The SSTARS (STeroids and Stents Against Re-Stenosis) Trial: different stent alloys and the use of peri-procedural oral corticosteroids to prevent in-segment restenosis after percutaneous coronary intervention.

Adam Z[1], Turley A[1], Mason JM[2], Kasim AS[3], Newby D[4], Mills N[4], Padfield G[4], Thompson L[1], Morley R[1], Hall JA[1], Wright RA[1], Muir DF[1], Sutton AGC[1], Swanson N[1], Carter J[1], Bilous R[1], Jones S[1], de Belder MA[1]

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[1]The James Cook University Hospital,
South Tees Hospitals NHS Trust,
Marton Rd,
Middlesbrough TS4 3BW
United Kingdom

[2]Warwick Medical School
University of Warwick
Coventry, CV4 7AL, United Kingdom

[3]School of Medicine, Pharmacy and Health
Durham University, Queen's Campus
Wolfson Research Institute, University Boulevard
Stockton-on-Tees, TS17 6BH, United Kingdom

[4]Royal Infirmary of Edinburgh,
Lothian University Hospitals NHS Trust,
Old Dalkeith Road,
Edinburgh EH16 4SA
Great Britain

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Corresponding author:

Dr Z Adam

The James Cook University Hospital

Marton Road

Middlesbrough TS4 3BW

UK

Email : zulfiquar.adam@nhs.net

Abstract

Background

Stent design and technological modifications to allow for anti-proliferative drug elution influence restenosis rates following percutaneous coronary intervention (PCI). We aimed to investigate whether peri-procedural administration of corticosteroids or the use of thinner strut cobalt alloy stents would reduce rates of binary angiographic restenosis (BAR) after PCI.

Methods

This was a two centre, mixed single and double blinded, randomised controlled trial using a factorial design. We compared (a) the use of prednisolone to placebo, starting at least six hours pre-PCI and continued for 28 days post-PCI, and (b) cobalt chromium (CoCr) to stainless steel (SS) alloy stents, in patients admitted for PCI. The primary end-point was BAR at six months.

Results

315 patients (359 lesions) were randomly assigned to either placebo (n=145) or prednisolone (n=170) and SS (n=160) or CoCr (n=160). The majority (58%) presented with an ACS, 11% had diabetes and 287 (91%) completed angiographic follow up. BAR occurred in 26 cases in the placebo group (19.7%) versus 31 cases in the prednisolone group (20.0%) respectively, p=1.00. For the comparison between SS and CoCr stents, BAR occurred in 32 patients (21.6%) versus 25 patients (18.0%) respectively, p=0.46.

Conclusion

Our study showed that treating patients with a moderately high dose of prednisolone for 28 days following PCI with BMS did not reduce the incidence of BAR. In addition, we showed no significant reduction in 6 month restenosis rates with stents composed of CoCr alloy compared to SS.

Keywords

Restenosis; Prednisolone; Cobalt chromium; Stainless Steel; Angioplasty

Introduction

Inflammation is one of the key mechanisms of restenosis after intra-coronary stent implantation[1]. An inflammatory cascade results in neo-intimal proliferation which, if excessive, results in restenosis. Drug eluting stents (DES), offering local delivery of immunosuppressive or anti-inflammatory drugs[2], have been the most successful means of reducing the need for target vessel revascularisation compared with bare metal stents (BMS)[2]. Despite the introduction of DES, BMS are still used in patients at low risk of restenosis and in patients for whom a short course of dual anti-platelet drug therapy is desirable(e.g. when there are concerns about risk of bleeding). DES are also more costly and so BMS may also be favoured for economic reasons in some health economies. There have also been concerns about stent thrombosis and accelerated neoatherosclerosis, particularly with first generation DES [3-5].

Issues for DES include drug delivery and polymer coatings (which themselves are associated with an inflammatory response). An alternative approach using systemic anti-inflammatory agents has also been tried. Corticosteroids mediate their effects primarily through the modulation of the cytosolic glucocorticoid receptor. Expression of anti-inflammatory proteins is upregulated and expression of pro-inflammatory proteins repressed, [6, 7] both of which may reduce restenosis.

The pathology of restenosis in BMS begins early after PCI and inflammatory reaction within the first 30 days is important[1]. Thus, both the timing and duration of corticosteroid therapy may be relevant to lowering restenosis rates and it may be important to suppress the inflammatory response prior to stent implantation. Corticosteroids have been studied in different contexts, including balloon angioplasty with and without stenting, and with variable duration of treatment both pre-procedure or post procedure. Results have been mixed [8-10].

Another important factor influencing restenosis in BMS is strut thickness. In stainless steel (SS) stents, restenosis occurs less frequently with thinner struts [11, 12]. These findings have influenced the drive towards the use of higher radial strength materials such as cobalt chromium (CoCr) alloys that allow reduction in strut thickness. Early registry studies supported this concept reporting restenosis in 15.7% of patients with cobalt alloys [13, 14] but there has been a lack of randomised data.

This trial investigated whether administration of corticosteroids (started several hours prior to PCI) or the use of CoCr stents would reduce the rate of binary angiographic restenosis (BAR) after PCI.

Methods

Study Design

Using a 2x2 factorial design, a two centre, randomised controlled trial compared the use of prednisolone to placebo and CoCr to SS steel alloy stents in patients admitted for PCI.

The trial featured a mixed single and double blinded randomised controlled design. Both the patients and the physicians performing PCI were blind to the prednisolone/placebo allocation but only the patients were blinded to the stent allocation. Patients were block randomised to prednisolone or placebo prior to angiography and subsequently to CoCr or SS stent once eligibility was confirmed. To provide a loading dose of prednisolone prior to the procedure, randomisation to prednisolone or placebo occurred in a 1:1 ratio prior to PCI. Patients eligible were randomised to either a CoCr or SS stent in a 1:1 ratio. Allocation of patients into intervention groups was achieved using a closed envelope system, managed by a research team working independently of the clinical team.

The primary objective was to show that prednisolone (compared with placebo) or CoCr stents (compared with SS stents) reduced 6 month BAR, defined within the stented segment plus five millimetres proximal and distal to this. Secondary objectives included investigation of the effects of the interventions on a number of pre-specified angiographic measures (see below), impact of highly sensitive (hs)-CRP, and assessment of patient safety. Major adverse cardiovascular and cerebrovascular events (MACCE: death, myocardial infarction, cerebrovascular event and target vessel revascularisation) were also recorded.

Setting

The study was performed in two tertiary cardiac units in the United Kingdom, The James Cook University Hospital in Middlesbrough and the Royal Infirmary of Edinburgh.

Recruitment

Patients eligible for the study were identified from the elective waiting list or were awaiting angiography after an acute coronary syndrome (ACS). Inclusion criteria for the double randomisation were: awaiting PCI for symptomatic coronary artery disease (elective or acute); documented myocardial ischaemia; coronary angiography demonstrating at least a 50% reduction of the luminal diameter (by visual estimate) in at least one native coronary artery; any lesion for which the operator (consultant interventional cardiologist) assessed a non-drug eluting stent was appropriate. Exclusion criteria included proposed use of a drug eluting stent in the study lesion(s);

left main stem stenosis ≥50%; primary PCI for ST elevation myocardial infarction; corticosteroid therapy for an alternative reason within 30 days of study enrolment; contraindication to corticosteroid use; previous recruitment to the trial; non-cardiac disease likely to cause death within six months; out of region hospital transfers.

Trials procedures

Prednisolone 40mg/day (or placebo) was started at least six hours pre-procedure and continued for 14 days, stepped down to 20mg/day from days 15-21 and 10mg/day from days 22-28.

Patients were pre-treated with clopidogrel. Coronary angiography was performed via femoral or radial artery puncture. After sheath insertion, a bolus of heparin was administered (dose: weight related with a minimum of 70u/kg). Before angiography, 200µg of intracoronary nitrate was administered. Lesions in large vessels (visual estimate of ≥3mm) were treated according to randomisation between the Multilink Zeta™ (SS) and Multilink Vision™ (CoCr) stents (Abbott Vascular, USA). Additional lesions in small vessels could be treated with Cypher Select™ stents (Cordis, USA), eluting sirolimus but as the trial progressed other second generation DES were also employed. Patients could be enrolled into the trial with lesions in small vessels if the operator thought it was reasonable to treat with a BMS.

Due to dual oral antiplatelet therapy plus oral corticosteroid use, all patients received empirical proton pump inhibitor cover (lansoprazole 30mg/day for 28-days) for the duration of the prednisolone course. Optimal medical therapy with beta-blockers, angiotensin-converting enzyme inhibitors and statins was encouraged; use of other agents was at the discretion of the attending physician. Patients were treated with aspirin 75mg daily indefinitely and clopidogrel 75mg daily for a minimum of four weeks.

All patients randomised were routinely brought back for repeat angiography. Quantitative coronary angiography (QCA) was performed as at the outset for all treated segments.

Angiographic measurements were made before predilatation (baseline), after the stenting procedure and at follow up using the Philips Inturis™ system by a research fellow (ZA) who performed the analysis independent of the clinical information. Measurements were made in diastole and performed in two orthogonal views. The contrast filled guiding or diagnostic catheter was used for magnification calibration. QCA measures included: minimal luminal diameter (MLD); reference diameter, derived as either an average of the proximal and distal reference diameters or the interpolated diameter derived by the software for the selected segment; percent diameter

stenosis; in-stent restenosis, defined as ≥50% diameter stenosis within the stent at follow up; in-segment restenosis, defined as ≥50% stenosis within the stented segment or within 5mm proximal or distal to the stent edges; acute gain, defined as the difference between MLD after stent implantation and the MLD before PCI; late loss, defined as the difference between the MLD after stent insertion and the MLD at follow up; net gain, defined as the difference between acute gain and late loss.

Biomarkers and monitoring of blood glucose

Hs-CRP and glycated haemoglobin (HbA1c) were measured at five time-points: at study entry, on the day of the procedure, at seven days, at 30 days and finally at six month follow up. Due to the potential problem of hyperglycaemia in patients randomised to corticosteroid treatment, all patients were given home glucose monitoring kits. Prior to hospital discharge they were instructed on the correct use of home monitoring. They were also educated on normal values and provided with contact details of the research team, in hours, or cardiology on call team, out of hours, for support and advice if their blood glucose recordings were high.

Safety

All patients were monitored for bleeding or for hyperglycaemia. Bleeding episodes were classified according to the Thrombolysis in Myocardial Infarction (TIMI) study group criteria for bleeding[15]. Adverse events were recorded according to expectedness and relatedness.

Statistical Analysis

The sample size for a 2x2 factorial design was calculated to detect an absolute difference in in-segment restenosis rates for both the stent and drug comparisons from 30% to 15%, assuming 5% alpha, 80% power and 15% loss to follow-up, indicating 137 patients per group (548 in total), and assuming no interaction between comparison groups. The planned sample size was not achieved and 315 patients were recruited within the constraints of unplanned complexities for patient identification and recruitment. The power calculation for the study was revisited prospectively before analysis of trial data and informed by recent evidence. Assuming restenosis occured in 30% of patients, and that both chromium cobalt stenting and prednisolone might halve the risk of restenosis, the average 'intervention rate' would be 11.25% and the average 'control' would be 22.5% within each comparison group. Assuming alpha of 5%, the trial had 72% power to detect an absolute difference of 11.25% between groups, using a two-sided test (nQuery+nTerim 2.0)

Analysis was performed by the principle of intention to treat (ITT), with analyses conducted according to assignment at randomisation[16, 17]. The intention to treat principle allows for modification due to missing data, for which there is no completely satisfactory remedy since strong assumptions are required regardless of the approach taken[18, 19]. Primary inference was based on the primary endpoint analysis as a difference in proportions, using Fisher's exact test [20] with statistical significance at the 5% level (2-sided), for combined stent groups and drug groups. Analyses of all secondary endpoints and adjusted analyses were considered supportive to the primary analysis so no adjustments for multiple comparisons were made.

Sensitivity analysis of the primary endpoint was performed at the level of the patient and lesion using generalized linear models (GLMs) with separate indicator variables for steroid and stent groups as well as their interactions. Secondary analyses explored changes in angiographic measures using GLMs [19, 21] and the role of covariates such as CRP level .

Patient demographics and study endpoints involving categorical variables were estimated using Fisher's exact test; continuous measures were evaluated using Student's t-test where appropriate, otherwise suitable non-parametric tests were used.

Ethics and governance

The conduct of the trial was subject to local site and London Multicentre Research Ethics Committee (MREC) approvals (ref: 04/MREC2/061) and registered with UK Trials (ISRCTN 05886349).

Results

Between January 2006 and May 2012, 315 patients were recruited and 359 lesions treated. The trial initially recruited mainly elective patients in whom angiographic status was known but over the course of the trial most patients underwent PCI immediately following angiography. In addition, a rapid increase in the use of DES made recruitment a challenge (see consort diagram, Figure 1). The mean age was 60 years (range 37 to 87 years), 85% were male, 42% were elective PCI cases and the mean number of lesions treated was 1.14 (range 1 to 4). Groups were similar at baseline, with no significant baseline differences (Table 1). Of 315 patients, 308 (98%) received the treatment allocated to them and there were no instances of treatment cross-over.

Angiographic measures

These are shown for primary target lesions in Table 2. There was no difference in stenosis by any measure pre or post PCI, or at follow up. This was also the case when the data were analysed using the interpolated reference diameter. Across all groups, average in-segment diameter stenosis was: 70.3% (95%CI: 68.8% to 71.7%) pre-PCI; 6.6% (95%CI: 5.9% to 7.3%) immediately post-PCI; and 35.2% (95%CI: 33.3% to 37.0%) at final follow up. Acute gain was 2.07mm (95%CI: 2.02 to 2.13mm), late loss 1.04mm (95%CI: -0.98 to 1.10mm) and net gain was 1.04 (95%CI: -0.97 to 1.12mm). The results were qualitatively the same for all lesions. The cumulative distribution of stenosis in target lesions is shown in Figure 2.

Endpoints

The primary endpoint of binary angiographic restenosis is reported in Table 3. There was no difference in restenosis between treatment groups. In-segment average restenosis across all groups was 19.1% (95%CI: 14.7% to 24.2%). However there was significant variation within the individual treatment combinations (varying from 11.7% to 26.4%) and a significant interaction was identified within a general-linear model. For in-stent average restenosis of target lesions the log-odds findings (x) were:

$$x = -2.024 + 0.804.drug + 0.999.stent - 1.555.drug{\cdot}stent$$
$$p<0.001 \qquad p=0.096 \qquad p=0.039 \qquad p=0.015$$

where *drug* is an indicator variable for prednisolone, *stent* is an indicator for stainless steel stent and *drug.stent* is the interaction term for *stent* and *drug* combined. Findings were qualitatively similar, regardless of the restenosis definition taken for target lesions or use of hierarchical models including all treated lesions. Analysis of stenosis percentage (y) using a general linear model did not find an interaction.

$$y = 33.40 + 3.11.drug + 3.20.stent - 5.82.drug{\cdot}stent$$
$$p<0.001 \qquad p=0.26 \qquad p=0.25 \qquad p=0.12$$

Findings were qualitatively similar, regardless of the restenosis definition taken for target lesions or use of hierarchical models including all treated lesions. The explanation for these findings is apparent in the comparison of cumulative stenosis rates comparing the treatment combinations (see Figure 2). Although there is no apparent difference over much of the distribution, there are apparent differences in the tail at the 50% stenosis point. Thus the finding may be an artefact of selectively dichotomising a continuous outcome and may not be of clinical importance.

There were no important differences in any other study endpoints, adverse or serious adverse events (Table 3).

Bleeding

Use of prednisolone did not influence the frequency of bleeding episodes: 7.6% vs. 5.5% for placebo, p=0.50). Almost all bleeds were minor and mainly related to femoral access (2.9% vs. 2.8% for placebo) at the time of the procedure. There was only one major bleeding episode (per rectum bleeding requiring transfusion). This occurred in the placebo group during the index admission and study medication was stopped.

Biomarkers and hyperglycaemia (Table 4)

Hs-CRP measurements were not available for 16 patients. The pre-PCI hs-CRP measurement was ≤5mg/l in 213 patients (71%) of whom only 28 (13%) had a raised CRP at day 7. Use of prednisolone was associated with a suppression of hs-CRP response at day 7 (-5.98 mg/L, 95%CI: -8.35 to -3.61, p<0.001) with a small rebound at day 30 (2.71mg/L, 95%CI: 0.78 to 4.65, p=0.006). There was no evidence of longer term changes at six months. There was no correlation between lowering hs-CRP and stenosis diameter at follow-up.

More patients had home blood glucose levels greater than 11mmol/l in the prednisolone than placebo group during follow-up: 22.9% vs. 6.9% respectively (p<0.001). This finding was apparent qualitatively in diabetic patients: 55.0% vs. 28.6% (p=0.17), as well as in non-diabetic patients: 18.7% vs. 4.6% respectively (p<0.001). In the majority of cases, dietary advice and reassurance was sufficient and there was no significant difference between the groups in use of additional oral hypoglycaemic therapy, insulin or need for study medication to be stopped. Glycated haemoglobin (Hb_{A1c}) was also monitored at five points during the trial. There were no clinically important differences between treatments during the trial.

Discussion

This trial was designed to address two separate questions. Was there was any benefit of (a) pre-procedural systemic corticosteroid therapy and (b) the use of thinner strut cobalt alloy stents in preventing BAR after BMS implantation? At the time of trial conception, both were seen as promising especially as there was concern about longer term safety with DES[4]. We found no benefit from the use of 28-days of prednisolone started at least six hours pre-procedurally or from the use of cobalt chromium stents.

Compared with previous randomised studies [9, 10] of corticosteroids, one of the key differences in design of this trial was the use of pre-procedural steroids and duration of treatment for 28 days. In the study by Lee *et al*., a single pulsed dose of intravenous methylprednisolone pre-procedure did not confer any benefit in reducing restenosis in BMS [9]. In The Immunosuppressive Therapy for the Prevention of Restenosis after Coronary Artery Stent Implantation (IMPRESS) study, prednisone administered 72 hours post procedure for 45 days in patients with elevated post-procedural CRP levels but normal pre-procedural CRP levels resulted in marked reductions in restenosis [10] with benefit extending clinically to five years [22]. There were only a small proportion (n=28/213) of such patients in our study, although our post procedure hs-CRP levels were measured at day 7. Our steroid protocol was designed to ensure therapeutic levels of anti-inflammatory activity before the initial injury from stenting as well as the resultant inflammation. Notably, we did not see any association between reducing hs-CRP and lowering restenosis. Our findings suggest that only a minority of elective and urgent patients fulfil the requirements of the IMPRESS protocol. Moreover, in routine clinical practice, the choice of stent at the time of the procedure cannot be determined by what the hs-CRP might be a few days later. Even in patients treated with BMS, the logistics of arranging for a routine hs-CRP measurement at 72 hours and then determining the use of steroids is difficult.

Our findings also differ from the most recent meta-analysis of five studies investigating the role of corticosteroids in reducing restenosis rates [23]. Separate analyses were performed for two trials involving balloon angioplasty alone [8, 24] and three involving BMS implantation [9, 10, 25]. Corticosteroids did reduce restenosis following BMS implantation (RR 0.60, 95% CI 0.37-0.97). Two of these trials, the study by Lee *et al*. and IMPRESS have been discussed above. In the Cortisone plus BMS or DES alone to Eliminate Restenosis (CEREA-DES) trial, the study endpoint was not angiographic restenosis but rather a combined clinical endpoint of major adverse cardiovascular events (MACE).In about half of these patients CRP was raised post PCI, defined as >3mg/l, and there was a significant reduction in MACE (23% vs. 8% for prednisone treated, p=0.03) but it is not clear whether this was driven by less restenosis; target lesion revascularisation was 12% vs. 8% (p=0.23) for BMS alone (n=125) compared to BMS plus oral prednisone (n=125)[25].

In both IMPRESS and CEREA-DES, the incidence of a raised CRP prior to treatment was higher than in our study (28%), suggesting that this might be an important feature to identify a group of patients likely to get a clinically important effect. Even though we included a relatively high proportion of patients following an acute coronary syndrome our results suggest that upstream steroid therapy will have no impact on restenosis in a population where the pre-procedural hs-CRP is not known.

Both IMPRESS and CEREA-DES utilised a high dose steroid regimen (reducing regimen of 1mg/kg for the first 10 days, 0.5 mg/kg from day 11 to day 30 and 0.25mg/kg from day 31 to 45). They did not include patients with diabetes. In our study, we included patients with diabetes and this influenced the steroid regimen, which was selected after discussion with our endocrine team to provide an effective anti-inflammatory dose used in other areas of medicine using a lower total and maximum dose of steroid in the early phase of treatment whilst minimising the risk of metabolic side effects. However, it is noteworthy that the results of the IMPRESS-LD study suggested that higher dose intensity for a longer period of time was required to reduce restenosis. The "low-dose" regimen in this small study itself included a loading of 1mg/kg for the first five days of treatment [26]. This may partly explain the difference in our findings. Prednisone (which is metabolised to prednisolone) was well tolerated but in our study, with more patients, we saw an increase in hyperglycaemia in patients on prednisolone, even amongst those without known diabetes. The potentially greater anti-inflammatory activity with higher doses of prednisolone may therefore come at the cost of increased adverse effects. It is also possible that any benefits from an anti-inflammatory reaction might be countered by a positive effect on tissue proliferation.

We also compared the use of thinner strut cobalt alloy stents with stainless steel stents. In The Intracoronary Stenting and Angiographic Results Strut Thickness Effect on Restenosis Outcome (ISAR- STEREO) trial, thinner strut SS stents compared with thicker strut stents with a similar design had significantly less late lumen loss and BAR (15% vs. 26%, p=0.003)[11] . Similarly the ISAR-STEREO 2 trial showed that thicker strut SS stents with a different design resulted in more restenosis compared to thin strut stents (31% vs. 18%, p<0.001)[12]. We tried to minimise other stent design factors by using stents of similar design (Multilink) but composed of the two different alloys. In our study, there was no significant reduction in restenosis rates in the thinner strut CoCr stent. The difference in strut thickness was more marked in the ISAR-STEREO trials (50µm vs. 140µm) compared to our study (81µm for the CoCr vs. 90-125µm variable strut thickness system for the SS stent which is thicker in straight areas and less in areas where the stent needs to bend). It also may be that the expected reduction of restenosis due to reduced strut thickness with CoCr might have been countered by some other unknown factor. Although our study did not show an advantage for the lower strut thickness stent using the CoCr alloy, it did not show a disadvantage and there may be other advantages from using the cobalt alloy, especially in improving trackability.

Only one other single centre randomised study from Brazil has compared the influence of metal alloy (SS vs. CoCr) on restenosis. In keeping with our findings there was no difference in this outcome [27]. Their study design was different from our study in that both types of stents were

implanted in the same patient but either in different vessels or in the same vessel if a gap greater than 10 mm could be left between the stents. There was also a larger proportion of patients with diabetes (36%) and higher rates of restenosis (34% vs. 32% SS compared to CoCr, p=0.80) than in our study. Moreover, a range of different SS stents were used in the comparison group with a considerable range in strut thickness. There is scant experimental data on the subject. A small non-randomised animal study comparing SS (120µm) and CoCr (90µm) stents implanted into normal porcine coronary arteries did not find an advantage of CoCr compared to SS with regards to late lumen loss and neointimal area from histopathological samples [28].

Our trial, although factorial in design, was not powered to detect a stent-drug interaction but nonetheless found one for the binary angiographic restenosis outcome. Within the stainless steel group, there is a numerical reduction in restenosis by prednisolone whereas the opposite occurs in the chromium cobalt group. The weight percentage of nickel and molybdenum is higher in 316L SS than CoCr [29] and the release of these metal ions may trigger local immune and inflammatory responses in susceptible individuals [30]. Whilst this may provide a plausible basis for a stent-drug interaction, it is more likely that this observation is a chance finding.

Study Limitations

The change in the pattern of PCI delivery over the course of the study, with a shift towards more acute cases and ad hoc PCI had an adverse influence on recruitment. Many patients were not eligible for the second randomisation. This was compounded by the rapidly increasing use of DES use, largely the result of a National Institute of Health and Care Excellence (NICE) recommendation that DES should be used in arteries less than 3mm in diameter or lesions greater than 15mm in length[31]. Patient concerns about side effects of prednisolone and the need for repeat coronary angiography were also factors. This ultimately led to the recruitment target not being met. We approached approximately four patients for every patient who consented to the first randomisation. Of those who consented, only about 1 in 3 was suitable for randomisation after angiography. However, based on the results observed, it is unlikely that a statistically significant difference would have been achieved if the recruitment target had been met.

Another potential limitation is lack of operator blinding to stent type. However, this would not have been easy to achieve considering the different appearances of the stents used and the primary endpoint of the trial, BAR, was assessed without knowledge of stent type deployed. Hence we do not believe this is a major failing. There was no core laboratory analysis of the angiograms but

analyses were performed by a single research fellow separate from the clinical team. Statistical analysis was performed independently from the clinical team.

Conclusion

Our study showed that treating patients upstream with a moderately high dose of prednisolone to cover most of the period of inflammation associated with restenosis in BMS did not reduce the incidence of binary angiographic restenosis. In addition, there was no significant reduction in restenosis rates with stents composed of cobalt chromium alloy compared to stainless steel.

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References

1. Farb A, Sangiorgi G, Carter AJ, Walley VM, Edwards WD, Schwartz RS, Virmani R. Pathology of acute and chronic coronary stenting in humans. *Circulation.* 1999;99(1):44-52.

2. Stettler C, Wandel S, Allemann S, Kastrati A, Morice MC, Schomig A, Pfisterer ME, Stone GW, Leon MB, de Lezo JS, Goy JJ, Park SJ, Sabate M, Suttorp MJ, Kelbaek H, Spaulding C, Menichelli M, Vermeersch P, Dirksen MT, Cervinka P, Petronio AS, Nordmann AJ, Diem P, Meier B, Zwahlen M, Reichenbach S, Trelle S, Windecker S, Juni P. Outcomes associated with drug-eluting and bare-metal stents: a collaborative network meta-analysis. *Lancet.* 2007;370(9591):937-948.

3. Hasegawa K, Tamai H, Kyo E, Kosuga K, Ikeguchi S, Hata T, Okada M, Fujita S, Tsuji T, Takeda S, Fukuhara R, Kikuta Y, Motohara S, Ono K, Takeuchi E. Histopathological findings of new in-stent lesions developed beyond five years. *Catheter Cardiovasc Interv.* 2006;68(4):554-558.

4. Camenzind E, Steg PG, Wijns W. Stent thrombosis late after implantation of first-generation drug-eluting stents: a cause for concern. *Circulation.* 2007;115(11):1440-1455; discussion 1455.

5. Nakazawa G, Vorpahl M, Finn AV, Narula J, Virmani R. One step forward and two steps back with drug-eluting-stents: from preventing restenosis to causing late thrombosis and nouveau atherosclerosis. *JACC Cardiovasc Imaging.* 2009;2(5):625-628.

6. Rhen T, Cidlowski JA. Antiinflammatory action of glucocorticoids--new mechanisms for old drugs. *N Engl J Med.* 2005;353(16):1711-1723.

7. Radke PW, Weber C, Kaiser A, Schober A, Hoffmann R. Dexamethasone and restenosis after coronary stent implantation: new indication for an old drug? *Curr Pharm Des.* 2004;10(4):349-355.

8. Stone GW, Rutherford BD, McConahay DR, Johnson WL, Giorgi LV, Ligon RW, Hartzler GO. A randomized trial of corticosteroids for the prevention of restenosis in 102 patients undergoing repeat coronary angioplasty. *Cathet Cardiovasc Diagn.* 1989;18(4):227-231.

9. Lee CW, Chae JK, Lim HY, Hong MK, Kim JJ, Park SW, Park SJ. Prospective randomized trial of corticosteroids for the prevention of restenosis after intracoronary stent implantation. *Am Heart J.* 1999;138(1 Pt 1):60-63.

10. Versaci F, Gaspardone A, Tomai F, Ribichini F, Russo P, Proietti I, Ghini AS, Ferrero V, Chiariello L, Gioffre PA, Romeo F, Crea F. Immunosuppressive Therapy for the Prevention of Restenosis after Coronary Artery Stent Implantation (IMPRESS Study). *J Am Coll Cardiol.* 2002;40(11):1935-1942.

11. Kastrati A, Mehilli J, Dirschinger J, Dotzer F, Schuhlen H, Neumann FJ, Fleckenstein M, Pfafferott C, Seyfarth M, Schomig A. Intracoronary stenting and angiographic results: strut thickness effect on restenosis outcome (ISAR-STEREO) trial. *Circulation.* 2001;103(23):2816-2821.

12. Pache J, Kastrati A, Mehilli J, Schuhlen H, Dotzer F, Hausleiter J, Fleckenstein M, Neumann FJ, Sattelberger U, Schmitt C, Muller M, Dirschinger J, Schomig A. Intracoronary stenting and angiographic results: strut thickness effect on restenosis outcome (ISAR-STEREO-2) trial. *J Am Coll Cardiol.* 2003;41(8):1283-1288.

13. Kereiakes DJ, Cox DA, Hermiller JB, Midei MG, Bachinsky WB, Nukta ED, Leon MB, Fink S, Marin L, Lansky AJ. Usefulness of a cobalt chromium coronary stent alloy. *Am J Cardiol.* 2003;92(4):463-466.

14. Sketch MH, Jr., Ball M, Rutherford B, Popma JJ, Russell C, Kereiakes DJ. Evaluation of the Medtronic (Driver) cobalt-chromium alloy coronary stent system. *Am J Cardiol.* 2005;95(1):8-12.

15. Rao AK, Pratt C, Berke A, Jaffe A, Ockene I, Schreiber TL, Bell WR, Knatterud G, Robertson TL, Terrin ML. Thrombolysis in Myocardial Infarction (TIMI) Trial--phase I: hemorrhagic

manifestations and changes in plasma fibrinogen and the fibrinolytic system in patients treated with recombinant tissue plasminogen activator and streptokinase. *J Am Coll Cardiol.* 1988;11(1):1-11.

16. Fisher LD, Dixon DO, Herson J, Frankowski RK, Hearron MS, Peace KE. *Intention to treat in clinical trials*. New York: Marcel Dekker; 1990.

17. Hennekens CH, Buring JE. *Epidemiology in Medicine*. Boston: Lippincott Williams and Wilkins; 1987.

18. DeMets DL. Statistical issues in interpreting clinical trials. *J Intern Med.* 2004;255(5):529-537.

19. Molenberghs G, Verbeke G. *Linear mixed models for longitudinal data*. New York: Springer-Verlaf; 2000.

20. Fleiss JL. *Statistical methods for rates and proportions*. Second ed. New York: John Wiley and Sons; 1981.

21. Graybill FA. *An Introduction to Linear Statistical Models*. New York: McGraw-Hill; 1961.

22. Ferrero V, Tomai F, Versaci F, Feola M, Proietti I, Rognoni A, Ghini AS, Gaspardone A, Vacca G, De Luca L, Vassanelli C, Ribichini F, Ferrero V, Tomai F, Versaci F, Feola M, Proietti I, Rognoni A, Ghini AS, Gaspardone A, Vacca G, De Luca L, Vassanelli C, Ribichini F. Long-term results of immunosuppressive oral prednisone after coronary angioplasty in non-diabetic patients with elevated C-reactive protein levels. *EuroIntervention.* 2009;5(2):250-254.

23. Sardar P, Chatterjee S, Mukherjee D, Garratt KN. Steroids for the prevention of restenosis in bare-metal stents--a systematic review and meta-analysis. *J Invasive Cardiol.* 2012;24(3):98-103.

24. Pepine CJ, Hirshfeld JW, Macdonald RG, Henderson MA, Bass TA, Goldberg S, Savage MP, Vetrovec G, Cowley M, Taussig AS, et al. A controlled trial of corticosteroids to prevent restenosis after coronary angioplasty. M-HEART Group. *Circulation.* 1990;81(6):1753-1761.

25. Ribichini F, Tomai F, De Luca G, Boccuzzi G, Presbitero P, Pesarini G, Ferrero V, Ghini AS, Abukaresh R, Aurigemma C, De Luca L, Zavalloni D, Soregaroli D, Marino P, Garbo R, Zanolla L, Vassanelli C, investigators C-D, Ribichini F, Tomai F, De Luca G, Boccuzzi G, Presbitero P, Pesarini G, Ferrero V, Ghini AS, Abukaresh R, Aurigemma C, De Luca L, Zavalloni D, Soregaroli D, Marino P, Garbo R, Zanolla L, Vassanelli C. Immunosuppressive therapy with oral prednisone to prevent restenosis after PCI. A multicenter randomized trial. *American Journal of Medicine.* 2011;124(5):434-443.

26. Ferrero V, Ribichini F, Rognoni A, Marino P, Brunelleschi S, Vassanelli C. Comparison of efficacy and safety of lower-dose to higher-dose oral prednisone after percutaneous coronary interventions (the IMPRESS-LD study). *Am J Cardiol.* 2007;99(8):1082-1086.

27. Abreu Filho LM, Forte AA, Sumita MK, Favarato D, Meireles GC, Abreu Filho LMd, Forte AAdC, Sumita MK, Favarato D, Meireles GCX. Influence of metal alloy and the profile of coronary stents in patients with multivessel coronary disease. *Clinics (Sao Paulo, Brazil).* 2011;66(6):985-989.

28. Milewski K, Zurakowski A, Pajak J, Pajak-Zielinska E, Liszka L, Buszman PP, Bis J, Debinski M, Buszman PE, Milewski K, Zurakowski A, Pajak J, Pajak-Zielinska E, Liszka L, Buszman PP, Bis J, Debinski M, Buszman PE. Comparison of thin-strut cobalt-chromium stents and stainless steel stents in a porcine model of neointimal hyperplasia. *Medical Science Monitor.* 2010;16(1):BR40-44.

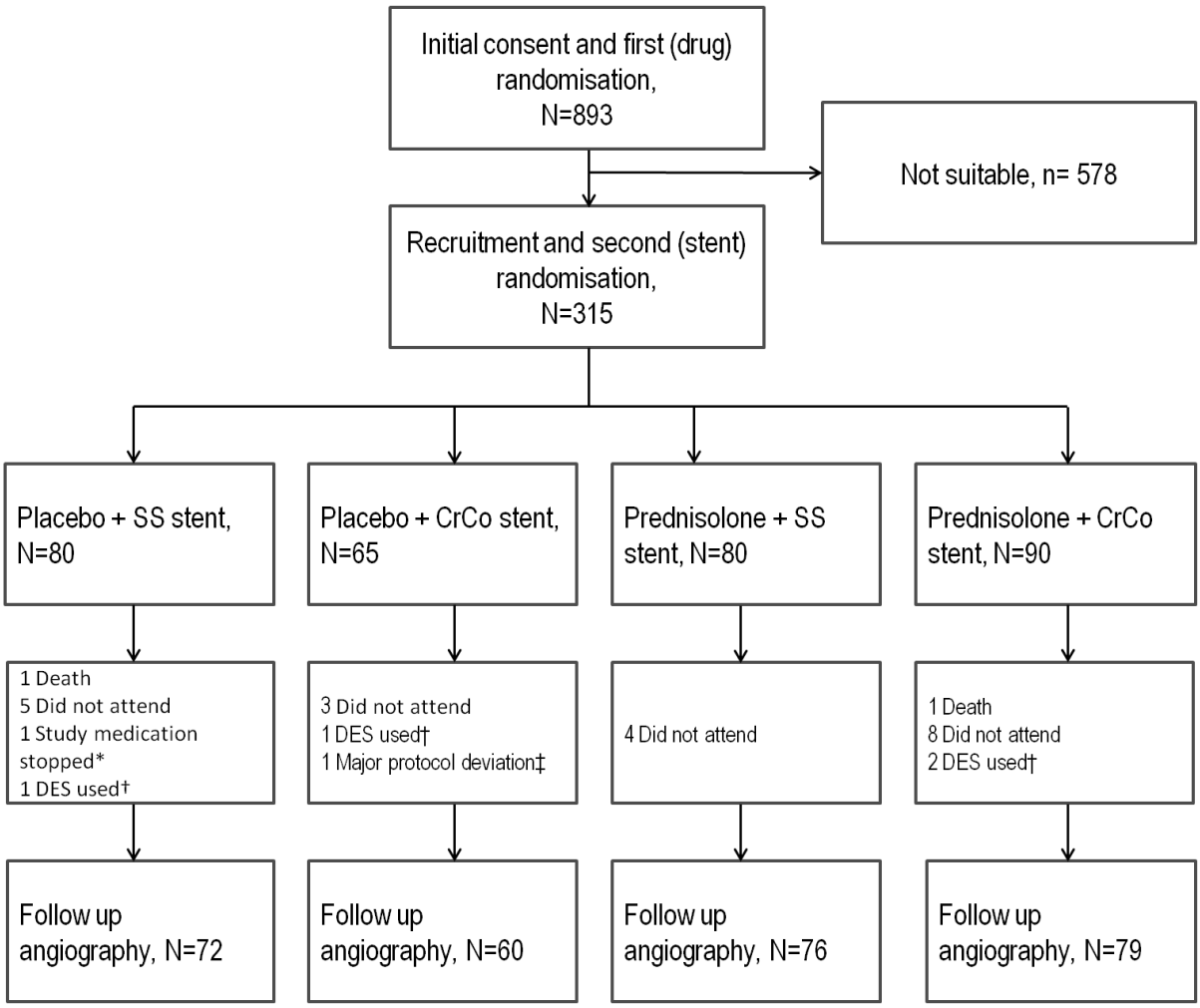
29. Mani G, Feldman MD, Patel D, Agrawal CM. Coronary stents: A materials perspective. *Biomaterials.* 2007;28(9):1689-1710.

30. Koster R, Vieluf D, Kiehn M, Sommerauer M, Kahler J, Baldus S, Meinertz T, Hamm CW. Nickel and molybdenum contact allergies in patients with coronary in-stent restenosis. *Lancet.* 2000;356(9245):1895-1897.

31. NICE technology appraisals [TA152] National Institute for Health and Care Excellence

Available at: https://www.nice.org.uk/guidance/ta152/chapter/1-Guidance. Accessed 30 October, 2015.

Figure 1. Consort diagram



*Physician directed

†Failure to deliver study stent

‡ Saphenous vein graft treated (study exclusion criteria).

Figure 2. Target lesion stenosis at six months

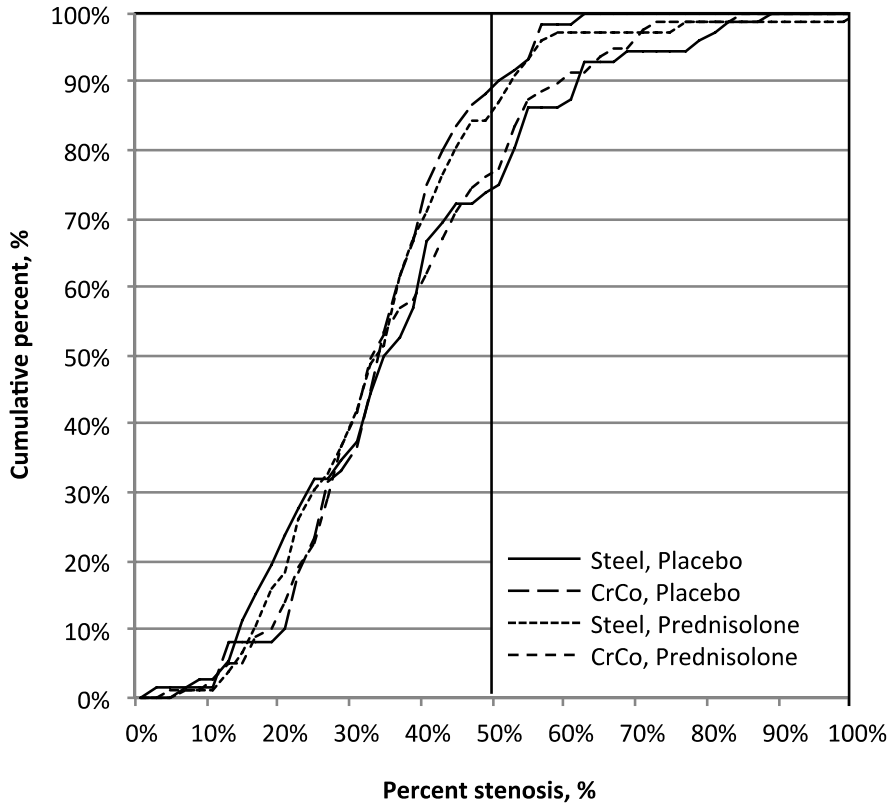


Table 1. Baseline patient characteristics

	Placebo, N=145				Prednisolone, N=170				Drug	Stent
	CoCr, n=65		SS, n=80		CoCr, n=90		SS, n=80		p	p
Actual treatment	64	(98.5%)	79	(98.8%)	87	(96.7%)	78	(97.5%)		
Elective PCI	26	(40.0%)	35	(43.8%)	37	(41.1%)	34	(42.5%)	1.00	0.73
Male	56	(86.2%)	68	(85.0%)	74	(82.2%)	71	(88.8%)	1.00	0.52
Age, y	60.2	(9.6)	60.0	(8.5)	59.5	(10.3)	62.2	(9.7)	0.54	0.23
Height, m	1.73	(0.08)	1.74	(0.09)	1.73	(0.09)	1.74	(0.08)	0.89	0.38
Weight, kg	85.5	(17.6)	87.5	(15.4)	88.9	(18.8)	86.7	(14.7)	0.50	0.82
Smoking status									0.67	0.53
never smoked	22	(33.8%)	30	(37.5%)	33	(36.7%)	24	(30.0%)		
ex-smoker	19	(29.2%)	30	(37.5%)	33	(36.7%)	33	(41.3%)		
current smoker	24	(36.9%)	20	(25.0%)	24	(26.7%)	23	(28.8%)		
History of hypertension	35	(53.8%)	42	(52.5%)	50	(55.6%)	35	(43.8%)	0.65	0.26
Family history of IHD	40	(61.5%)	42	(52.5%)	50	(55.6%)	45	(56.3%)	0.91	0.57
Previous MI	9	(13.8%)	10	(12.5%)	8	(8.9%)	12	(15.0%)	0.73	0.50
Previous CABG	3	(4.6%)	0	(0.0%)	1	(1.1%)	1	(1.3%)	0.67	0.21
Previous PCI	0	(0.0%)	3	(3.8%)	5	(5.6%)	7	(8.8%)	0.06	0.29
Previous TIA/CVA	1	(1.5%)	1	(1.3%)	3	(3.3%)	4	(5.0%)	0.19	1.00
History of peripheral VD	1	(1.5%)	4	(5.0%)	4	(4.4%)	0	(0.0%)	0.74	0.75
History of LVSD	2	(3.1%)	7	(8.8%)	3	(3.3%)	5	(6.3%)	0.62	0.13
Renal disease	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	-	-
Diabetes (I or II)	6	(9.2%)	8	(10.0%)	13	(14.4%)	7	(8.8%)	0.59	0.47
Insulin diabetic	1	(1.5%)	2	(2.5%)	2	(2.2%)	0	(0.0%)	0.67	0.68
HbA1c, %	5.75	(0.85)	5.86	(0.97)	5.83	(0.87)	5.71	(0.50)	0.75	0.88
Hypercholesterolaemia	61	(93.8%)	72	(90.0%)	76	(84.4%)	70	(87.5%)	0.11	1.00
Cholesterol, mmol/L	4.9	(1.1)	4.6	(1.3)	4.8	(1.3)	4.5	(1.0)	0.46	0.04
Creatinine value, µmol/L	91.1	(17.4)	94.0	(18.8)	90.5	(20.3)	93.4	(15.5)	0.67	0.15
Troponin, µg/L	1.35	(4.65)	4.63	(11.54)	1.39	(2.75)	1.98	(5.52)	0.17	0.07
CRP, mg/L	6.31	(14.53)	8.32	(13.11)	5.39	(11.77)	6.36	(15.07)	0.35	0.35
Number of lesions									0.46	0.72
1	59	(90.8%)	71	(88.8%)	77	(85.6%)	69	(86.3%)		
2	4	(6.2%)	9	(11.3%)	12	(13.3%)	10	(12.5%)		
3	1	(1.5%)	0	(0.0%)	1	(1.1%)	1	(1.3%)		
4	1	(1.5%)	0	(0.0%)	0	(0.0%)	0	(0.0%)		
Indication for PCI									0.58	0.81
elective	26	(40.0%)	35	(43.8%)	37	(41.1%)	34	(42.5%)		
unstable angina	11	(16.9%)	6	(7.5%)	14	(15.6%)	14	(17.5%)		
non-STEMI	25	(38.5%)	32	(40.0%)	34	(37.8%)	29	(36.3%)		
STEMI	3	(4.6%)	7	(8.8%)	5	(5.6%)	3	(3.8%)		
GPIIb/IIIa type									0.88	0.21
none	38	(58.5%)	47	(58.8%)	53	(58.9%)	44	(55.0%)		
Abciximab	26	(40.0%)	30	(37.5%)	37	(41.1%)	32	(40.0%)		
Tirofiban	1	(1.5%)	2	(2.5%)	0	(0.0%)	4	(5.0%)		
Lesion length, mm	14.0	(6.4)	13.3	(7.0)	13.8	(8.2)	14.5	(6.4)	0.49	0.98
Stent length, mm	19.2	(6.9)	20.1	(9.2)	20.7	(10.2)	21.2	(8.4)	0.24	0.55

Chromium Cobalt, CoCr; Stainless Steel, SS
Count data shown as: count (%); comparisons: Fisher's exact test
Numeric data shown as: mean (SD); comparisons: independent samples t-test

Table 2. Vessel measurements (target lesion)

	Placebo				Prednisolone				Drug				Stent			
	CoCr		SS		CoCr		SS		Prednisolone-Placebo				SS-CoCr			
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Diff.	95% CI		p	Diff.	95% CI		p
Reference diameters, mm																
Pre-PCI	3.19	(0.41)	3.13	(0.43)	3.21	(0.44)	3.21	(0.41)	0.06	-0.03	0.15	0.21	-0.03	-0.13	0.06	0.51
Post-PCI	3.24	(0.39)	3.13	(0.39)	3.29	(0.43)	3.27	(0.35)	0.10	0.01	0.19	0.03	-0.07	-0.16	0.02	0.13
6-month	3.05	(0.42)	3.02	(0.40)	3.08	(0.43)	3.09	(0.37)	0.05	-0.04	0.15	0.28	-0.02	-0.11	0.08	0.75
Minimum luminal diameters, mm																
Pre-PCI [A]	0.97	(0.46)	0.93	(0.41)	0.95	(0.46)	0.95	(0.41)	0.00	-0.10	0.10	0.99	-0.02	-0.11	0.08	0.74
Post-PCI [B]	3.02	(0.33)	2.98	(0.37)	3.04	(0.42)	3.04	(0.35)	0.05	-0.04	0.13	0.29	-0.03	-0.11	0.06	0.50
6-month [C]	2.04	(0.49)	1.91	(0.62)	1.96	(0.57)	2.05	(0.57)	0.03	-0.10	0.17	0.61	-0.01	-0.14	0.12	0.87
Acute Gain [B]-[A]	2.05	(0.50)	2.04	(0.47)	2.10	(0.54)	2.09	(0.47)	0.05	-0.06	0.16	0.42	-0.01	-0.12	0.10	0.85
Late loss [B]-[C]	0.95	(0.37)	1.08	(0.56)	1.13	(0.53)	0.99	(0.50)	0.04	-0.08	0.16	0.49	-0.02	-0.13	0.10	0.79
Net gain [A]-[C]	0.97	(0.59)	1.08	(0.58)	1.10	(0.62)	1.03	(.68)	0.04	-0.10	0.19	0.57	-0.01	-0.16	0.13	0.87
Diameter stenosis, %																
Pre-PCI	69.6%	(14.0%)	70.1%	(12.6%)	70.5%	(13.8%)	70.7%	(11.2%)	0.7%	-2.1%	3.6%	0.62	0.3%	-2.5%	3.2%	0.83
Post-PCI	6.9%	(6.4%)	5.1%	(5.2%)	7.2%	(6.6%)	7.1%	(5.6%)	1.3%	0.0%	2.6%	0.06	-1.0%	-2.3%	0.4%	0.15
6-month	33.4%	(12.3%)	36.6%	(18.7%)	36.5%	(16.2%)	33.9%	(15.3%)	0.1%	-3.6%	3.8%	0.97	0.0%	-3.7%	3.7%	0.98

Table 3. Study events

	Placebo, N=145				Prednisolone, N=170				Drug			Stent		
	CoCr, n=65		SS, n=80		CoCr, n=90		SS, n=80		Placebo	Pred.		CoCr	SS	
	Count	%	Count	%	Count	%	Count	%	%	%	p	%	%	p
Primary endpoint*														
Restenosis (by any measure)+	7	(11.7%)	19	(26.4%)	18	(22.8%)	13	(17.1%)	19.7%	20.0%	1.00	18.0%	21.6%	0.46
in-segment average	7	(11.7%)	19	(26.4%)	18	(22.8%)	13	(17.1%)	19.7%	20.0%	1.00	18.0%	21.6%	0.46
Secondary endpoints														
Target lesion revascularisation	1	(1.5%)	9	(11.2%)	5	(5.6%)	6	(7.5%)	6.9%	6.5%	1.00	3.9%	9.4%	0.07
Target vessel revascularisation	2	(3.1%)	9	(11.2%)	6	(6.7%)	6	(7.5%)	7.6%	7.1%	1.00	5.2%	9.4%	0.19
Any endpoint or SAE	8	(12.3%)	20	(25.0%)	20	(22.2%)	13	(16.3%)	19.3%	19.4%	1.00	18.1%	20.6%	0.67
MACCE														
composite	2	(3.1%)	10	(12.5%)	6	(6.7%)	6	(7.5%)	8.3%	7.1%	0.83	5.2%	10.0%	0.14
death	0	(0.0%)	1	(1.3%)	1	(1.1%)	0	(0.0%)	0.7%	0.6%	1.00	0.6%	0.6%	1.00
MI	1	(1.5%)	1	(1.3%)	1	(1.1%)	0	(0.0%)	1.4%	0.6%	0.60	1.3%	0.6%	0.62
CVA	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0.0%	0.0%	-	0.0%	0.0%	-
Target vessel revascularisation	2	(3.1%)	9	(11.3%)	6	(6.7%)	6	(7.5%)	7.6%	7.1%	1.00	5.2%	9.4%	0.19

Count data shown as: count (%); comparisons: group %, Fisher's exact test

* Analysed as target lesion (i.e. one lesion per patient) + 287 patients completed final follow-up angiography (CoCr /Placebo, n=60; SS/Placebo=72; CoCr/Prednisolone=79; SS/Prednisolone=76)

MACCE, major adverse cardiovascular cerebrovascular events; MI, myocardial infarction; CVA, cerebrovascular accident

Table 4. Study markers

	Placebo				Prednisolone				Drug			Stent		
	CoCr		SS		CoCr		SS		Prednisolone-Placebo			SS- CoCr		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	95% CI		p	95% CI		p
hs-CRP, mg/L														
admission	6.31	(14.53)	8.32	(13.11)	5.39	(11.77)	6.36	(15.07)	-4.90	1.72	0.35	-1.73	4.83	0.35
pre-procedure	5.36	(12.77)	6.66	(10.50)	4.51	(11.32)	6.69	(15.19)	-3.56	2.53	0.74	-1.22	4.83	0.24
7 days	7.25	(9.38)	7.57	(16.14)	1.86	(6.99)	0.96	(3.01)	-8.35	-3.61	<0.001	-2.31	2.62	0.90
30 days	4.11	(9.85)	3.33	(6.38)	5.79	(6.56)	7.03	(9.43)	0.78	4.65	0.006	-1.79	2.12	0.87
6 months	1.48	(1.77)	3.29	(4.31)	2.45	(4.51)	4.36	(12.82)	-1.09	2.79	0.39	-0.15	3.69	0.07
HbA_{1c}, %														
admission	5.75	(0.85)	5.86	(0.97)	5.83	(0.87)	5.71	(0.50)	-0.23	0.16	0.75	-0.21	0.18	0.88
7 days	5.76	(0.84)	5.81	(0.89)	5.97	(0.99)	5.88	(0.53)	-0.05	0.34	0.16	-0.23	0.16	0.73
30 days	5.72	(0.67)	5.75	(0.60)	6.01	(1.24)	5.95	(0.55)	0.05	0.44	0.016	-0.23	0.16	0.73
6 months	5.75	(0.67)	5.95	(0.83)	5.96	(1.14)	5.82	(0.51)	-0.17	0.24	0.75	-0.19	0.23	0.85
Time to 30d FU (d)	37.6	(104.5)	32.6	(6.9)	40.9	(79.0)	28.4	(41.6)	-15.1	15.2	1.00	-24.0	6.1	0.24
Time to 6m FU (d)	210	(37)	204	(37)	203	(34)	201	(28)	-12.9	3.0	0.22	-11.3	4.6	0.41