.9)</td>
<td>72 (54.1)</td>
<td>51 (62.2)</td>
<td>0.2</td>
</tr>
<tr>
<td>Three vessel CAD, n (%)</td>
<td>90 (41.9)</td>
<td>46 (34.6)</td>
<td>44 (53.7)</td>
<td>0.006</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>53.1±9.7</td>
<td>53.8±9.1</td>
<td>51.7±9.7</td>
<td>0.1</td>
</tr>
</tbody>
</table>

Medical therapy at admission:
- Oral anticoagulant agents, n (%)<br>- Diuretics, n (%)<br>- Statins, n (%)<br>- ACE-inhibitors or ARBs, n (%)<br>- Aspirin, n (%)<br>- Thienopyridine-derived agents, n (%)<br>- Calcium channel blockers, n (%)<br>- β-blockers, n (%)<br>

Medical therapy at follow-up***:
- Oral anticoagulant agents, n (%)<br>- Diuretics, n (%)<br>- Statins, n (%)<br>- ACE-inhibitors or ARBs, n (%)<br>- Aspirin, n (%)<br>- Thienopyridine-derived agents, n (%)<br>- Calcium channel blockers, n (%)<br>- β-blockers, n (%)<br>

ACE indicates angiotensin-converting enzyme; ARBs: angiotensin receptor blockers; ACS: acute coronary syndrome; CAD: coronary artery disease; CABG: coronary artery bypass grafting; eGFR: estimated glomerular filtration rate; HR: heart rate; MI: myocardial infarction; PCI: percutaneous coronary intervention; SBP: systolic blood pressure

*Obesity was defined as BMI ≥30; **Dyslipidemia was defined as a total cholesterol concentration >5.69 mmol/L, a triglyceride concentration >1.69 mmol/L, an HDL cholesterol concentration <1.03 mmol/L, and/or having received treatment for dyslipidemia. ***among the 204 patients alive at follow-up.

Values are mean ± SD or number (percent of total). †Comparisons of the continuous or discrete variables between patient groups have been performed using unpaired t-test or Chi-square test, respectively.
Table 2. Angiographic and procedural characteristics.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Coronary vessels treated with Multi-link Vision</th>
<th>Coronary vessels treated with Xience V</th>
<th>P value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location of treated vessel, n (%)</td>
<td></td>
<td></td>
<td>0.57</td>
</tr>
<tr>
<td>Left anterior descending coronary artery</td>
<td>94 (36.9)</td>
<td>106 (41.2)</td>
<td></td>
</tr>
<tr>
<td>Left circumflex coronary artery</td>
<td>83 (32.5)</td>
<td>80 (31.1)</td>
<td></td>
</tr>
<tr>
<td>Right coronary artery</td>
<td>78 (30.6)</td>
<td>71 (27.6)</td>
<td></td>
</tr>
<tr>
<td>Vessel site, n (%)*</td>
<td></td>
<td></td>
<td>0.37</td>
</tr>
<tr>
<td>Proximal</td>
<td>158 (52.4)</td>
<td>172 (56.2)</td>
<td></td>
</tr>
<tr>
<td>Middle-distal</td>
<td>143 (47.6)</td>
<td>134 (43.8)</td>
<td></td>
</tr>
<tr>
<td>Lesion type, n (%)*</td>
<td></td>
<td></td>
<td>0.93</td>
</tr>
<tr>
<td>A-B1</td>
<td>121 (40.2)</td>
<td>122 (39.9)</td>
<td></td>
</tr>
<tr>
<td>B2-C</td>
<td>180 (59.8)</td>
<td>184 (60.1)</td>
<td></td>
</tr>
<tr>
<td>CTO, n (%)*</td>
<td>12 (4.0)</td>
<td>13 (4.2)</td>
<td>1.0</td>
</tr>
<tr>
<td>Bifurcation lesions, n (%)*</td>
<td>46 (15.3)</td>
<td>51 (16.7)</td>
<td>0.65</td>
</tr>
<tr>
<td>Baseline TIMI flow, n (%)</td>
<td></td>
<td></td>
<td>0.43</td>
</tr>
<tr>
<td>0-1</td>
<td>25 (9.8)</td>
<td>16 (6.2)</td>
<td></td>
</tr>
<tr>
<td>2-3</td>
<td>230 (90.2)</td>
<td>241 (93.8)</td>
<td></td>
</tr>
<tr>
<td>Post-procedural TIMI flow, n (%)</td>
<td></td>
<td></td>
<td>0.95</td>
</tr>
<tr>
<td>0-1</td>
<td>1 (0.4)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>2-3</td>
<td>254 (99.6)</td>
<td>257 (100)</td>
<td></td>
</tr>
<tr>
<td>Direct stenting, n (%)</td>
<td>84 (33.1)</td>
<td>56 (21.9)</td>
<td>0.005</td>
</tr>
<tr>
<td>Post-dilation, n (%)</td>
<td>116 (45.7)</td>
<td>156 (60.9)</td>
<td>0.007</td>
</tr>
<tr>
<td>Rotablator, n (%)</td>
<td>3 (1.2)</td>
<td>4 (1.6)</td>
<td>0.72</td>
</tr>
<tr>
<td>Total lesion length, mm</td>
<td>19.3±8.0</td>
<td>20.6±10.8</td>
<td>0.14</td>
</tr>
<tr>
<td>Total stent length, mm</td>
<td>19.6±7.9</td>
<td>24.7±11.3</td>
<td>0.001</td>
</tr>
<tr>
<td>Number of stents per vessel</td>
<td>1.2±0.4</td>
<td>1.3±0.5</td>
<td>0.001</td>
</tr>
<tr>
<td>Reference vessel diameter, mm</td>
<td>2.86±0.5</td>
<td>2.78±0.4</td>
<td>0.07</td>
</tr>
<tr>
<td>Stent diameter, mm</td>
<td>3.02±0.5</td>
<td>2.89±0.4</td>
<td>0.002</td>
</tr>
<tr>
<td>Pre-procedural MLD, mm</td>
<td>0.54±0.38</td>
<td>0.48±0.31</td>
<td>0.07</td>
</tr>
<tr>
<td>Post-procedural MLD, mm</td>
<td>2.66±0.4</td>
<td>2.59±0.4</td>
<td>0.87</td>
</tr>
<tr>
<td>Pre-procedural diameter stenosis, %</td>
<td>81.0±12.2</td>
<td>82.4±10.5</td>
<td>0.17</td>
</tr>
<tr>
<td>Post-procedural diameter stenosis, %</td>
<td>8.9±6.1</td>
<td>8.6±6.3</td>
<td>0.61</td>
</tr>
</tbody>
</table>

CTO: chronic total occlusion; DES: drug-eluting stent; MLD: minimal luminal diameter.
* Percentages refer to 607 treated lesions (301 with Multilink Vision and 306 with Xience V, respectively).
Values are mean ± SD or number (percent of total). †Comparisons of the continuous or discrete variables have been performed using a paired t-test or a McNemar test, respectively.
Table 3. Clinical events at 1 and 12 months in the overall population

<table>
<thead>
<tr>
<th>Events, n (%)</th>
<th>Overall n=215</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cardiac death</td>
</tr>
<tr>
<td>30 DAYS</td>
<td>0</td>
</tr>
<tr>
<td>12 MONTHS</td>
<td>3 (1.4)</td>
</tr>
</tbody>
</table>

MI: myocardial infarction; SAT: subacute thrombosis; TLR: target lesion revascularization; TVR: target vessel revascularization

Table 4. Multivariate analysis of predictors of the ID-TVR at 1 year.

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of stent (BMS versus DES)</td>
<td>4.95 (2.1-11.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Treated vessel</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAD versus combined Cx-RCA</td>
<td>0.90 (0.4-1.5)</td>
<td>0.8</td>
</tr>
<tr>
<td>Cx versus combined LAD-RCA</td>
<td>2.36 (0.8-6.4)</td>
<td>0.09</td>
</tr>
<tr>
<td>RCA versus combined LAD-Cx</td>
<td>0.35 (0.1-1.1)</td>
<td>0.5</td>
</tr>
<tr>
<td>Lesion location (Proximal versus Distal)</td>
<td>1.54 (0.7-3.1)</td>
<td>0.1</td>
</tr>
<tr>
<td>Lesion type (A-B1 versus B2-C)</td>
<td>0.89 (0.4-1.9)</td>
<td>0.9</td>
</tr>
<tr>
<td>Stent length (mm)</td>
<td>1.00 (0.9-1.0)</td>
<td>0.8</td>
</tr>
<tr>
<td>Pre-procedural reference vessel diameter (mm)</td>
<td>0.32 (0.1-0.7)</td>
<td>0.006</td>
</tr>
<tr>
<td>Pre-procedural minimal lumen diameter (mm)</td>
<td>1.57 (0.3-7.5)</td>
<td>0.4</td>
</tr>
<tr>
<td>Pre-procedural diameter stenosis (mm)</td>
<td>1.02 (0.9-1.0)</td>
<td>0.2</td>
</tr>
</tbody>
</table>

BMS: bare-metal stent; Cx: circumflex coronary artery; DES: drug-eluting stent; LAD: left anterior descending coronary artery; RCA: right coronary artery
Figure Legends:

Figure 1. RENAL-DES study flow-chart

Figure 2. Incidence of ischemia-driven target vessel revascularization at 12 months (primary endpoint) in the overall population and among patients with moderate CKD (eGFR: 30 to 59 ml/min) and severe CKD and/or kidney failure (eGFR: <30 ml/min).
Consecutive Pts with eGFR <60 mL/min

Coronary Angiogram and Verification of Inclusion/Exclusion Criteria
N=415

Exclusion from Enrollment after Joint Evaluation of Cardiovascular Team

Randomization for Coronary Vessel (intra-individual design)
N=215 (51.8%), 512 coronary vessels

In-Hospital Follow-Up (clinical and laboratory)

One-month Follow-Up (by phone and laboratory)

12-month Follow-Up (clinical visit and Gated-SPECT 201-Tl)

Symptoms/Signs of Ischemia

Repeat Coronary Angiography
N=36

Figure 1
Figure 2

Bar chart showing the percent of ischemia-driven target vessel revascularization for different patient groups:

- **Overall population (Primary endpoint)**: 11.4% for Multi-link Vision, 2.7% for Xience V, with a p-value of <0.001.
- **Moderate CKD**: 7.3% for Multi-link Vision, 2.6% for Xience V, with a p-value of 0.03.
- **Severe CKD/Dialysis**: 24.2% for Multi-link Vision, 3.1% for Xience V, with a p-value of 0.005.

The chart compares the revascularization rates between Multi-link Vision and Xience V for each patient group.
Randomized Comparison of XiEnce-V and Multi-link VisioN Coronary Stents in the sAme muLtivessel Patient with Chronic kiDnEy diSease (RENAL-DES) Study

Fabrizio Tomai, Flavio Ribichini, Leonardo De Luca, Alessandro Petrolini, Anna S. Ghini, Luca Weltert, Carmen Spaccarotella, Igino Proietti, Carlo Trani, Francesco Nudi, Michele Pighi and Corrado Vassanelli

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SUPPLEMENTAL MATERIAL

Randomized comparison of XiEnce-V and Multi-link VisioN coronary stents in the same multivessel patient with chronic kidney disease (RENAL-DES) study.

Fabrizio Tomai¹, MD, FACC, FESC; Flavio Ribichini², MD; Leonardo De Luca¹, MD, FACC, PhD; Alessandro Petrolini¹, MD; Anna S. Ghini¹, MD, PhD; Luca Weltert¹, MD; Carmen Spaccarotella³, MD; Igino Proietti⁴, MD; Carlo Trani⁵, MD; Francesco Nudi⁶, MD; Michele Pighi², MD; Corrado Vassanelli², MD, FESC.

¹ Department of Cardiovascular Sciences, European Hospital, Rome; ² Division of Cardiology of the Department of Medicine, University of Verona; ³ Institute of Cardiology, University Magna Grecia, Catanzaro; ⁴ Department of Cardiology, Vannini Hospital, Rome; ⁵ Institute of Cardiology, Cattolica University, Rome; ⁶ Division of Nuclear Medicine, Madonna della Fiducia Clinic, Rome; Italy.
SUPPLEMENTAL METHODS

Biochemical determinations

Besides routine determinations, blood samples for creatinine and cystatin C serum levels has been obtained at admission, 3-5 days, 30 days, and at 9 and 12 months, except in patients in dialysis. Troponin I (ng/mL), CK-MB and C-reactive protein levels has been determined at admission, 6 and 24 hours after PCI and at discharge.

Blood cell counting with formula, glycemia and urinary protein values has been also verified all patients during hospitalization, at 30 days, and at 9 and 12 months.

Prevention of contrast induced nephropathy

For the prevention of contrast induced nephropathy all patients has been treated according to the following protocols:

a) Patients at high risk (creatinine clearance ≤30 ml/min):

1) 0.9% Saline solution:
   • 1 ml/Kg/h for 24 hours (to be started 12 hours before the procedure)
   • reduce to 0.5 ml/Kg/min if ejection fraction ≤0.45 or NYHA class ≥II

2) 0.84% Sodium bicarbonate:
   • Bolus: ml/h= body weight in Kg x 0.462 mEq (for 60 minutes)
   • IV infusion: ml/h=(body weight in Kg x 0.154 mEq)/6 (for 6 hours)

3) N-Acetylcysteine:
   • 600 mg per os BID (the day before and the day scheduled for procedure)

b) Patients at moderate-low risk (creatinine clearance 31-60 ml/min):

1) 0.9% Saline solution:
   • 1 ml/Kg/h for 24 hours (to be started 12 hours before the procedure)
reduce to 0.5 ml/Kg/min if ejection fraction ≤0.45 or NYHA class ≥II

2) N-Acetylcysteine:

- 600 mg *per os* BID (the day before and the day scheduled for procedure).
SUPPLEMENTAL FIGURE LEGEND

Figure 1S. Example of a patient with renal dysfunction and two-vessel coronary artery
disease enrolled in the RENAL-DES study. After randomization, this patient was treated with
two Xience-V on left circumflex and one Vision on left anterior descending. Seven months
after stent implantations, he experienced a recurrence of angina and underwent a coronary
angiography that documented a significant and diffuse restenosis of the bare-metal stent.

FIGURE 1S.
SUPPLEMENTAL REFERENCES


Appendix

List of participants:

F. Tomai, L. De Luca, A. Petrolini, A.S. Ghini, L. Weltert, Department of Cardiovascular Sciences, Division of Cardiology, European Hospital, Rome; L. Altamura, P. Corvo, G. De Persio, Interventional Cardiology Unit, Aurelia Hospital, Rome; C. Spaccarotella, C. Indolfi, Institute of Cardiology, Magna Grecia University, Catanzaro; I. Proietti, S. Musarò, Division of Cardiology, Figlie di S. Camillo Hospital, Rome; C. Trani, F. Burzotta, G. Lanza, C. Aurigemma, Institute of Cardiology, A. Gemelli University, Rome; F. Nudi, M. Vetere, Division of Nuclear Medicine, Madonna della Fiducia Clinic, Rome; F. Ribichini, V. Ferrero, M. Pighi, G. Pesarini, A. Mugnolo, A. Fede, C. Vassanelli. Division of Cardiology, of the Department of Medicine, University of Verona, Italy.

Clinical Events Committee:

G. Sardella, Department of Cardiovascular Sciences, La Sapienza University, Rome; G. Patti, Campus Bio-Medico University of Rome, Rome, Italy.