Long-term clinical follow-up of the multicentre, randomized study to test immunosuppressive therapy with oral prednisone for the prevention of restenosis after percutaneous coronary interventions: Cortisone plus BMS or DES veRsus BMS alone to EliminAte Restenosis (CEREA-DES)

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Aims To analyse the clinical outcome at 4 years in patients with coronary artery disease treated with bare metal stents (BMS) vs. BMS and oral prednisone, or drug-eluting stents (DES), all assuming similar adjunctive medical treatment.

Methods and results Five Italian hospitals enrolled 375 non-diabetic, ischaemic patients without contraindications to dual anti-platelet treatment or corticosteroid therapy in a randomized controlled study. The primary endpoint was the event-free survival of cardiovascular death, myocardial infarction, and recurrence of ischaemia needing repeated target vessel revascularization at 1 year, and this was significantly lower in the BMS group (80.8%) compared with the prednisone (88.0%) and DES group (88.8%; P = 0.04 and 0.006, respectively). The long-term analysis of the primary endpoint was a pre-specified aim of the trial, and was performed at 1447 days (median, IQ range = 1210–1641). Patients receiving BMS alone had significantly lower event-free survival (75.3%) compared with 84.1% in the prednisone group (HR: 0.447; 95% CI: 0.25–0.80, P = 0.007) and 80.6% in DES patients (HR: 0.519; 95% CI: 0.29–0.93, P = 0.03). Prednisone-treated patients did not develop new treatment-related clinical problems. Drug-eluting stents patients suffered more very late stent thrombosis as a cause of spontaneous myocardial infarction. The need for target vessel revascularization remained lower in the prednisone and DES groups (13.6 and 15.2%, respectively), compared with BMS (23.2%).

Conclusions The clinical benefits of prednisone compared with BMS only persisted almost unchanged at 4 years. Drug-eluting stents performed better than BMS at long-term, although the advantages observed at 1 year were in part attenuated because of the occurrence of very late stent thrombosis and late revascularizations.

Clinical Trial NCT 00369356.

Keywords Randomized clinical trial • Long-term follow-up • Coronary artery disease • Stent • Prednisone

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Introduction

The assessment at long term of the clinical results of revascularization procedures is necessary to estimate the real advantages (or pitfalls) of new technologies and new treatment strategies.

This manuscript reports the long-term clinical outcome observed in patients with coronary artery disease (CAD) treated with percutaneous coronary interventions (PCI) using three different forms of a randomly assigned revascularization treatment, on top of optimal medical therapy: (i) bare metal stent (BMS group); (ii) sirolimus or paclitaxel drug-eluting stent implantation (DES group); or (iii) BMS followed by a 40-day oral treatment with prednisone (prednisone group), as detailed in the study protocol.1

The use of systemic treatment with prednisone given orally after BMS implantation has shown efficacy in reducing restenosis at mid- and long-term in non-diabetic patients with a persistent inflammatory state, as indicated by elevated C-reactive protein levels.2–4 Being inflammation one of the principal components of stent restenosis,5,6 the use of a systemic anti-inflammatory and/or immunosuppressive therapy to prevent it, may be a reasonable option.7–9

The anti-restenotic alternatives offered by a locally delivered treatment (like DES) or a systemic pharmacologic therapy (like oral prednisone) bare two substantial differences: DES have high efficacy but also the potential for local vascular toxicity; a systemic treatment may cause undesired side-effects, but may also act on the global vascular system with the potential of affecting atherosclerotic progression in non-treated lesions. However, despite the attractive rational of this hypothesis, very little is known on such effects at the long term.

Growing evidence suggests that atherosclerotic progression may cause more ischaemic recurrences than DES failure itself.10,11 Furthermore, in-stent late neo-atherogenesis has been identified as a main reason of very-late PCI failure often presenting with acute coronary syndromes. This histopathological process is substantially different to the neointimal proliferation that causes conventional stent restenosis; it has been observed rarely and very late after BMS implantation (>6 years) but occurs earlier and more frequently after implantation of drug-active stents,12 and is retained to play a main role in the process of late DES failure. Conversely, systemic medical treatment continues to provide evidence of sustained benefit in terms of secondary prevention of cardiovascular events at long term.13–15

The principal aim of this study is to demonstrate the clinical effects at the long term of a short immunosuppressive and anti-inflammatory treatment with prednisone in patients with advanced CAD treated with PCI and BMS implantation on top of optimal medical therapy.

Methods

CEREA-DES is an independent, investigator-initiated study. The study protocol was approved by the Ethics Committee of each of the participating centres. The study is registered at the Osservatorio Nazionale Sulla Sperimentazione Clinica dei Medicinali. Ministero della Sanità della Repubblica Italiana (EudraCT 2006-000770-75), and in the USA as a Clinical Trial NCT 00369356. The full protocol of the study is available for consultation of details on the methodology and rational.1 All patients provided written informed consent prior to catheterization for participation in the study.

Study population

Consecutive patients undergoing coronary angiography were considered suitable for inclusion in the study when showing significant CAD (either single or multi-vessel involvement), with signs or symptoms of myocardial ischaemia, amenable for PCI. Exclusion criteria were: diabetes; age over 80 years old; recent Q-wave myocardial infarction (<2 weeks); uncontrolled hypertension; gastric ulcer; neoplasia; severe renal failure (creatinine >2.5 mg/dL); left main disease; contraindications to high-doses of steroids; known contraindications to dual antiplatelet therapy for at least 6 months; and the lack of signed informed consent.

Patients were assigned to one of the three study arms: BMS implantation (control group), BMS implantation followed by medical treatment with oral prednisone, (prednisone group) of DES. Random allocation of patients in treatment groups could be obtained 24/24 h through an electronic system. External randomization followed a sequence based on pseudorandom numbers generated by a computer program. The brand of BMS implanted was left to the operator’s preference. The use of DES was limited to the paclitaxel-eluting stent (Taxus Liberte™, Boston Scientific, Marlborough, MA, USA) and the sirolimus-eluting stent (Cypher Select®, Cordis, Johnson & Johnson, New Brunswick, NJ, USA). Technical details of PCI have been reported elsewhere.7

Medication

Before PCI all patients were pre-treated with a loading dose of either ticlopidine 500 or clopidogrel 300 mg, and conventional doses of aspirin (325–500 mg in patients with acute coronary syndromes and 100–160 mg in stable patients). After successful stent implantation all patients received standard medications, including aspirin 100–160 mg, ticlopidine 250 mg b.i.d. or clopidogrel 75 mg/day for 1 month. Patients receiving DES were under double anti-platelet treatment for a minimum of 6 months, up to 1 year, independently of clinical presentation. For patients receiving BMS because of stable ischaemia, the double anti-platelet treatment was withdrawn after 1 month. It was instead continued for 1 year in those treated because of acute coronary syndromes. Prednisone was administered at 1 mg/kg for the first 15 days; 0.5 mg/kg from Day 16 to 30; 0.25 mg/kg from Day 31 to 40.12 The drug was associated to a gastro-protective anti-acid therapy during the whole period of steroid treatment, ideally a proton pump inhibitor 20 mg twice daily; and 20–40 mg/day of oral thiazide to reduce liquid retention and blood pressure and prevent calcium depletion.9 Treatment with prednisone was started ideally the same day of PCI, after the procedure and in all cases within 48 h.

Data management, definitions, and study endpoints

The primary endpoint of the study was the survival free of major adverse cardiac events (MACEs) at 12 months as analysed by means of a Cox proportional hazard regression analysis. Major adverse cardiac events are cardiac death, myocardial infarction (either non-Q wave or Q-wave), and the need to repeat revascularization (on the same vessel/s treated) because of the recurrence of angina at rest, under effort, or the evidence of ischaemia by instrumental means, i.e. repeated target vessel revascularization (TVR). The definition of the clinical events and other details of the study protocol are published elsewhere.1 All adverse events were adjudicated and classified by an
event adjudication committee, unaware of the patient’s assigned treatment after review of original source documentation.

The aim of the present report was the assessment of the clinical outcome at 4 years by evaluating the event-free survival of the MACE’s included in the primary endpoint of the study.

The additional evaluation of major bleeding events (i.e. spontaneous bleeding needing hospitalization, bleeding causing by other associated pathologies while under anti-platelet treatment and requiring hospitalization, and/or blood transfusion), late and very late stent thrombosis according to the Academic Research Consortium definitions, and the assessment of possible adverse effects of the corticosteroid treatment at 4 years (i.e. clinical occurrence of newly diagnosed diabetes, peptic ulcer, refractory hypertension, auto-immune disease or cancer) were secondary endpoints of the study.

Follow-up

A follow-up visit was performed at 1 month after the procedure in order to assess the therapeutic compliance as well as the occurrence of any side-effect of the medical therapy. A physical examination and exercise testing were performed in all patients at 6 months to detect any early recurrence of symptoms or silent myocardial ischaemia. A long-term follow-up was planned at 1 year by means of a direct visit, and at 2, 3, and 4 years by telephone interviews, and, in case of any reported cardiac or other vascular symptom during the interview, a complete clinical examination was performed in the outpatient clinic including additional examination as needed.2

Statistical methods

The aim of the statistical analysis is to compare the results of the control group (BMS) against the two forms of alternative treatment: added prednisone or DES, according to the intention-to-treat principle. Evaluation of the event-free survival was hierarchical for the analysis of the primary endpoint at 1 year and at long term, considering always the most severe event when more than one occurred. Cumulative incidence of events at long term is also provided. Continuous data are described as mean ± SD, unless skewed, when median and inter-quartiles ranges are used. Categorical variables are reported as counts and percentage. The homogeneity of baseline, procedural, and medical therapy data was assessed with multi-comparison tests. The Brandt–Snedecor test was used for categorical variables and variance analysis (ANOVA with the Bonferroni method) for continuous data. Therefore, each variable of the treatment groups was compared with the control group generating two significance values (BMS vs. BMS and prednisone (p1), and BMS vs. DES (p2). All significance levels were corrected for the multiple comparisons.

Kaplan–Meier Survival plots were obtained for the evaluation of the primary endpoint. The association between each form of treatment and the primary endpoint at 4 years was assessed by means of a Cox proportional hazard regression analysis, after verification of the proportionality assumption by the straightforward approach of graphic log(−log) analysis. A probability equal or < 5% was considered significant for two-sided statistics. MS Excel version 2003 and SPSS version 15 were used for computer-aided data analysis and figure generation.

Results

The detailed information regarding the baseline characteristics of patients enrolled in the study have been published previously and shown briefly in Table 1. As expected from its randomized nature, there were no differences among groups. As per protocol, 125 patients were actually treated with BMS, 127 with DES, and 122 with prednisone after BMS. At 1 year patients treated with BMS had a significantly worse event-free survival (80.8%) compared with those treated with the addition of oral prednisone (88%, HR: 0.505; 95% CI: 0.26–0.98, P = 0.04) or with DES (88.8%, HR: 0.388; 95% CI: 0.19–0.76, P = 0.006).

The median follow-up duration of the observation was 1447 days (IQ range 1210–1641) and was similar for the three groups. BMS: 1461 (1219–1644), prednisone: 1449 (1205–1664), and DES: 1420 (1213–1617).

Of the 375 patients enrolled, 4-year follow-up was available for 365 (123 patients with BMS: 98.4%, 121 patients treated with prednisone: 96.8%, and 121 patients with DES: 96.8%). Seven patients died before scheduled long-term follow-up visit; one patient in the DES group and one in the prednisone group could not be contacted (lost at follow-up) at 4 years; finally, one patient in the prednisone group refused to give consent for further contacts after 1 year. These three lost patients were considered as censored for the analyses at the moment of the latest clinical contact.

Patients receiving BMS alone when compared with those treated with prednisone or DES had a significantly lower event-free survival at 4 years. In fact, according to the intention to treat analysis it was 75.3% compared with 84.1% in the prednisone group (HR: 0.447; 95% CI: 0.29–0.80, P = 0.007) and 80.6% in the DES group (HR: 0.519; 95% CI: 0.29–0.93, P = 0.03) (Figure 1). The per-protocol analysis further reinforced this difference: prednisone, HR: 0.423; 95% CI: 0.24–0.74, P = 0.003 and DES, HR: 0.521; 95% CI: 0.28–0.99, P = 0.05. When major bleedings were included into the composite clinical endpoint, the net clinical outcome did not change, since only three cases of major bleeding (one per each treatment group) occurred between 1 and 4 years. Use of dual anti-platelet therapy at 1 year was more frequent in DES patients and the dual regimen was prolonged for another year in 28 BMS and 25 prednisone patients (Table 2). At 4 years, it was still used in 29 DES patients (23.2%), compared with 6 (4.8%) and 4 (3.2%) patients in the BMS and the prednisone groups, respectively, being this the only significant difference related to the medical treatment among groups at 4 years.

Differences in terms of MACE and its landmark analysis (30 days, 1 year, between 1 and 4 years, and up to 4 years) are shown in Tables 2 and 3. Mortality at 4 years was similar among the three groups and all cases were attributed a possible cardiovascular nature. Spontaneous MI related to the target vessel within 1 year occurred in two patients of the BMS group (due to subacute stent thrombosis in one case, and due to occlusive restenosis in the second). At long term, three DES patients had spontaneous MI due to very late (definite) stent thrombosis. A possible stent thrombosis was adjudicated as a cause of sudden death in one DES patient (Table 3). All these events occurred under single anti-platelet regimen and had no correlation with recent therapeutic changes.

The need for TVR at long-term remained higher in the BMS group (23.2%), compared with prednisone (13.6%), or to DES (15.2%), although these differences did not attain statistical significance. Non-TVR rates in the prednisone group were 4.8%, compared with 7.2% in the BMS and 12% in the DES group, and the
The occurrence of newly diagnosed diabetes, peptic ulcer, refractory hypertension, auto-immune disease or cancer in the three groups was clinically irrelevant and homogeneously distributed.

At univariate analysis generic variables associated with the occurrence of MACE were baseline levels of creatinine (HR: 2.89, 95% CI: 0.96–8.69, \( P = 0.05 \)), smoking habit (HR: 1.67, 95% CI:...
1.05–2.66, \( P = 0.03 \)), the presence of triple-vessel disease (HR: 1.53, 95% CI: 1.13–2.08, \( P = 0.005 \)), the length (HR: 1.05, 95% CI: 1.00–1.01, \( P = 0.02 \)), and the diameter of the stents (HR: 0.42, 95% CI: 0.25–0.67, \( P = 0.001 \)). In the multivariate model, all the same variables, except the baseline creatinine levels, emerged as independent predictors on MACE. Treatment with prednisone significantly reduced the HR for the occurrence of MACE compared with BMS (HR \( = 0.447 \), 95% CI: 0.29–0.80, \( P = 0.007 \)). The treatment with DES compared with BMS yielded an HR of 0.519 with a 95% CI: 0.29–0.97 and \( P = 0.05 \).

**Discussion**

Drug-eluting stents have substantially reduced the recurrence of ischaemia at short-to mid-term, and this benefit is sustained also at 4–5 years compared with BMS. However, the need for repeated revascularization procedures in the same lesion (TLR) after DES implant increased in randomized studies from 7.2 and 11.6% for Cypher and Taxus at 1 year, up to 15 and 18% at 5 years, respectively, percentages that suggest a “late catch-up phenomenon”. Also important is the need for new revascularization procedures after PCI driven by the progression of atherosclerosis in other than the initially treated sites, an eventuality that doubled the incidence of target vessel myocardial infarction and re-interventions from 10 to 11% at 1 year, to 20–21%, at 2 years of the index treatment in the Resolute AC trial, despite the use of second generation DES. In fact, the occurrence of neo-atherosclerosis within DES, and atherosclerosis progression in other than the PCI-treated sites, are both strong determinants of the long-term clinical outcome of catheter-based revascularization techniques, despite the improved local efficacy and global safety of new generation DES. A subtle but progressive deterioration of the excellent early results of first-generation DES observed in large series, is confirmed in our study. Both, late DES restenosis and very late DES thrombosis accounted for most of these adverse events, in particular after the third year of follow-up. This happened despite the maintenance of optimal medical therapy during 4 years of regular medical controls, an attitude that may have contributed to improve the clinical outcome in all patients.

At 1 year, our study demonstrated that the addition of prednisone after BMS, or the implantation of DES, yielded similar
event-free survival, and that both strategies performed significantly better than BMS alone.\(^7\) The analysis at the long term of the prednisone therapy after stenting, discloses the following principal observations.

First, the clinical benefit observed at 1 year remain almost unchanged at 4 years, with a very low incidence of cardiac events occurring between 1 and 4 years; i.e. only one case of late restenosis, and none of late or very late stent thrombosis. Of note, these long-term results are almost identical to those previously reported following preliminary experiences with oral prednisone after BMS implantation in patients with single or with multi-vessel CAD at 5-year follow-up.\(^4\) Secondly, it is that the use of a short, high-dose cycle of oral prednisone as in the IMPRESS and the CEREA studies\(^8\) – \(^10\) does not correlate with the occurrence of other newly diagnosed diseases such as diabetes mellitus, gastric or suprarenal disorders or refractory hypertension; and thirdly, is the trend observed towards a lower need for new revascularizations at the long term, compared with the other two groups. This may suggest a beneficial effect of the immunosuppressive and/or anti-inflammatory cycle against atherosclerosis progression in the coronary vascular tree.

Other experiences with systemic drug therapy to prevent restenosis have been reported some years ago, in particular with the administration of oral rapamycin.\(^21\) – \(^23\) Despite favourable short-term results, long-term clinical outcome has shown some reduced anti-restenotic efficacy compared with that observed at 1 year.\(^19\), \(^20\) Similarly to prednisone, the anti-proliferative efficacy of orally administered rapamycin is dose dependent, but unlike prednisone, it induces different effects in the reparative process that follows artery wall injury after stent implantation in the experimental model.\(^24\), \(^25\) Furthermore, it has a lower tolerability profile at the effective dose required in humans compared with prednisone.\(^9\) – \(^19\), \(^21\)

It is unarguable that DESs are highly effective in reducing in-stent restenosis, intended as a local phenomenon, due to their potent anti-proliferative effect. Nevertheless, the need to re-intervene on the same vessel or on other vessels at long-term follow-up increases with time at a higher rate compared with BMS, likely because of a more intense induction of neatherosclerosis that follows the implantation of the Taxus or Cypher stents, a permanent endothelial damage being considered to play a main role in this sustained plaque progression.\(^12\) A lower need for repeated interventions in different segments of the treated vessel and in other than the treated vessels (non-TLR+non-TVr) following immunosuppression with prednisone, may suggest a global beneficial effect of the treatment. This, if proved by adequately conceived investigations, may benefit patients undergoing PCI irrespective of the type of stent implanted. The anti-proliferative effectiveness of the steroid treatment mediated by persistent and effective inhibition of monocyte activation and cytokines release, as demonstrated in a subgroup of patients of the CEREA-DES, provides mechanistic support to this hypothesis.\(^26\) Furthermore, relatively short cycles of immunosuppression with steroids have shown similar efficacy at long term compared with prolonged steroid exposition in several diseases of known inflammatory nature, such as, cystic fibrosis, acute and recurrent periartiditis, retroperitoneal fibrosis, and kidney transplant patients, among others.\(^27\) – \(^29\)

The comprehensive interpretation of these observations, and their potential clinical impact, raises important questions that warrant further investigation.

### Clinical implications and conclusions

Our study shows that a relatively short cycle of high-dose prednisone treatment given orally after BMS implantation in non-diabetic patients with advanced CAD, improves the clinical outcome of PCI performed in patients receiving BMS, by reducing the cumulative incidence of MACE at long term. The significant clinical benefit observed at 1 year (HR: 0.505; 95% CI: 0.260–0.981) was further incremented along time up to 4 years (HR: 0.447; 95% CI: 0.249–0.803) without the occurrence of undesirable adverse effects that may be attributable to the steroid treatment itself.

<table>
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<tr>
<th>Table 2 One-year outcome and anti-platelet regimen</th>
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<tr>
<td>BMS, n = 125 (%)</td>
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<td>30-days (hierarchical)</td>
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<tr>
<td>Cardiac death</td>
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<td>QWMI(^a)</td>
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<td>NQWMI(^b)</td>
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<td>TVR(^c)</td>
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<td>Aspirin</td>
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<td>Thienopyridine</td>
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<td>1-year (hierarchical)</td>
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<td>All death</td>
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<td>1-year (cumulative)</td>
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<td>Cardiac death</td>
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<td>Non-TVR</td>
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<td>Dual anti-platelet therapy beyond 12 months</td>
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There were no other significant differences among groups. MACE, major adverse cardiac event; MI, myocardial infarction; QWMI, Q-wave myocardial infarction; NQWMI, non-Q-wave myocardial infarction; TLR, target lesion revascularization; TVR, target vessel revascularization.\(^a\) Subacute stent thrombosis.\(^b\) Procedural MI.\(^c\) P < 0.05 vs. BMS group.**P < 0.001 vs. BMS and prednisone groups.
The strategy of using prednisone, on top of optimal medical therapy, after BMS implantation in patients without contraindications, may prove particularly suited in suboptimal candidates for prolonged intense anti-platelet therapy. Furthermore, the present study, as well as other previous experiences, has shown that the systemic effect of the drug provides restenosis protection also in complex patients with diffuse disease, long lesions, or bifurcations treated with balloon angioplasty and spot and provisional stenting. Furthermore, due to the irrelevant economic cost of the drug, this strategy may help patients (and doctors) in situations of economic restrictions wherever the cost of DES is still an issue.

**Study limitations**

The study was designed as a superiority trial, to compare DES, and BMS plus prednisone, with BMS. The direct comparison of the two study groups (DES vs. prednisone) as a non-inferiority trial would be of greater interest. However, the sample size required for a pairwise comparison of the three groups is beyond the possibility of an investigator-initiated study. Indeed, even keeping the non-inferiority margin as high as 25%, 2507 patients per arm would be required in order to obtain an 80% power. Under a clinical standpoint, prednisone treatment and dual anti-platelet therapy require accurate monitoring of side-effects, and this has precluded the possibility of performing the study in a blinded fashion. The exclusion of diabetic patients is a main limitation to the applicability of this treatment and a possible determinant of the global incidence of MACEs. Finally, our DES patients underwent Cypher and Taxus implantation, new generation DES may permit shorter periods of dual anti-platelet therapy with better safety profile.

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**Conflict of interest:** none declared.

**References**

BMS alone to eliminate restenosis (CEREA-DES) - study design and rationale.

Appendix

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Percutaneous implantation of a 26 mm Edwards SAPIEN-XT aortic valve prosthesis in a degenerated 30 mm mitral annuloplasty ring

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A 80-year-old male presented with New York Heart Association (NYHA) IV functional class and peripheral oedema 6 years after mitral valve (MV) surgery comprising restrictive annuloplasty (St Jude Medical Seguin ring, 30 mm), implantation of neo-chordae and pericardial patch plastic of the posterior MV leaflet. Echocardiography showed severe MV stenosis [Panel A, two-dimensional (2D) Doppler trace of the MV; Panel B, 3D transoesophageal echocardiography (TEE) of the annuloplasty ring and MV orifice]. Open-heart surgery was declined because of relevant co-morbidities (logistic EuroSCORE 37.4%; STS-Score: 9.3%). Therefore, a percutaneous transvenous MV implantation with a ‘valve-in-ring’ technique was planned. To assess feasibility, ex vivo implantation of a transfemoral balloon expandable aortic valve (TAVI) bioprosthesis (Sapien XT, Edwards Life-sciences, Irvine, CA, USA) in a SJM Seguin 30 mm ring was performed, which confirmed stable positioning of a 26 mm prosthesis inside the rounded MV ring with some extent of a periprosthetic leakage (Panel C, * indicates periprosthetic leakage). Therefore, we planned the valve expansion with adding 2 mL of extra fluid to the recommended balloon-volume for this TAVI prosthesis. Thereafter, a transfemoral delivery system for TAVI was used to deliver the stented valve in the mitral position over a transvenous, transseptal antegrade approach (Panel D, fluoroscopy of the aortic valve insertion). The bioprosthesis was deployed successfully within the non-fluoroscopic MV ring under TEE guidance. Three-dimensional echocardiography confirmed proper positioning and function of the bioprosthesis with acute reduction of the measurable transvalvular pressure gradient, and without periprosthetic leakage (Panel E, 3D TEE en face view of the acute procedural result; Panel F, 2D TEE with Doppler trace of the MV). The patient was discharged on Day 7 after the procedure with improved functional NYHA class II.

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