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RANDOMISED CLINICAL TRIAL

Editor's Choice – Two Year Results of the Randomised DISCOVER Trial Comparing Covered Versus Bare Metal Stents in the Common Iliac Artery

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WHAT THIS PAPER ADDS

This study compared covered and bare metal balloon expandable stents for advanced atherosclerotic lesions in the common iliac artery, which were defined as either a stenosis $>$ 3 cm in length or occlusion. Optimal treatment of inflow and outflow disease was mandatory, and meticulous verification of technical success was performed using bidirectional angiography and intra-arterial trans-lesional pressure gradient measurement. Under these conditions, both stent types showed excellent results after two years of follow up, with no between group differences for freedom from restenosis or target lesion revascularisation rates.

Objective: It has been suggested that covered stents (CS) may lower restenosis rates compared with bare metal stents (BMS) after endovascular treatment of the common iliac artery. This trial aimed to provide additional evidence on the efficacy of CS *vs.* BMS in the common iliac artery.

Methods: This multicentre, randomised, single blind controlled superiority trial compared balloon expandable CS and balloon expandable BMS for advanced atherosclerotic lesions in the common iliac artery; this was defined as a stenosis $>$ 3 cm in length or occlusion. The primary end point was freedom from binary restenosis after two years of follow up. The study was conducted according to the principles of the Declaration of Helsinki (version: October 2008) and registered with the Dutch Trial register (NTR3381).

Results: One hundred and seventy-four limbs were included between 2012 and 2019 with 87 limbs in each group. Six patients crossed over from the BMS group to the CS group but were analysed according to an intention to treat principle. Freedom from binary restenosis after two years of follow up was 84.7% (95% CI 76.7 — 92.7%) in the BMS group and 89.1% (95% CI 82.4 — 95.8%) in the CS group ($p = .40$). Freedom from occlusion was 95.0% (95% CI 90.3 — 95.7%) in the BMS group and 96.4% (95% CI 92.5 — 100%) in the CS group ($p = .66$). Freedom from target lesion revascularisation was 91.1% (95% CI 84.8 — 97.3%) and 95.2% (95% CI 90.7 —99.7%), respectively ($p = .31$). Technical success, complications, haemodynamic success, and clinical success were also comparable between both groups. Per-protocol analysis did not affect the outcomes of the study.

Conclusion: No difference was found between balloon expandable CS and BMS for treating advanced atherosclerotic lesions of the common iliac artery.

Keywords: Aortoiliac occlusive disease, Bare metal stents, Common iliac artery, Covered stents, Peripheral artery disease, Randomised controlled trial
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INTRODUCTION

Endovascular interventions for aorto-iliac occlusive disease are associated with decreased mortality and morbidity rates compared with open surgical repair, at the cost of decreased primary patency rates.[1] A recent meta-analysis showed primary patency rates at five years ranging from 65 — 85% for endovascular treatment compared with 85 — 95% for surgical bypass.[2]

The use of covered stents may be one way of lowering restenosis rates. It is hypothesised that neointimal hyperplasia, leading to restenosis, may be reduced by the polytetrafluoroethylene cover on the stent. It may either act by providing a direct barrier to neointimal hyperplasia growing through the stent struts or by excluding the damaged endothelium from bloodborne pro-inflammatory cytokines and macrophages.[3] One randomised controlled trial showed a significantly higher freedom from binary restenosis rate after covered stent placement compared with bare metal stents for aorto-iliac occlusive disease. Subgroup analysis showed that this effect was strongest in TransAtlantic Inter-Society Consensus II (TASC II) C and D lesions and persisted for up to five years of follow up.[4,5] A more recent meta-analysis including non-randomised series also failed to show a difference in primary patency between covered stents and bare metal stents.[6]

This article describes the results of the Dutch Iliac Stent trial: COVERed balloon expandable *vs.* uncovered balloon expandable stents in the common iliac artery (DISCOVER). This study aimed to compare the efficacy of covered balloon expandable stents (CS) and bare metal balloon expandable stents (BMS) for the treatment of stenoses $>$ 3 cm in length and occlusions of the common iliac artery (CIA).

METHODS

The full study protocol for this trial has been published previously.[7] The study was a randomised, controlled, single blind, multicentre superiority trial. Medical ethical approval was obtained from the Medical Ethical Review Committee of each participating hospital. The study was conducted according to the principles of the Declaration of Helsinki (version: October 2008)[8] and registered in the Dutch Trial register (NTR3381).[9] This article was written in concordance with the recommendations in the Consolidated Standards of Reporting Trials (CONSORT) statement.[10]

Objectives

The objective was to compare the efficacy of CS with BMS for the treatment of advanced atherosclerotic lesions of the CIA. The primary end point was freedom from binary restenosis rate at 2 years of follow up. This was defined as the percentage of limbs with the absence of $>$ 50% stenosis in or within 1 cm of the stent edge. A complete overview of end points and definitions was provided in the previously published protocol.[7]

Study population

Patients with symptomatic, advanced atherosclerotic lesions of the CIA presenting at one of the participating hospitals were included. An advanced atherosclerotic lesion was defined as a stenosis $>$ 3 cm in length or an occlusion of any length. The length of stenosis was assessed during the intra-procedural angiogram after guidewire passage, after which the definitive decision to include or exclude the patient was made. If both sides were eligible for inclusion, the most symptomatic side was included and randomised, and both sides received the allocated stent.

Inclusion criteria included age $>$ 18 years and a signed informed consent form. Exclusion criteria were mostly conditions that would preclude the patient from adhering to study procedures or completing follow up. Patients with acute occlusions and those with concomitant aortic disease for which Covered Endovascular Reconstruction of the Aortic Bifurcation[11] (CERAB) was deemed necessary pre-procedurally were also excluded. Patients with claudication were only included when they had persistent debilitating symptoms after six months of supervised exercise therapy, were prescribed optical medical therapy, and had been advised to stop smoking. A full list of inclusion and exclusion criteria was provided in the study protocol.[7]

All participating centres were large vascular centres, and procedures were performed by vascular surgeons and interventional radiologists who had broad experience in iliac artery stenting.

Sample size calculation

A freedom from binary restenosis rate of 90% in the CS group *vs.* 72% in the BMS group at two years of follow up was expected, based on the available literature at the time.[7,12,13] An α error level of 0.05 and a β error level of 0.2 were chosen, which led to a required size of 79 patients per group. Anticipating a loss to follow up of 10%, the total number of patients to be included was 174.

Randomisation, blinding, and treatment allocation

Patients were randomised 1:1 to the CS or BMS group. The online randomisation program Trans European Network for Clinical Trial Services (http://tenalea.net) was used. Rather than stratification, a minimisation algorithm was used to ensure comparable groups.[14] Parameters that were used for minimisation were occlusion *vs.* stenosis, endovascular *vs.* hybrid procedures, and critical limb ischaemia *vs.* intermittent claudication. The treating physicians could not be blinded due to the nature of the study. Patients were blinded for the allocated treatment, as were the vascular technicians performing the post-procedural ankle brachial index and duplex ultrasonography, and the research nurses who performed post-procedural follow up and scoring of events.

Treatment

The aim of the treatment was to obtain a patent CIA with unobstructed inflow and outflow via at least the superficial or deep femoral artery. Therefore, the CIA was treated and, if indicated, any concomitant lesion in the aorta, external iliac artery (EIA), and common femoral artery (CFA). This

strategy corresponds with daily practice. The CIA was treated with percutaneous or hybrid (i.e., with concomitant CFA endarterectomy) transluminal angioplasty with stent placement. After passage of the guidewire, and in the case of stenosis confirming a length of $>$ 3 cm with angiography, the patient was randomised to CS or BMS. No more than 0.5 mm oversizing of the stent relative to the reference diameter of the artery was allowed. Following placement of the stent, technical success was verified with bidirectional angiography and trans-lesional pressure gradient measurement. For residual stenosis $>$ 30% or systolic pressure gradient $>$ 10 mmHg, additional PTA and or stent placement was mandatory until technical success was achieved. Technical success was defined as successful vascular access and completion of the endovascular procedure with $<$ 30% residual diameter reduction of the treated lesion on completion angiography and systolic pressure gradient $<$ 10 mmHg. Device success was defined as exact deployment of the device according to the instructions for use. Procedural success was defined as a combination of technical success, device success, and absence of procedural complications.

The CS that was used was the Advanta V12 polytetrafluoroethylene covered stent (Getinge Maquet, Rastatt, Germany); this was the only CS used in the participating centres during the trial. The BMS that could be used were at the discretion of the treating physician: Omnilink Elite stent (Abbott Laboratories, North Chicago, IL, USA), Express LD Iliac stent (Boston Scientific, Natick, MA, USA), Palmaz Genesis stent (Cordis Corporation, Bridgewater, NJ, USA), and Scuba stent (INVATEC S.p.A, Roncadelle, Italy).

The choice of additional treatment for the aorta, EIA, and CFA was at the discretion of the treating physician, this included: percutaneous transluminal angioplasty, balloon expandable or self expanding stents or stent grafts, remote endarterectomy of the EIA, and endarterectomy with or without patch angioplasty of the CFA, provided adequate inflow and outflow were achieved.

During the intervention, all patients received a dose of at least 5 000 units of heparin. After the intervention, all patients received a statin indefinitely and dual antiplatelet therapy (DAPT) consisting of acetylsalicylic acid 80 mg once daily and clopidogrel 75 mg once daily for one month, followed by single antiplatelet therapy indefinitely. At the start of the trial, this was acetylsalicylic acid 80 mg once daily, and from 2016 onward clopidogrel 75 mg once daily, in concordance with an update of the Dutch guidelines.[15]

Baseline characteristics

A full overview of definitions of the baseline characteristics can be found in the study protocol.[7]

Follow up

Follow up was scheduled at one, six, 12, and 24 months post-procedure. Follow up included ankle brachial index with treadmill test and duplex ultrasonography (except for the1 month assessment where no duplex was performed). Parameters scored during follow up included occurrence of restenosis or occlusion, Rutherford stage, functional and haemodynamic status, and occurrence of complications, amputation, or death.

Changes to the protocol

- Calcification was scored as none, mild ($<$ 25% circumference), moderate (25 $-$ 50%), or severe ($>$ 50%).[16]
- No definition was given for clinical success in the protocol; this was defined as improvement of at least one Rutherford category, except for patients with tissue loss (Rutherford 5 and 6) who must have at least improved to a level of claudication (i.e., Rutherford $\leq$ 3) to be considered successful.[17]
- After the first month of DAPT, the protocol dictated acetylsalicylic acid 80 mg once daily, indefinitely. From 2016 onward this was changed to clopidogrel 75 mg once daily, in concordance with an update of the Dutch guidelines.[15]

Statistical analysis

Baseline characteristics of both groups were presented with descriptive analysis. For continuous data, averages with standard deviation were calculated for both groups after checking for normal distribution using data visualisation with a histogram. Frequencies were calculated for categorical data. All analyses were performed based on an intention to treat principle. A per protocol analysis was additionally performed for the primary end point. A p value of $<$ .05 was considered statistically significant.

The Kaplan—Meier method was used to estimate the freedom from binary restenosis rate and the log rank statistic to assess the efficacy of CS compared with BMS with respect to the primary end point. The secondary end points, freedom from occlusion rate, and freedom from re-occlusion rate were also calculated with actuarial (Kaplan—Meier) analysis and expressed as a percentage with a standard error and 95% confidence intervals (CI). Hazard ratios (HR) across different subgroups were calculated using Cox logistic regression analysis and visualised using forest plots.

A χ^2 test was used to compare the other categorical secondary end point variables between the two groups and the Student t test to compare the continuous secondary end points between the treatment groups.

Logistic regression analysis was performed to assess predictors of binary restenosis. Possible parameters that could predict binary restenosis were assessed using the Wald test. Parameters with a p value of $\leq$ .50 were included in the multivariable analysis. Next, stepwise backward logistic regression was performed with a cut off p value of .10 for entry or removal into the model until a fitting model was reached.

All statistical analyses were performed with SPSS 26.0 software (IBM, Armonk, NY, USA).

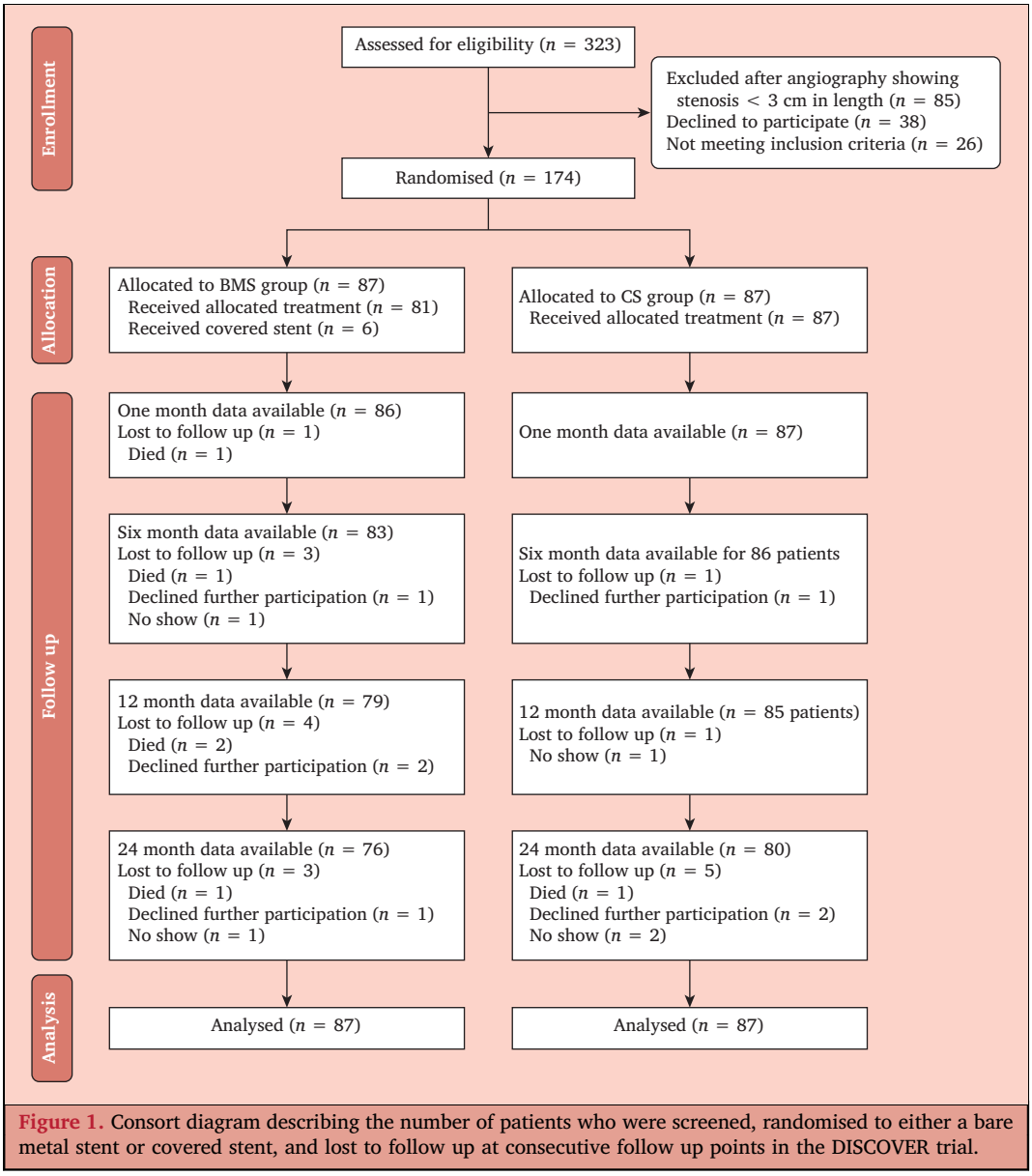

Figure 1. Consort diagram describing the number of patients who were screened, randomised to either a bare metal stent or covered stent, and lost to follow up at consecutive follow up points in the DISCOVER trial.

RESULTS

The trial included 174 patients from May 2012 until September 2019 when inclusion was completed; there were 87 patients per group (Fig. 1). More than half of the patients were included in the centre that initiated the study; this was due to slower than anticipated inclusion in the other participating centres. For this reason, more centres were added during study enrolment (see Supplementary Table S1 for numbers of included patients per centre). The other main reason for the slower than expected recruitment was that the great majority of stenoses were found to be < 3 cm and therefore excluded.

One patient in the CS group had a stenosis in the EIA rather than the CIA, and one patient in the BMS group was treated with a self expanding stent. Six patients in the BMS group had a CS for various reasons (Table 1). All of these patients remained in the study and were analysed according to the intention to treat principle. Six patients died during

Table 1. Reasons for crossover to the covered stent group in six of 87 patients who were randomised to the bare metal stent group in the DISCOVER trial, comparing bare metal stents and covered stents for common iliac artery atherosclerotic lesions

Reason for crossover
Fresh thrombus, preference for covered stent
PTA balloon bursting multiple times with residual stenosis, treated successfully with a covered stent without balloon bursting and no residual stenosis
Migrating plaque proximally, for which additional covered stent placement was performed
Conversion to CERAB due to arterial blush at aorto-iliac bifurcation
Flaring of the stent was considered necessary; this was not possible with the available bare metal stent
Conversion to CERAB due to dissection

CERAB = covered endovascular reconstruction of aortic bifurcation; PTA = percutaneous transluminal angioplasty.

Table 2. Patient characteristics for 174 patients who were treated with either a bare metal stent or covered stent for common iliac artery atherosclerotic lesions in the DISCOVER trial

Patient characteristics	Bare metal stent (n = 87)	Covered stent (n = 87)
Age − y	60±10 (40–90)	62±9 (42–86)
Male	49 (56.3)	49 (56.3)
Comorbidities		
Hypertension	52 (59.7)	53 (60.9)
Dyslipidaemia	52 (59.7)	44 (50.6)
Diabetes	16 (18.4)	12 (13.8)
Ischaemic heart disease	18 (20.7)	22 (25.3)
Congestive heart failure	3 (3.4)	1 (1.1)
Renal insufficiency	8 (9.2)	8 (9.2)
Cerebrovascular disease	7 (8.0)	9 (10.3))
Smoking, current	43 (49.4)	46 (52.9)
Smoking, past	40 (46.0)	36 (41.4)
Rutherford class		
1	14 (16.1)	8 (9.2)
2	27 (31.0)	23 (26.4)
3	21 (24.1)	30 (34.5)
4	21 (24.1)	18 (20.7)
5	4 (4.6)	8 (9.2)
Resting ABI*	0.56±0.24	0.50±0.22
Pre-intervention use of statin	74 (85.0)	76 (87.3)
Pre-intervention use of TAI	85 (97.7)	81 (93.1)
Acetylsalicylic acid	69 (79.3)	70 (80.5)
Clopidogrel	18 (20.7)	12 (13.8)
Dipyridamole	1 (1.1)	1 (1.1)
Ticagrelor	4 (4.6)	2 (2.3)
Pre-intervention use of AC	5 (5.7)	6 (6.9)
VKA	3 (3.4)	4 (4.6)
DOAC	2 (2.3)	2 (2.3)
No pre-operative TAI or AC	0 (0)	1 (1.1)

Data are presented as mean ± standard deviation (range) or n (%). ABI = ankle brachial index; AC = anticoagulant; DOAC = direct oral anticoagulant; TAI = thrombocyte aggregation inhibitor; VKA = vitamin K antagonist.
* Number of patients per group = 79.

Table 3. Lesion characteristics for 174 patients who were treated with either a bare metal stent or covered stent for common iliac artery atherosclerotic lesions in the DISCOVER trial

Lesion characteristics	Bare metal stent (n = 87)	Covered stent (n = 87)
Occlusion	61 (70.1)	62 (71.3)
Stenosis	26 (29.9)	25 (28.7)
Length of stenosis − mm	38±8 (30–50)	37±7 (30–60)
Degree of stenosis − %	68±14 (50–90)	70±15 (50–95)
*Degree of calcification**		
None	3 (4.4)	3 (4.3)
Mild	24 (35.3)	28 (40.0)
Moderate	22 (32.4)	19 (27.1)
Severe	19 (27.9)	20 (28.6)
TASC II class		
A	19 (21.8)	13 (14.9)
B	47 (54.0)	49 (56.3)
C	5 (5.7)	4 (4.6)
D	16 (18.4)	21 (24.1)
Reference vessel diameter − mm	8.4±0.9 (6–10)	8.2±0.8 (6–10)
Randomised side		
Left	46 (52.9)	43 (49.4)
Right	41 (47.1)	44 (50.6)

Data are presented as mean ± standard deviation (range) or n (%). TASC II = Trans-Atlantic Inter-Society Consensus II.
* Data unavailable for patients where no pre-operative computed tomography angiography was available; patients with bare metal stent n = 68, patients with covered stent n = 70.

the study period and 12 were lost to follow up (Fig. 1), so full data at 24 months of follow up were available for 156 patients (89.7%).

Baseline patient and lesion characteristics are described in Tables 2 and 3. Procedural characteristics are summarised in Table 4. The contralateral CIA was treated in 31 patients in the CS group compared with 19 patients in the BMS group, mainly because they more often had bilateral disease (stenosis or occlusion). Kissing stents were placed in 15 patients in the BMS group and 27 patients in the CS group. *Ad hoc* subgroup analysis and additional sensitivity analysis using a multivariable model were performed to exclude possible bias due this difference, see below.

Short term outcomes

Procedural outcomes are summarised in Table 5. Technical success was achieved in all patients. One minimal stent dislodgement occurred in the CS group. Peri-procedural complications occurred in 8.0% of patients in the BMS group and 12.6% in the CS group. Most of these complications could be resolved with adjunctive endovascular procedures such as additional balloon angioplasty or stent placement. This resulted in a procedural success of 92.0% in the BMS group *vs.* 87.4% in the CS group (p = .32).

Post-procedural complications occurred in 18.4% of patients in the BMS group and 21.8% in the CS group (Supplementary Table S2). For endovascular procedures only, excluding hybrid procedures, complication rates were 13.3% and 18.3%, respectively. These were mostly minor access site related complications such as haematomas and post-procedural limb oedema. Overall major complications rates were 6.9% in the BMS group and 8.0% in the CS group (p = .77); for endovascular procedures only these were 4.0% and 5.6%, respectively (p = .64). Major complications are summarised in Supplementary Table S3.

Clinical success at one month was 90.6% in the BMS group and 94.3% in the CS group (p = .36). For distribution of Rutherford categories pre- and post-procedurally, see Supplementary Table S4. Ankle brachial index test results at rest and after exercise at baseline and each of the follow up times are summarised in Supplementary Table S5. Clinical failures were mostly patients with claudication who experienced subjective improvement in complaints but remained in the same Rutherford category as per the objective criteria.[17] At one month of follow up, there was one patient with persisting Rutherford 5 in the CS group and one patient with

Table 4. Procedure characteristics for 174 patients who were treated with either a bare metal stent or covered stent for common iliac artery atherosclerotic lesions in the DISCOVER trial

Procedure characteristics	Bare metal stent (n = 87)	Covered stent (n = 87)
Endovascular or hybrid procedure		
Endovascular	75 (86.2)	71 (81.6)
Hybrid	12 (13.8)	16 (18.4)
Treatment of ipsilateral EIA	20 (23.0)	15 (17.4)
PTA	7 (8.0)	2 (2.3)
Stent	9 (10.3)	6 (7.0)
RIAE	4 (4.6)	7 (8.1)
CFA endarterectomy	12 (13.8)	16 (18.4)
Treatment of contralateral CIA	23 (26.4)	43 (49.4)
PTA	1 (1.1)	6 (6.9)
Stent	22 (25.2)	37 (42.5)
Reason for treating contralateral CIA[*]		
Stenosis	19 (82.6)	27 (62.8)
Occlusion	0 (0)	4 (9.3)
Protection of contralateral side[†]	3 (13.0)	8 (18.6)
Peri-procedural complication	1 (4.3)	4 (9.3)
Protrusion of stent into the aorta[‡]		
None	7 (31.8)	10 (27.0)
<10 mm	6 (27.2)	15 (40.5)
≥10 mm	9 (40.9)	12 (32.4)
Stent diameter − mm		
6	2 (2.3)	1 (1.1)
7	8 (9.2)	11 (12.6)
8	33 (37.9)	48 (55.2)
9	37 (42.5)	20 (23.0)
10	7 (8.0)	7 (8.0)
Post-operative DAPT[§]	85 (97.7)	81 (93.1)
Post-operative statin	79 (90.8)	82 (94.3)

Data are presented as n (%). CFA = common femoral artery; CIA = common iliac artery; DAPT = dual antiplatelet therapy; EIA = external iliac artery; PTA = percutaneous transluminal angioplasty; RIAE = remote iliac artery endarterectomy; SD = standard deviation.
* Total number of patients with bare metal stent n = 23 and covered stent n = 43.
† Total number of patients with bare metal stent n = 22 and covered stent n = 37.
‡ These were cases with an ostial lesion without contralateral (significant) stenosis or occlusion, where a kissing stent or balloon was placed to avoid dislodging the atheroma to the contralateral side.
§ Including patients who were on anticoagulation, who received single antiplatelet therapy for one month rather than DAPT.

Table 5. Immediate outcomes after angioplasty and stent placement for 174 patients who were treated with either a bare metal stent or covered stent for common iliac artery atherosclerotic lesions in the DISCOVER trial

Immediate outcomes	Bare-metal stent (n = 87)	Covered stent (n = 87)	p value
Technical success[*]	87 (100)	87 (100)	NP
Device success	87 (100)	86 (98.9)[†]	NP
Peri-procedural complications[‡]	7 (8)	11 (12.6)	.32
Major complications	2 (2.3)	2 (2.3)	.99
Puncture site bleeding requiring surgical closure	1 (1.1)	1 (1.1)	.99
EIA rupture (during RIAE) requiring surgical reconstruction (interposition graft)	–	1 (1.1)	NP
IIA occlusion – symptomatic	1 (1.1)		NP
Minor complications[§]	6 (6.9)	11 (11.5)	.20
Plaque migration	2 (2.3)	4 (4.6)	.41
Dissection	3 (3.4)	6 (7.0)	.30
Arterial blush	1 (1.1)	–	NP
Procedural success	80 (92.0)	76 (87.4)	.32
Mean improvement in ABI	0.38±26	0.42±0.25	.33

Data are presented as mean ± standard deviation (range) or n (%). ABI = ankle brachial index; BMS = bare metal stent; DAPT = dual antiplatelet therapy; EAI = external iliac artery; IIA = internal iliac artery; NP = not possible; RIAE = remote iliac artery endarterectomy.
* Intra-operative complications led to loss of procedural success but not loss of technical success, provided a patent CIA with < 30% residual diameter reduction and a translesional systolic pressure gradient of < 10 mmHg was achieved on completion angiography.
† One case of minimal stent dislodgement.
‡ Some patients had more than one complication.
§ All were resolved intra-procedurally using adjunctive endovascular interventions (i.e., repeat angioplasty, additional stent placement).

persisting Rutherford 4 in the BMS group. Both patients underwent additional femoropopliteal revascularisation resulting in complete ulcer healing and relief of rest pain, respectively. Clinical success at two years was 92.2% in the BMS group *vs.* 97.2% in the CS group (p = .17).

Follow up

After two years of follow up, freedom from binary restenosis was 84.7% (95% CI 76.7 — 92.7%) in the BMS group and 89.1% (95% CI 82.4 — 95.8%) in the CS group (p = .40, log rank test; Fig. 2). Freedom from occlusion was 95.0% (95% CI 90.3 — 95.7%) in the BMS group and 96.4% (95% CI 92.5 — 100%) in the CS group (p = .66, log rank test; Fig. 3). Freedom from target lesion revascularisation was 91.1% (95% CI 84.8 — 97.3%) and 95.2% (95% CI 90.7 — 99.7%), respectively (p = .31, log rank test; Fig. 4). Characteristics of the restenoses and occlusions are summarised in Supplementary Table S6; most restenoses were located at the proximal edge of the stent, and this was comparable between both groups.

The target extremity revascularisation rate was 8.5% in the BMS group and 8.3% in the CS group (p = .94, log rank). During follow up, 16 additional procedures were performed in the randomised leg and are summarised in Supplementary Table S7.

No major or minor amputations occurred during the follow up period. The all cause mortality rate was 6.0% in the BMS group and 1.2% in the CS group (p = .10, log rank test). Cause of death was malignancy in all but one patient, who died of pneumonia within 30 days of the intervention.

Per protocol analysis

For the per protocol analysis, the six patients who were randomised to the BMS group but received a covered stent were crossed over to the CS group. The patient who

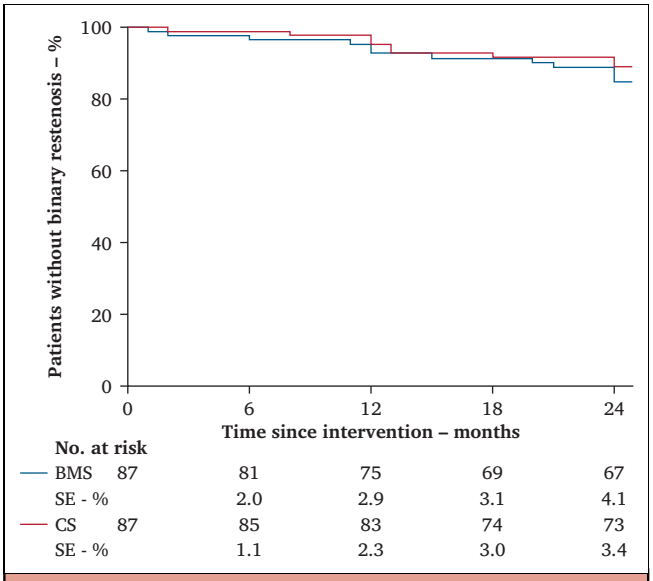

Figure 2. Cumulative Kaplan–Meier estimate of freedom from binary restenosis during follow up for 87 patients randomised to bare metal stents (BMS) and 87 patients randomised to covered stents (CS). A p value for the difference between groups = .40 (log rank test). SE = standard error.

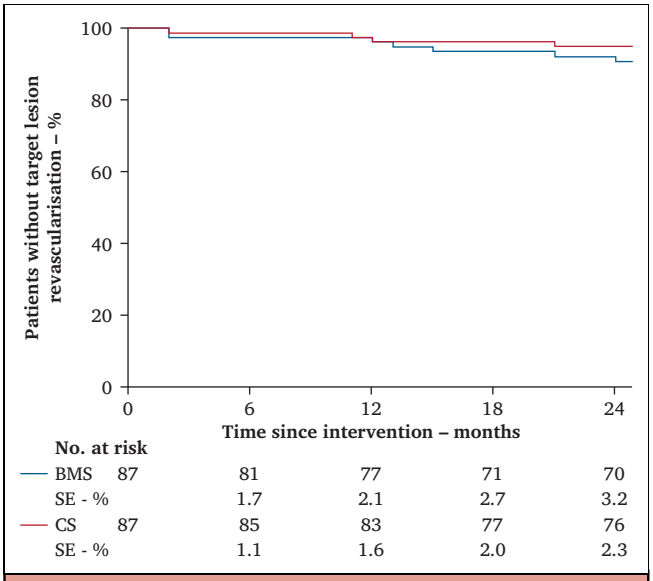

Figure 4. Cumulative Kaplan–Meier estimate of freedom from target lesion revascularisation during follow up for 87 patients randomised to bare metal stents (BMS) and 87 patients randomised to covered stents (CS). A p value for the difference between groups = .31 (log rank test). SE = standard error.

received a self expanding stent and the patient who was treated in the EIA were excluded. Freedom from binary restenosis at two years was 83.3% (95% CI 74.7 — 91.9%) in the BMS group and 89.7% (95% CI 83.2 — 96.2%) in the CS group ($p = .24$, log rank test).

Subgroup analyses

Subgroup analyses were performed for patient related and lesion related factors (Supplementary Figs. S1 and S2). There was no difference in the primary outcome in any of the evaluated subgroups, but this trial was not powered for these analyses.

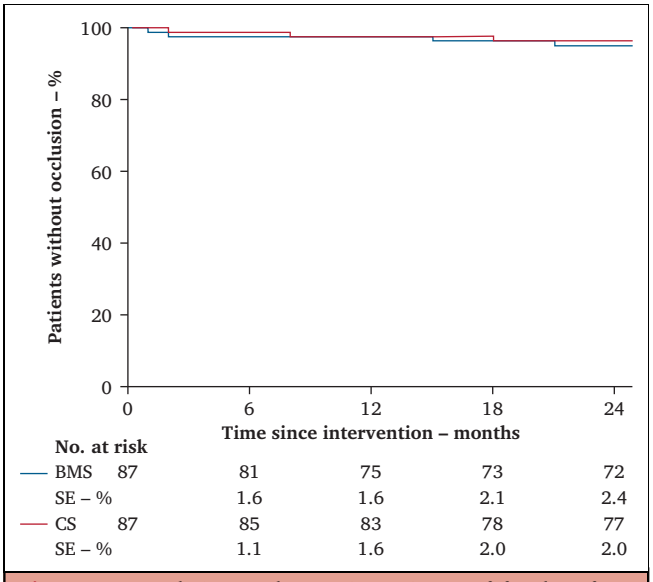

Figure 3. Cumulative Kaplan–Meier estimate of freedom from occlusion during follow up for 87 patients randomised to bare metal stents (BMS) and 87 patients randomised to covered stents (CS). A p value for the difference between groups = .66 (log rank test). SE = standard error.

Multivariable analysis

Figure 5A shows the results of univariable analysis for all assessed parameters possibly predicting binary restenosis. Figure 5B shows the final model after multivariable analysis. Presence of moderate or heavy calcification was found to predict a lower risk of binary restenosis ($p = .021$). To explore the impact of the higher number of kissing stents in the CS group, one final model was constructed in which the use of kissing stents and the type of stent used were added to the model (Fig. 5C). In this model, neither the use of kissing stents nor the type of stent used was identified as a predictor of binary restenosis.

DISCUSSION

This article describes the two year results from the DISCOVER trial, a randomised controlled trial comparing BMS and CS for the treatment of advanced atherosclerotic lesions of the CIA. The primary end point of the study was freedom from binary restenosis after two years of follow up. No difference was found between BMS and CS, which persisted after per protocol analysis and multivariable analysis, and no differences were found for any of the secondary end points. There was a crossover rate of 7% from the BMS to the CS group for various technical reasons, indicating the importance of CS as a bailout device.

This trial defined advanced CIA lesions as a stenosis > 3 cm or an occlusion. A length of 3 cm was chosen to define a long stenosis, as this length was used as a cut off point in the original TASC classification and no other definition was available. It consciously avoided using the TASC II

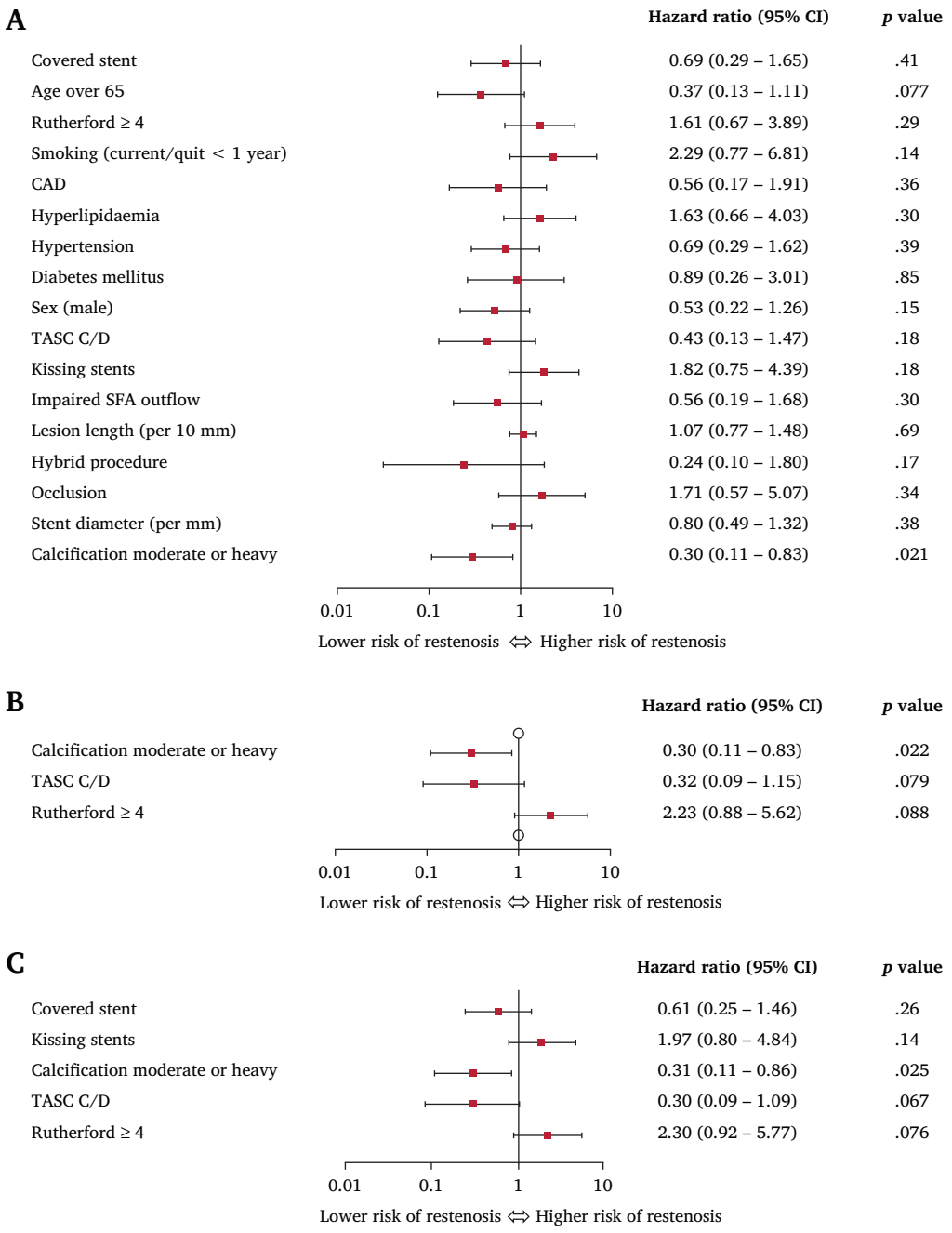

Figure 5. (A) Univariable analysis demonstrating the hazard ratio of restenosis for each parameter that was considered for inclusion in the multivariable model. Multivariable analyses demonstrating (B) the final model after multivariable analysis and (C) addition of kissing stents and type of stent used. CAD = coronary artery disease; CI = confidence interval; SFA = superficial femoral artery; TASC = Trans-Atlantic Society Consensus.

classification to classify advanced CIA disease because the TASC II classification considers the complete bilateral aorto-iliac segment including the aorta, CFA, and EIA. Therefore, a focal CIA stenosis with concomitant EIA and CFA lesions contralaterally will be TASC C or D, whereas an isolated, calcified, long chronic CIA occlusion will be a TASC B. However, in the authors' opinion, the former would not be considered an advanced CIA lesion, whilst the latter would.

The results from the current trial contrast with the results from COBEST,[4,5] which also compared CS and BMS for aorto-iliac occlusive disease. In COBEST, a significantly increased freedom from binary restenosis rate was observed for CS. The freedom from binary restenosis rate in COBEST at one month dropped to 85% in the BMS group, which was still near 100% in the CS group. In their subgroup analysis of TASC C and D lesions, the primary patency in the BMS group dropped to 75% at one month; this is much lower than results from the current

and other studies on iliac stenting.[2] This difference in patency between both groups at one month persisted during follow up, but did not actually increase even after five years of follow up. The authors of COBEST have not discussed this striking result, but a potential explanation may be suboptimally treated outflow. Although the reported number of patients with TASC II C or D lesions, and thus with more concomitant lesions, was higher in COBEST than in the current study (38.1% *vs.* 26.4%), the number of concomitant lesions that were treated was much lower: 5.4% *vs.* 16.1% for the CFA and 8.3% *vs.* 20.1% for the EIA.

Another explanation for the differences between the COBEST and DISCOVER trial might be the meticulous verification of technical success in the current study, with both bidirectional angiography and pressure gradient measurement after stent placement, and additional PTA and or stent placement when residual stenosis was identified; the COBEST trial did not report how technical success was verified.

Complication rates in the current trial were higher than those published in a recent meta-analysis, with a reported average of 13.4%,[1] although there was no difference between the groups. This might be explained by the fact that nearly 20% of the procedures were hybrid procedures, 30% of the patients had chronic limb threatening ischaemia, almost 70% of lesions were chronic occlusions, and that this was a prospective trial with meticulous complication registration. A recent case series of 130 patients treated with CERAB, with a comparable patient population, showed major complication rates similar to the current study.[18]

The presence of moderate or heavy calcification was found to predict a lower risk of binary restenosis in the multivariable analysis, although these results should be interpreted with caution given the low number of events. In the ICE trial, heavy calcification was also found to protect against occurrence of restenosis in the multivariable model, although in this trial it did not reach significance (HR 0.40; 95% CI 0.15 − 1.07; $p = .069$). Perhaps these types of lesions are less biologically active and thus have a lower tendency to form neointimal hyperplasia.

The current ESVS guidelines provide no recommendations on the choice between either stent,[19,20] and based on these results the authors believe that future guidelines should not recommend CS over BMS for treating atherosclerotic lesions of the CIA.

Limitations

This study had some limitations. It was anticipated that inclusion of all 174 patients would take two years, whilst it took more than seven years; this may have introduced selection bias.

During the study period, the Dutch guidelines were updated to advise clopidogrel rather than acetylsalicylic acid after procedures for peripheral arterial disease, and the study protocol was updated accordingly. Furthermore, there were more patients with kissing stents in the CS group, and presence of kissing stents, especially with significant protrusion into the aorta, has been shown to influence restenosis rates in some studies. To correct for this imbalance, additional subgroup analysis and multivariable modelling was performed.

Conclusion

After two years of follow up, bare metal stents and covered balloon expandable stents both showed excellent results for treating advanced atherosclerotic lesions of the CIA. No difference was identified between either stent type regarding freedom from restenosis or any of the secondary outcomes. Based on these results, the routine use of covered stents to treat CIA occlusive disease cannot be advocated.

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APPENDIX A. SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejvs.2022.11.008.

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COUP D'OEIL

Huge Aortic Aneurysm? Massive Fistula!

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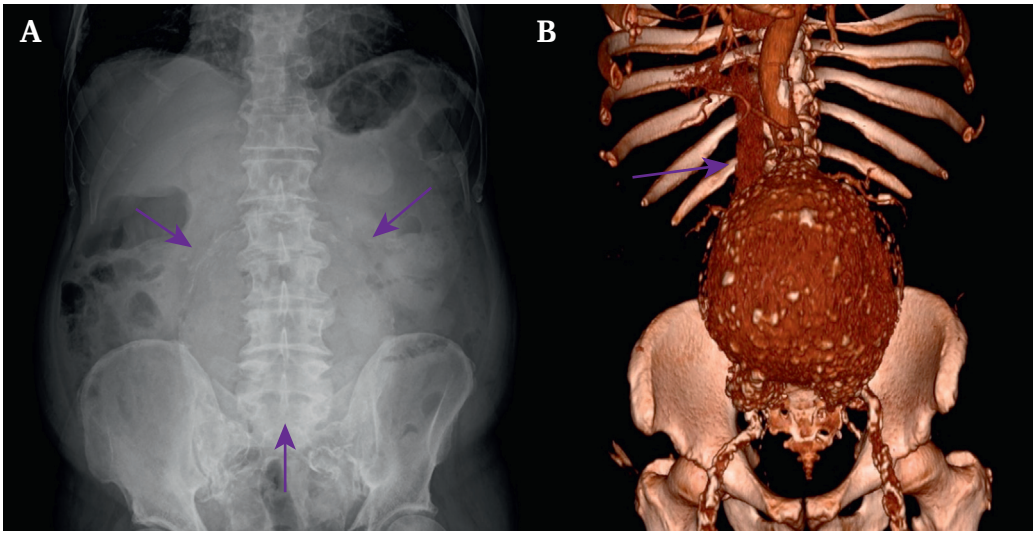

A 73 year old man presented with lumbar pain, dyspnoea, and oliguria. A tender pulsatile abdominal mass with a thrill and bilateral lower limb oedema were noted. Abdominal X-ray revealed a giant calcified spherical mass (A, arrows). Computed tomography angiography showed a 14 cm infrarenal abdominal aortic aneurysm associated with filling of the inferior vena cava with contrast in the arterial phase filling (B, arrow). Blood results revealed a serum creatinine of 5.2 mg/dL and N-terminal pro B-type natriuretic peptide of 25 000 pg/dL. The patient underwent open surgical aneurysm and aortocaval fistula repair (aortobifemoral graft) and was discharged on post-operative day 10.

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