Aortoiliac stenting, how blood flow and stents interact

Erik Groot Jebbink

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Academic thesis, University of Twente, Enschede, the Netherlands, with a summary in Dutch

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PRINTED BY Gildeprint – www.gildeprint.nl

ISBN 978-90-365-4425-5

DOI 10.3990/1.9789036544252

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The author gratefully acknowledges financial support for the publication of this thesis by:

Maquet Netherlands BV

Angiocare BV

ChipSoft

Technical Medicine and ECTM, University of Twente

Financial support by the Dutch Heart Foundation for the publication of this thesis is gratefully acknowledged

AORTOILIAC STENTING, HOW BLOOD FLOW AND STENTS INTERACT

DISSERTATION

to obtain the degree of doctor
at the University of Twente, on the authority of
the Rector Magnificus, prof. dr. T.T.M. Palstra,
on account of the decision of the graduation committee,
to be publicly defended on
Friday the 1st of December, 2017 at 12:45

by

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Introduction

In the Netherlands the prevalence of peripheral arterial disease (PAD), based on measurement of the ankle-brachial index (ABI), is estimated to be 19.1 % in people aged 55 and over, of which 6.3 % report symptoms of intermittent claudication (IC). The prevalence rapidly increases to over 40 % in the population aged 80 and over¹. Most lesions associated with PAD are located in the infrainguinal region and only a fraction of PAD is aortoiliac occlusive disease (AIOD), surprisingly IC symptoms are caused by AIOD in 53 % of the female patients aged below 40². AIOD comprises all narrowing vascular lesions (stenosis and occlusions) that form in the distal aorta, the aortic bifurcation and the common iliac arteries. Usually AIOD begins at the aortic bifurcation and progresses distally into the iliac arteries and proximally into the aorta³. AIOD may impact the quality of life (QoL) significantly, when the disease progresses from intermittent claudication to critical limb ischemia (including ischemic rest pain, ulcers/gangrene and risk of amputation). In this thesis the focus is on AIOD.

As a first measure to objectify AIOD the ABI is well-known. ABI is the ratio of the systolic blood pressure at the ankle to the systolic blood pressure at the upper arm, were a number of > 1.0 rules out PAD (single measurement, 99 % negative predictive value). ABI values ≤ 0.9 confirms the diagnosis of lower-extremity PAD. ABI between 0.91 and 1.0 is considered borderline in terms of cardiovascular risk, justifying further evaluation. ABI measurements between 0.8 and 1.0 require repeated measurements (three times) to reach 95 % certainty⁴. When the ABI drops below 0.9 this independently correlates with impaired QoL, especially for physical activity in older adults⁵. QoL is a critical element for older people, even more than survival. This shows that AIOD can become very incapacitating and that proper disease management is crucial to warrant a good QoL.

If adequate collateralization is present patients can manage their levels of claudication nonoperatively for many years, especially in combination with supervised walking exercise⁶. Supervised walking exercise is the first line of therapy at all times. In combination with secondary medical prevention this lowers the risk for cardiovascular events and increases survival (Figure 1), mediated by several risk factors: male gender, age, diabetes, smoking, hypertension and dyslipidemia.

When patients develop disabling IC not responding to supervised walking exercise or critical limb ischemia (CLI) surgical intervention may become inevitable. Since the early sixties the aorto-bi-femoral bypass (ABFB) is the gold standard in the treatment of AIOD with high graft durability (coined patency) during long-term follow-up. Although the good long-term primary patency results are accompanied by substantial postoperative mortality and (major) complications. Primary patency is defined as a patent graft obtained without the need for additional or secondary surgical or endovascular procedures.

The high mortality and complication rate of ABFB justified the search for less invasive treatment options and in the early 90's the first AIOD lesions were treated minimal invasively or "with endovascular techniques" using percutaneous techniques, requiring catheter mounted balloons and the Palmaz balloon-expandable stent⁷. Due to the fact that AIOD lesions often involve the distal aorta, aortic bifurcation and both iliac arteries, a treatment algorithm was needed that could resolve the complete lesion, or reconstruct the aortic bifurcation in order to treat from healthy to healthy tissue. The kissing stent (KS) technique was introduced to fulfill this need. With this technique stents are deployed simultaneously in the iliac arteries and the stents protrude into the aorta where they abut or "kiss". Since the nineties many papers (with low numbers of patients) were published regarding the results of the KS technique, short-term results could match with ABFB results, however long-term results did not, especially in complex lesions.

However, endovascular treatment did lower the postoperative mortality and major complication rate. Over time techniques improved and more advanced stents came to the market, enabling the treatment of more complex lesions, with acceptable patency results. This also introduced a wide variety of treatment protocols and cohorts of patients are usually not easy to compare between studies. Chapter two and three of this thesis describe a systematic review and individual patient data analysis to research

Figure 1. The increase in mortality with peripheral arterial disease is related to its severity.

Reproduced from Norgren et al.²³

the influence of treatment protocols and lesion severity on primary patency results, complication rate and clinical outcome of KS.

In recent years there has been increased emphasis on the influence of the geometry of the KS configuration with respect to primary patency results. Greiner et al. showed that stent protrusion into the aorta does influence primary patency⁸. At this point the concept of mismatch or “dead zones” was introduced, this relates to a suboptimal conformation of the cephalic ends of the KS configuration with respect to the aortic wall. Furthermore, the use of bare metal stents covered with expanded polytetrafluoroethylene (ePTFE) seemed to improve patency results, possibly due to a reduction of vessel ingrowth between the struts of the bare stents^{9–12}.

The concepts of mismatch and covered stents were used to develop a technique to reconstruct the aortic bifurcation in a more anatomical fashion¹³. This technique, coined the covered endovascular reconstruction of the aortic bifurcation (CERAB), makes use of three instead of two stents. A stent is deployed in the distal aorta, proximally sealing with the aortic wall, leaving the distal part at a smaller diameter, creating a funnel shape. Two limbs are placed in the distal part of the funnel and deployed simultaneously. Stretching the distal funnel and creating a tight seal between the funnel and the limbs, all steps are schematically depicted in Figure 2. However, the question remains if the CERAB does actually lower the mismatch and is an improved reconstruction. Chapter four and five compare the in vitro and in vivo geometry of different KS and the CERAB configurations, comparing mismatch and conformation to the vessel wall.

Figure 2.

- A** the aortic cuff is deployed in the distal aorta and proximally aligned with the aortic wall.
- B** The cuff is now funnel shaped and both iliac limbs are placed in the narrow distal part.
- C** both limbs are inflated simultaneously to complete the CERAB configuration and create a neobifurcation.

Reproduced from Goverde et al.¹³

Studies published on the KS technique often hypothesize about the possible mechanism why mismatch areas influence stent patency^{14,15}. Perturbation of blood flow and the following cascade of detrimental effects is often briefly mentioned. Of course patient outcome is the most important parameter when researching the performance of endovascular techniques. However, to advance the field of endovascular treatment local insight in the behavior of different stents is crucial to improve its outcome for patients. The intricate interaction between stents, blood flow and the vessel wall influences stent patency¹⁶. Blood flow creates shearing forces on the vessel wall (wall shear stress (WSS), Figure 3), these forces mediate the arrangement and permeability of endothelial cells. This in turn regulates the progression of atherosclerotic and thrombotic processes¹⁷. Low values of WSS contribute to the development and rupture of atherosclerotic plaque^{18,19}. Furthermore if the low WSS has an oscillatory nature this also enhances the progression of atherosclerosis at a specific site in the vascular system. The oscillatory nature is captured by the oscillatory shear index (OSI)²⁰. Moore et al. showed that at sites with high prevalence of atherosclerosis the conditions of low and oscillating WSS hold true²¹. The aortic bifurcation is such a site where atherosclerosis has a high prevalence, mediated by low WSS and a high OSI index²². When studying the observed flow patterns in areas of low WSS and high OSI recirculation of flow is often observed, creating forces that are not perpendicular to the wall, causing a decrease in WSS. Recirculation can also be expected

Figure 3. Definition of the wall shear stress or endothelial shear rate.

Reproduced from J.J. Wentzel et al.²⁴

when the KS or CERAB geometry cause mismatch areas, Chapter six and seven of this thesis elaborate on the effects of the geometry of the KS and CERAB configuration on blood flow, WSS and OSI using in vitro experiments.

As mentioned before, clinical outcome is a very relevant parameter to test the performance of a stent configuration. Chapter eight describes the midterm results on the use of the CERAB configuration in the treatment AIOD lesions, regarding primary patency, clinical improvement and complication rate.

There is more to an endovascular technique than just clinical outcome, incorporating knowledge on the local characteristics of the configuration will give a more complete overview of the technique. In this thesis we hope to show that combining several clinical and technical parameters produces a more firm and useful body of knowledge for, in this case, stent configurations used in the treatment of AIOD. Ultimately aiding in the optimization of techniques and QoL of the patient.

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Systematic review of results of kissing stents in the treatment of aortoiliac occlusive disease

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Adapted from **Annals of Vascular Surgery**
2017, Volume 42, Pages 328–336.

ABSTRACT

BACKGROUND Endovascular treatment of AIOD involving the aortic bifurcation is challenging. The gold standard is open surgery with patency rates up to 90 % at 5 years, but has considerable morbidity and mortality. The KS technique was introduced as an alternative. The goal of this review is to give an overview of the current results and role of the KS technique in AIOD treatment.

METHODS The Cochrane guidelines were used to assure a systematic method. A search query designed in the Scopus search interface was used to identify relevant studies. Abstracts from the search were screened against the inclusion and exclusion criteria. During full-text reading, methodological quality was scored using a critical review list tailored to the topic of AIOD. Thereafter, study data were extracted and pooled for further analysis.

RESULTS In total, 143 abstracts were retrieved using Scopus, 116 were rejected and 7 more were rejected after full-text screening. One study was included after cross referencing. Twenty-one studies presented 1390 patients. Rutherford classification 1/2/3 was the indication in 76.2 % of patients, and 48.4 % of the lesions were classified as Trans-Atlantic Inter-Society Consensus C or D. The technical success rate was 98.7 %, and the complication rate was 10.8 %. Clinical improvement at 30 days was achieved in 89.9 %. Primary patency at 12, 24, and 60 months was 89.3 %, 78.6 %, and 69.0 %, respectively.

CONCLUSIONS KS treatment of AIOD yields acceptable mid-term results, with high technical success rates and mostly minor complications occur. The long-term patency cannot yet match that of open surgery, underlining the need for further research that provides insight into factors related to reocclusion.

INTRODUCTION

The aortic bifurcation is a common location of atherosclerosis, potentially leading to symptoms such as disabling intermittent claudication or critical limb ischemia. The disease prevalence is in the range of 3–10 %, increasing to 15–20 % in persons aged over 70¹. Surgical reconstruction by means of aorto-bi-femoral/iliac bypass or endarterectomy of the occluded segment has 5-year patency rates up to 90 % and is therefore considered the gold standard for type C and D lesions according to the Trans-Atlantic Inter-Society Consensus Document (TASC II) for AIOD¹. Open surgery is, however, associated with a 3.3–4.3 %, 30-day mortality rate². Postoperative complications arise in 5–10 % of cases and are either related to preoperative comorbid conditions such as myocardial infarction, congestive heart failure, pulmonary insufficiency, and renal insufficiency, or directly related to the aortic reconstruction such as hemorrhage, embolization, or thrombosis of the distal arteries³. De Vries and Hunink reported a significant decrease in 30-day mortality from 4.6 % to 3.3 % when comparing studies published before 1975 with studies published after 1975. However, Chiu et al.⁴ reported that the 30-day mortality after open repair did not significantly change.

The noteworthy morbidity and mortality after open repair justified the exploration of minimal invasive methods. In the past decades, endovascular techniques for treatment of AIOD emerged. Simultaneously deployed bilateral iliac stents, the so-called KS technique, enable the endovascular treatment of lesions that include the aortic bifurcation. Several studies have been published about the outcome of KS, with varying results. Factors reported to affect patency include the protrusion length of the stents into the aorta, a systematic pre- and/or postdilatation, a crossing position of the stent, stent characteristics, and postinterventional anticoagulant medication. However, a review of the current standard, KS, is lacking. The goal of this systematic review is to assess the technical success rate, procedural protocols, adverse events, and clinical outcome after KS technique in the treatment of AIOD. The latter contributes to better information for patients regarding the expected outcome and risks.

MATERIALS AND METHODS

A systematic review was conducted on the results obtained using KS treatment. The Cochrane guidelines were used to develop a systematic method⁵. The interface used for searching was Scopus (Elsevier B.V., Amsterdam, The Netherlands), which includes MEDLINE and EMBASE. Articles were included until September 2016.

STUDY SELECTION The abstracts of the articles were independently screened by 3 investigators (SH, JWL, and EGJ) and the decision for full-text assessment was based on the following criteria:

- Patient number > 3
- Patients diagnosed with AOID
- KS technique
- English or Dutch language
- Study describes original data
- Not only technical description

Any disagreements were resolved by discussion to reach consensus. No search was performed to retrieve any unpublished data or abstracts. Full-text versions were subsequently studied by SH and EGJ. Inclusion required that the data were analyzed per patient. If data were analyzed per limb, conversion to per patient analysis should be possible. Reference lists were screened for eligible studies.

METHODOLOGICAL QUALITY ASSESSMENT Methodological quality of the included articles was assessed using a critical review list. A combined list from the MOOSE group, previous reviews in the area of endovascular treatment, and the Agency for Healthcare Research and Quality was formed. Thereafter, the list (Supplemental Table 1) was tailored to fit the current important criteria (patency, lesion characteristics, etc.)⁶⁻⁸. Each item was graded from 0 to 2 depending on the information available in the article; cut-off criteria were determined by the authors. The maximum score for quality of the articles was 26. The scoring was performed to be able to compare reporting quality of the studies, and articles were not excluded based on the quality assessment.

DATA EXTRACTION Data extraction was performed by SH and EGJ individually, merging was done together, and any discrepancies were resolved with a check in the full-text article.

DATA POOLING Although there were differences in the definitions per study, we used the stratification applied by the authors per study, if applicable. Pooling did not depend on the method for determining the pooled parameter. Data are reported in mean $\pm$ standard deviation, unless otherwise stated. To examine trends in the data, the studies were split

into 2 groups: studies published before 2010 and studies published in or after 2010. The 3-year patency rates were included in the 24-month patency rate ($n = 2$) and 48 months in the 5-year patency rates ($n = 2$).

RESULTS

STUDY SELECTION Figure 1 depicts the flow chart of the study selection. Consequently, 21 articles were included in the study⁹⁻²⁹. One article compared 2 patient groups and reported a full dataset for each group²¹. These groups were analyzed as separate articles for data extraction, but during quality assessment we calculated as one. The mean years of data collection were 6.2 ± 3.6 years (range 2-16). Table 1 gives an overview of the included studies.

QUALITY ASSESSMENT The quality score of the articles ranged from 12 to 22, with a mean of 18.2. All studies were retrospective, consecutive case studies and only one described a multicenter study²². The majority of the studies ($n = 15$) did not describe explicit exclusion criteria. Table 1 includes the total quality score per study. A detailed overview of the scoring per article can be found in Supplemental Table 2. Nine studies also provided additional details on lesion length, vessel diameter, stenoses versus occlusions, and the exact locations of lesions. Overall, the interventional technique was clearly described.

Only 5 studies had no patients lost to follow-up, while 6 others did not describe whether there were any patients lost to follow-up. Thirteen studies provided a clear description of the follow-up schedule.

Fourteen studies used the TASC classification (TASC I: $n = 2$; TASC II: $n = 12$). Eighteen studies presented patency rates, including a clear definition, whereas 3 studies only presented the initial results of the technique. In 15 studies, the assessment of patency was based on clinical evaluation combined with either duplex ultrasound or angiography.

Figure 1. Flow chart illustrating study selection.

Five studies only used clinical evaluation with or without ABI. The majority provided data on the mortality rate, except for the 2 studies reporting initial results of the KS technique, and 2 studies with long-term follow-up did not describe mortality at all.

The description of adverse events varied widely among studies. All except 2 provided details on complications, and 19 of 21 also divided adverse events into minor and major. However, definitions of minor and major adverse events differed between studies.

Table 1. Included studies for the current review.

FIRST AUTHOR	PUBLICATION YEAR	STUDY RANGE	STUDY TYPE	INCLUDED # OF PATIENTS	QUALITY SCORE TOTAL*
Mendelsohn	1998	1994–1997	R	20	17
Scheinert	1999	1991–1998	R	48	13
Haulon	2002	1993–1998	R	106	18
Mohamed	2002	1997–2001	R	24	20
Greiner	2005	1997–2005	R	41	19
Houston	2007	1992–1994	R	43	20
Bjorses	2008	1995–2004	R	173	20
Sharafuddin	2008	1998–2005	R	66	20
Sabri	2010	2002–2007	R	54	22
Mouanoutoua	2003	1995–2002	R	50	16
Yilmaz	2006	1994–2006	R	68	22
Sixt	2013	1996–2006	R	135	19
Dohi	2013	2005–2012	R	25	15
Abello	2012	1999–2001	R	80	18
Strecker	1993	—	R	18	12
Hinnen	2015	1995–2011	R	215	19
Moon	2015	2007–2012	R	21	12
Pulli	2015	2005–2012	R	41	22
Suh	2015	2005–2012	R	30	21
Meng	2016	2007–2014	R	63	20
Grimme	2015	2003–2009	R	69	17

#: number; R = retrospective. *After consensus between the two observers SH and EGJ.

PREOPERATIVE CHARACTERISTICS

Patient demography In total, 21 studies (22 patient groups) were included, presenting results of KS procedures in 1390 patients. Patient demography for all studies is depicted in Table 2. A detailed overview of the baseline patient characteristics per study can be found in Supplemental Table 3. Hypertension (HT) and hyperlipidemia (HL) were most common with prevalences varying from 37.5–96 % and 20.8–90 %, respectively. The prevalence of diabetes mellitus (DM) was 8.3–60.3 %, while 29.4–100 % of patients were current smokers.

Clinical classification and lesion type The majority (76.2 %) of patients were classified as Rutherford 1, 2, or 3 with a range from 32.6 % to 100 %. Twelve percent were classified as Rutherford 4 (range 4.2–58.1 %) and 8.7 % were classified as Rutherford 5 or 6 (range 2.4–34.8 %).

Table 2. Patient demographics and risk factors.

PARAMETER	# OF STUDIES REPORTING DATA	MEAN (RANGE)
Sample size	22	63.2 (18–215)
Age, (year)	21	61.4 (32–88)
Men (%)	21	65.5 (39.5–100)
<i>Risk factors</i>		
Smoking (%)	21	66.9 (29.4–100)
DM (%)	21	26.1 (8.3–60.3)
HT (%)	20	59.9 (37.5–96.2)
HL (%)	19	58.7 (20.8–90)
CVD (%)	16	47.7 (17.1–85)
<i>Rutherford*</i>		
R0 (%)	1	37.5 †
R1/2/3 (%)	20	73.7 (32.6–100)
R4 (%)	16	18 (4.2–58.1)
R5/6 (%)	12	13.4 (2.4–34.8)
<i>TASC II/I</i>		
TASC A (%)	13	23.6
TASC B (%)	13	28.2
TASC C (%)	13	17.5
TASC D (%)	13	30.9

#: number; DM: diabetes mellitus; HT: hypertension; HL: hyperlipidaemia; CVD: cardiovascular disease.

*Not all studies reported full Rutherford scale. †Single value, only one manuscript reported patients for Rutherford category 0.

Of the studies that provided the TASC classification ($n = 14$), 48.8 % included mainly TASC C and D lesions, while the other half included mainly category A and B lesions. Details per study can be found in Supplemental Table 3. The majority of studies provided lesion details.

PROCEDURAL DETAILS The mean technical success rate of 21 studies was 98.7 %. All but 4 studies had a 100 % immediate technical success. Fifteen studies reported the total number of deployed stents and the type of stent used, and percentages cannot be reported because individual patient data are lacking. Sixteen studies reported whether the arteries were predilated (systematically [$n = 3$], selective [$n = 10$], or not at all [$n = 3$]). Overall procedural data are presented in Table 3. A detailed overview of the procedural details per study can be found in Supplemental Table 4.

Most studies had a preference for either the self-expanding (SE) or balloon-expandable (BE) stents. One study also reported the number of used BE and SE combinations¹⁸. Thirteen of the 21 studies reported that stents were postdilated (systematically [$n = 7$], routinely [$n = 2$], selective [$n = 4$]). Protrusion of stents into the aorta was described by all but one study; the protrusion length varied from 1 to 40 mm depending on lesion anatomy. Eighteen studies reported on hybrid procedures. Hybrid procedures were performed with a mean of 17 ± 16.8 % (range 2–63 %). The administration of heparin during the procedure varied widely between studies, and the amounts reported ranges from 2500 to 10000 units. Postoperative infusion of heparin was described in 5 studies. Three studies did not describe peroperative anticoagulant therapy. One study combined KS placement with thrombolytic therapy in all patients²⁴.

Table 3. Procedural details.

PARAMETER	# OF STUDIES REPORTING DATA	MEAN	(RANGE)
Mean occlusion length (mm)	11	58.6	(6.7–145)
Mean stenotic length (mm)	6	55.22	(17–158)
BE stents (%)	12	51.2	(14–100)
SE stents (%)	11	55	(9.8–100)
Technical success (%)	19	98.7	(89–100)
Additional treatments (%)	19	34.4	(4.9–100)
Overall complications (%)	20	10.8	(1.4–22)
Minor complications (%)	14	9.1	(0–22)
Major complications (%)	16	5.8	(0–14.6)

#: number; BE: Balloon-expandable; SE: Self-expanding.

FOLLOW-UP AND PATENCY RATES The mean follow-up across studies was 26.6 ± 9.6 months (range 0–144), as shown in Table 4. A detailed overview of the follow-up details per study can be found in Supplemental Table 5.

Lost to follow-up information was provided by 14 of 21 studies with a mean percentage of $13 \pm 19.4\%$ (range 0–68.1%). Medical therapy during follow-up usually ($n = 16$ studies) consisted of single antiplatelet therapy using acetylsalicylic acid (ASA), although the dosage varied widely (75–325 mg daily). In 8 studies this was combined with clopidogrel. The use of statins was described in 3 studies.

Thirty-day outcome and complications Data on clinical improvement 30-days after intervention were provided by 12 of 21 studies. Overall, $89.9 \pm 9.6\%$ of patients showed a clinical improvement at 30 days (range 70.8–100%).

All but one study reported on complications of the KS procedure, as shown in Table 5. The overall complication rate was $10.8 \pm 5.7\%$, while the rate of minor complications was $9 \pm 5.7\%$. Major complications were reported in $5.8 \pm 4.4\%$ of cases ($n = 16$ studies).

Table 4. Follow-up data.

PARAMETER	# OF STUDIES REPORTING DATA	MEAN (RANGE)
Mean FU (months)	16	26.7 (0–144)
Patients lost to FU (%)	11	9.6 (0–47)
Reinterventions (%)	19	20.9 (0–62.5)
30d clinical improvement (%)	12	89.9 (70.8–100)
Procedural mortality (%)	8	1
30-day mortality (%)	10	1 (0–4.5)
Primary patency (%)		
12m (%)	13	89.3 (76–97.8)
24m (%)	13	78.6 (58–92)
60m (%)	9	69 (63–81)
Assisted secondary patency (%)		
12m (%)	4	92.3 (84–99)
24m (%)	4	83.9 (69–94)
60m (%)	6	77.3 (64–94)
Secondary patency (%)		
12m (%)	7	94.2 (88–100)
24m (%)	8	94.7 (83–100)
60m (%)	8	83.1 (69–93)

#: number; FU: Follow-up

Table 5 reports complication details. One procedure-related mortality was reported (acute occlusion of the distal aorta and brainstem hemorrhage).

Patency rates A combination of ABI measurements and duplex ultrasound was most commonly used ($n = 11$) to report patency. Fifteen studies also based patency on clinical judgment.

The 12-month patency rates were 89.3 %, 92.3 %, and 92.3 % for the primary, assisted-primary, and secondary patency, respectively. The 24-month patency rates were 78.7 %, 83.9 %, and 94.2 % for the primary, assisted, and secondary patency, respectively. The reported primary patency at 60 months was 69 % ($n = 9$ studies), with an assisted patency of 77.3 % and a secondary patency of 83 %. Three studies reported a 10-year secondary patency of 87.3 %.

All but one study reported on the number of reinterventions performed during follow-up; the percentage of reinterventions varied from 0–62.5 % (mean across studies 20.9 ± 15.9 %).

Amputations and mortality Eight studies described a total of 3 minor and 7 major amputations. Of these, 1 major and 3 minor amputations were planned amputations and performed during the same session as the KS procedure.

Table 5. Specification of reported adverse events per article (when reported).

AUTHOR	YEAR	EVENT						
		Rupture	Bleeding from puncture site	Thrombosis	Dissection	Distal embolisation	Pseudo aneurysm	Groin hematoma
Scheinert	1999						1	2
Haulon	2002							15
Mohamed	2002						1	4
Greiner	2005	1		1	3		5	
Bjorses	2008	3	1			3	1	11
Mouanoutoua	2003				1	2		3
Yilmaz	2006					2	2	3
Abello	2012				2			
Strecker	1993							2
Hinnen	2015		5			1	5	
Moon	2015			2				3
Pulli	2015			1	1	3		
Suh	2015			2			1	
Meng	2016							3
	Total	4	6	6	7	11	16	46

Thirteen studies reported mortality of which 12 reported 30-day mortality (mean 1, range 0–3); 4 studies had no 30-day mortality, 3 studies had 1 death, 1 study had 2, and 2 had 3 deaths during the first 30 postoperative days. An overview of mortality rates per study can be found in Supplemental Table 6.

Only 4 studies reported 12-month mortality numbers (1 study: $n = 1$; 3 studies: $n = 0$). In total, 24-month mortality numbers were described by 6 studies; 3 studies had no mortality, 1 study had 12.5 %, and 1 had 9.3 % during 24-month follow-up. One study had a high mortality rate of 28.8 % inherent to the known increased cardiovascular risk and the high incidence of malignancies in this patient group, according to the authors¹⁶.

TRENDS OVER TIME After separating studies into 2 groups (before 2010, $n = 11$, including 657 patients; after 2010, $n = 10$, including 733 patients), few parameters significantly differed. Patients included in studies published after 2010 more frequently had DM (19.3 % vs. 33.6 %, $p = 0.012$) and HT (50.4 % vs. 69.5 %, $p = 0.021$). Furthermore, less patients with Rutherford category 5 and 6 were included in studies published after 2010 (18.9 % vs. 8 %, $p = 0.057$). The reported 24-month secondary patency significantly decreased in the publications after 2010, from 97.8 % to 90.8 % ($p = 0.016$), while there was no difference in primary patency and secondary patency at 1 year. Other important parameters did not significantly differ.

DISCUSSION

The KS technique is nowadays firmly embedded in the treatment options of AIOD including the aortic bifurcation. This review has shown a high technical success rate, an overall postoperative adverse event rate of 10.8 %, and a primary patency rate at 12, 24, and 60 months of 89.3 %, 78.6 %, and 69.0 %, respectively.

In the past 2 decades, over 21 studies have been published on the results of the KS technique in AIOD. All of them were retrospective cohort studies. Although standards to report endovascular procedures in literature are available, they are not fully embedded in the community³⁰. This is reflected by the wide variation in the description of the KS procedures and resulting patient data. To be able to compare and evaluate the results between studies, clear definitions on, for example, technical and clinical success are required. In the reviewed literature, these definitions were not always clear or even not described.

CLASSIFICATION OF DISEASE Overall, 73.7 % of patients included in this review were treated with KS for intermittent claudication, whereas half the lesions were classified as TASC C or D lesions. This is a concerning percentage, underlining the fact that greater education and outreach is needed on the role of medical management stated in clinical practice guidelines for patients with claudication. In addition, less TASC D lesions were treated in our review group when compared with the open reconstruction group of Kashyap et al. (50 % vs. 77.0 %)³¹. Thus, the severity of the treated lesions was higher in studies concerning open reconstruction of aortoiliac lesions, indicating that KSs are not main stream for complicated lesions. However, Björkses et al. reported no difference in outcome between TASC A and B or TASC C and D lesions treated with KS. In our opinion, this is surprising because procedures are technically more complex with increasing TASC category and the risk for rupture might be higher.

PROCEDURAL DETAILS Within the studied publications, there was a wide diversity in procedural protocols with regard to the used stent type (BE versus SE), stent design (closed cell versus open cell, covered versus bare stent), standard pre- and/or postdilatation, and whether protrusion into the aorta was considered to be beneficial or not. The choice of stent type was not substantiated by most authors; some authors preferred the use of SE stents in long tortuous lesions and the use of BE stents in short and calcified lesions. Björkses et al. did not find differences in patency between SE and BE stents. Sabri et al. concluded that the use of covered stents gave superior results over bare metal stents (primary patency rate at 1 year of 92 % and 78 %, for covered and bare metal stents, respectively). However, more recent studies do not report an increase in the use of covered stents in KS configurations. Predilatation was mostly done in selective cases, with long calcified lesions. Others refrained from predilatation because of the

possible risk on distal embolization¹⁹. Distal embolization was recorded 11 times in 5 studies (3.2 %) and is the third most recorded complication after pseudoaneurysms and groin complications.

Several studies reported on the number of hybrid procedures that were performed to optimize the outflow. This may well improve outcome of KS configurations, as was previously suggested, although series are still limited³². For future research, incorporating individual patient data of the previous, this would be a parameter of particular interest.

ANTICOAGULANT THERAPY

Peroperative The usage and dosage of intraoperative heparin fluctuated between studies. A recent review on the use of heparin in infrainguinal arterial bypass surgery concluded that the benefit of intraoperative administration of heparin is not yet proven in a randomized controlled trial³³. A previous study was also unable to demonstrate any evidence on the beneficiary effect of prophylactic perioperative use of heparin during surgery for abdominal aortic aneurysms³⁴. Evidence suggesting that the use of low molecular weight heparin produces better results in infrainguinal bypass surgery is emerging but still inconclusive³³.

During follow-up In several studies, ASA was prescribed as antiplatelet therapy, while others added clopidogrel. Antiplatelet therapy is indicated to reduce the risk of myocardial infarction and vascular death in AIOD patients; this also holds in combination with clopidogrel in high risk patients³⁵. A 2001 Cochrane review (updated in 2014) concluded that there is no evidence that supports the use of heparin, low-molecular-weight heparin (LMWH), and oral anticoagulants for treatment of IC in terms of pain-free walking distance, ABI, or progression to intervention³⁶. The 2012 Cochrane review by Robertson et al. concluded that there is only limited evidence suggesting a reduction in restenosis/reocclusion at 6 months after percutaneous transluminal angioplasty using antiplatelet drugs, compared with placebo or control groups. This also includes the use of dual platelet therapy (ASA and clopidogrel) compared with ASA only.

COMPLICATIONS The most frequently reported complication was a groin hematoma. The application of closure devices could reduce this frequently seen complication; however, Das et al. (2011) performed a meta-analysis and reported no statistically significant difference between manual compression and the application of a closure device in the interventional radiology setting. A 2015 review from Patel et al. concluded that closure devices are effective in achieving hemostasis with a similar complication rate as manual compression.

FOLLOW-UP Although most protocols incorporated some imaging modality to objectify patency, some studies only reported patency based on clinical judgment. This has reduced the ability to reliably compare patency rates between studies. Moreover, the strategy toward reinterventions was not consistent, which clearly may have influenced the secondary patency rate. Despite the fair 24-month patency results, the rate of reinterventions ranges between 0 % and 62.5 % with a mean of 20.9 %.

The 24-month primary and secondary patency rates in the present study are 78.6 % and 94.7 %, respectively. In the meta-analysis by Chiu et al., a 24-month primary patency of 90 % for open aorta-bi-femoral bypass surgery was described with an operative mortality of 4.1 %. In the literature reviewed in this study, only one procedural death was reported. The study of Kashyap et al. indicated that endovascular therapy rivals open reconstruction with respect to secondary patency, limb salvage, and survival. Our results confirm this as the secondary patency rate at 24 months was within the same range as those of surgical treatments. However, a review of Indes et al.³⁷ concluded that open bypass surgery is still superior to endovascular treatment for AIOD (pooled data on 1-, 3-, and 5-year primary patency: 94.8 % vs. 86 %, 86 % vs. 80 %, 90 % vs. 86.5 %), although with increased risk for adverse events and mortality.

PREDICTORS OF PATENCY Geometrical factors may affect performance of KS. Greiner et al.¹⁵ studied the effect of limb crossing/protrusion of KS. The findings were in favor of the noncrossing group with 2-year primary patency rates of 94.1 % for the “noncrossing” group and 33.2 % for the “crossing” group. This difference emphasizes the need for detailed research toward the geometrical differences of various KS configurations. The results of Greiner are supported by the findings of Sharafuddin et al.¹⁹, who found that the size of mismatch between the stent and vessel wall was predictive for stent patency. They concluded that matching of stents to the specific anatomy increases patency. Why the mismatch between the vessel lumen and KS configuration decreases patency is not clear. Possibly flow disturbances occur at the proximal part of the configuration, altering the wall shear stress, causing a reaction of the endothelium (neointimal hyperplasia). Improvements to the KS configuration might improve patency. The recently developed CERAB technique may be a step forward in improving the results³⁸. The CERAB configuration uses a third stent to form a funnel around the proximal ends of the KS configuration, eliminating the mismatch area and possibly improving the local flow regime at the proximal inflow of the KS configuration. A recently published study on the CERAB configuration shows promising results, 1- and 2-year primary patency rates of 87.3 % and 82.3 % respectively, while mainly (85.4 %) TASC D lesions were treated³⁹.

TRENDS OVER TIME When studying results obtained before and after 2010, it seems clear that the topic of KSs caught more attention in the last 6 years, as the same number of studies ($n = 10$) was published in the period between 1990 and 2010. Patients had more comorbidities (DM and HT) but clinical staging was less severe before treatment, suggesting that treatment was considered at an earlier stage. Reporting bias does not seem to be an issue here, because every study reported all relevant comorbidities. The secondary patency seemed to decrease at 24 months. It is unclear how this occurred but it might be related to a changed treatment strategy toward reinterventions. Overall, the results seem to have stabilized with respect to primary patency, complications, and lesion severity.

LIMITATIONS The current study has several limitations. Clinical characteristics of the treated patients varied across studies, as reflected by the large ranges, for instance, the presence of HT (37.5–96 %). All studies were retrospective in design, which introduced a selection bias for endovascular treatment. Most studies do not state if endovascular treatment is the first choice of treatment or if patient's health would not allow open surgery; this increases the heterogeneity of the results. During data extraction several comparisons were done to determine if parameters were suggestive for improved stent patency. We were not able to draw robust conclusions because of inhomogeneous data. If individual patient data were available more extensive analyses could be performed. This would lead to increased level of evidence and recommendations on the optimal KS technique and follow-up protocol.

CONCLUSION

The present systematic review of outcome after KS technique for AIOD revealed significant heterogeneity among studied literature which hampers overall comparison. However, the early and mid-term patency rates of KS treatment are acceptable, without a striking evolvement during time. Nevertheless, the scarcely reported long-term primary patency cannot yet match that of open reconstructive surgery. Further research is needed to assess factors related to early stent failure.

The authors want to thank J.G.M. Becht, PhD, for the help with the design of the search query: inclusion, exclusion, and logic combination of search terms.

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SUPPLEMENTARY DATA

Supplemental Table 1. Criteria for methodological quality assessment.

PARAMETER	CRITERIA AND SCORE
Study design	A. Retrospective = 0 B. Prospective = 1 C. Prospectively randomized = 2
Study population	A. Not Mentioned = 0 B. Only in- or exclusion criteria mentioned = 1 C. Both in- or exclusion criteria mentioned = 2
Patient characteristics	A. Not mentioned = 0 B. Clinical Classification or DM/HT/Smoking/HL = 1 C. DM/HT/Smoking/HL and clinical classification = 2
Lesion description	A. No TASC, no lesion description = 0 B. Length of the lesion, localization, ratio stenosis occlusive = 1 C. Only TASC I/II applied = 1 D. B+C = 2
Technique description	A. Pre dilatation B. Post dilatation C. Stent choice per lesion D. Stent overlap E. Stent localization F. Definition technical success G. Medication H. Rationale for endovascular intervention Nothing described = 0 Between 1 and 4 points described = 1 > 4 points described = 2
Lost to follow-up	A. Not described = 0 B. Large loss to follow-up = 0 C. Small loss to follow-up = 1 D. No loss to follow-up = 2
Patency described	A. No = 0 B. Yes = 2
Assessment of patency	A. Not described = 0 B. Clinical = 1 C. Clinical + ABI = 1 D. Imaging + clinical = 2
Definition of outcome	A. Not mentioned = 0 B. Well defined = 2
Description of Follow-up protocol	A. Not mentioned = 0 B. Poorly described = 1 C. Well described = 2
Indication for intervention	A. Not mentioned = 0 B. Poorly described = 1 C. Well described = 2
Mortality number	A. Not mentioned = 0 B. Described = 2
Complication numbers given	A. Not mentioned = 0 B. Given without subdivision = 1 C. Given, subdivision in Major/Minor = 2

DM: diabetes mellitus; HT: hypertension; HL: hyperlipidemia; TASC: Trans-Atlantic Inter-Society Consensus.

Supplemental Table 2. Quality assessment of included studies.

FIRST AUTHOR	YEAR	TOTAL SCORE	STUDY DESIGN	POPULATION	PATIENT CHARACTERISTICS	LESION DESCRIPTION	TECHNIQUE DESCRIPTION	FU COMPLETE	PATENCY DESCRIPTION	ASSESSMENT OF PATENCY	DEFINITIONS OF OUTCOME	FU DESCRIPTION	INDICATION FOR INTERVENTION DESCRIBED.	MORTALITY # GIVEN	COMPLICATION # GIVEN
Mendelsohn	1998	17	0	2	2	1	2	2	0	1	0	1	2	2	2
Scheinert	1999	13	0	0	2	1	2	1	0	2	0	2	1	0	2
Haulon	2002	18	0	2	2	0	2	1	2	2	2	1	2	0	2
Mohamed	2002	20	0	0	2	1	2	2	2	2	2	2	2	2	1
Greiner	2005	19	0	0	2	2	2	0	2	2	2	2	2	2	1
Houston	2007	20	0	2	2	2	1	1	2	2	2	2	2	2	0
Bjorses	2008	20	0	0	2	1	2	1	2	2	2	2	2	2	2
Sharafuddin	2008	20	0	0	2	2	2	0	2	2	2	2	2	2	2
Sabri	2010	22	0	0	2	2	2	2	2	2	2	2	2	2	2
Mouanoutoua	2003	16	0	0	2	0	2	2	2	1	0	1	2	2	2
Yilmaz	2006	22	0	2	2	2	2	1	2	1	2	2	2	2	2
Sixt	2013	19	0	1	2	2	1	0	2	2	2	2	2	2	1
Dohi	2013	15	0	0	2	2	1	0	2	1	2	2	2	0	1
Abello	2012	18	0	0	2	2	1	1	2	2	2	1	2	2	1
Strecker	1993	12	0	0	2	1	2	1	0	1	0	1	2	0	2
Hinnen	2015	19	0	1	2	1	2	0	2	1	2	2	2	2	2
Moon	2015	12	0	0	2	1	2	0	2	0	0	0	2	2	1
Pulli	2015	22	1	1	2	1	2	1	2	2	2	2	2	2	2
Suh	2015	21	0	2	2	1	2	0	2	2	2	2	2	2	2
Meng	2016	20	0	1	2	2	1	2	2	1	2	1	2	2	2
Hinnen	2015	17	0	1	2	1	1	1	2	2	2	0	2	2	1

FU: follow-up; #: number

Supplemental Table 3 Baseline patient characteristics.

FIRST AUTHOR	YEAR	# OF PATIENTS	DATA COLLECTION (Y)		MEAN AGE (SD) (Y)		HT (%)	DM (%)	HL (%)	SMOKING (%)	CVD (%)	RO (%)	R1/2/3 (%)	R4 (%)	R5/6 (%)	TASCA (%)	TASCB (%)	TASCC (%)	TASCD (%)
Mendelsohn	1998	20	2.0	55.0	58.4 (12.3)	70.0	35.0	90.0	65.0	85.0		100.0							
Scheinert	1999	48	7.0	60.4	59.0 (10.2)	75.0	10.4	47.9	85.4			95.8	4.2						
Haulon	2002	106	3.0	91.5	52.5 (10.2)	41.5	8.5	54.7	93.4			100.0							
Mohamed	2002	24	3.0	50.0	66.4	37.5	8.3	20.8	58.3			66.7	8.3	25.0					
Greiner	2005	41	8.0	53.7	60.8	48.8	19.5	41.5	56.1			51.2	22.0	14.6	4.9	9.8	24.4	61.0	
Houston	2007	43	2.0	39.5	64.0		23.3		81.4	25.6		32.6	58.1	9.3	0	27.9	53.5	18.6	
Bjorses	2008	173	9.0	45.7	64.2	45.1	18.5		58.4	26.0		72.8	9.8	17.3	15.0	33.5	10.4	41.0	
Sharafuddin	2008	66	7.0	69.7	64.0 (11)	50.0	31.8	74.2	89.4	48.5		42.4	22.7	34.8					
Sabri*	2010	26	2.0	65.4	61.0	96.2	50.0	69.2	38.5	50.0		80.8			26.9	34.6	23.1	15.4	
Sabri	2010	28	2.0	53.6	61.0	89.3	39.3	75.0	46.4	46.4		75.0			46.4	46.4	7.1	0	
Mouanoutoua	2003	50	7.0	56.0	62.0 (6.4)	42.0	14.0	38.0	44.0	82.0		70.0	18.0	12.0					
Yilmaz	2006	68	12.0	94.1	55.0 (11)	38.2	20.6	47.1	29.4	47.1		94.1	5.9		35.3	57.4	7.4	0	
Sixt	2013	135	10.0																
Dohi	2013	25	6.0	80.0	71.0 (9.4)	72.0	44.0	44.0	52.0	44.0		76.0	20.0	4.0	0	0	0	100.0	
Abello	2012	80	2.0	73.8	58.0 (12)	42.5	27.5	60.0	91.3		37.5	46.3	10.0	6.3	66.3	16.3	17.5	0	
Strecker	1993	18		61.1	61.0	55.6	22.2	77.8	100.0	22.2		88.9	11.1						
Hinnen	2015	215	16.0	62.8	61.0	45.6	20.9	54.0	54.9	47.4		83.7	7.9	7.0	56.3	27.4	0.9	13.5	
Moon	2015	21	5.0	100.0	53.0	71.4	33.3	61.9	71.4	47.6		61.9	38.1	23.8	9.5	23.8	33.3	38.1	
Pulli	2015	41	7.0	75.6	64.6	78.0	17.1	56.1	87.8	17.1		80.5	17.1	2.4	14.6	19.5	12.2	53.7	
Suh	2015	30	7.0	86.7	67.1	80.0	23.3	83.3	53.3	53.3									
Meng	2016	63	7.0	58.7	66.0	81.0	60.3	47.6	61.9	82.5		71.4	28.6		0	39.7	33.3	27.0	
Grimme	2015	69	6.0	42.0	59.0	39.1	20.3	72.5	88.4	39.1		84.1	5.8	4.3	31.9	30.4	4.3	33.3	

#: number; HT: hypertension; DM: diabetes mellitus; HL: hyperlipidaemia; CVD: cardiovascular disease in medical history; R: Rutherford. Fontaine to Rutherford conversion: Fontaine 1 = Rutherford 0; Fontaine 2 = Rutherford 1, 2, 3; Fontaine 3 = Rutherford 4; Fontaine 4 = Rutherford 5, 6. *Covered stent group.

Supplemental Table 4. Procedural details.

FIRST AUTHOR	YEAR	# OCCLUSIVE LESIONS	# STENOTIC LESIONS	MEAN OCCLUSION LENGTH (mm)	MEAN STENOSIS LENGTH (mm)	BE STENTS (%)	SE STENTS (%)	TECHNICAL SUCCESS (%)	ADDITIONAL TREATMENTS (%)	MINOR COMPLICATIONS (%)	MAJOR COMPLICATIONS (%)
Mendelsohn	1998	0	20			100.0		100	60.0		5.0
Scheinert	1999	23	32	6.7				100	14.6	6.3	0
Haulon	2002		55			41.5	58.5	100	16.0	14.2	
Mohamed	2002	20	14	59.0	43		100.0	100	12.5	20.8	
Greiner	2005	24	58	23.9				92	61.0	7.3	14.6
Houston	2007	12	31	42.9	37	23.3	76.7				
Bjorses	2008	9	104	28.7		30.1	50.9		31.8	10.4	3.5
Sharafuddin	2008	28		83.2	59	9.8	90.2	94	30.3	7.6	6.1
Sabri*	2010	12	22					100	73.1		11.5
Sabri	2010	3	27					100	53.6		7.1
Mouanoutoua	2003	6	43			86.0	14.0	100	22.0	6.0	4.0
Yilmaz	2006	26	68	23.0		76.5	23.5	100	11.8	8.8	2.9
Sixt	2013							100			
Dohi	2013	11		145.0		17.6	82.4	100	20.0	8.0	0
Abello	2012	10†	70		17.3†	58.5	41.5	89		0	5.0
Strecker	1993	8	20	14.2	18	100.0		100	83.3	11.1	0
Hinnen	2015							100	14.88	0.9	5.1
Moon	2015							100	23.81	19.0	
Pulli	2015	32	9	158	157.5	9.76	34.15	100	4.88		7.3
Suh	2015	20	10					100	10.00		13.3
Meng	2016				60.0	60.87	34.16	100	100.00	6.3	7.9
Grimme	2015					100.00			10.14		

#: number; BE: balloon-expandable; SE: self-expanding. *Covered stent group. †10 patients presented with both occlusive and stenotic lesions; only combined lesion length provided.

Supplemental Table 5

FIRST AUTHOR	YEAR	MEAN FU (SD) (M)	PATIENTS LOST TO FU (%)	REINTERVENTIONS (%)	30D CLINICAL IMPROVEMENT (%)	PATENCY 12M			PATENCY 24M			PATENCY 60M		
						p	a	s	p	a	s	p	a	s
Mendelsohn	1998	10 (7)	5.0											
Scheinert	1999	18	14.6	10.4	100.0	97.8			87		100			
Haulon	2002	30 (11)	4.7	17	96.2	89.5			81		98			
Mohamed	2002	24		62.5	70.8	81.5	84		58	84	100			
Greiner	2005				80.5				61	69				
Houston*	2007		11.6	25.6					89	93		82		93
Bjorses	2008	36 (28)	12.7	17.3	83.8	97.0	99	100	88	94	97	65	73	83
Sharafuddin	2008	37 (27)		15.2								81	94	
Sabri†	2010	20		7.7	92.3	92.0			92					
Sabri	2010	25		42.9	85.7	78.0			62					
Mouanoutoua	2003	20 (12)	0	8.0					92		100			
Yilmaz	2006	35 (31)	19.1	45.6		76.0	90	94				63	64	81
Sixt	2013			3.7		91.0		95						
Dohi	2013	28 (24)		20.0	96.0									
Abello	2012		7.5	40.0	93.8		96					65	81	
Strecker	1993	11	0	0	100.0	97.8			87		100			
Hinnen	2015	31		19.53	79.5				75	86	91	70	81	91
Moon	2015	41		28.57		89.6		94				64		69
Pulli	2015	22		12.20								71	71	83
Suh	2015	39		10.00		97.0			87					
Meng	2016		0.0	11.11	100.0	87.3		95	77		93	71		90
Grimme	2015		68.1	21.74		88.1		88	79		83	72		75

FU: follow-up; p: primary, a: assisted, s: secondary patency. *Follow-up data also provided 10 years primary patency of 68 % and a secondary assisted patency of 86 %. †Covered stent group.

Supplemental Table 6. Reported mortality rates, procedural, 30 days, 12 and 24months per study.

FIRST AUTHOR	YEAR	n	PROCEDURAL (%)	30 DAYS (%)	12 MONTHS (%)	24 MONTHS (%)
Mendelsohn	1998	20	0		5	
Scheinert	1999	48				
Haulon	2002	106				
Mohamed	2002	24				12.5
Greiner	2005	41		0		
Houston	2007	43	0	2.3		9.3
Bjorses	2008	173		1.15		
Sharafuddin	2008	66		4.5		28.8
Sabri*	2010	26		0	0	0
Sabri	2010	28				
Mouanoutoua	2003	50		2	0	0
Yilmaz	2006	68	0	0		
Sixt	2013	135				
Dohi	2013					
Abello	2012	80	0			
Strecker	1993	18				
Hinnen	2015	215	0.5	1.4		
Moon	2015	21				
Pulli	2015	41	0	0	0	0
Suh	2015	30	0			
Meng	2016	63	0			
Grimme	2015	69		1.4		

*Covered stent group.

Individual patient data analyses after kissing stent treatment

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ABSTRACT

INTRODUCTION The kissing stent (KS) technique is a popular treatment strategy for aortoiliac occlusive disease (AIOD). In the past two decades several retrospective cohort studies have been published regarding the outcome of this technique with mixed results. The goal of this study was to make a quantitative analysis based on an individual patient data (IPD) analysis of patients after kissing stent treatment.

METHODS The Scopus search engine was used to execute a search query to identify eligible papers. After abstract screening full text versions of the included papers were studied. Authors of included papers were approached to consider joining the IPD consortium. After agreement, data was sent anonymously and databases were merged. Backward logistic regression was used to identify outcome predictors. Kaplan-Meier curves were used to calculate patency rates.

RESULTS In total data from 5 papers was included, representing 605 of 1480 patients presented in literature (40.9 %). Baseline Rutherford classification was 1 (7.6 %), 2 (16.3 %), 3 (60.1 %), 4 (9.4 %), 5 (5.9 %) or 6 (0.5 %) and 52.9 % of the treated lesions were classified as TASC A and B. Cumulative primary and secondary patency after 12, 24, and 60 months was 86.1 %, 81.2 %, 72.8 % and 94.8 %, 93.0 %, 88.8 %, respectively. Primary patency significantly increased after 2005 ($p = 0.005$). Backward logistic regression only revealed aging as a significant but modest predictor to preserve primary patency ($OR = 0.92$, $p < 0.005$). Any previous endovascular intervention performed ($OR = 3.00$, $p = 0.007$) was the main predictor for loss of secondary patency, aging ($OR = 0.95$, $p = 0.020$), history of cardiovascular disease ($OR = 0.25$, $p = 0.029$), and using self-expanding stents instead of balloon-expandable stents ($OR = 0.40$, $p = 0.026$) were predictors of preserving secondary patency.

CONCLUSION The KS stent technique is related to competitive patency rates up to 2 years FU, with high technical success, and acceptable complication rates, also in case of TASC C and D lesions. The results improve over time and results after 2005 rival those of open surgery, indicating an endovascular-first approach in case of all AIOD lesions is supported by data from our current IPD analysis for KS treatment.

INTRODUCTION

KS treatment encompasses a well-accepted intervention for AIOD. The technique has several established benefits over open surgery: shorter length of hospital stay, lower 30-day mortality, lower 30-day major complication rate and comparable short-term outcome^{1,2}. The long-term outcome, however, cannot match that of open surgery, due to a high rate of reinterventions to assure stent patency³⁻⁶. Data published on the results of KS treatment usually include a relatively low sample size (mean 63.2, range: 18-215; Chapter 2), hampering robust conclusions. This can be attributed to the low prevalence of bilateral AIOD, including the aortic bifurcation and distal aorta. The heterogeneity of included patient groups reduces the comparability with respect to open surgery. More recent results suggest that KS treatment can also be an appropriate choice in more severe lesions, classified as TASC C and D^{1,7-9}. Also, while comparing the KS technique to other techniques, choices within the treatment protocol, which could potentially influence stent patency, are a much-debated topic. For instance, choices on pre- and post-dilatation differ between studies and may influence patency by increasing the cross-sectional area of the stented lumen as to enhance conformation to the vessel wall. The choice of balloon-expandable or self-expanding stents could also influence stent patency, based on the fact that self-expanding stents often have a better conformation to the vessel wall in turn causing less blood flow perturbations¹⁰⁻¹² (Chapter 4). The addition of an ePTFE cover might enhance patency by limiting cell ingrowth, however, when protruding (or the KS “cross”) in the distal aorta this conformation may cause dead space in which blood flow can recirculate, causing edge stenosis at the inflow and thrombus formation¹³ (Chapter 6). Our group recently published a systematic review on the results reported using kissing stents (including 21 studies), but the lack of IPD prevented an in-depth analysis of the aforementioned points. To this end, a consortium was established to pool the data available on kissing stent treatment and perform an IPD analyses. The goal was to evaluate short and long term technical and clinical outcomes after KS treatment in a large sample size. We evaluated possible predictors of failure/reintervention and aim to provide evidence-based protocol advice for KS treatment.

METHODS

DATA SOURCES The search query built for our systematic review (Chapter 2) was re-executed on 1–5–2017 using the Scopus database, to add the most recent publications. This strategy followed the guidelines from the preferred items for systematic reviews and meta-analysis (PRISMA) group¹⁴ (Chapter 2). To perform the IPD analyses the PRISMA–IPD statement was used¹⁵. Authors of eligible papers published after the year 2000 were approached by electronic mail to consider joining the consortium and a communication log was kept to overview all responses. If authors did not respond to the request a second letter was sent, if this remained unanswered the study was excluded.

Clinical investigation agreements were signed to formalize the collaboration and expectations. Data transfer agreements were signed and datasets were anonymized before transferring. The original principal investigators already obtained ethical approval prior to inclusion in the IPD. The study was approved by the local institutional review board.

MERGING OF THE DATA Prior to merging the individually obtained databases an SPSS (Version 24, IBM Corp., Armonk, NY, USA) database was constructed, according to the reporting standards¹⁶ (Chapter 2). In the conversion process fields of the original study database were mapped to the prebuild database. This was documented in a conversion log, which was saved per study. When applicable a conversion scheme was also saved in the log, based on the value label defined for the original field and IPD field. After initial mapping and conversion, a check of the conversion log and data copying per study cohort was performed. Any discrepancies on the meaning of column headings or definitions were resolved by discussion with the author. Per study a copy of the IPD database was saved. These were thereafter merged into one final database. All fields in the prebuild IPD database that contained no data in the final database were removed.

OUTCOME Primary study outcome was the cumulative patency results at 24 months. Secondary outcomes were: patency at 30 days, 6, 12 and 60 months, complication rate (major/minor), improvement in Rutherford stage and improvement in ABI. Additionally the predictive value of protrusion length, pre and post dilatation, stent type and patient demographics on primary patency was evaluated.

DEFINITIONS Definitions for cardiovascular risk factors were based on the latest reporting standards¹⁶, if applicable. Units for length, diameter, blood pressure, etc. were predefined and conversion was applied if needed. If no standard definition was available, labels per database were added if not yet available in the master database. Definitions for patency were used as adopted by the authors. Clinical improvement was defined as an

increase of ABI of at least 0.1 and a decrease of Rutherford of at least 1, between baseline and the first postoperative measurement.

STATISTICS Continuous variables are presented as median followed by range, since the data was not normally distributed (tested using the Kolmogorov-Smirnov test). Categorical variables are presented as counts followed by percentage.

Pre- and post-procedural comparisons of continuous variables were analyzed with ANOVA for repeated measures. Dichotomous variables were compared with a Fischer's exact test. The Chi square (X^2) test was used for comparing non-numeric categorical variables. Changes in parameters during follow-up time (30 days, 1 year, 2 years and 5 years) were calculated and analyzed using ANOVA for repeated measures.

Primary and secondary patency rates were determined on an intention to treat basis with Kaplan-Meier (KM) analyses. Logistic regression analyses (backward) was used to identify predictors of primary patency (reintervention or restenosis) and secondary patency (i.e. definitive failure). The Hosmer-Lemeshow test was used to check the goodness of fit of the model. Variables were included based on the correlation with outcome (if correlation $p < 0.05$; variables were entered into the regression model). The following parameters were included in the model for primary patency: age, preoperative ABI, hypertension, diabetes mellitus, stent crossing, TASC II category (A+B and C+D). For the secondary patency age, hypertension, smoking, CVD, previous (endo) vascular interventions and stent type were included as predictors. The Kruskal-Wallis test was used to evaluate the categorical parameters between included study groups, ANOVA was used for continuous parameters. Differences were considered significant for p -values < 0.05 .

RESULTS

After execution and interpretation of the search query 21 papers were included^{1-10,17-27}. Contact details of 19 corresponding authors of studies were available. Eight authors responded, two could not locate the original data files (data were published early 2000) and one did not have the resources to file an institutional review board (IRB) request and anonymize the database. The inclusion flow chart is presented in Figure 1. In total 6 databases were obtained (from 5 authors, Sabri et al.²⁴ included two separate groups), containing data of 605 patients, out of the 1480 presented in literature (40.9%)^{3,8,9,19,24}. Four publications reported on single center data, Dorigo et al.²⁸ published data collected in three centers. All patients were treated between April 1995 and February 2014. Patient demographics are presented in Table 1. Indication for intervention was IC in 84 % of patients, compared to 16 % of patients with CLI. Lesions were classified as TASC A or B in 52.9 % and TASC C and D in 47.1 %. Vascular interventions (either endovascular or

Figure 1. IPD inclusion flow diagram. The green boxes indicate results used from our previous systematic review.

surgical, both aortoiliac and more distal) were performed before in 27.3 % of patients. The median follow-up was 24 months (range 0–120 months). Follow-up was available at 30 days, 1, 2 and 5 years in 561, 399, 330 and 113 cases. Overall survival at 30 days, 1, 2 and 5 years was 98.9 %, 95.9 %, 91.5 % and 76.9 %.

Table 1. Patient and lesion characteristics

	# VALID	MEDIAN (RANGE)	
Age	604	61 (35–98)	
		n	%
Men	605	341	56.4
Risk factors			
Smoking, current or past (quit < 10)	599	395	65.9
Diabetes Mellitus	589	149	25.3
Hypertension	594	384	64.6
Hyperlipidemia	567	393	69.3
Cardiac disease	599	199	33.2
Renal disease	387	26	6.7
Cerebrovascular disease	282	37	13.1
Rutherford category	594		
1		45	7.6
2		97	16.3
3		357	60.1
4		56	9.4
5		35	5.9
6		3	0.5
TASC classification	600		
A		190	31.7
B		127	21.2
C		88	14.7
D		195	32.5
	# VALID	MEDIAN (RANGE)	
ABI preoperative			
Left	411	0.70 (0.09–1.44)	
Right	408	0.72 (0.09–1.30)	
		n	%
Previous vascular intervention	439	120	27.3
Type of previous intervention			
PBA	58	4	6.9
PBA+stent distal to iliac region		31	53.4
PBA+stent iliac region		7	12.1
Bypass surgery		9	15.5
Stent in bifurcation prostheses		7	12.1

#: number; ABI: ankle brachial index; PBA: plain balloon angiography

VARIATION ACROSS STUDIES Table 2 gives an overview of demographic parameters and outcome variables. The variable research group was added to the logistic regression model, this did not prove to be a parameter with significant predictive power ($B = -0.02$, $S.E. = 0.11$, $odds = 0.9$, $p = 0.9$)

Table 2. Demographics and outcome per study

PARAMETER	HINNEN ³ et al.	SIXT ⁹ et al.	SABRI ²⁴ et al. (B)	SABRI ²⁴ et al. (C)	GRIMME ¹⁹ et al.	DORIGO et al. ²⁸	p-VALUE
	<i>Median (range)</i>						
Age	60.0 (36–89)	59.0 (40–87)	60.0 (38–82)	62.5 (39–79)	58 (35–80)	67 (38–98)	< 0.005
	<i>n (%)</i>						
Men	135 (62.8)	44 (32.6)	15 (53.6)	18 (69.2)	32 (43.8)	97 (75.8)	< 0.005
<i>Risk factors</i>							
Smoking, current or past	118 (54.9)	103 (76.3)	23 (82.1)	20 (76.9)	65 (89.0)	66 (51.6)	< 0.005
Diabetes Mellitus	45 (20.9)	30 (22.2)	16 (57.1)	13 (50.0)	14 (19.2)	35 (27.3)	0.007
Hypertension	97 (47.1)	98 (72.6)	25 (89.3)	25 (96.2)	30 (42.3)	109 (85.2)	< 0.005
Hyperlipidemia	116 (54.0)	116 (85.9)	21 (75.0)	18 (69.2)	54 (74.0)	68 (53.1)	< 0.005
Cardiac disease	72 (34.4)	51 (37.8)	13 (46.4)	13 (50.0)	19 (26.0)	31 (24.2)	0.021
Renal disease		8 (5.9)	0.0	3 (11.5)	7 (10.0)	8 (6.3)	0.360
Cerebrovascular disease	30 (14.4)				7 (9.6)		0.300
<i>Rutherford</i>							< 0.005
1	1 (0.5)	5 (3.8)	19 (67.9)	20 (76.9)			
2	54 (25.5)	22 (16.8)			21 (30.4)		
3	125 (59.0)	91 (69.5)	2 (7.1)	1 (3.8)	41 (59.4)	97 (75.8)	
4	17 (8.0)	4 (3.1)	5 (17.9)	11.5	4 (5.8)	23 (18.0)	
5	15 (7.1)	6 (4.6)	2 (7.1)	7.7	3 (4.3)	7 (5.5)	
6		2 (1.5)				1 (0.8)	
TASC							< 0.005
A	120 (57.1)	28 (20.7)	13 (46.4)	7 (26.9)	22 (30.1)		
B	59 (28.1)	21 (15.6)	13 (46.4)	10 (38.5)	24 (32.9)		
C	2 (1.0)	25 (18.5)	2 (7.1)	5 (19.2)	3 (4.1)	51 (39.8)	
D	29 (13.8)	61 (45.2)		4 (15.4)	24 (32.9)	77 (60.2)	
Previous endovascular intervention	28 (13.0)	32 (33.0)	13 (46.4)	16 (61.5)	31 (42.5)		< 0.005
<i>Type of stents</i>							
							< 0.005
Self-expanding	138 (92.0)	60 (45.5)	1 (3.6)			106 (82.8)	
Balloon-expandable	12 (8.0)	63 (47.7)	27 (96.4)		73 (100.0)	5 (3.9)	
Covered balloon-expandable				26 (100.0)		17 (13.3)	
Primary patency lost	59 (27.4)	16 (11.9)	12 (42.9)	2 (7.7)	20 (27.4)	14 (11.3)	< 0.005
Secondary patency lost	17 (7.9)	5 (3.7)			17 (23.3)	5 (4.0)	< 0.005

B: bare stent group; C: covered stent group

Table 3. Procedure details

	# VALID	n	%		# VALID	n	%
Technical success	532	527	99.1	Additional treatment	269	43	12.8
Type of stents	528			Type of additional treatment	221		
Balloon-expandable		180	34.1	None		183	82.8
Covered balloon-expandable		43	8.1	PBA distal of kissing stents		2	0.9
Self-expanding		305	57.8	Bypass surgery		19	8.6
Crossing	346	233	67.3	Endarterectomy		11	5.0
				TEA femoral artery		6	2.7

#: number; PBA: plain balloon angiography; TEA: trombo-endarterectomy

PROCEDURAL RESULTS Overall a technical success rate of 99.1% was achieved. The vast majority (91.9%) was treated with bare metal stents of which in 57.8% of cases self-expanding stents were used. Covered balloon-expandable stents were used in 8.1% of the cases. In 67.3% of cases the stents protruded into the distal aorta and crossed. In 12.8% an additional treatment was performed along with the primary KS treatment. Details are presented in Table 3.

CLINICAL OUTCOMES UNTIL 1 MONTH FOLLOW-UP At discharge the ABI had significantly improved with respect to the baseline measurements ($p < 0.001$). Shift in Rutherford class between pre and postoperative is presented in Figure 2. Clinical improvement (based on both the discharge Rutherford scoring and ABI) could be established, in 66.5% of the cases. In case of no clinical improvement, the ABI did improve but the Rutherford classification did not in 65.1% of the cases, in 15.1% of cases the

Figure 2. Overview of Rutherford distribution at baseline and discharge.

Table 4. Clinical outcome

	# VALID	MEDIAN (RANGE)		# VALID	n	%
ABI at discharge			Complication	558	46	8.2
Left	426	1.00 (0.23–1.38)	Complication type	348		
Right	417	1.00 (0.27–1.33)	None		313	89.9
			Bleeding		8	2.3
			False aneurysm		6	1.7
			Dissection		4	1.1
			Thrombosis		3	0.9
			Cardiac		3	0.9
			Hematoma		2	0.6
			Wound complication		2	0.6
			Embolus		2	0.6
			Pulmonary embolism		1	0.3
			Procedural death		1	0.3
			IIA overstented		1	0.3
			Contrast reaction		1	0.3
Rutherford at discharge	389					
0		209	53.7			
1		35	9.0			
2		46	11.8			
3		84	21.6			
4		8	2.1			
5		5	1.3			
6		2	0.5			
Clinical improvement	287	156	49.1			

#: number; ABI: ankle brachial index; IIA: internal iliac artery

Rutherford classification did not improve but the ABI did and in 19.8 % of the cases both the ABI and the Rutherford did not improve. The 30-day complication rate was 8.2 % (n = 46 patients); the most frequently observed complication was perioperative bleeding (2.3 %). Details regarding the type of complication are depicted in Table 4.

FOLLOW-UP Table 5 describes the available data per FU period (as opposed to only the final FU). An increase in stent failure (loss of primary patency), definitive stent failure (loss of secondary patency) and reinterventions in terms of percentage can be observed as FU progresses while the number of patients available for follow-up decreases.

PATENCY The included papers used different definitions for primary patency, three papers defined primary patency as the absence of restenosis (< 50% based on duplex or peak systolic velocity (PSV) < 2.5)^{9,19,24}. While two other papers defined primary patency as the absence of a reintervention of the target lesion^{3,8}. Primary patency rates for 6, 12,

Table 5. Follow-up information

FU INTERVAL	FU n (%)	FAILURE n (%)	DEFINITIVE FAILURE n (%)	REINTERVENTIONS n (%)
30d	235 (39)	18 (8)	8 (4)	19 (8)
1y	134 (22)	15 (11)	6 (5)	14 (10)
2y	183 (30)	67 (37)	12 (7)	49 (26)
5y	72 (12)	28 (39)	9 (13)	25 (35)

FU: follow-up

24, 36, 48 and 60 months are 87.6 %, 86.1 %, 81.2 %, 76.6 %, 75.3 % and 72.8 %, respectively. Secondary patency results for 6, 12, 24, 36, 48 and 60 months are 96.0 %, 94.8 %, 93.0 %, 91.4 %, 90.0 %, 88.8 %, respectively. Detailed results are presented in Figure 3. Figure 4 shows the patency per site and Figure 5 shows the patency rates per TASC classification (A+B and C+D). Half of the procedures were performed before 2005, the other half in or after 2005. When comparing the patency rates, the primary patency before 2005 was significantly lower compared to the results obtained after 2005 ($p = 0.005$). This excluded the data from Sabri et al., as the medical ethical board prohibited the exchange of dates. Only the patients included from the cohort of Dorigo et al. were predominantly treated after 2005 ($n = 121$, 95 %), for other groups the procedures were divided roughly 50/50 over the period before and after 2005. An overview of the patency before and after 2005 is depicted in Figure 6.

Figure 3. Kaplan–Meier survival curve for the primary and secondary patency

PREDICTORS OF DEFINITIVE FAILURE AND REINTERVENTIONS Backward logistic regression was applied to identify predictors of primary and secondary patency. Only aging (odds ratio (OR) = 0.92, $p < 0.005$) significantly albeit modestly, predicted preservation of primary patency. Previous (endo)vascular intervention (OR = 3.00, $p = 0.007$) was a significant predictor for loss of secondary patency. Furthermore modest but significant contributions of age (OR = 0.95, $p = 0.020$), history of CVD (OR = 0.25, $p = 0.029$), and the use of self-expanding stents (OR = 0.40, $p = 0.026$) were found to preserve secondary patency. Details are depicted in Table 6.

Figure 4. Primary and secondary patency, split by site ($p < 0.005$, for both).

Figure 5. Primary patency by TASC classification ($p = 0.047$)

Figure 6. Patency values before and after 2005 ($p = 0.005$).

Table 6. Details for PP and SP predictors

INCLUDED FOR PP	B (S.E.)	LOWER	ODDS RATIO	UPPER	SIG.
Age	-0.08 (0.02)	0.88	0.92	0.96	< 0.005
INCLUDED FOR SP	B (S.E.)	LOWER	ODDS RATIO	UPPER	SIG.
Previous (endo)vascular intervention	1.1 (0.41)	1.35	3.00	6.63	0.01
Age	-0.05 (0.02)	0.91	0.95	1.00	0.02
History of CVD	-1.39 (0.64)	0.07	0.25	0.87	0.03
SE vs. BE	-0.93 (0.42)	0.18	0.40	0.90	0.03

Model statistics: $R^2 = 0.18$; Cox & Snell = 0.1; Nagelkerke = 0.2. Model chi-square = 30.86; $p < 0.005$.

PP: primary patency; S.E.: standard error; SP: secondary patency; CVD: cardiovascular disease; SE: self-expanding; BE: balloon-expandable; Sig.: significance.

DISCUSSION

The current study included the IPD of 605 patients with AIOD treated with the KS technique, which is the largest group presented in literature, to our knowledge. The 24 month overall primary and secondary patency was 81.2 % and 93 % respectively. There still seems to be a gap with results from open surgery, with an average 2-year primary patency of 93 %. The current KS cohort consisted of 32.5 % TASC D lesions, with a primary patency at two years of 87.7 %, which was similar to TASC C lesions (primary patency: 88.8 %). The TASC C and D lesions performed significantly better than TASC A (primary patency: 77.1 %) and B lesions (primary patency: 71.4 %). This finding is surprising and contrary to previous studies, which have shown no difference in outcome between TASC lesion category and primary patency^{1,9,17,29}. Furthermore, the TASC II consensus document states that generally the outcome gradually worsens with increasing extent of the disease³⁰. This observation may be related to an increased learning curve, as more complex lesions are likely to be treated with more experience and progress in the treatment of cardiovascular risk factors. This is reflected by the observation that more complex lesions were treated in the latest time interval.

Apart from open surgery the CERAB is another technique to treat severe AIOD. Initial primary patency results at two years are around 87%, treating primarily TASC D lesions³¹, which is in line with the results from this IPD analysis. That study, however included all patients from the first in human and a learning curve bias was likely. In the current study, overall 195 lesions were classified as TASC D, but 138 (70.7 %) of these lesions are from the study groups of Sixt (n = 61) and Dorigo (n = 77), indicating a heterogeneity in treatment strategy between study groups. These results call for a one-to-one comparison of both the CERAB and KS technique for severe AIOD.

To investigate any change in outcome over time, the cohort was split in a group treated prior to 2005 and in or after 2005. This threshold is, somewhat arbitrarily based on the fact that 2005 is the median year of procedure in the current cohort. This analysis showed that there is a significant difference in patency results obtained prior and after 2005. Applying our backward logistic regression model on the groups before and after 2005 did not yield different results with respect to predictors for outcome. After 2005 more self-expanding stents were deployed (66.9 % vs. 55.8 %) and stents were placed less often in a configuration that protruded in the aorta (73.7 % vs. 86.5 %). After 2005 more TASC D lesions were included (40.4 % vs. 27.8 %). The latter is, however, contradicting as TASC D lesions include lesions that cross the bifurcation, when treating these lesions from healthy-to-healthy tissue protrusion of the stents is often needed. Lesions treated with self-expanding stents that do not protrude into the aorta may influence the improved patency results after 2005. The recently published ICE-trial also indicates superior

results of self-expanding stents for the treatment of lesions in the iliac vasculature with respect to restenosis rate³². Our current dataset showed that primary patency is not significantly influenced by procedural choices, like type of stent, protrusion and patient demography (apart from age). Only the type of stent and previous interventions predicted preservation of secondary patency with self-expanding stents proving superior to balloon expandable stents. Based on these results no change of recommendations for the future treatment of patients with the KS technique can be established.

After analysis of the FU per interval the results show that there is an increase in the number of primary failures and reinterventions at two years. This indicates that it might be beneficial to schedule one more FU moment between 12 and 24 months, to have an early diagnoses of KS configurations that are at risk. Apart from primary failures there is also an increase of definitive failures seen at 2-year FU.

When reporting FU results the studies that were included in this KS IPD analysis mainly used ABI and Rutherford classification to report postoperative clinical outcome. During FU the ABI was seldom reported and patency was mostly based on duplex ultrasound and observed symptoms. This choice maybe justified by the fact that in case of no clinical improvement this was mainly due to an absence of improvement in Rutherford staging, making this an important marker.

This IPD has several limitations, mostly due to the fact that all groups have focused on a different set of parameters in their databases, coded using different definitions. This limits the number of parameters available for the merged datasets, introducing missing data. In case of primary patency two different definitions were used; this could not be re-coded due to lack of data during the FU intervals. Not all data could be retrieved, highlighting the importance of proper storage of research data. Furthermore, symptoms were not regularly reported during the FU period, therefore clinically driven reinterventions could not be analyzed. No information about serious adverse events was available. The aforementioned hampers the construction of models (due to exclusion in case of missing data) that can correctly predict failure of primary patency. The technical success rates have to be regarded with care as definitions were not always reported and in case of a technical failure it was not always clear how this was dealt with. The number of patients included was only 41 % (6 out of 19 studies) of the data that is available in literature, in some cases the corresponding author did not reply to our request. In a field where patient cohorts are usually small, this may hamper robust conclusions and may limit the advancement of knowledge, outcome and technique of the KS treatment. Unfortunately, the present IPD analysis did not allow us to draw robust conclusions on choice of patient categories that can be best treated with KS.

CONCLUSION

The current KS IPD analysis has shown that acceptable patency rates can be obtained at 2 year FU, with high levels technical success, and acceptable complication rates, also in the cases of TASC D lesions. Guidelines with respect to treatment choices could not be developed based on the current dataset. However, outcome seems to improve over time and results after 2005 rival those of open surgery, indicating that an endovascular-first approach in case of all AIOD lesions is supported by data from the current IPD analysis for KS treatment.

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Geometrical consequences of kissing stents and the covered endovascular reconstruction of the aortic bifurcation configuration in an in vitro model for endovascular reconstruction of aortic bifurcation

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Adapted from **the Journal of Vascular Surgery**
2015, Volume 61, Issue 5, Pages 1306-1311.

ABSTRACT

OBJECTIVE KS are commonly used to treat aortoiliac occlusive disease, but patency results are often lower than those of isolated stents. The CERAB technique was recently introduced to reconstruct the aortic bifurcation in a more anatomical and physiological fashion. The aim of this study is to compare the geometrical consequences of various stent configurations in vitro.

METHODS Anatomic vessel phantoms of the aortoiliac bifurcation were created to accommodate stent configurations. Self-expanding nitinol KS, balloon-expandable covered KS, and two versions of the CERAB configuration were deployed, one with the iliac legs positioned inside the tapered part of the aortic cuff (1) and one with the legs deployed above this level (2). Computed tomography data were obtained to assess the geometry. The conformation ratio (D-ratio) was calculated by use of the ratio of the major and minor axes. The proximal mismatch area, mean mismatch area, and total mismatch volume were calculated.

RESULTS The highest D-ratios were observed in the nitinol KS and the CERAB configuration, implying an ideal “double-D” shape. The proximal and mean mismatch areas were four- to sixfold lower in the CERAB (1) configuration when compared with nitinol KS and CERAB (2), respectively, whereas the covered KS had the highest mismatch area. Nitinol and covered KS had the largest mismatch volume, whereas the mismatch volume was the lowest in the CERAB (1) configuration.

CONCLUSIONS Although nitinol self-expanding stents have a high stent conformation, the lowest radial mismatch was found in the CERAB (1) configuration, supporting the hypothesis that the CERAB configuration is the most anatomical and physiological reconstruction of the aortic bifurcation. Within the CERAB configuration, the two limbs are ideally positioned inside the tapering portion of the cuff, minimizing mismatch.

INTRODUCTION

Endovascular treatments of extensive lesions involving the aortic bifurcation are among the most challenging indications in endovascular surgery. According to existing guidelines, surgery is the gold standard for bilateral and extensive occlusive disease on the basis of good long-term patency rates¹. The 30-day mortality rate for an aorto-bifemoral bypass, however, is 4 %, with an early local and systemic morbidity rate of 6 % and 16 %, respectively². These complications justify the search for minimally invasive alternatives. Stents in KS position have frequently been used to reconstruct the aortic bifurcation, and several modifications exist. The 1-year primary patency rate of KS varies between 70 % and 100 %, with a morbidity rate of 6 % to 24 %, including distal embolization in up to 8 % of cases³. The use of covered stents appears to improve patency rates⁴. Various aspects of the KS configuration may affect patency rates, including the positioning of the stents and the discrepancy between the stented lumen and the aortic lumen, the so-called radial mismatch⁵. The latter causes flow perturbations and thrombus formation that in turn may decrease stent patency⁶. Choosing a configuration with the lowest radial mismatch may thus be crucial, and, for this reason, the CERAB technique was recently developed in an attempt to reconstruct the aortic bifurcation in a more anatomical and physiological fashion⁷.

With the use of this technique, a covered stent is expanded 15 to 20 mm above the aortic bifurcation and this stent is proximally adapted to the aortic wall with a larger balloon, thereby creating a cone-shaped stent. Two iliac covered stents are then placed in the distal conic segment and simultaneously inflated, making a tight connection with the aortic stent, as if they were molded together, thus simulating a new bifurcation. The aortic cuff covers the free-floating proximal ends of the iliac stents that reside in the distal aorta and might thus prevent unwanted flow perturbations around the protruding part of the stents, guiding the flow into the limbs like a funnel.

In the present study, we have assessed radial mismatch and stent conformation of four different stent configurations with the use of identical, in vitro, rigid phantoms to mimic the vessel anatomy. Results are discussed in view of the current available theoretical and clinical experience on stent patency in the aortoiliac region.

METHODS

To assess radial mismatch and differences in stent conformation between various stent configurations, four identical rigid aortoiliac bifurcation models were created, partly adopted from Chong et al.⁸ First, a literature survey was performed to obtain geometrical data of the aortoiliac anatomy^{9,10,11}. Data from 47 cadavers and 55 biplanar angiograms were combined to obtain the key geometry features as presented in Table 1. The combined data were used to create a model with the use of Computer-Aided Design (CAD) software (SolidWorks 2012; SolidWorks Corp, Concord, Mass). The final model included the abdominal aorta, the aortic bifurcation, the renal arteries, and both common iliac arteries. The CAD design was used to make a solid three-dimensional printed model of the vessel lumen, which, in turn, was used to make a silicone mold (620/TL95 silicone rubber; NKC, Harjon B.V., Dordrecht, The Netherlands). This was used to create wax castings of the vessel lumen. The spray-painted wax casting was placed inside a rectangular container. De-aerated clear silicone rubber (Sylgard 184; Dow Corning GmBH, Wiesbaden, Germany) was poured inside the container and set to dry at 35 °C overnight. Thereafter, the temperature was increased to 120 °C to melt the wax vessel lumen.

Table 1. Anatomical parameters used to design the bifurcation model

PARAMETER	DIMENSIONS MEAN (STANDARD DEVIATION)
Diam. abdominal aorta at inflow (mm)	22 (3.5)
Diam. abdominal aorta at renal artery (mm)	19 (3.3)
Diam. abdominal aorta at IMA (mm)	17 (3.6)
Diam. abdominal aorta at bifurcation (mm)	16 (1.6)
Diam. renal artery left/right (mm)	6 (1.3)
Diam. CIA left/right (mm)	8 (1.7)
Distance from aortic bifurcation to renal arteries left/right (mm)	86 (1.7)
Length of CIA left (mm)	55 (3.2)
Length of CIA right (mm)	57 (6.1)
Length of renal artery left (mm)	12 (a)
Length of renal artery right (mm)	29 (a)
Branching angle renal artery left (degrees)	65 (16)
Branching angle renal artery right (degrees)	61 (17)
Take of angle CIA left (degrees)	20 (5.9)
Take of angle CIA right (degrees)	30 (6.8)
Angle of aorta (degrees)	16 (3.3)

CIA: Common iliac artery; Diam.: diameter; IMA: inferior mesenteric artery.

All vessels are symmetrically round, and dimensions are rounded to whole millimeters.

(a) No standard deviation available.

Figure 1. Still color photographs, Rontgen images, and bronchoscopic images of

- A** Self-expanding nitinol kissing stents (KS)
- B** Balloon-expandable covered kissing (CK) stents
- C** Covered Endovascular Reconstruction of the Aortic Bifurcation (CERAB)-1 with the limbs starting in the tapered part of the aortic cuff
- D** CERAB-2 with the iliac limbs starting just above the tapered segment of the aortic cuff.

The stent configurations were constructed by two experienced vascular surgeons (PG, MR) with the use of regular guide wires and catheters. Four different configurations were created. One bare metal kissing (BMK) stent configuration was made using two 10-mm self-expanding nitinol stents (S.M.A.R.T Control; Cordis Corp, Miami, Fla). After deployment, these nitinol stents were flushed with hot water (40 °C) and dilated to ensure full deployment of the nitinol. In the second model, a covered kissing (CK) stent configuration, consisting of two 8-mm ePTFE covered stents (V12; Atrium Maquet Getinge, Hudson, NH), was placed. In the third and fourth model, a CERAB configuration was placed by use of one 12 × 61-mm covered stent that was dilated to 16 mm in the proximal two-thirds of the stent length and two 8 × 38-mm (CERAB-1) or 8 × 59-mm (CERAB-2) limbs. In the first CERAB (CERAB-1) configuration, these two limbs were placed exactly in the tapered part of the aortic cuff only (10 mm above the distal margin of the cuff), as the technique intended⁷. In the second CERAB configuration (CERAB-2), the two limbs were deployed above the conic segment of the aortic cuff (25 mm above the distal margin of the cuff), which in theory would be a suboptimal position. All ePTFE-covered stents were submerged in water (40 °C, 2 minutes) before placement, preventing rupture of the ePTFE.

The models were imaged by means of four modalities: still color photographs, X-ray photographs, computed tomography (CT) scanning, and bronchoscopic imaging (Figure 1). The photographs (A900; Sony, Tokyo, Japan) were made in the anterior-posterior direction, and the lumen of the model was filled with a solution of water and glycerol (ratio, 44:56 wt/wt) to match the refractive index of the silicone and fluid-filled vessel lumen. When the refractive index is matched, clear undisturbed photographs can be obtained. X-ray images were also obtained in the anterior-posterior position. To inspect the proximal stent geometry, a bronchoscope (EB-1970K 2.8; Pentax Corporation, Tokyo, Japan) was inserted into the model to obtain close-up photographs. CT imaging (Brilliance 40 slice; Philips Medical, Best, The Netherlands) was performed for each model. The following scan settings were used: slice thickness 1 mm; adjacent increment; kV 120; mAs/slice 365; field of view, 180 mm. Matlab (2012A; The MathWorks Inc, Natick, Mass) was used to analyze the CT data. A software tool was designed to segment the mismatch volume in each slice by hand, with the use of a polygon approximation. All pixels within the segmented area are summed and multiplied by the pixel size to obtain the mismatch area. The proximal mismatch area was determined on the first CT slice with both limbs in view. The mean mismatch area was calculated by averaging the mismatch area determined per 1-mm slice over the entire mismatch segment. One-millimeter coupes were chosen to obtain sufficient data points for calculating the mean mismatch area. The mismatch segment is the cranio-caudal length, where a discrepancy exists between the stented lumen and the aortic lumen. The mean mismatch area was

calculated as $\text{sum}(\text{mismatch area per slice})/\text{number of slices}$. The total mismatch volume was calculated summing the slice area multiplied with the slice thickness (1 mm). To assess the stent conformation (double-D shape) ellipses (with 5 degrees of freedom: x, y, minor axes, major axes, and angle) were fitted to the stent lumen of each slice in the CT data. Thereafter, the ratio between the major and minor axes was used as a measure for stent conformation (D-ratio). Ratios higher than 1 indicate a more elliptical (or “D”) shape, with a maximum of 2. Two researchers independently performed the measurements, and the results were averaged.

RESULTS

STENT CONFORMATION In Figure 2, the D-ratio for the four stent configurations is shown. When focusing on the inflow segment of the limbs, the BMK stents and CERAB limbs had the highest (1.6 and 1.4) D-ratios, meaning that these configurations had the highest stent conformation to the aortic wall and aortic cuff, respectively. The BMK stents retain a D-shape over the full length in the aorta, which is not seen with the other configurations. The D-ratio of the CERAB-2 rises, with a maximum of 1.6, when the limbs enter the tapered part of the aortic cuff. More proximally and distally, the ratio is between 1 and 1.4, indicating a round conformation. The CK stents have a mean D-ratio of 1.15, pointing toward a double-barrel configuration. None of the configurations exhibited large D-ratio differences between the left and right limbs; the average difference between the left and right limbs was 0.11, 0.048, 0.036, and 0.049 for the BMK stents, CK stents, CERAB-1, and CERAB-2, respectively.

Figure 2. D-ratios of the four different configurations. A ratio of 1 indicates a circular conformation of the stent, whereas ratios higher than 1 indicate more elliptical conformation. Starting point of the graph is the proximal side of the iliac limbs.

BMK: Bare metal kissing; CERAB: Covered Endovascular Reconstruction of the Aortic Bifurcation; CK: covered kissing.

PROXIMAL MISMATCH AREA Figure 3 presents the axial slices of the configurations at the inflow portion of the limbs. In Figure 3, A, it is shown that the BMK stents are flattened in the middle, creating a double D configuration. In contrast, the CK stents are crossed and obtain a more round double-barrel geometry, because the kissing parts of the stents do not flatten (Figure 3, B). The limbs of the CERAB-1 configuration (Figure 3, C) are forced into a double-D shape by the tapering part of the aortic cuff. In contrast, the CERAB-2 configuration has a more round inflow lumen of both limbs (Figure 3, D). At the proximal inflow part, the total mismatch area was the lowest in the CERAB-1 configuration (4.04 mm^2), compared with 24.75 mm^2 , 56.68 mm^2 , and 22.5 mm^2 for the BMK, CK, and CERAB-2, respectively.

Figure 3. Axial slices of the computed tomography (CT) scans of the inflow portions of the four models.

- A** Self-expanding nitinol kissing stents (KS);
- B** Balloon-expandable covered kissing (CK) stents;
- C** Covered Endovascular Reconstruction of the Aortic Bifurcation (CERAB)-1 with the limbs starting in the tapered part of the aortic cuff;
- D** CERAB-2 with the iliac limbs starting just above the tapered segment of the aortic cuff.

MEAN MISMATCH AREA The mean total mismatch areas are presented in Table 2. The CK stents have a mean total mismatch area (53.48 mm^2) that is more than twice that of the BMK stents (21.38 mm^2). The CERAB-1 configuration has only one-sixth of the mean mismatch area (3.1 mm^2) of the BMK stents. The CERAB-2 configuration has a total mean mismatch area (12.65 mm^2) that was four times that of the first CERAB configuration, but it was still much lower than those of the two KS configurations.

TOTAL MISMATCH VOLUME The results of the three-dimensional total mismatch volume are depicted in Figure 4. The BMK stents have a long but straight mismatch volume along the aorta. The CK stents had the largest mismatch volume. The mismatch volume of the CK stents is twisted, and the two lumina join at the bifurcation as the result of crossing of the stents. The CERAB-1 has a thin and short total mismatch volume, whereas the CERAB-2 has a longer, cone-shaped volume. The total volume per stent configuration can be seen in Table 2. CK stents had the largest mismatch volume (2163.3 mm^3), whereas the mismatch volume was lowest (30.25 mm^3) in the CERAB-1 configuration: 30 times lower than the BMK (903.34 mm^3). When comparing the two CERAB configurations, it can be seen that the mismatch volume of the CERAB-1 configuration is almost nine times lower than that of the CERAB-2 configuration.

Table 2. Mean mismatch areas and volumes of the four different configurations

CONFIGURATION	MISMATCH AREA mm^2						MISMATCH VOLUME mm^3		
	Prox. left	Prox. right	Prox. left + right	Mean left	Mean right	Mean left + right	Left	Right	Total
A, BMK stents	12.10	13.2	24.75	10.02	11.37	21.38	417.07	486.27	903.34
B, CK stents	27.64	30.43	56.68	26.1	27.4	53.48	1031.45	1131.85	2163.3
C, CERAB-1	2.3	1.74	4.04	1.45	1.66	3.11	14.06	16.19	30.25
D, CERAB-2	14.45	8.10	22.5	7.97	4.68	12.65	149.10	88.89	237.99

BMK: Bare metal kissing; CERAB: Covered Endovascular Reconstruction of the Aortic Bifurcation; CK: covered kissing;
Prox.: proximal.

Figure 4. Geometric mismatch volumes of the four stent configurations as measured with a custom written script, used to segment the whole mismatch volume in each slice by hand, through the use of a polygon approximation.

- A** Self-expanding nitinol kissing stents (KS);
- B** Balloon-expandable covered kissing (CK) stents;
- C** Covered Endovascular Reconstruction of the Aortic Bifurcation (CERAB)-1 with the limbs starting in the tapered part of the aortic cuff;
- D** CERAB-2 with the iliac limbs starting just above the tapered segment of the aortic cuff.

DISCUSSION

Results of the present study show that different stent configurations may result in large variations in stent conformation, mismatch area (up to sixfold difference), and mismatch volume (up to 30-fold difference). The CERAB configuration with the limbs starting in the tapering part of the aortic cuff, as they are intended to do, was related to the best geometrical conditions, meaning the lowest radial mismatch and a high stent conformation. Both CERAB configurations were related to a lower mismatch area and mismatch volume when compared with the KS configurations, but this was above all true for the CERAB-1 configuration. Within the BMK configuration, however, the D-ratio was the highest, indicating that nitinol stents have the highest conformation to the vessel wall. Nevertheless, the radial mismatch was much lower in the CERAB configurations because the aortic cuff had adapted to the outline of both limbs and thus these limbs no longer need to conform to the aortic wall. Therefore, the D-ratio in these configurations is lower but eventually the radial mismatch is much lower.

Radial mismatch is considered among the most important factors affecting patency of KS^{5,12-14}. After insertion of KS, the outer stent lumen is still perfused, creating a stagnant blood column in the residual space. Previous studies have shown that the decrease in blood flow and the flow through stented vessel lumen resulted in lower shear stress associated with increased neointimal thickening¹⁵. These findings were confirmed by the histopathological finding of mesenchymal tissue, intimal hyperplasia, and organizing thrombus in the space between the opposing stents, within the lumen of the stents, and at the level of the stent overlapping in the distal aorta¹³.

At least two conditions of Virchow's triad are met: perturbed and stagnant flow and the inevitable endothelial damage caused by the deployed stents. Additionally, stent protrusion in the distal aorta may also influence patency, as does the crossover position of the stents¹². These factors have not been assessed in the present study and warrant further investigation.

In our study, the CK had the highest mismatch and the lowest stent conformation ratio, which is in accord with the findings of Hughes et al.¹⁴ Clinical data, however, indicate a superiority of CK above BMK stents⁴. The 1- and 2-year patency rates of balloon-expandable covered stents were superior to those of balloon-expandable bare metal stents. In the present study, however, balloon-expandable bare metal stents were not assessed. Although clinical data are still lacking, *in vitro* data suggest that the use of self-expanding nitinol KS is to be preferred above bare metal balloon-expandable stents because of significant reduction in mismatch area¹⁴. Moreover, it is crucial to emphasize that the effect of radial mismatch on patency rates of covered stents may differ from that of bare metal stents, because the covering material will prevent flow through the

radial mismatch area into the stented lumen. Obviously, this may reduce the occurrence of recirculation, turbulence, and stasis of blood. In turn, this may affect the shear stress phenomenon and thus leaves bare metal stents vulnerable to thrombosis and in-stent restenosis caused by intimal hyperplasia. Additional flow studies are indicated to elucidate this differential effect of radial mismatch on flow patterns and eventually, the patency rates of different configurations.

In this study, we have used a vascular model, based on measurements performed in cadavers. As an alternative, measurements performed on CT data could have been used, providing even more detailed anatomic information. We re-created the mean anatomic environment in which the deployed stents behaved as they would have in vivo. When using a straight tube model, crossing and twisting of the stents is less likely to occur, influencing the mismatch area. Nevertheless, the current model does not correct for the potential effect of calcifications and obviously, the anatomical variations in patients. Furthermore, the influence of the rigidity of the model on stent behavior is unknown and might influence the obtained results. The stents used in the current study were chosen because they represent three widely used options for aortoiliac stenting. However, many different variables can be altered when placing KS, for example, flaring of the proximal part, crossing of the stents, and increasing or decreasing the protrusion of the stents into the aorta. All of these variables could influence the mismatch area but were not taken into account in this study. We acknowledge the fact that this study only includes geometric behavior of different stent configurations. There is abundant room for further progress in determining the influences of flow and mechanical parameters in combination with several stent configurations. Furthermore, the stents were only deployed once per configuration; despite the fact that two experienced vascular surgeons deployed the stents, this may limit the reproducibility of our results. As a result, no statistical analysis could be performed on the data.

CONCLUSIONS

Although nitinol self-expanding stents had the highest stent conformation to the model wall, the lowest radial mismatch was found in the CERAB configurations, supporting the hypothesis that the CERAB configuration is a more anatomical and physiological reconstruction of the aortic bifurcation. Within the CERAB configuration, the lowest mismatch is achieved when placing the two limbs inside the tapered portion of the cuff.

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In vivo geometry of the kissing stent and covered endovascular reconstruction of the aortic bifurcation configurations in aortoiliac occlusive disease

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Adapted from **Vascular**
2017, in press.

ABSTRACT

OBJECTIVES Various configurations of KS configurations exist and patency rates vary. In response the covered endovascular reconstruction of the aortic bifurcation configuration was designed to minimize mismatch and improve outcome. The aim of the current study is to compare geometrical mismatch of kissing stent with the covered endovascular reconstruction of the aortic bifurcation configuration in vivo.

METHODS Post-operative computed tomographic data and patient demographics from 11 covered endovascular reconstruction of the aortic bifurcation and 11 matched kissing stent patients were included. A free hand region of interest and ellipse fitting method were applied to determine mismatch areas and volumes. Conformation of the stents to the vessel wall was expressed using the D-ratio.

RESULTS Patients were mostly treated for Rutherford category 2 and 3 (64 %) with a lesion classification of TASC C and D in 82 %. Radial mismatch area and volume for the covered endovascular reconstruction of the aortic bifurcation group was significantly lower compared to the kissing stent configuration ($p < 0.05$). The D-ratio did not significantly differ between groups. Measurements were performed with good intra-class correlation. There were no significant differences in the post-procedural aortoiliac anatomy.

CONCLUSIONS The present study shows that radial mismatch exists in vivo and that large differences in mismatch exist, in favour of the covered endovascular reconstruction of the aortic bifurcation configuration. Future research should determine if the decreased radial mismatch results in improved local flow profiles and subsequent clinical outcome.

INTRODUCTION

The KS configuration is frequently used for AIOD and there is a shift towards endovascular treatment of more complex lesions (type TASC C and D). KS configurations usually protrude into the distal aorta to treat the lesions completely. Due to incomplete contact between the stent and vessel lumen, mismatch areas are created. These areas are referred to as 'radial mismatch' or 'protrusion mismatch' (Figure 1) and several studies have indicated a negative relation between mismatch and stent patency¹⁻⁶. The underlying principle is likely to be flow perturbations that, in turn, could cause low WSS and thrombus formation (Chapter 6). The CERAB technique was developed in an attempt to reconstruct the native aortic bifurcation in a more physiological fashion^{7,8}. With this technique a covered stent is expanded 15–20 mm above the aortic bifurcation and proximally adapted to the aortic wall with a larger balloon, thereby creating a cone-shaped stent. Two iliac covered stents are placed in the distal conic segment and simultaneously inflated, making a tight connection with the aortic stent thus creating a new bifurcation. Previously, we have shown in vitro that the CERAB indeed better resembled the normal anatomy compared to KS (Chapter 4). It is questionable, however, how these results translate to the in vivo situation as local anatomy, including calcified lesions, might affect mismatch areas. In the present study, we compared the anatomy and stent geometry of two cohorts of patients treated with either the KS or CERAB technique with the primary outcome measure being radial mismatch.

Figure 1. Overview of the KS technique (left) using two self-expanding stents and the CERAB technique (right) using three balloon-expandable stents. For each configuration two cross sections are shown to depict the size of the in vitro radial mismatch. CERAB: covered endovascular reconstruction of the aortic bifurcation; KS: kissing stent.

METHODS

PATIENT SELECTION Patients treated with the CERAB or KS configuration were identified in two hospitals. One centre solely applied the KS technique using two simultaneously deployed self-expanding, bare metal, nitinol stents (Wallstent, Schneider Inc., Minneapolis, MN, USA). These stents were deployed with the proximal end into the aorta and post-dilated⁹. The second centre solely applied the CERAB technique in case of AIOD using balloon-expandable covered stents (Advanta V12, Atrium Maquet, Getinge, Hudson, MA, USA) as previously described⁸. Post-operative anticoagulation consisted of clopidogrel (3–6 months) and acetylsalicylic acid (lifetime) or marcoumar (3 months) and acetylsalicylic (lifetime), for the CERAB and KS groups, respectively. Treatment of AIOD was only indicated if the aortoiliac lesions were hemodynamically significant (> 70 % on computed tomographic angiography (CT-A) or Peak Systolic Velocity ratio > 2.5).

Inclusion criteria were:

- KS or CERAB as primary treatment option.
- Primary patency achieved at 3 months.
- 3 month post-operative CT-A data available.

Exclusion criteria were:

- KS or CERAB configuration extending into an aneurysmatic infrarenal aorta.

Three month post-operative CT-A imaging after KS or CERAB treatment is not standard care at both hospitals and, as such, the included CT-A scans were mostly indicated for other reasons. In order to have comparable groups the patients in the KS group were matched to the CERAB population, in subsequent order: TASC II classification, age (in a range of 5 years) and gender. No matching was performed based on the lesion types within TASC II categories. No data on patient outcome were retrieved, as the groups are too small for reliable outcome comparison. Human investigation review board approval was obtained for this study; patient informed consent did not have to be obtained.

DATA ANALYSIS Anatomical characteristics were analysed using postoperative CT-A data using the Terarecon (Aquarius, Foster City, CA, USA) software tool. A centre lumen line (CLL) was automatically constructed and manually checked in all cases. Thereafter outer to outer diameter (front to back and left to right for each slice) and length measurements were performed along the CLL. Length and diameter measurements in the aorta were performed from the lowest renal artery to the apex of the aortic bifurcation. Measurements in both iliac arteries were performed from the apex of the aortic bifurcation to the apex of the iliac bifurcation. In all cases step size along the CLL was 10 mm. Furthermore, the stent placement with respect to the aortic bifurcation was determined. The mismatch area and stent confirmation ('double-D' shape) were determined using a dedicated tool designed in Matlab (Chapter 4).

The mismatch area was determined using two methods, a manual segmentation (region of interest (ROI) method) and an ellipse approximation (correction was applied for overlapping ellipses). Figure 2 gives an overview of both methods. In case of a KS configuration the three ellipses were fitted on the vessel wall and stent perimeter. With the CERAB configurations the ellipses were fitted to the perimeter of the body and both legs. Stent conformation was expressed as D-ratio, calculated as the ratio between the major and minor axes of the ellipses fitted to the stent lumen (the blue circles in Figure 2, A).

For the KS patients CT scans were made with a slice thickness between 1 and 3 mm, 120 kVp (135 kVp in one case) and mAs ranging between 45 and 235. The CT scans of the CERAB patients were made with a slice thickness between 1 and 4 mm, 110 or 120 kVp, mAs between 35 and 107. The matrix size was 512×512 pixels for all scans.

STATISTICAL ANALYSIS Data are presented as mean and standard variation, unless stated otherwise. The Shapiro-Wilk test was used to test for normality. Although data were normally distributed non-parametric testing was used due to the small sample size per group. Non-parametric testing (Mann-Whitney U test) was used to compare the patient anatomy, stent characteristics, mean radial mismatch, total mismatch volume and D-ratio. The non-parametric Chi-square test was used to compare risk factors, the Rutherford category and the TASC category. Bland-Altman plots were used to compare the ROI and ellipse method. To assess the consistency and reproducibility of the measurements the intra-class correlation (ICC) and 95 % confidence interval (CI) were

Figure 2. Overview of both segmentation methods, shown with the CERAB configuration.

- A** Application of three ellipses to represent the configuration, the yellow ellipse defines the CERAB cuff (in case of a KS configuration this is the vessel wall), the two blue circles represent the lumina of both stents.
- B** Manual segmentation of the mismatch area (ROI) between the stents and the cuff (in case of a KS configuration this is the vessel wall).

CERAB: covered endovascular reconstruction of the aortic bifurcation; KS: kissing stent; ROI: region of interest.

displayed for all measurements, and an ICC > 0.7 was considered as good agreement between the observers. All measurements were performed by two researchers (TTM and EGJ). A significance level of 5 % was used. All statistical analyses were performed using IBM SPSS Statistics for Windows, version 23 (IBM Corp, Armonk, NY, USA).

RESULTS

PATIENT DEMOGRAPHICS Eleven CERAB patients, treated between April 2012 and October 2013, and 24 KS patients, treated between January 2005 and August 2014, met the inclusion criteria. Four patients in the KS group were excluded because of an infrarenal aortic aneurysm. For the remaining 20 KS patients a best match was determined with the 11 included CERAB patients. In total, 22 patients were included in this study, 11 in the CERAB group and 11 in the KS group. The mean age for the CERAB and KS cohort was 65.4 (SD 9.3) and 58.0 (SD 11.6) years, respectively ($p = 0.13$). Demographic data are summarized in Table 1. The post-procedural aortoiliac anatomy of both groups is comparable (Table 2). For the CERAB configuration the mean overlap between cuff and limbs is 17.1 mm (SD 6.4 mm). A full overview of the stent characteristics is given in Table 3.

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Table 1. Demographic data of CERAB and KS patients

CLINICAL CHARACTERISTICS	CERAB		KS		p-VALUE
	n	%	n	%	
Gender:					
Male	8	73	4	36	0.087
Risk factors:					
Smoking	9	82	4	36	0.03
Hypertension	4	36	4	36	1
Diabetes mellitus	3	27	5	45	0.38
Dyslipidemia	7	64	9	82	0.34
Preinterventional category:					0.71
Rutherford cat 2	3	27	1	9	
Rutherford cat 3	4	45	6	55	
Rutherford cat 4	2	18	2	18	
Rutherford cat 5	0	0	0	0	
Rutherford cat 6	2	18	2	18	
TASC II classification:					0.12
A	0	0	1	9	
B	0	0	3	27	
C	4	36	1	9	
D	7	64	6	55	

CERAB: covered endovascular reconstruction of the aortic bifurcation; KS: kissing stent.

Risk factor definitions: smoking: active smoker or former smoker that stopped smoking less than five years pre intervention. Hypertension: patients on antihypertensive medication or BP > 140/90. Diabetes: patients on an antidiabetic medication (insulin and/or oral medication).

Table 2. Postoperative anatomic comparison

SEGMENT	CERAB MEAN (SD)	KS MEAN (SD)
Length Aorta (mm)	97.5 (11.3)	94.7 (9.3)
Length CIA right (mm)	58 (21.0)	60.9 (14.8)
Length CIA left (mm)	57.2 (19.0)	57.4 (17.2)
Diameter aorta (mm)	18.8 (2.6)	19.8 (2.7)
Diameter CIA right (mm)	10.9 (1.8)	11.3 (1.7)
Diameter CIA left (mm)	11 (1.4)	11.3 (1.3)
Angle Aorta (degrees)	24.6 (7.0)	19.7 (8.1)
Angle CIA right (degrees)	29.3 (9.6)	29 (8.1)
Angle CIA left (degrees)	21.8 (9.5)	28.3 (8.4)

CERAB: covered endovascular reconstruction of the aortic bifurcation; KS: kissing stent; CIA: common iliac artery

Table 3. Stent placement

SEGMENT (mm)	CERAB MEAN (SD)	KS MEAN (SD)
Distance right limb, protrusion	35.3 (12.7)	40 (11.5)
Distance left limb, protrusion	35.3 (12.0)	38.9 (11.6)
Distance right limb, distal edge to bifurcation	23.9 (9.7)	67.6 (36.2)*
Distance left limb, distal edge to bifurcation	24.0 (14.6)	72.8 (34.2)*
Distance CERAB cuff, prox. edge to bifurcation	65.4 (15.1)	NA
Distance CERAB cuff, distal edge to bifurcation	18.2 (8.8)	NA

CERAB: covered endovascular reconstruction of the aortic bifurcation; KS: kissing stent; NA: not applicable

* denotes $p < 0.05$

Table 4. Geometric analysis

METHOD	AREA (mm ²)/VOLUME (mm ³)	CERAB MEAN (SD)	KS MEAN (SD)
Ellipse	Radial mismatch area	14.1 (4.2)	172.7 (70.0)*
	Radial mismatch volume	307.7 (131.2)	7268 (3810.9)*
ROI	Radial mismatch area	11.0 (4.8)	165.8 (71.5)*
	Radial mismatch volume	240 (127.3)	7047.0 (3239.0)*

CERAB: covered endovascular reconstruction of the aortic bifurcation; KS: kissing stent; ROI: region of interest

*denotes $p < 0.05$

MEAN MISMATCH AREA The mismatch area was 13-fold higher in the KS cohort compared to the CERAB cohort for the ellipse method ($p < 0.05$) (Table 4). For the ROI method the mismatch area was 16-fold higher for the KS cohort with respect to the CERAB cohort ($p < 0.05$).

TOTAL MISMATCH VOLUME Total mismatch volume was higher in the KS group for both the ellipse and ROI method ($p < 0.05$). With the ellipse method a 24-fold increase was observed for the KS cohort ($p < 0.05$) while the ROI method depicted a 30-fold increase ($p < 0.05$).

STENT CONFORMATION The obtained D-ratio was not significantly different between groups (CERAB 1.20 and KS 1.15, respectively, $p > 0.05$). The mean area difference between the left and right stent area for the CERAB was 4.3 mm^2 , for the KS a difference of 16.8 mm^2 was noted ($p < 0.05$).

COMPARISON OF METHODS AND RESEARCHERS Bland-Altman plots were created to compare the ellipse and ROI method (Figure 3) without significant difference between the two methods. For the ellipse method the ICC was 78 % (CI 9.6–94.3 %) for the CERAB

Figure 3. Left: Bland-Altman plot for the ROI and ellipse method, calculated area. Right: Bland-Altman plot for the ROI and ellipse method calculated volume. The green line indicates mean difference and the dotted lines indicate 2 SD difference from the mean. ROI: region of interest.

and 80 % (0.4 to 96 %) for the KS measurements. For the ROI method the ICC was 87.5 % (CI 40–97 %) for the CERAB and 80 % (CI 22–95 %) of the KS measurements.

DISCUSSION

In the present study, we have shown that CERAB is an improved reconstruction of the aortic bifurcation, in terms of mismatch, compared to KS. Others previously showed a relation between protrusion (i.e. mismatch) and patency^{3,5}. Significant differences exist (up to 16-fold area increase) between the mismatch areas of KS and CERAB, in favour of the latter. Mismatch volumes showed even larger differences, however, this could be due to the fact that protrusion length of the KS configuration exceeds that of the CERAB in all cases.

These results confirm earlier in vitro data (Chapter 4), but that study largely underestimated the mismatch size for both the KS (21.4 mm² vs. 165.8 mm²) and CERAB (3.1 mm² vs. 11.0 mm²). A better agreement between the in vivo and in vitro mismatch measurements could have been anticipated for CERAB, as mismatch between cuff and limbs is less depending on anatomy than the mismatch between the KS and the vessel wall. In case of a suboptimal placed CERAB in vitro, with the limbs protruding in the already flared proximal part of the aortic cuff, the in vitro results better match the observed in vivo results (11 mm² vs 12.6 mm²), suggesting that there is room for improvement in clinical practice. Precise placement of the limbs inside the non-tapered part of the cuff is important to minimize the mismatch area. To discard radial mismatch as a parameter of interest, the use of the AFX stent (Endologix Inc., Irvine, CA, USA) might be a good solution when treating AIOD, as this is a one piece bifurcation graft¹⁰.

The high D-ratios (1.6 and 1.4) observed in vitro for the KS and CERAB configuration, respectively, were not observed in the current study (1.15 and 1.2). Possibly the rigid walls of the vessel phantom, used in the in vitro studies, forced the stents more into a double D-shape or the in vitro oversizing was larger compared to the stents used in the present series. The demonstrated mismatch in vivo is an important parameter for research. Previous in vitro research showed flow stagnation between the neobifurcation and anatomical bifurcation in the KS configuration. A covered KS configuration showed large vortices at the mismatch areas at the neobifurcation, causing pathologic proximal WSS and OSI values (Chapter 6). The CERAB showed only small flow recirculation in the cuff, without affecting WSS and OSI values. Basic knowledge on this subject can aid the choice of the optimal stent configuration for AOID treatment.

Limitations of the current study are the fact that post-operative CT-A data were only available for a limited number of patients treated. However, given the highly statistical significance of the differences it is debatable whether a larger sample size would affect the outcome. Scoring of calcifications was not applied to investigate the possible influence on mismatch area. Furthermore no follow-up data was used in this study to verify if the large difference in mismatch had any effects on patency. The sample sizes were

considered too small to reliably observe any difference in clinical outcome and would render any conclusion on clinical impact unreliable. Data from two sites was included for analysis, in order to reduce selection and performance bias. However, this could also have introduced differences in pre, per and post-operative care and in imaging protocols, which might have influenced the observed differences. Nevertheless the observed differences in geometry were highly significant so that this potential confounder was not considered to be likely. The current study only included self-expanding bare metal KS as a comparison for the CERAB configuration. The results could be different with balloon-expandable stents, but also in different configurations like crossing or non-crossing positions. The self-expanding bare metal configuration is, however, a very relevant configuration as observed in a recent review which showed that 50 % of cases were treated with self-expanding bare metal KS (Chapter 2).

CONCLUSION

We demonstrated that radial mismatch is present and that large differences are present between KS and CERAB, with a decreased geometrical mismatch in favour of the latter. In vitro measurements have underestimated the average mismatch area and volume in comparison with the in vivo situation.

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Hemodynamic comparison of stent configurations used for aortoiliac occlusive disease

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Adapted from **the Journal of Vascular Surgery**
2017, Volume 66, Issue 1, Pages 251-260.e1.

ABSTRACT

BACKGROUND Endovascular treatment of aortoiliac occlusive disease entails the use of multiple stents to reconstruct the aortic bifurcation. Different configurations have been applied and geometric variations exist, as quantified in previous work. Other studies concluded that specific stent geometry seems to affect patency. These variations may affect local flow patterns, resulting in different WSS and OSI. The aim of this study was to compare the effect of different stent configurations on flow perturbations (recirculation and fluid stasis), WSS, and OSI in an in vitro setup.

METHODS Three different stent configurations were deployed in transparent silicone models: BMK stents, CK stents, and the CERAB configuration. Transparent covered stents were created with polyurethane to enable visualization. Models were placed in a circulation setup under physiologic flow conditions. Time-resolved laser particle image velocimetry techniques were used to quantify the flow, and WSS and OSI were calculated.

RESULTS The BMK configuration did not show flow disturbances at the inflow section, and WSS values were similar to the control. An area of persistent low flow was observed throughout the cardiac cycle in the area between the anatomic bifurcation and neobifurcation. The CK model showed recirculation zones near the inflow area of the stents with a resulting low average WSS value and high OSI. The proximal inflow of the CERAB configuration did not show flow disturbances, and WSS values were comparable to control. Near the inflow of the limbs, a minor zone of recirculation was observed without changes in WSS values. Flow, WSS, and OSI on the lateral wall of the proximal iliac artery were undisturbed in all models.

CONCLUSIONS The studied aortoiliac stent configurations have distinct locations where flow disturbances occur, and these are related to the radial mismatch. The CERAB configuration is the most unimpaired physiologic reconstruction, whereas BMK and CK stents have their typical zones of flow recirculation.

INTRODUCTION

Endovascular reconstruction of the aortic bifurcation using kissing stents is an established procedure for occlusive aortoiliac lesions. Although guidelines still advise open surgery as the “gold standard” for extensive lesions, progress is being made in endovascular treatment of TransAtlantic Inter-Society Consensus C and D lesions^{1,2}. Endovascular treatment is attractive because of its minimally invasive nature, high technical success, and low morbidity and mortality rates³. Long-term patency rates, however, still cannot match those of open surgery, 90 % at 5 years vs 69 % (range, 63–81 %) for the kissing stent configuration (Chapter 2). In addition, the complication and mortality rates of open surgery seem to have reached a plateau level and do not seem to improve anymore⁴. The thrust toward improved outcome of endovascular techniques has resulted in several variations using covered stents, balloon-expandable stents, or self-expanding stents^{5–7}. A number of clinical studies reporting on the results of kissing stents have been published, wherein disturbed flow due to radial mismatch after stent placement was associated with stent patency^{7–9}. Radial mismatch is defined as the discrepancy between the stented lumen and the vessel lumen after stent placement. Furthermore, the protrusion of the proximal part of the stents, creating radial mismatch, in the distal aorta could have an impact on patency^{7,9}. Protrusion, however, is often needed to treat lesions that include the distal part of the aorta, creating a zone of mismatch between stent and vessel wall^{10,11}.

Innovations in kissing stent configuration design were suggested to overcome protrusion-related patency decrease. A recent development is the CERAB technique that preserves the bifurcation using three covered stents¹². Initial clinical data are promising, with 1-year primary and secondary patency rates of 87 % and 95 %, respectively, in a group of 103 patients with 88 % TransAtlantic Inter-Society Consensus II D lesions¹³. Previously we showed that the CERAB significantly decreases the radial mismatch (Chapter 4).

Recent literature indicated that there is a strong correlation between disturbed blood flow and onset and progression of atherosclerosis, thrombus formation, and intimal hyperplasia in stented arteries¹⁴. The parameter of interest in the last is blood flow-induced shear stress acting on the arterial wall, referred to as WSS. In the presence of risk factors for atherosclerosis, low WSS is associated with local endothelial dysfunction and development of intimal hyperplasia, whereas high shear stress is atheroprotective¹⁵. Furthermore, large oscillations in WSS also correlate with areas of intimal hyperplasia and progression of atherosclerosis. These oscillations are captured in the OSI, highlighting areas of disturbed flow along the vessel wall¹⁶. The aim of this study was to investigate the influence of three frequently used stent configurations on local flow patterns, WSS, and OSI.

METHODS

MODELS AND STENTS In vitro experiments were conducted using four identical aortoiliac bifurcation models. The production process of the models was previously described (Chapter 4). The models are rigid; however, minimal influence on flow phenomena is expected, especially because the vascular system of elderly diseased patients is considered low in compliance. Three stent configurations were studied: a BMK stent model using two 10-mm self-expanding nitinol stents (S.M.A.R.T CONTROL; Cordis Corporation, Miami, Fla); a CK stent model using two inhouse covered 8-mm balloon-expandable stents; and a CERAB model using three in-house covered stents, two 8-mm and one 12-mm balloon-expandable stents. The configurations are depicted in Figure 1, and a fourth model acted as a control. The in-house covered stents were based on the platform of the Advanta V12 stents (Atrium Maquet Getinge, Hudson, NH). To create transparent covered stents for the CK and CERAB models, the bare Advanta V12 stent mesh was coated with a transparent polyurethane (Tecoflex TPU clear; The Lubrizol Corporation, Wickliffe, Ohio) cover using a dip coating process¹⁷. Thickness

Figure 1. The three studied stent configurations as used in the clinical setting. During the flow studies, the white polytetrafluorethylene cover was replaced by transparent polyurethane. The orange, purple, gray, and yellow lines indicate locations of wall shear stress (WSS) calculations; the yellow dots indicate distance = 0.

- I Self-expanding nitinol bare-metal kissing (BMK) stents
- II Balloon-expandable covered kissing (CK) stents
- III Covered endovascular reconstruction of the aortic bifurcation (CERAB) configuration, consisting of a body and two limbs created with balloon-expandable covered stents.

The green areas were excluded from analysis because no flow was observed. The yellow arrows indicate the mean flow direction and direction of the laser sheet for all configurations.

of the polyurethane layer was judged by visual inspection. This process allowed the visualization of flow patterns inside the stent configurations.

FLOW CIRCUIT Models were placed in a flow circuit (as depicted in Supplementary Figure 1) in which pulsatile flow was generated. Figure 2, A depicts the waveform used to control the pumps (12 V, Kavan, type 0190.121; Kavan GmbH, Nürnberg, Germany), which was originally described by Lee and Chen¹⁸. Flow sensors (type UF8B; Cynergy3 Components Ltd, Wimborne, Dorset, United Kingdom) at the inlet and four outlet vessels were used to monitor the system and to adjust the outflow. The two iliac vessels were connected to a single compliance, peripheral resistance, and a single flow sensor. Studies were carried out under human resting conditions, using a mean inflow of 1.6 L/min and a heart rate of 60 beats/min. The outflow of each vessel was equally set at 25 % of the inflow¹⁹. Besides flow, the pressure was recorded using a guide wire-mounted pressure sensor (PressureWire Certus; St. Jude Medical, St. Paul, Minn), placed in the distal part of the aorta model (Figure 2, B). Each outflow vessel was fitted with a needle valve to set the mean arterial pressure within physiologic ranges (mean of ± 90 mmHg). The distal

Figure 2.

- A** Black line, Waveform used to control the pumps.
Green line, Flow waveform obtained with flow sensor at the inlet of the system.
The yellow dots indicate sites used for analysis.
- B** Accompanying pressure waveform, obtained at the aortic bifurcation.

ESV, End-systolic velocity; PDV, peak diastolic velocity; PSV, peak systolic velocity.

compliance vessel was used to set the variation around the mean pressure (± 20 mmHg). The circulating bloodmimicking fluid (BMF) was a mixture of water (47.4 %), glycerol (36.9 %), and sodium iodide (15.7 %), both to resolve the refractive index mismatch between the BMF and the models and to obtain a physiologic liquid (4.3 cP; density, 1244 kg/m^3)²⁰.

FLOW VISUALIZATION, PARTICLE IMAGE VELOCIMETRY²¹ Rhodamine-coated fluorescent polymethyl methacrylate particles (size, 1–20 μm ; density, 1190 kg/m^3) were suspended in the BMF solution. Particle images were obtained using a pulsed laser sheet (LDY303HE; Litron, Warwickshire, England) in synchronization with a high-speed camera (FASTCAM SA-X2; Photron, Tokyo, Japan), and data were captured at 2000 Hz, resolution 1024×1024 (8 bit/pixel). The camera was positioned at a 90-degree angle to the laser sheet; the laser sheet was placed in the center of the stented lumen. A region of interest where the laser entered the model (right side) was used for analysis because of maximal signal intensity at the wall, as indicated in Figure 1. For the control and BMK stent configurations, images were obtained at the proximal inflow and at the neobifurcation, including the iliac outflow. For the CK stent and CERAB configurations, the anatomic bifurcation was not included because these areas are excluded by the covered stent configuration and no flow was observed (as indicated in Figure 1).

DATA PROCESSING Background subtraction was applied to remove nonmoving, stationary areas. Automatic wall detection through thresholding was applied to segment the flow lumen. Thereafter, PIVlab 1.35 was used to process the image pairs using correlation-based analysis methods²². Validation was done using thresholding and a normalized median check²³. For each model and location, 12 cardiac cycles were obtained and averaged to obtain 1 averaged cycle per measurement location. Thereafter, the direction of the flow was calculated for each vector, based on the mean flow direction. Using a MATLAB (version 2013a; The MathWorks Inc, Natick, Mass) script, WSS ($\mu \frac{\delta u}{\delta y}$) and OSI ($\frac{|NEG WSS|}{|POS WSS| + |NEG WSS|}$) values were calculated along the vessel wall (orange lines in Figure 1)²⁴. NEG WSS and POS WSS indicate the area under the WSS vs time curve when the WSS is negative and positive, respectively. Therefore, the OSI indicates the WSS direction with respect to the mean blood flow direction during the cardiac cycle. The OSI can vary from 0 to 1, 0 meaning no cyclic variation, 1 a continuous 180-degree change in the WSS direction. Time points, as indicated in Figure 2, A, for peak systolic velocity (PSV), end-systolic velocity (ESV), and peak diastolic velocity (PDV), were chosen to compare flow patterns between the models.

RESULTS

The results of the experimental data are presented in text per stent; the figures are grouped per location to facilitate comparison of the stents. The flow fields and WSS values at the bifurcation for the control and BMK stents are shown in Figures 3 and 4, respectively. The flow fields, WSS values, and OSI at the inflow of the control, BMK stents, CK stents, and CERAB are shown in Figures 5–7, respectively. Figure 8 depicts the WSS values for inflow of the CERAB vs the control.

Figure 3. Peak systolic velocity (PSV), end-systolic velocity (ESV), and peak diastolic velocity (PDV) time points for the bifurcation site of the bare-metal kissing (BMK) stent (lower) configuration compared with the control (upper). The dotted pink line indicates the kissing boundaries of the BMK stents.

Figure 4. Wall shear stress (WSS) values along the right lateral wall for the control and bare-metal kissing (BMK) stent configuration. Distance = 0 is the yellow dot on the purple line in Figure 1.

BMK CONFIGURATION

BMK proximal The inflow for both BMK stents is undisturbed and oriented forward toward the PSV (Figure 5), very much resembling the flow features of the control model. Proximal to the BMK configuration, a double-lobed velocity profile already takes shape. During the ESV time point, flow reversal occurs, but flow remains undisturbed.

Figure 5. Peak systolic velocity (PSV), end-systolic velocity (ESV), and peak diastolic velocity (PDV) time points, proximal to the stent configuration for the bare-metal kissing (BMK) stents, covered kissing (CK) stents, and covered endovascular reconstruction of the aortic bifurcation (CERAB) compared with the control. Stent mesh is shown in red.

Flow returns to a forward direction during the PDV. WSS along the proximal wall is comparable between the BMK configuration and control (Figure 6). However, during ESV, the WSS is more negative for the control model (average, -0.27 Pa). The OSI calculations also show a relatively low OSI for the BMK configuration with respect to the control (0.15 vs 0.30; Figure 7).

BMK neobifurcation The flow direction of the BMK bifurcation is oriented in a forward direction at PSV. No recirculation of flow is present; however, two clear flow lumina are formed (double-peaked velocity profile, Figure 5). Between the anatomic bifurcation and neobifurcation of the BMK configuration, a stagnation zone is observed (Figure 3, bottom). Separation zones are present at the lateral wall of the control model while advancing toward ESV, inducing reverse flow, gradually expanding toward the vessel center. At ESV, backward flow is observed in the complete field of view. The BMK configuration also experiences these flow separations, but to a lesser extent. The two-lumen flow breaks up and flow swirls through the stent struts. Furthermore, flow starts to recirculate at the apex of the bifurcation (Figure 3, bottom middle). A fully forward-oriented flow field is restored toward the PDV for both configurations, again with a stagnation zone between the neobifurcation and anatomic bifurcation of the BMK stents. WSS values along the lateral arterial walls are similar for the BMK stents and control during PSV (Figure 4). During ESV, the WSS values for the control model are more negative, and at peak diastole this effect is not seen anymore. The OSI shows a clear peak for both the BMK stent and control at the location of the lateral wall of the bifurcation (0.24 and 0.34, respectively). WSS and OSI values could not be obtained at the neobifurcation of the BMK configuration.

BMK iliac Outflow of the BMK configuration is comparable to the control during the three phases of the cardiac cycle. This is also reflected in the OSI (0.08 vs 0.10) and average WSS (0.77 Pa vs 0.84 Pa).

Figure 6. Wall shear stress (WSS) values along the right artery wall proximal to the stent configuration for the baremetal kissing (BMK) stent, covered kissing (CK) stent, and covered endovascular reconstruction of the aortic bifurcation (CERAB) configuration compared with the control shown for peak systolic velocity (PSV), endsystolic velocity (ESV), and peak diastolic velocity (PDV) time points. Distance = 0 is the yellow dot on the orange line in Figure 1.

CK CONFIGURATION

CK proximal For the CK configuration, flow is accelerating toward the inflow of the CK limb. During PSV and PDV, the flow is undisturbed and forward oriented. Toward the ESV point, flow reversal occurs (Figure 5).

CK neobifurcation Recirculation zones are present at both vessel walls near the proximal edge of the mismatch zones of the CK limbs (Figure 5, CK). These recirculation zones get larger toward the PSV. Backflow is observed during deceleration toward the ESV phase, starting at the wall and growing toward the vessel center. WSS values for the CK stents are about five times lower compared with the control model (time average WSS: control 0.16 Pa vs CK 0.03 Pa) during the PSV and PDV (Figure 6). During the ESV point, the WSS values for the control are mostly negative; values for the CK stents are again close to zero (average, -0.02 Pa; Figure 6, purple line). The CK configuration exhibits an increasing OSI toward the inflow, indicating large changes between forward and reverse flow while moving toward the CK inflow (Figure 7, purple line). No data are obtained at the anatomic bifurcation because no blood flow was observed in this region.

CK iliac Iliac outflow is organized similar to the flow fields observed in the control model. However, both OSI (0.41 vs 0.1) and WSS (0.43 Pa vs 0.84 Pa) differ with respect to the control.

Figure 7. Oscillating shear index (OSI) values along the vessel wall. Distance = 0 is the yellow dot on the orange line in Figure 1.

BMK, Bare-metal kissing stent; CERAB, covered endovascular reconstruction of the aortic bifurcation; CK, covered kissing stent.

CERAB CONFIGURATION

CERAB inflow Comparison of the inflow of the CERAB configuration and the same location for the control model yielded comparable results. Small differences occur as the flow velocity increases toward the PSV; fluid inside the cuff seems to be accelerated toward the limbs. This effect is not seen toward the bifurcation in the control situation. The flow reversal for the control model is less prominent in comparison to the CERAB configuration from the PSV toward the ESV (data not shown). WSS values are comparable between the control model and CERAB inflow (Figure 8). The OSI values for the CERAB and control are 0.11 and 0.3, respectively.

CERAB neobifurcation At the neobifurcation of the CERAB, where the limbs enter the cuff, a minor zone of recirculation occurs between the cuff and limb on the right side only toward the ESV point. During the deceleration toward the ESV, backflow is observed, starting at the wall and growing toward the vessel center (Figure 5, bottom row). WSS values are similar to the control model (Figure 6, magenta line). The OSI values are 0.15 on average. No data were obtained at the anatomic bifurcation because this area is excluded from the circulation by the covered stents.

CERAB iliac Iliac outflow is comparable to the outflow of the control model. This is also reflected by the OSI (0.12 vs 0.10) and WSS (0.77 Pa vs 0.84 Pa) values.

Figure 8. Wall shear stress (WSS) values along the right artery wall proximal to the stent configuration for the control and covered endovascular reconstruction of the aortic bifurcation (CERAB) inflow shown for peak systolic velocity (PSV), end-systolic velocity (ESV), and peak diastolic velocity (PDV) time points. Distance = 0 is the yellow dot on the yellow line in Figure 1.

DISCUSSION

In this study, we have demonstrated that the CERAB configuration is a more physiologic reconstruction of the aortic bifurcation than CK or BMK configurations. Both CK and BMK stents have areas of recirculation that are related to zones of mismatch. In a previous study, we already showed that choice of stent geometry and proper placement of the configuration significantly influence the radial mismatch (Chapter 4). The latter is linked to stent patency with the notion that blood flow perturbations influence thrombus formation (short term) and vessel wall ingrowth (long term) mediated by WSS changes⁷⁻⁹.

In comparing the bifurcation of the BMK stent and control, a flow stagnation was observed between the anatomic bifurcation and neobifurcation during the whole cardiac cycle. Furthermore, the velocity profile over the luminal radius is clearly double lobed (decreasing central in the lumen) for the BMK configuration, indicating that the stent struts situated central in the aortic lumen (kissing part of the configuration) create large drag forces on the flowing blood. Saker et al. pointed out histopathologic findings of mesenchymal tissue, intimal hyperplasia, and organizing thrombus in this area and attributed this to stagnant blood flow⁸. Our in vitro results indeed confirm the presence of stagnant blood flow in this zone of mismatch. Furthermore, during the ESV time point, recirculation occurs at the site of the anatomic bifurcation and neobifurcation, increasing the mass transfer between blood and the vessel wall²⁵. However, the WSS values for the BMK stent in comparison to the control along the lateral and medial iliac wall (iliac data not shown) differ only during the end-systolic period, indicating that flow stagnation in the mismatch area might be the largest point of concern for the BMK configuration. WSS and OSI values, unfortunately, could not be obtained at the zone of recirculation because of stent porosity. Hence, there is no confining wall, and only shear rates can be obtained.

It seems well established that geometry, such as curved vessels and bifurcation sites, is linked to disturbed blood flow and low mean or low oscillatory WSS values, which make these locations prone to development of atherosclerosis and restenosis²⁶. However, a review by Peiffer et al. showed that the low oscillatory shear theory might be less robust than is commonly assumed²⁷.

Recirculation zones were continuously present at the inflow of the CK configuration, also reflected in low WSS values (time average, 0.025 Pa) proximal to the CK configuration. Taylor et al. and Sugimoto et al. presented values between 0.2 and 0.3 Pa for the same vessel segment in a healthy aorta^{28,29}. This is in line with our control results (mean WSS, 0.16 Pa) and values reported earlier in the literature^{30,31}. Furthermore, for the CK configuration, OSI values increase from 0.2 proximal to 0.9 at the inflow, indicating mainly reversely oriented flow at the mismatch area near the inflow during the cardiac

cycle. Low WSS and high OSI are linked to intimal hyperplasia and might explain the occurrence of edge stenosis in these configurations³². The recirculation observed at the inflow of the CK configuration also increases the residence time and therefore the possibility for blood substances to exchange with the vessel wall, facilitating the buildup of fat and inflammatory cells. Clinically, CK stents seem to outperform BMK stents (92 % vs 72 % 1-year primary patency rate, respectively), although results are conflicting^{6,33,34}. In the comparative study of Sabri et al., stent protrusion of > 1 cm was observed in only 5 of 26 patients treated with a CK configuration, indicating that mismatch areas were not numerous⁶. The study of Greiner et al. indicated that protrusion of bare-metal stents (both bare-metal self-expanding and balloon-expandable stents) could influence patency⁹. In relation to this, our results show significant drag induced by the metal mesh of the bare-metal stent configuration, possibly causing stasis of blood, leading to thrombus formation and eventually stent failure. However, in relation to the results we obtained, it is difficult to say if the presence of a stagnation zone between the neobifurcation and anatomic bifurcation is of more importance than the geometric mismatch area seen at the inflow of the CK stent, although our results suggest a higher impact on local flow dynamics (comparing WSS and OSI) for the CK stents in comparison to the BMK stents. Moreover, a full explanation cannot be obtained from the present results; possibly the influence on an even smaller scale needs to be assessed and taken into account (flow around the struts)³⁵.

A minor zone of recirculation was present in the overlap of the CERAB body and limbs without affecting WSS. Previously, we have shown that a proper placement of the two limbs in the smaller part of the aortic cuff is essential to reduce mismatch in CERAB. A more cranial placement in the aortic cuff (ie, in the already flared part of the cuff) increases mismatch, and this could affect flow patterns in this section. Proper placement of the CERAB limbs in the cuff ensures minimal mismatch areas with minimal flow disturbances as a consequence, emphasized by the undisturbed WSS values at the inflow of the CERAB configuration. Further studies that take limb placement with the CERAB into account will need to be undertaken. In the current study, we used 10-mm self-expanding BMK stents to create a D shape, as is typically done in clinical practice. The CK configuration, with 8-mm stents, was not flared after placement because our literature review did not reveal a clear consensus on flaring. However, flaring could influence the obtained results, and a more detailed study is required in the future.

To date, only one other study presented in vitro results of flow visualization after stent placement at the aortic bifurcation³⁶. The recirculation observed by Fabregues et al. in the vertex of the healthy bifurcation is also observed in our measurements. They also showed that recirculation zones occur in the mismatch area between the distal aorta and proximal stent. However, mockups of clinically used stents were used, and stents were

placed only unilaterally, something not regularly performed in clinical practice, and results are reported only qualitatively. Furthermore, to our knowledge, no computational fluid dynamics (CFD) has been performed to investigate the matter, and WSS values have not been reported. In vitro testing of a range of situations and flow parameters would require the construction of new models for each and every configuration. On the other hand, CFD simulations offer great application potential. However, accurate creation of the CFD mesh (including material properties) and reliable modeling of the fluid-structure interaction are challenging.

LIMITATIONS In this study, balloon-expandable baremetal stents were not included and no variation in mismatch area within stent configurations was taken into account, limiting the generalization of the results. In future research, the balloon-expandable bare-metal stent will be included. In addition, blood flow is not a two-dimensional phenomenon as flow features also develop in a three-dimensional manner. The measurement technique currently used does not permit capture of these three-dimensional features, and this could potentially influence the conclusions drawn from the present data.

The flow setup used here can produce reproducible inflow characteristics, with low variability between cycles and between measurements. Furthermore, the measured inflow signal was comparable to the theoretically derived signal, apart from a small mismatch at the diastolic peak, which consistently occurred at a later time span. This could lead to minor deviations in WSS values with respect to the theoretical values. The wall of our model was assumed to be rigid, and the influence on flow characteristics was assumed to be modest³⁷. The typical vascular system of patients treated with aortoiliac stents is often heavily calcified and rigid, bringing the resemblance of the model closer to reality. In calculating WSS values, accurate wall detection is important. Potters et al. showed that inaccurate wall detection can lead to systematic errors of up to 40 %³⁸. For optical access, the CK stents were covered with a transparent polyurethane, introducing material properties different from the original polytetrafluorethylene cover, which could have influenced our WSS results. However, our aim was to compare stents with and without cover, not to perfectly mimic the polytetrafluorethylene material properties. The BMF used is a newtonian fluid, whereas blood is a non-newtonian fluid. However, in large vessels, blood can be assumed to behave like a newtonian fluid³⁹. Current experiments are conducted under resting conditions at the lower end at 60 beats/min. For patients treated with aortoiliac stents, this assumption holds most of the time; however, exercise conditions do occur, and it would be interesting to study the local influence of a higher heartbeat rate. During exercise, the resistance of the iliac outflow decreases, and less backflow is expected during the end-systolic phase⁴⁰. The mismatch areas that arise after placement of the stents in the models are subjected to relatively

slow and stagnant flows. There is a possibility, however, that the stagnant volume can thrombose and fills up over time, excluding this volume from the circulation. In vivo, this clearly would be a possibility, thereby limiting the impact of the mismatch zones.

CONCLUSIONS

The studied aortoiliac stent configurations have distinct locations where flow disturbances occur, and these are related to the radial mismatch. The CERAB configuration appears to be the most unimpaired physiologic reconstruction, whereas BMK and CK stents have their typical zones of flow recirculation. In combination with clinical data, this work can provide the necessary evidence that the use of the CERAB configuration outperforms the use of only kissing stents for the reconstruction of the aortic bifurcation in aortoiliac occlusive disease.

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SUPPLEMENTARY FIGURE

Supplementary Figure 1. Flow circuit.

The green squares (1, 2, and 3) indicate the measurement zones.

Influence of iliac stenotic lesions on endovascular flow patterns near the covered endovascular reconstruction of the aortic bifurcation stent configuration

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Adapted from **the Journal of Endovascular Therapy**
2017, in press.

ABSTRACT

PURPOSE CERAB is an endovascular treatment modality for AIOD with promising early patient outcome and stent hemodynamics. Proper distal runoff is identified as an important parameter to ensure patency. The aim of this study is to investigate the effect of distal stenotic lesions on flow patterns near the CERAB configuration.

METHOD Laser particle image velocimetry (PIV) measurements were performed in in vitro models of the aortic bifurcation with and without a CERAB configuration in place. A hemodynamic (HD) non-significant (ΔP : 9 mmHg) and significant (ΔP : 26 mmHg) stenosis and total occlusion were simulated in the left iliac artery. Velocity fields and time-averaged wall shear stress (TAWSS) were calculated.

RESULTS HD significant distal lesions did not influence the inflow patterns and TAWSS (0.5–0.6 Pa) in both models. HD significant distal stenotic lesions caused a twofold decrease in peak outflow velocities (control: 106 vs. 56 cm/s, CERAB: 96 vs 54 cm/s) and a threefold decrease in TAWSS (control: 1.34 vs. 0.44 Pa, CERAB: 0.75 vs 0.21 Pa). In the CERAB outflow, there was a 2-fold decrease in WSS compared to the control, independent of lesion severity.

CONCLUSION This in vitro study shows, that distal stenotic lesions influence aortic bifurcation outflow patterns and TAWSS, and more extensively in the CERAB configuration. Distal stenotic lesions could therefore increase the risk of disease progression and loss of stent patency. In vivo studies are necessary to confirm these observations.

INTRODUCTION

Traditionally, the treatment of choice for extensive AIOD has been open surgery, while the KS technique has been applied in the last decades for the less complex lesions. A recent alternative therapy for extensive disease is the CERAB.

Satisfying early results have been reported for the CERAB procedure, with primary patency rates of 87 % and 82 % at one and two years follow-up, respectively. The secondary patency rate is 95 % at both time points in a group with over 80 % TASC II D lesions¹. This patient selection makes it difficult to compare the results to studies on other endovascular techniques that have included fewer type D lesions¹. We recently showed, in an in vitro setup, that regional flow patterns around the CERAB configuration are more comparable to physiologic flow than those in bare metal or covered KS (Chapter 6). (Patho) physiologic WSS values at the in- and outflow of the configurations are also of interest as they may promote the development of atherosclerotic plaque and in turn could affect stent patency, due to occurrence of restenosis². However, it is still unclear how these flow patterns and WSS values are influenced by comorbidities, for example as a result of flow limiting stenotic lesions in the iliac artery, distal to the stent configurations. These lesions may cause a poor runoff, which has been identified as a risk factor for the failure of stent grafts³⁻⁶. A previous study evaluating the CERAB technique also suggested that outflow obstructions distal to CERAB stents could reduce primary patency¹. Therefore, this study aims to investigate the influence of distal stenotic lesions on endovascular flow patterns and to quantify WSS values near the CERAB configuration.

METHODS

Laser PIV measurements were performed to obtain velocity vector fields of a rigid in vitro model of the abdominal aorta, with renal arteries and CIA and a CERAB configuration in place. The CERAB configuration was deployed using in-house fully covered stents based on the platform of the Advanta V12 stents (Atrium Maquet Getinge, Hudson, NH, USA), as depicted in Figure 1 (Chapter 6). Two 8-mm Atrium V12 stents (the limbs) were placed within the distal part of a funnel shaped V12 large diameter tapered stent (16 mm at proximal edge, gradually narrowing distally to 12 mm). The neobifurcation starts approximately 20 mm proximal to the anatomic bifurcation (as illustrated in Figure 1). Measurements performed this model were compared to a control model without stents.

EXPERIMENTAL SETUP The flow models and experimental setup were previously described (Groot Jebbink et al.⁷, Chapters 4 and 6) and are shown in Figure 2. Systolic and diastolic blood pressures were set to 130 mmHg and 90 mmHg, respectively. A heart rate of 60 bpm with a mean suprarenal inflow of 1.6 L/min, divided equally over both renal and both iliac vessels, was created to represent physiologic pulsatile flow conditions (Figure 3)⁸.

Figure 1. Covered endovascular reconstruction of the aortic bifurcation (CERAB), placed in an in vitro model of the infra renal aorta (filled with blood mimicking fluid, BMF), using Atrium V12 stents. The white PTFE cover is replaced by transparent polyurethane to obtain optical access.

The black lines indicate the vessel walls, which are otherwise invisible due to refractive index matching between the vessel phantom (cast from PDMS) and the BMF. *u* and *v* represent the direction components of the velocity vector. The two headed arrow indicates the distance between the anatomical bifurcation and the neobifurcation.

Figure 2. Schematic representation of the experimental setup.

- 1 Inflow region of interest (ROI).
- 2 Outflow ROI.

The dashed lines indicate the contours of the CERAB deployed in the vessel phantom. The setup was based on a second order Windkessel model. The inlet section (approx. 100 cm) ensures fully developed flow entering the model. Peripheral resistance was controlled with needle valves. The compliance distal to the vessel phantom was used to model the peripheral dispensability of the vessels. The circulating blood mimicking fluid (BMF) was a mixture of water (47.4 %), glycerol (36.9 %) and sodium iodide (15.7 %). The resistance was added to mimic an outflow stenosis.

Light from a continuous wave laser (Cohlibri, $\lambda = 532$ nm, LIGHTLINE lasertechnik GmbH, Osnabrück, Germany) was transformed into a laser sheet (40 mm width, thickness < 1 mm) using cylindrical lenses. The laser sheet illuminated the central plane of the model. A high speed camera (Fastcam SA-X2, Photron Inc, Tokyo, Japan) was used to capture the fluorescence from the tracer particles (size, 1–20 μm , Dantec Dynamics A/S, Skovlunde, Denmark) during 12 heartbeats at 1000 frames per second (fps) at the inflow and at 2000 fps at the outflow of the CERAB configuration. The frame rate was chosen to maximize the correlation peaks of particle displacement with respect to the

Figure 3. Suprarenal flow pattern used as input for the model.

The magenta line indicates the flow profile that was used to control the gear pumps.

The green line indicates the measured flow at the inlet section of the setup.

observed velocities of the ROI. The outflow of the iliac vessels contain higher peak velocity values requiring a frame rate of 2000 fps, at the inflow 1000 fps was sufficient. A long-pass filter, with a cutoff wavelength of 625 nm, was used to filter out reflecting laser light at 532 nm.

MEASUREMENTS Images were captured in two ROI at the inflow (distal aorta) and outflow (left CIA), depicted as positions 1 and 2 in Figure 2. In order to assess the influence of distal stenotic lesions, 4 measurements were performed in each ROI using modified iliac outflow conditions in both the control and CERAB model, an overview is given in Table 1. To simulate the stenoses, inserts with a reduced diameter and a length of 1 cm were placed in the 8-mm outflow tube of the left iliac artery. Pressure gradients across the stenotic lesions were measured twice, during a separate experiment (using the same setup and conditions), with a built-in pressure sensor (40PC015G1A, Honeywell International Inc., USA) distal to the stenosis location. Systolic pressure at the bifurcation was used to calculate the pressure difference. All pressure measurements were performed in duplo and the results of each sample location were averaged.

A healthy distal artery, hemodynamic non-significant stenosis, hemodynamic significant stenosis and a total occlusion were simulated (details are presented in Table 1). Total occlusion was simulated through clamping of the vessel, only for the inflow ROI measurements, because during total occlusion no flow and consequently no shearing force was present in the left CIA. The obtained pressure gradients across the stenotic lesions corresponded with physiological observations^{9,10}.

DATA ANALYSIS PIV analysis was performed through pairwise cross-correlation in all captured images using PIVlab¹¹. Pre- and post-processing was performed using Matlab (The MathWorks Inc, USA) (Chapter 6). Velocity vector fields during PSV and ESV were obtained.

WSS was calculated as $\mu \frac{\delta u}{\delta y}$ where u is the velocity along the vessel wall, y is the height above the vessel wall, $\frac{\delta u}{\delta y}$ the flow gradient perpendicular to the vessel wall and μ is the dynamic viscosity of the BMF (as indicated in Figure 1). WSS analysis was performed

Table 1. Overview of the measurements obtained for both regions of interest

MEASUREMENT #	CONTROL	CERAB	LUMEN DIAMETER (mm)	LUMEN LOSS (%)	PRESSURE DIFFERENCE (mmHg)
1	No stenosis	No stenosis	8	0	NA
2	Insignificant stenosis	Insignificant stenosis	5	38	9
3	Significant stenosis	Significant stenosis	3	63	26
4	Occlusion	Occlusion	0	100	NA

#: number

for the wall segments captured in each ROI through interpolation of the velocity data at multiple normal vectors, perpendicular to the vessel wall, using the no-slip boundary condition for viscous fluids. TAWSS was plotted against vessel length and TAWSS values are shown for the left aortic wall in the inflow ROI and lateral iliac wall in the outflow ROI. Similar TAWSS values were found at the opposite vessel walls. WSS analysis was less accurate inside the CERAB configuration (and not relevant in this study) and was therefore not evaluated.

RESULTS

INFLOW ROI Similar and undisturbed flow patterns were seen in the inflow ROI of the control model and CERAB model with a healthy distal artery, both during PSV and EDV. During ESV, backflow velocities near the vessel walls was higher compared to the velocities in the center of the vessel lumen in both models (Figure 4, bottom).

The flow pattern in the inflow ROI of the control model was not influenced by distal stenosis (both non-significant and significant) or occlusion. In the CERAB model, a total occlusion of the distal artery caused an asymmetric flow during ESV, but not during PSV (Figure 4, right). During ESV, backflow from the unaffected CIA was jetted into the proximal CERAB cuff and concurrent recirculation was observed.

Figure 4. Flow velocity vector fields at the inflow of the CERAB model with a healthy distal artery (left) and total occlusion (right) during PSV (upper) and ESV (lower). Stent mesh indicated in red. The center graph shows axial velocity profiles for both the healthy distal artery and total occlusion situation in the CERAB model during PSV.

In both models, distal stenosis (both non-significant and significant) did not influence TAWSS (Figure 5). In the control model, a 20 % decrease in TAWSS was observed due to the total occlusion of the left CIA. This was not seen in the CERAB configuration (Figure 5).

OUTFLOW ROI In the proximal part of the outflow ROI, in case of healthy distal arteries, flow velocity during PSV was 40 % lower in the control model than in the CERAB model (57 vs. 95 cm/s). In the distal part of the ROI, similar peak flow velocities were seen in the control model and the CERAB model (Figure 6). In the outflow ROI, a more developed, parabolic axial flow profile was present in the CERAB model, compared with control,

Figure 5. Time averaged wall shear stress (TAWSS) at the left aortic vessel wall in the inflow ROI of the control and CERAB model. The vertical black dashed line represents the proximal edge of the CERAB cuff.

Figure 6. Velocity-vs-time plot of outflow ROI in the control and CERAB model. Locations of velocities are indicated by the red dots in the top right panels.

with lower flow velocities near the vessel wall (Figure 7). This causes a smaller velocity gradient, with respect to the control (Figure 7).

In both the CERAB model and the control model, a decrease in velocity during PSV was seen across the vessel lumen with increasing stenosis severity (Figure 7). The non-significant stenosis caused a small drop in PSV, while a significant stenosis caused a 53 % and 56 % decrease (control: 106 vs. 56 cm/s, CERAB: 96 vs 54 cm/s).

In the control model, an earlier onset of backflow, or flow reversal (FR), was seen with increased stenosis severity (FR in Figure 8). The second moment of flow reversal (back to forward flow) remained the same, indicating that distal stenosis caused a longer duration of backflow. This effect was not observed in the CERAB model.

In both the stented and the control model, TAWSS in the outflow ROI decreased due to distal stenosis (Figure 9). In the models with a significant stenosis, there was a 3-fold decrease in TAWSS, compared to the models with healthy distal arteries (average 2–4 cm, control: 0.44 Pa vs. 1.34 Pa, CERAB: 0.21 Pa vs. 0.75 Pa). In the CERAB model, TAWSS was 2 times lower than in the control model, independent of stenosis severity (average 2–4 cm, healthy: 0.75 Pa vs. 1.34 Pa, significant stenosis: 0.21 Pa vs. 0.44 Pa).

Figure 7. Flow velocity vector fields of the outflow ROI in the control (upper) and CERAB (lower) model during PSV. The graphs show axial velocity profiles for the three stages of distal outflow stenosis in both the control (upper) and CERAB (lower) model during PSV.

Figure 8. Velocity-vs-time plots of outflow ROI in the control and CERAB model. Locations of velocities are indicated by the red dots in the top right panels. FR = moment of flow reversal.

Figure 9. Time averaged wall shear stress (TAWSS) in the outflow ROI (left iliac artery, lateral wall) of the control model and CERAB model. Length 0 zero is just distal of the bifurcation. The vertical black dashed line represents the distal edge of the left CERAB limb.

DISCUSSION

In this study we have shown that the inflow section of the CERAB and control model are not influenced by outflow stenosis, but an occlusion causes jetting from the non-occluded limb into the cuff of the CERAB and a 20 % decrease in TAWSS occurs in the control model. In the inflow ROI, the highest velocities during ESV were found near the vessel wall. This was caused by backward flow from the distal aorta towards the renal arteries during ESV. Holenstein and colleagues attributed the occurrence of back flow to differences in resistance between the renal system and peripheral system of the legs¹². Velocities near the vessel wall also returned to a forward direction earlier than in the center of the vessel, indicating the presence of a Womersley velocity profile¹³. These phenomena are also known to occur in vivo, which confirms the similarity between the flow conditions in the used models and human physiology.

When comparing the flow velocity measurements during PSV in the control at the location of the anatomical bifurcation with the same location in the CERAB model, a 40 % decrease was observed. This can be explained by the fact that the CERAB limbs keep the flow lumen at 8 mm starting at the neobifurcation, whereas the native bifurcation widens before it narrows into the CIA (branch to trunk ratio larger than 1). This influences the observed flow profiles and TAWSS values in the distal iliac vessels.

The observed flow profile in the control model was more blunt or plug-shaped, while in the CERAB the profile was more parabolic, causing a smaller velocity gradient and resulting in lower TAWSS values. This can be attributed to the fact that the outflow profile of the CERAB can develop (i.e. become more parabolic) over a longer distance (approximately 20 mm) compared to the control. Therefore, prior to the introduction of distal stenosis, the TAWSS near the CERAB outflow was already two times lower, compared to the control model.

Introducing stenosis in the distal outflow section of both control and CERAB caused a twofold decrease in flow velocity and a threefold drop in TAWSS values. Several studies have previously shown that areas with low TAWSS correspond to regions that may exhibit atherosclerotic lesions, leading to the belief that low TAWSS causes an increased risk on the formation of atherosclerotic plaques¹⁴⁻¹⁶. This means that low TAWSS due to a distal stenosis could increase the risk of new or progressive plaque formation and therefore may accelerate disease progression, with potential detrimental consequences for graft patency.

In the outflow tract of the CERAB configuration, a twofold decrease in WSS was seen compared to the control model, independent of the occurrence or severity of a distal stenotic lesion. This indicates that the risk of accelerated disease progression due to distal stenosis might well be greater in patients treated with a CERAB, compared to untreated

patients. Progression of atherosclerosis can lead to failure of the CERAB configuration, which may lead to acute limb ischemia. Besides the possible mid- to long-term effects, more acute modes of failure could be attributed to the fact that low WSS also increases the risk of thrombosis¹⁷. Clinical results reported by our group on the CERAB technique observed early thrombosis in two patients 3 weeks postoperative¹⁸.

In a previous study by Grimme et al. it was shown that outflow impairment near the CERAB configuration can cause occlusion of the stents and should therefore be monitored intensively and treated early¹. This study provides in vitro data on local hemodynamics that suggests that stenotic lesions more distal to the CERAB configuration could have the same effect. Treatment of this type of lesion, when significant, should therefore be considered in patients with a CERAB configuration, regardless of the presence or absence of symptoms. In the case of non-significant stenosis, an increase in follow-up intensity should be considered. In patients with a stenotic lesion around the femoral bifurcation prior to CERAB, placement of the stent configuration should likely be combined with femoral endarterectomy in a hybrid procedure¹⁹.

The lower WSS values in the outflow tract of the CERAB configuration seem to be unrelated to the proximal cuff, but rather to the distal leg. Therefore, this finding could also apply to stent configurations that create a neobifurcation, such as kissing stents or grafts used for open surgery, as the extension of iliac lumen gives rise to a more developed flow profile, with lower TAWSS values. A previous in vitro study by Walker et al. also showed lower WSS downstream of a stent wire, lending credibility to this assumption²⁰. This would mean that treatment of stenosis distal to a stent should be considered in all patients, not only in patients with a CERAB configuration.

Besides WSS, the oscillatory nature of WSS also correlates with the progression and development of atherosclerosis²¹. This is reported using the oscillatory shear index (OSI); higher values indicate a balanced variation between the positive and negative direction of WSS. The metric was not included in the results because the observed pattern depicted the inverse of the WSS curves. With increasing stenosis severity the PSV decreased (positive WSS), balancing with the backflow (negative WSS) component causing an increase in OSI.

LIMITATIONS Several limitations, inherent to in vitro studies, influenced the results of this study, such as compliance of the vessels, interaction between stent and vascular endothelium and movement of the vessels, which were not modelled in the in vitro setup. Stent covers made of a transparent polyurethane were used to simulate the geometry of the CERAB, while obtaining optical access. We did not attempt to mimic the material properties of ePTFE. Furthermore, direct measurement of WSS using PIV techniques is not possible. Therefore, WSS values are always based on the velocity profile normal to

the wall, which can only be obtained at a finite distance from the wall. This necessitates an interpolation of the flow profile to the wall, possibly introducing a measurement error. A high spatial and temporal resolution in combination with accurate wall detection is therefore needed to calculate the WSS with reasonable accuracy.

Lower WSS distal to the stents, such as observed in this *in vitro* study, may not be present *in vivo*, e.g. due to the reorganization of endothelial cells around the stent edges and the compliance of arteries. Thus, *in vivo* studies to quantify endovascular flow patterns around stents are required. It should, however, be noted that *in vivo* flow quantification, with a high spatial and temporal resolution is not trivial. Aside from resolution constraints, MRI-based techniques for *in vivo* flow quantification in stents create considerable, material-dependent, artifacts which may inhibit quantitative analysis near the stent configuration²². Contrast-enhanced, high-frame rate, ultrasound-based techniques (echoPIV) could prove to be a convenient modality to quantify the in- and outflow of stent configurations. Until now, echoPIV techniques are only used in superficial arteries and cardiac applications, in a research setting²³. Furthermore, clinical follow-up studies should be performed to investigate the effect of WSS on stent patency results and subsequent clinical outcome.

Another relevant difference between the *in vitro* model and human physiology is the iliac outflow tract of the present measurement setup. Both iliac vessels were connected to a single compliance and resistance. Therefore, during measurements, a decreased flow in the stenotic vessel automatically led to an increased flow in the contralateral vessel. In human physiology, the demand of oxygen is regulated for each organ individually by adjusting vascular resistance. Thus, in principle a different redistribution of flow could take place. However, the redistribution of flow through the entire body due to a stenosis in a single vessel is complex and was therefore not simulated in this study. Furthermore, a left right comparison was not attempted. However, a future study accurately modeling the flow distribution would be of interest, the addition of contralateral stenosis would further strengthen this.

CONCLUSION

This in vitro study shows, that stenotic lesions distal to the aortic bifurcation cause a decrease in peak flow velocities and a corresponding decrease in TAWSS in the outflow tract of both the control and CERAB model. In the outflow tract of the CERAB configuration, TAWSS was lower than in the control model, independent of the severity of the distal stenotic lesion, indicating that local accelerated disease progression could be larger in patients treated with a CERAB. Therefore, treatment of stenotic lesions distal to a CERAB configuration could be indicated, regardless of the presence or absence of symptoms. In vivo assessment of local flow patterns in combination with patient follow-up is required to verify these findings.

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Three year outcome of the Covered Endovascular Reconstruction of the Aortic Bifurcation (CERAB) technique for aortoiliac occlusive disease

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Adapted from **the Journal of Vascular Surgery**
2017, in press.

ABSTRACT

OBJECTIVE The objective of the current study was to demonstrate the three year outcome of the CERAB technique for the treatment of extensive AIOD)

METHODS Between February 2009 and July 2016, all patients treated with the CERAB technique for AIOD were identified in the local databases of two centers and analyzed. Demographics and lesion characteristics were scored. FU consisted of clinical assessment, duplex ultrasound and ABI. Patency rates and clinically driven target lesion revascularization (CD-TLR) were calculated by Kaplan–Meier analysis.

RESULTS 130 patients (69 male and 61 female) were treated of which 68 % patients were diagnosed with intermittent claudication and 32 % suffered from critical limb ischemia. The vast majority (89 %) were TASC II D lesions and the remaining were TASC II B and C (both 5 %). Median follow-up was 24 months (range 0–67 months). The technical success rate was 97 % and 67 % of cases were performed completely percutaneously. The ABI improved significantly from 0.65 ± 0.22 preoperatively to 0.88 ± 0.15 after the procedure. The 30-day minor and major complication rate was 33 % and 7 %. The median hospital stay was 2 days (range 1–76 days). At 1 and 3-years FU 94 % and 96 % of the patients clinically improved at least 1 Rutherford category (2 % and 0 % unchanged, 4 % and 4 % worsened). Limb salvage rate at 1-year was 98 % and 97 % at three year follow-up. Primary, primary-assisted and secondary patency was 86 %/91 %/97 % at 1-year, 84 %/89 %/97 % at 2-year and 82 %/87 %/97 % at 3-year FU. Freedom from CD-TLR was 87 % at 1-year and 86 % at both 2 and 3-year FU.

CONCLUSIONS The CERAB technique is a safe and feasible technique for the treatment of extensive aortoiliac occlusive disease with good three year results regarding patency and clinical improvement.

INTRODUCTION

The last decades have shown a clear trend towards endovascular interventions as the first-line treatment strategy for AIOD, also as a solution for complex lesions. Endovascular treatment of AIOD has been related to less morbidity and a shorter hospital stay, compared to open surgery¹. In addition, open reconstruction is related to late complications, including incisional hernia formation. The kissing stent (KS) technique, using two stents abutting or 'kissing' in the central lumen of the distal aorta, is most commonly used when the aortic bifurcation is involved. A recent review showed that the primary patency of KS at 2-year follow-up is 79 %, with 48 % TASC C or D lesions treated². The geometry of the KS configuration was previously identified as a risk factor for re-stenosis and thrombosis³⁻⁵. The cross configuration in KS influences the mismatch areas between the stent and vessel wall that, in turn, causes flow disturbances. This is thought to be the main cause of impaired patency, related to neointimal hyperplasia induced by low oscillating wall shear stress and stagnant blood flow⁶. To overcome these disadvantages and to achieve better long-term patency, our groups introduced a new technique in 2013 named the CERAB technique⁷. We previously showed that this configuration is related to a superior flow geometry and more physiological flow patterns, in vitro (Chapters 4 and 6). In 2015 the early results of the CERAB technique were published with 1-year primary and secondary patency rates of 87 % and 95 %, respectively. These were considered to be promising, particularly since they included all treated patients from two sites including the first-in-man⁸. In the present study we have evaluated three year outcomes of the same cohort and updated it with the more recently treated patients.

METHODS

PATIENTS All patients treated with the CERAB technique between February 2009 and July 2016 in two hospitals, the Rijnstate Hospital Arnhem (Netherlands) and the ZNA Vascular Clinic (Belgium) were identified and analyzed retrospectively. Human investigation review board approval was obtained for this study and patient informed consent was not required, related to the retrospective design. Patients treated for acute limb ischemia and/or with chimney configurations were excluded from the analysis⁹. Prior to endovascular treatment all patients were treated with anti-platelet therapy, statins and (supervised) walking exercise. Medical files were screened for demographic data, clinical status, using the Rutherford classification for chronic ischemia¹⁰, complications and information on follow-up. Lesions were categorized according to the TASC II criteria by assessing the CT-A scans^{11,12}. Procedural reports were used to extract information on the procedure and the stent types used. The pre-treatment runoff resistance score for the iliac outflow was calculated based on the runoff grading scheme as proposed by Rutherford et al.¹⁰ A three point degree of stenosis scale was used to gauge the resistance, < 50 % stenosis = 0, > 50 % stenosis = 1 and occlusion = 2, based on duplex ultrasound. Weighting units are divided among the relative contribution to runoff; 2 for the external iliac artery (EIA) and 1 for the internal iliac artery (IIA). The maximal combined runoff score for left and right was 12 (left+right = $(2 \cdot 2 + 2 \cdot 1) + (2 \cdot 2 + 2 \cdot 1)$). Follow-up was scheduled after 6 weeks, 6, 12, 24, 36, 48 and 60 months and consisted of clinical assessment and duplex ultrasound with ABI measurements. Due to the low number of patients with a completed FU of 48 and 60 months FU up till 36 months is reported in the Results section.

CERAB PROCEDURE Suitability for the technique was evaluated based on CT-A imaging. Details on the CERAB technique have been described before⁷. Briefly, two introducer sheaths are placed in the common femoral arteries. The lesion is crossed either endoluminally or subintimally, depending on the lesion characteristics (Figure 1, A, verifying re-entrance). After pre-dilatation, a 9 Fr introducer sheath is inserted above the proximal margin of the aortic lesion. Thereafter, a 12-mm balloon-expandable ePTFE covered stent (Atrium Advanta V12, Maquet Getinge, Hudson, NH, USA) is deployed in the distal aorta. The distal end of the stent is placed approximately 15 to 20 millimeters above the bifurcation to facilitate canalization. This stent is flared proximally with a balloon adapted to the native diameter of the distal aorta, typically with a diameter of 16 mm, to ensure full apposition to the aortic wall. This creates a funnel-shaped stent with a distal segment that is still 12 mm in diameter. Subsequently, two iliac covered stents, typically 8 mm, are positioned in the conic segment and simultaneously inflated (Figure 1, B). As treatment planning is always from healthy-to-healthy tissue, in some cases distal extensions are required (Figure 1, B). In these cases we try to preserve the

internal iliac arteries, if patent, using a bare metal stent at these locations to prevent buttock claudication and erectile dysfunction. Post procedure, patients receive statin treatment and dual antiplatelet therapy for at least six months after which single antiplatelet and statin therapy is continued.

DEFINITIONS Primary outcome of the study was the 3-year primary patency. Secondary outcome measures included assisted-primary patency, secondary patency, freedom from CD-TLR, technical success, clinical improvement, length of hospital stay, 30 day morbidity, mortality and secondary interventions. Patency was determined by means of duplex ultrasound ($PSV < 2.5$). Primary patency was defined as patency that is obtained without the need for additional or secondary surgical or endovascular procedures¹³. Assisted-primary patency is defined as patency of the configuration achieved with the use of an additional or secondary surgical or endovascular procedure, as long as

Figure 1.

A Angiography of a 54-year old male patient with intermittent claudication and an occlusion of the distal aorta.

B Control angiography after reconstruction with the CERAB technique, with bilateral extensions, landing just above the iliac bifurcation. The aortic cuff is deployed 15–20 mm proximal to the anatomical bifurcation. On the completion angiography the caudal lumbar arteries are visible. Lumbar filling can occur because of three reasons. First, the artery can originate proximal to the aortic cuff. Secondly, because of flow of contrast between the aortic cuff and aortic wall in case of an incomplete apposition. And finally, because contrast may flow through the small gutters between the aortic cuff and the iliac limbs.

occlusion of the treated segment has not occurred¹³. Secondary patency was defined as the patency achieved by all procedures to recanalize an occluded CERAB configuration, preserving the configuration. Freedom from CD-TLR was defined as the time between the procedure and any revascularization based on restenosis and or occlusion and return or increase of symptoms. Technical success was achieved when blood flow was restored with less than 30 % residual stenosis. Restenosis was defined as a PSV ratio > 2.5, measured proximal, in or distal to the graft on duplex ultrasound. Major and minor complications were registered up until 30 days after the procedure. Complications leading to transient impairment were scored as minor. Complications leading to permanent damage or death were scored as major¹³. Limb salvage rate was defined as all patients without above the ankle amputations.

STATISTICS Data are presented as mean ± standard variation, unless stated otherwise. The Shapiro–Wilk test was used to test for normality. Statistical analysis was performed using SPSS 24 (IBM Corp. in Armonk, NY, USA). The non-parametric Chi-square test was used to test for differences in outcome with respect to previous vascular interventions, learning curve, IC vs. CLI and impaired runoff. The paired student T-test was used to compare ABI pre- and postoperative. An ANOVA for repeated measures was used to test the difference in Rutherford category pre- and postoperative. Univariate analysis was used to identify any correlation between smoking, diabetes, hypertension, renal status, cardiac status and pulmonary status and patency. Kaplan–Meier survival analysis was used to calculate patency numbers. The Log-rank test was used to compare the resulting survival curves. Statistical significance was defined as $p < 0.05$.

Table 1. Patient characteristics

	MEAN (RANGE)			n	%		n	%
Age	61	(36–81)	ASA category:			Pre-operative runoff score:		
	n	%	1	0	0	0	53	43
Gender:			2	73	57	1	3	2
Male	69	53	3	50	39	2	11	9
Risk factors:			4	6	5	3	5	4
Current smoking	100	78	Rutherford category:			4	19	15
Diabetes mellitus	46	35	1	1	1	5	5	4
Hypertension	96	74	2	0	0	6	10	8
Hyperlipidemia	121	93	3	84	66	7	3	2
Cardiac disease	61	47	4	22	17	8	5	4
Pulmonary disease	51	39	5	18	14	9	3	2
Carotid disease	26	20	6	2	2	10	4	3
Renal disease	25	19				12	3	2

RESULTS

During the study period a total of 130 patients (69 male and 61 female) were treated with the CERAB technique at the two sites. Patient characteristics are depicted in Table 1 and Figure 2. One patient was classified as Rutherford category 1, as he was preventively treated for an aortobifemoral prosthesis at risk for occlusion because of high grade stenosis at the proximal anastomosis. The majority of lesions (n = 116, 89 %) were classified as TASC II D, the remaining were TASC II B and C (both n = 7, 5%). Seven patients had previously undergone a surgical reconstruction of the aortoiliac segment: five aorto-bi-iliac bypasses, one ileo-femoral and one femoro-femoral crossover bypass. Another 46 patients (35 %) had previously undergone an endovascular intervention; 46 % of these interventions were angioplasties of the common iliac artery (in 17 % kissing balloon) and 37 % were angioplasties with stenting of the common iliac artery (31 % KS), Table 1 provides details on the remaining interventions. Prior to the intervention 35 % (n = 44) had no stenosis in one of the outflow vessels, 35 % (n = 44) had a stenosis and 30 % (n = 38) had an occlusion in one of the outflow vessels (either left or right). Further details per vessel segment are presented in Table 1. Median follow-up was 23.5 months (range 0–67 months). Follow-up at 24 and 36 months was available in 56 and 37 cases, respectively.

PROCEDURAL RESULTS The technical success rate was 97 %. In 4 cases technical success was not obtained; in three patients no re-entry could be obtained and in one the lesion could not be passed. All technical failures occurred within the first 40 treated patients

Table 1 (cont'd). Patient characteristics

		n	%			% (OPEN; STENOSIS; OCCLUDED)	
Intervention history:				Outflow vessels:		Right	Left
Previous aortoiliac intervention		53	41	External iliac artery		59; 30; 11	67; 22; 10
PBA	CIA	18	14	Internal iliac artery		66; 21; 14	61; 22; 17
	CIA kissing	3	2	Common femoral artery		71; 26; 3	76; 22; 2
	EIA	3	2	Superficial femoral artery		67; 29; 5	66; 27; 7
	SFA	2	2	Deep femoral artery		91; 8; 18	90; 10; 0
PBA + stent	CIA	13	10				
	CIA kissing	4	3				
	EIA	2	2				
	SFA	1	1				
Surgical treatment aorto-iliac segment		7	5				
Amputation		0	0				

ASA: American Society of Anesthesiologists physical status classification system; PBA: plain balloon angioplasty; CIA: common iliac artery; EIA: external iliac artery; SFA: superficial femoral artery.

(case 20, 24, 37 and 39). Most procedures were performed by bilateral percutaneous access of the common femoral arteries (n = 87, 67 %). In 15 % of cases (n = 20) a surgical cut down of both femoral arteries was performed, combined with an endarterectomy of the common femoral artery in 65 % of them (n = 13). In 18 % of the procedures (n = 23) a percutaneous access technique was used on one side and surgical cut down was performed on the contralateral side. At the location of the cut down this was combined with an endarterectomy in 52 % of the procedures. Brachial access was used in two procedures.

Three covered stents were used in 55 % (n = 67) of the cases, 4 in 19 % (n = 23), 5 in 22 % (n = 27) and more than 6 stents in 4 % (n = 5). The aortic stent was predominantly used in the dimensions 12 × 41 mm (n = 77) or 12 × 61 mm (n = 34). Limbs (left + right) were deployed with a diameter x length of 8 × 59 mm (n = 190), 8 × 38 mm (n = 30) and 6 × 59 mm (n = 10). In a number of cases the limb was extended into the external iliac artery to reach healthy tissue (14 % to the right and 15 % to the left side). The mean procedure time was 152.7 ± 88 minutes and mean amount of contrast used was 122.5 ± 62.4 mL. Median hospital stay was 2 days (range 1 to 76 days); 54 % of the patients stayed in hospital for 1-2 days; 29 % of the patients stayed 3-5 days and 6 % were admitted for longer than 5 days.

In 11 % of the cases there were procedural complications, including unintentional dissection, arterial rupture or thrombosis (Table 2) and all of them were solved during the initial procedure. In one patient an extensive bleeding in the left common iliac artery led to a resuscitation after cardiac arrest and subsequent prolonged intensive care unit (ICU) and hospital stay (76 days). The patient died with an unknown cause of death 3 months after discharge.

Figure 2. Distribution of Rutherford categories within the cohort during follow-up. Between parenthesis the number at risk for each follow-up period.

CLINICAL OUTCOME Postoperative complications are depicted in Table 2. Minor complications occurred in 43 cases (33 %), in 33 cases (77 %) these were hematoma, ecchymosis or leg edema. A re-intervention was necessary in 2 cases with a minor complication, both requiring thrombin injection for a false aneurysm at the access site. In 8 % of the treated patients major postoperative complications occurred: stent collapse in

Table 2. Complications

	n	SEVERITY/COMMENTS
<i>Procedural, major (no minor reported)</i>		
Dissection	6	All resolved with endovascular repair in the same procedure (PBA or stenting), no influence on health
Bleeding	2	One led to resuscitation after cardiac arrest during the procedure
Rupture	2	All resolved in the same procedure with endovascular repair, no influence on health
Dislocation of stent	1	Migration of the CERAB body, correction unsuccessful, however, CERAB completed
Stent deformation	1	Treated with PBA
Thrombus formation	2	All treated in the same procedure (thrombectomy), no influence on health
<i>Post procedure, major</i>		
Stent deformation	3	Recovery after re-intervention. Stent collapse (one limb crushing the other limb), PBA in 2 cases, aortobifemoral graft in 1 case.
Pneumonia	2	Leading to death in one case. Second case same patient as MOF case.
Thrombose	2	Recovery after intervention, 1 thrombectomy and 1 thrombolysis treatment.
CFA occlusion related to closure device	1	Recovery after intervention, removal of the closure device.
Multi organ failure	1	ICU stay with complete recovery, patient deceased six months postoperatively
Acute renal insufficiency	1	Permanent impairment requiring dialysis. Patient deceased 4 months postoperatively.
<i>Post procedure, minor</i>		
Groin hematoma	15	Temporary impairment in two patients.
Edema legs	18	Temporary impairment
Re-bleed	2	Temporary impairment, conservative treatment with bandaging.
Pseudo aneurysm of the CFA	3	Recovery after intervention, thrombin injection in two cases, other case only temporary impairment.
Fever unknown cause	2	Temporary impairment, no focus found near the CERAB, no intervention.
Atrial fibrillation	1	Temporary impairment, treated with medication.
Wound infection	1	Temporary impairment, resolved after treatment with antibiotics.
Wound dehiscence	1	Temporary impairment, no treatment.

PBA: plain balloon angioplasty; MOF: multi organ failure; CFA: common femoral artery; ICU: intensive care unit; GFR: glomerular filtration rate.

one of the limbs in three cases; in one case the CERAB was explanted and replaced with an aorto-bi-femoral graft and in two cases a kissing balloon technique was used to restore the flow lumen of the collapsed limb (Figure 3). Another patient was re-operated for an occlusion of the femoral artery attributed to a misplaced closure device. In two cases an early thrombosis of the CERAB occurred, both 3 weeks postoperatively. Both were successfully treated; one by thrombectomy and the other by thrombolysis. Postoperative deterioration of chronic renal insufficiency occurred in one patient without the need for dialysis. This patient, treated for Rutherford category 5, died 4 months postoperative. The 30-day mortality rate was 0 %.

Clinical improvement, expressed as an increase of at least one Rutherford category, at 6 weeks follow-up was 87 %. No improvement was observed in 11 % of the patients and in 3 % it worsened (max. 1 category). The median Rutherford category changed from 3 (min: 1, max: 6) preoperative to a median of 0 (min: 0, max: 5) postoperative ($p < 0.05$). At 24 and 36 months the median Rutherford category was 0 (min: 0, max: 6) and 0 (min: 0,

Figure 3. Limb crush examples as observed in two cases. Treatment was performed using a kissing balloon technique. Post-op computed tomography shows restoration of the crushed lumen.

max: 6), both significantly different with respect to the preoperative staging, an overview is given in Figure 2. The ABI significantly improved from 0.65 ± 0.22 preoperatively to 0.88 ± 0.15 after the procedure ($p < 0.05$). At 24 and 36 months the ABI was 0.97 ± 0.14 and 0.99 ± 0.14 .

In total 3 % of patients underwent toe amputations, three within 30 days and one during the procedure (unrelated to the procedure). The preoperative Rutherford classification was 5 in two cases and 6 in two cases. After 3-year follow-up 4 (3 %) major amputations

#: number; S.E.: standard error

Figure 4. Kaplan–Meier curve presenting the primary patency (PP), primary assisted patency (PAP), secondary patency (SP) and clinically driven target lesion revascularization (CD-TLR) for the follow-up moments, including number at risk and standard error.

(under or above the knee) were performed, at 6 months (n = 1), 12 months (n = 1) and 24 months (n = 2) FU, respectively. The initial Rutherford classification was 4 in three cases and 5 in one case. Limb salvage rate at 1-year was 98 % and 97 % at three year follow-up. The overall survival at 1 and 3-year FU was 93 % and 88 %, respectively. In total 12 patients died during the 3-year follow-up.

PATENCY The patency rates are depicted in Figure 4. The primary patency was 86 % after 12 months, 84 % after 24 months and 82 % after 36 months. Univariate analyses showed no significant relation between primary patency and smoking, diabetes, hypertension, renal insufficiency or coronary disease. No differences in outcome were observed between the first 20 treated in each clinic and the patients treated thereafter (p = 0.54 and p = 0.28), and as such a clear learning curve effect could not be established.

Outcome between patients with and without a history of previous vascular interventions (either surgical or endovascular) was not significantly different (p = 0.26). More details are presented in Table 3. There was no significant difference (p = 0.24) in primary patency for patients with an increased runoff score (score 1–12) prior to treatment and patients without (score 0). Furthermore, grouped initial Rutherford indication (IC vs. CLI) did not influence the primary patency results (p = 0.61).

REINTERVENTIONS During the follow-up period CERAB-related reinterventions were performed in 18 patients (14 %) (Table 4). 72 % of the patients received one or two reinterventions and the majority of them were performed within the first 12 months after the initial procedure (88 %). Apart from reinterventions other (endo)vascular interventions were performed in 27 patients (21 %). In 67 % of the cases this was either a PBA or PBA and stenting of the outflow arteries.

Table 3. Patency results based on history of (endo)vascular treatment

	YES (%) (n = 46)	NO (%) (n = 80)
<i>1-year follow-up</i>		
Primary patency	80	88
Primary assisted patency	91	97
Secondary patency	98	98
<i>3-year follow-up</i>		
Primary patency	76	85
Primary assisted patency	83	88
Secondary patency	94	98

Table 4. (Re)interventions during follow up

	# INTERVENTIONS		# INTERVENTIONS
<i>Reinterventions (related to the CERAB, in 18 patients)</i>		<i>Other intervention (not related to the CERAB, in 27 patients)</i>	
6 weeks	4	6 weeks	14
6 months	15	6 months	6
12 months	11	12 months	7
24 months	3	24 months	9
36 months	1	36 months	6
total	34	total	42
<i>Number of reinterventions per patient</i>		<i>Number of other interventions per patient</i>	
1	9	1	18
2	4	2	5
3	3	3	2
4	2	4	2
<i>Type of reinterventions</i>		<i>Type of other intervention</i>	
Embolectomy (iliac artery + aorta)	10	PBA	CIA 1
Kissing PBA, iliac artery limbs	7		EIA 5
PBA + stent iliac limbs (extension or in-stent)	6		SFA 3
Thrombolysis	5		PA 1
Unilateral PBA, iliac limb	3	PBA + Stent	CIA 3
Surgery (aorto-bi-femoral or axillo-femoral bypass)	2		EIA 5
PBA + stent aorta	1		SFA 8
			PA 2
		Thrombolysis	2
		Thrombectomy	2
		Endarterectomy CFA	3
		Surgical Bypass (femoro-popliteal or femoro-tibial)	4
		Superior mesenteric artery stent	2
		Unknown	1

#: number; PBA: plain balloon angioplasty; CIA: common iliac artery; EIA: external iliac artery; CFA: common femoral artery; SFA: superficial femoral artery; PA: popliteal artery.

DISCUSSION

In the present study we have demonstrated that patency and clinical outcome of the CERAB technique for extensive AIOD is satisfying, with three-year primary, primary-assisted and secondary patency rates of 82 %, 87 % and 97 %, respectively. The technical success rate was 100 % in the last 90 procedures, and in many of them open surgery would have been the only alternative treatment modality. Technically, there are no anatomical or morphological lesion boundaries for indication of the CERAB technique. The amount of (circular) calcification is not considered to be an exclusion criterion for the technique. In cases presenting lesions just distal to the renal arteries the chimney CERAB technique of the inferior mesenteric artery was applied (not included in the present study)⁹. However, the overall health situation of the patient has to be taken into account and in relatively fit patients open surgical repair may be preferred over the use of chimney's in the visceral arteries.

Eighty-eight percent of reinterventions were performed within the first year after treatment, which is reflected in the stable patency rates afterwards. These results stand firm amidst results that are obtained with the KS technique, with 2-year primary patency of 79 % (range 58–92 %) and also compared to aorto-bi-femoral grafts, with a 2-year primary patency of 93 % (range 87–98 %)^{2,14,15}. It should be noted, however, that more complex lesions were treated in the current study, when compared to most results reported for KS and open repair, both 50 % TASC C and D lesions, making the comparison less reliable^{2,14}. Only the cohort of Dorigo and colleagues had a comparable distribution of the TASC categories¹⁵.

Flow and geometry seem to be important factors in view of stent patency. In previously published papers we studied the influence of the KS and CERAB technique on radial mismatch and blood flow using in vitro modeling (Chapters 4 and 6). The effects of different stent configurations on flow perturbations were investigated and these studies showed that the CERAB configuration is the most unimpaired physiologic reconstruction with only a few zones of recirculation and little fluid stasis. Lowering flow disturbances and radial mismatch, i.e. mimicking a native bifurcation, could lower thrombus formation and thereby restenosis¹⁶.

The 30-day major complication rate of 8 % is low in comparison to the 30-day major complication rate of 20 % reported after aorto-bi-femoral and aorto-bi-iliac bypass procedures¹⁷ and in line with respect to those observed after KS treatment (5.8 % ± 4.4 %, TASC C and D in 50 % of cases)². Therefore, the results of this study show that the technique is indeed a valuable alternative for these treatment options.

The relation between patency and outflow has previously been shown for KS by several studies^{4,14} while it was not observed by others^{18,19}. Therefore, the impact of impaired runoff in aortoiliac stenting remains under debate. Studies that did observe the aforementioned relation pointed out that the atherosclerotic process might be more virulent in patients with extensive PAD and impaired runoff. This underlines the importance of proper risk management using statins, antiplatelet drugs and walking exercise. However, the optimal duration of double antiplatelet therapy has never been studied in this respect, and should be the topic of further research.

First signs of patency loss are usually observed on duplex ultrasound. According to the study of Chong et al. PSV values above average are commonly reported during duplex follow-up in the CERAB configuration, and could require a CT-A for further assessment²⁰. CT-A data often reports a patent configuration, therefore Chong and colleagues proposed a tool to predict the maximal PSV in the CERAB. In future studies it would be interesting to incorporate such tools and to evaluate their predictive value.

Most reinterventions were performed within the first 12 months after treatment. This emphasizes that strict follow-up in the first 12 months is paramount to detect onset of re-stenosis, while follow-up afterwards could be less frequent. With this FU schedule a secondary patency rate of 97 % can be achieved at three-year follow-up.

In the present study, patency was defined according to the reporting standards, as recently described by Stoner et al.¹³. In other studies, including our first paper on the outcome after CERAB, another definition was used, that includes the presence of a significant stenosis as loss of primary patency⁸. In the current cohort there were only two cases with such a stenosis left untreated, and as such the influence on the results is only minimal with a 3-year primary patency of 81 % vs. 82 %. Standardization of definitions and adherence to reporting standards is key and requires attention when comparing data from different studies.

In the current cohort four technical failures were reported and in all cases the lesion could not be passed from a retrograde direction. Brachial access was not attempted in these cases. Nowadays, brachial access is applied in our centers in challenging cases and is a viable option in case of a failed retrograde approach²¹. When comparing the major complication rate with the complications observed in our early series, a 4-fold increase was noted (2 % vs 8 %). This could be related to the fact that over time more complex lesions were considered to be suitable for the technique and also underlines frailty of this group of patients. Three of the complications were caused by a crushed iliac stent in the aortic cuff (two examples shown in Figure 3). In one of them this was likely to be a technical error where the aortic cuff was post-dilated after positioning of the limbs, thereby crushing the contralateral limb. In the other two cases no clear reason was

observed, however, could have been related to the heavily calcified lesions. Improvement of stent design and additional knowledge on stent mechanics may also contribute to the prevention of this complication. In addition, a relining stent could be used to add radial force to the CERAB configuration. However, relining the CERAB configuration as a preventive measure would significantly increase cost. Furthermore, to our knowledge no lesion morphology or geometry characteristics can predict stent crushing. When diagnosing stent collapse, PBA in combination with relining could be beneficial, since the original configuration might be weakened.

The choice of stents was based on studies that reported a superior patency of covered stents over bare metal stents in treatment of TASC C and D lesions²²⁻²⁵. In 45 % of the cases we could not complete the procedure with three stents only, emphasizing the need for longer 8 mm diameter limbs (currently limited to 58 mm length). In the current cohort the CERAB was mostly constructed using Advanta Atrium V12 stents. Due to manufacturing problems since 2015 the large diameter Atrium Maquet V12 stents are no longer available. In search of alternatives the LifeStream (BARD Peripheral Vascular, Tempe, AZ, USA) and more recently the Begraft and Begraft Aortic (Bentley Innomed GmbH, Hechingen, Germany) were used for this indication. Future research should point out what the differences are between these three balloon-expandable stents with respect to placement accuracy, radial force, durability of the ePTFE layer and patency. Parallel to the introduction of the CERAB the use of the AFX unibody bifurcation endograft (Endologix Inc, Irvine, Calif, USA) was described for treatment of AIOD^{26,27}. The benefit of this stent is the fact that radial mismatch is completely prevented, but being a self-expanding stent the AFX stent has less radial force.

The present study is limited by the fact that it describes the first experience of a novel technique. With gaining experience results were likely to improve, but broadening indication for the technique during time may also have affected results. Furthermore, the retrospective analyses of our registry limited us to draw firm conclusions on causation of failure of patency. Moreover, the 3-year follow-up was not completed for the entire cohort, and as such only reflects early experience. Nevertheless, the standard error of the patency rate estimate was below 10 %.

CONCLUSION

This study has shown that the CERAB technique is related to good three year results, with regard to patency and clinical outcome, in patients treated for mostly TASC II D lesions. Long-term studies should establish its role in these patients and risk-prediction tools need to be assessed.

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General discussion

INTRODUCTION The field of biological fluid mechanics has contributed largely to our understanding of blood flow and blood flow interactions in the human body. People like John Womersley, Donald McDonald and Michael O'Rourke unraveled important concepts regarding the underlying mechanism of the cardiovascular system¹. Most of their work is directed towards understanding the cardiovascular system through modelling. Within the vascular community pioneers like Julio Palmaz started to treat stenotic lesions using endovascular techniques in the early nineties, driven by the high morbidity and complication rate seen with open surgical techniques, especially in case of AIOD. Many cohort studies followed, describing the results obtained with endovascular techniques, like the KS technique. Several design iterations were performed in an effort to optimize the patency results, this also led to the introduction of the CERAB technique. The ideas for these design improvements are mostly based on hypothesis regarding the local interactions between the stent geometry, blood flow and the vessel wall. In this thesis we aimed to combine insights from the fields of biological fluid mechanics and endovascular surgery to unravel the local hemodynamics in order to better substantiate the choice of stent geometry to optimize patency results for patients with AIOD treated with endovascular techniques.

CURRENT TREATMENT OPTIONS Regarding the current status of endovascular treatment of AIOD, chapter two shows that studies have only been performed with a retrospective design, including a low number of patients (63.2 on average). More than half of the patients included were treated for relative mild lesions (TASC A and B) and a Rutherford category of 1, 2 or 3 in 73.7 % of the cases. This shows that lifestyle changes and exercise therapy are not the first line of treatment in many cases, while good results can be obtained in early stages of AIOD². Education on this point is therefore needed. Furthermore, endovascular treatment protocols differ between studies in the use of pre- and post-dilation, type of stent (covered, balloon-expandable and self-expanding) and postoperative medication. This makes the study groups very heterogeneous, hard to compare and shows that consensus is lacking. Based on the evolution of endovascular techniques and surgical techniques in general, an increase of patency results over the years could be expected. However, we did not observe such a trend, possibly due to the fact that more complex lesions are included, dampening the effect of improved techniques. Furthermore, since 2010, the body of literature regarding the KS technique doubled, groups that more recently started to use the technique might be more eager to publish the results, dampening the effect of improved skills.

To further substantiate conclusions based on current literature and correct for the large differences between patient cohorts, an IPD analysis was issued after finishing the review, including 605 patients. Backward logistic regression analysis was used to identify outcome predictors for primary patency. However, no predictors regarding

the treatment protocol could be identified for the primary patency. Secondary patency is influenced by the choice of stents, in favor of self-expanding stents. Furthermore secondary patency is influenced by previous (endo)vascular procedures that have been performed. This indicates that the primary patency results obtained with both balloon- and self-expanding stents do not differ based on our cohort, furthermore treatment choices like: stent protrusion, pre and post dilatation did not influence patency. When dividing the cohort in patients treated before and after 2005 an significant increase in primary patency was observed. Indicating endovascular techniques are still changing, for the better. Lastly we observed that treated TASC C and D lesions perform better than TASC A and B lesions, possibly because the outcome is monitored more strictly and the improvement more prominent.

STENT GEOMETRY Flow studies without a thorough understanding of the concerning geometry are hard to interpret. Regarding stent geometry we have shown, using in vitro models, that mismatch areas are always present when using the KS or CERAB technique. Lending credit to the hypothesis that these mismatch areas cause flow perturbations, triggering the cascade of stent failure due to stent thrombosis and neointimal hyperplasia³. The size of the mismatch area and volume largely differs between stent configurations. Self-expanding BMK stents better conform to the vessel wall, creating a larger D-ratio (measure to express conformability of two stents in a single vessel) and smaller mismatch area, with respect to balloon-expandable stents. Adding a third stent, like with the CERAB technique, drastically decreases the size of the mismatch area with respect to the most optimal KS configuration. The location of the limbs inside the cuff is of utmost importance in order to minimize the mismatch area, this makes it an important step when deploying the CERAB configuration. To assure that the in vitro results are valid, we also performed an in vivo analysis to quantify the mismatch area. In vivo data shows that reduction of mismatch is not that easily achieved in the clinical situation, as the mismatch areas measured are a factor 4 to 8 higher compared to the in vitro data. In vivo the CERAB also showed superior result with respect to the KS configurations. Correct (over)sizing of stents is crucial in this case to reduce the amount of radial mismatch. Furthermore high resolution intraoperative imaging and tools to clearly mark the stent edges can further reduce radial mismatch.

STENTS & BLOOD FLOW, IN VITRO QUANTIFICATION Having quantified the geometry, in vitro flow studies were performed to compare the influence of the stent geometry on pulsatile blood flow in a controlled situation. Laser PIV techniques were used to visualize and quantify local flow patterns near the stent configurations under physiological flow conditions. Flow fields, WSS and the OSI were analyzed. Recirculation of flow was observed during the complete cardiac cycle near the inflow of the CK

stent configuration. This caused WSS values five times lower compared to the control situation and OSI values that are 3 times higher compared to the control. This indicates the local detrimental effect of covered stents that protrude into the distal aorta. Causing unfavorable conditions for long-term patency, as low and oscillatory WSS contribute to the development of atherosclerosis and increase the risk of thrombosis⁴. When performing follow-up of CK stents extra attention for the inflow of the stents is therefore recommended to issue timely re-interventions. The BMK stent configuration shows better conformation to the aortic wall and a clear double lobed velocity profile in the aortic segment of the configuration, however, without consequences for the WSS and OSI values as they are in the same range as the control and CERAB at the inflow. The BMK stent configuration shows a zone of stagnant blood flow between the anatomic bifurcation and neo bifurcation, which makes this location vulnerable for thrombus formation. Something Saker et al. also showed in their paper on the histopathology after KS treatment³. While the inflow and neobifurcation show WSS values in range with the control, the iliac outflow of the CERAB shows WSS values that are two times lower compared to the control. This can be attributed to the more parabolic outflow profile formed due to the more proximal neo bifurcation of the CERAB in comparison to the control which shows a plug shaped outflow profile. This makes the outflow of the CERAB a point of concern during FU. Furthermore, the introduction of an unilateral symptomatic outflow stenosis causes a threefold drop in WSS for both the control and CERAB, indicating timely treatment of outflow stenosis is warranted to maintain patency of the CERAB configuration.

CLINICAL PERFORMANCE As already briefly introduced, this thesis combines both technical and clinical research to give insight in the performance of endovascular AIOD treatment techniques. Regarding the clinical part, we have shown that the CERAB technique is applicable with high technical success in a cohort with mainly challenging TASC D lesions (89.2%). The three year primary patency results are falling behind 10% with those observed after aortobifemoral grafting. Although these cohorts only contained TASC D lesions in up to 50% of the patients. Like any surgical technique the CERAB also has several points of concern. These mainly lie in deployment and seal between the limbs and the cuff. In the current cohort we observed kinking or crushing of a stent limb in 4 cases. Regarding patency loss we observed 6 cases where patency was lost due to the development of an edge stenosis in the outflow and in two cases stents occluded due to outflow limitations⁵. Given the results from our in vitro analysis of the CERAB outflow these failures may be attributed to the observed low and oscillating WSS. Possibly the use of conic limbs preserves the plug shaped outflow profile retaining a WSS value within the normal range.

Good reference values for WSS are not available and only limited data is available regarding the aortoiliac region, based on small cohorts⁶. Furthermore age, blood pressure, exercise and body mass index seem to have an important effect on the WSS values, making measurements highly patient specific^{7,8}. Methods to determine WSS always depend on two inputs: reliable velocity estimation near the vessel wall and reliable estimation of the vessel wall. Both are challenging to obtain and a gold standard is not available (either in vivo or in vitro)^{9,10}. Over the years many papers supporting the theory that low and oscillatory WSS promotes the development of atherosclerosis, a review of Peiffer et al. challenges this theory after reviewing the methods applied to come to a conclusion¹¹. This underlines the fact that there is no gold standard available and WSS data should be interpreted with great cause.

FUTURE PERSPECTIVES Since the introduction of the CERAB technique several new balloon-expandable stents have come to the market. Calling for a review with respect to the combination of stents that are applied in the CERAB configuration. Besides clinical and technical performance of these stents, mechanical characterization is a key step in understanding the differences between these stents and should be subject of future research.

Quantification and understanding of the flow of fluids has been a the subject of research for several centuries. In the last decades bio fluids were mainly studies using in vitro, animal or computer models. The use of in vitro modeling comes with several advantages, like the ability to setup a controlled environment with respect to boundary conditions, geometry and the choice of high resolution imaging techniques. Of course any simulation is a simplification of reality, leaving room for doubt about the translation of the observed results to the patient population. Future perspectives lay in improvements of materials to realistically mimic the vessel wall and also application of inflow conditions that arise due to cardiac pathologies.

The use of in vivo techniques to quantify blood flow is slowly emerging, the obtained spatial resolution is nowhere near that of established laser PIV techniques. However, the use of high frame rate (>1000 fps), plane wave, contrast enhanced ultrasound techniques could be a great step forward to build an iterative circle between in vitro and in vivo research. This enables us to further unravel, verify, and utilize interactions between blood flow, stents and the vascular system. Besides knowledge driven research, applied research of quantification of in vivo blood flow on a patient level may contribute to more personalized vascular care and risk assessment. This does not only apply to stenotic lesions but also to aneurysmatic disease. Based on the observed flow profiles before and after treatment, choices could be substantiated regarding treatment and follow-up scheduling.

GENERAL CONCLUSION

The work presented in this thesis shows that the clinical results obtained with the KS technique are fair and can be improved based on pre- and perioperative choices. The local geometry largely differs between stent configurations used for treatment of AIOD. Furthermore, we have shown that the stent geometry influences blood flow, subsequently causing stasis of blood and influencing the shearing forces on the vessel wall to a pathologic point. The CERAB configuration causes less flow perturbations at the inflow and neobifurcation. However, the long non-tapered limbs of the CERAB cause outflow conditions with low WSS values, amplified in the presence of outflow stenosis distal to the CERAB configuration. Clinical results obtained with the CERAB are promising, certainly given the fact that mostly TASC D lesions were included.

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English Summary

This thesis describes several chapters related to the subject of AIOD. AIOD arises from stenotic lesions that form near the aortic bifurcation, including the distal aorta and the proximal iliac arteries. The chapters in this thesis address both clinical subjects as well as subjects that combine biofluidics, medical insights and their clinical implications. The goal main goal is to form better substantiated choices in the treatment of AIOD to improve the long-term outcome.

The prevalence of PAD, of which AIOD is a subgroup, in the Netherlands in the population above 55 years old is estimated to be 19.1 %. This is based on a subcohort of the Rotterdam study¹. In the population of PAD patients only 6.3 presents with symptoms like IC symptoms, which in turn influence walking distance. When the walking distance drastically decreases this can become very incapacitating. When treatment is indicative a minimal invasive treatment option is often the standard of care. With this treatment option the vessels are treated from the inside (endovascular).

In the first chapter of this thesis the currently available literature on the treatment of AIOD is reviewed. The gold standard for AIOD treatment, when using endovascular techniques, is the KS method. Using this method two stents are deployed simultaneously in both iliac arteries, the stent about or 'kiss' in the distal aorta, hence the name 'kissing stents'. The technique renders reasonable patency results with respect to the invasive option of open surgery. However, after two years the patency results of the kissing stents are 15 % lower with respect to the results obtained with open surgery. Furthermore, a large diversity in the choice of treatment protocol was observed. The location of deployment of the stents (with respect to the aortic bifurcation) differs as well as the type of stent. Due to the fact that the IPD was not available we were not able to draw firm conclusions and we could not give recommendations with respect to standardization of the treatment protocol. To overcome these limitations the IPD was requested from all studies included in the review. Five authors committed to this request, supplying the data for 605 patients treated for AIOD with the KS technique. Analysis of this dataset showed no influence of stent type or other choices in the treatment protocol on the primary patency. Splitting the cohort in patients treated before and after 2005 showed that there is a significant improved in patency for patients treated after 2005.

During the following chapters we compared the geometry of different stent configurations when these are placed near the aortic bifurcation. Previous studies showed that that the geometry influences the patency. Area's between the vessel wall and the stent (coined mismatch areas) might cause blood flow perturbations triggering a cascade of thrombus formation, neointima hyperplasia and finally restenosis or reocclusion. To resolve these mismatch area's the CERAB technique was introduced. With this technique three instead of two stents are used, the third stent is placed in the distal aorta, creating a funnel (or cuff) to guide the blood flow in the two iliac limbs.

However, the exact differences between the geometry of the stents is not clear. Using in vitro models, making the configurations anatomy independent, we showed that the CERAB significantly decreases the mismatch area's with respect to the KS configurations. To optimize the mismatch minimization it is of utmost importance to focus on the placement of the limbs inside the cuff. This study was also repeated in two groups of patients, treated either with the KS technique or CERAB technique. The results also showed a significant difference between the CERAB and KS technique, with respect to mismatch area. However, the differences were not as large as observed with the in vitro results. This shows that optimal deployment of the CERAB in vivo is still challenging.

Having identified the geometric differences between the KS and CERAB technique we shifted our focus to the interaction between the stent configuration and blood flow. The in vitro models were incorporated in an experimental setup to simulate blood flow in the infrarenal aorta and the iliac arteries. Using laser based particle image velocimetry, high resolution (both spatial and temporal) measurements were performed to obtain vector velocity fields near the in and out flow of the stent configurations. Results show that large areas of flow recirculation arise near the inflow of the covered kissing stent configuration during the whole cardiac cycle. These recirculation areas increase the risk of thrombosis and the wall shear stress is decreased. Low wall shear stress can cause in neoplasm the vessel wall. The bare metal stent configuration did not have recirculation at the inflow, however, between the neobifurcation and the anatomic bifurcation stasis of blood occurs. This may cause thrombus forming, as was observed bij Saker et al.². In case of the CERAB configuration, no recirculation was observed near the inflow, small recirculation of blood was observed near the neobifurcation, wall shear stress levels are comparable to the control model.

Thereafter we investigated the outflow of the CERAB configuration using our in vitro setup, because clinical results showed that most graft failure is observed at the outflow, most likely due to distal stenosis. This study showed that, independently of distal stenosis severity the wall shear stress was two times lower with respect to the control situation. The low wall shear stress is probably related to the more developed outflow profile of the CERAB configuration, giving rise to a less steep velocity gradient. When introducing a significant distal stenosis, the wall shear stress is three times lower than the control situation. Thus, in spite of the favorable inflow characteristics, the outflow should be monitored closely during FU, based on both the clinical and experimental results.

Apart from investigating the local blood flow the clinical performance of the CERAB is also of importance. The last chapter of this thesis presents the 3-year follow-up results of patients treated with the CERAB technique in both the Rijnstate ziekenhuis Arnhem and the Ziekenhuis Netwerk Antwerpen. We showed that the 3-year primary patency is 82.1 %, the secondary patency is 97 %. These results are promising, given the fact that

most lesions treated are TASC D lesions. In comparison to the KS technique a margin of 5.5 % in patency is gained after three years (76.6 % vs. 81.1 %). The complication rate of the CERAB technique is in the same range as the KS technique in case of AIOD treatment.

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Nederlandse samenvatting

In dit proefschrift wordt een reeks van studies beschreven over de aandoening aorto-iliacaal stenotisch (vernauwend) vaatlijden (AISV). Het aorto-iliacale gebied omvat de distale aorta (grote buikslagader), de bifurcatie (afsplitsing) en de proximale iliacaal vaten (liesvaten). De studies uit dit proefschrift richten zich zowel op klinische vraagstukken rondom de behandeling van dit ziektebeeld als vraagstukken op het grensvlak tussen de technische mogelijkheden en de klinische implicaties daarvan. Het uiteindelijke doel is om tot een beter onderbouwde keuze voor een behandeling te komen en de langetermijntoekomst van de behandeling verder te optimaliseren.

De prevalentie van perifeer arterieel vaatlijden in de Nederlandse populatie boven de 55 jaar, waarvan AISV een subgroep is, wordt geschat op 19.1 %. Dit is gebaseerd op een sub-cohort uit de Rotterdam studie¹. 6.3 % van deze mensen heeft ook daadwerkelijk symptomen, zoals claudicatio intermittens (etalagebenen). Wanneer deze klachten toenemen kunnen ze als zeer invaliderend ervaren worden, doordat ze veel pijnklachten veroorzaken en de loopafstand danig wordt verkleind. Wanneer men overgaat tot behandeling, wordt tegenwoordig vaak gekozen voor een minimaal invasieve behandeling. Hierbij worden de bloedvaten van binnenuit behandeld, door vanuit de lies stents te plaatsen. Dit wordt ook wel endovasculair behandelen genoemd.

In dit proefschrift is allereerst gekeken naar de huidige stand van zaken in de literatuur rondom de behandeling van AISV, doormiddel van het uitvoeren van een systematische review. Hieruit komt naar voren dat de gouden standaard, wat betreft endovasculair behandelen, het toepassen van 'kissing' stents is. Bij deze methode wordt via beide iliacaal vaten een stent opgevoerd en tegelijkertijd ontplooid, waarbij de uiteinden elkaar raken in de aorta (vandaar de naam 'kissing'). Het blijkt dat met deze techniek redelijk tot goede resultaten worden gehaald in vergelijking met de meer invasieve broekprothese (geweven vervanging van het bloedvat, welke wordt ingehecht op de plek waar het ziekte vat is verwijderd). Echter, twee jaar na de plaatsing zijn 15 % meer broekprotheses open dan kissing stents. Er wordt een grote verscheidenheid aan behandelprotocollen binnen de verschillende centra beschreven, waarbij ook de manieren van plaatsing en het soort stent sterk verschillen. Op basis van deze eerste review was het niet mogelijk om aanbevelingen te doen over standaardisatie van het behandelprotocol, omdat alleen de gemiddeldes per studiegroep beschikbaar waren. Om deze reden zijn de data van alle individuele patiënten opgevraagd bij de auteurs van alle studies die in deze systematische review werden geïnccludeerd. Uiteindelijk is de data van 5 studies geïnccludeerd, met in totaal 605 patiënten, behandeld met kissing stents voor AISV. Analyse van de data toonde aan dat er geen invloed is van behandelkeuzes (stent type, wel of geen predilatatie of de manier van plaatsen) op de uitkomst. Wel lijken stents geplaatst na 2005 het beter te doen dan stents geplaatst voor 2005, wat wijst op een verbetering van endovasculaire technieken voor de behandeling van AISV.

In het vervolg van dit proefschrift is onderzoek verricht naar de geometrie van stents wanneer deze geplaatst worden nabij de aortabifurcatie. Het lijkt namelijk zo te zijn dat de geometrie van invloed is op de levensduur van de stents. Ruimtes tussen de stents en de vaatwand zorgen mogelijk voor een verstoring van de bloedstroom, wat voor stolling en reactie van de vaatwand zorgt. Hierdoor ontstaat restenose. Verschillende kissing stent configuraties zijn vergeleken met een techniek die enkele jaren geleden werd geïntroduceerd, de CERAB-techniek. Bij deze techniek wordt gebruik gemaakt van drie in plaats van twee stents. De derde stent vormt een trechter met in het smalste gedeelte de twee kissing stents. De hypothese is dat hiermee de ruimte tussen de stents en de vaatwand in de distale aorta wordt verkleind. Middels in vitro modellen hebben we aangetoond dat bij de CERAB-techniek deze ruimtes inderdaad kleiner zijn ten opzichte van de kissing stent configuratie. Om de ruimte te minimaliseren is het belangrijk om de kissing stents nauwkeurig te plaatsen. Deze studie is ook uitgevoerd bij twee patiëntgroepen waarbij één cohort behandeld is met kissing stents en het andere met de CERAB-techniek. Ook hier was het verschil tussen de CERAB en kissing stents groot, maar niet zo groot als de verschillen gemeten met de in vitro studie. Dit toont aan dat het in de praktijk lastig kan zijn om de optimale configuratie te bereiken.

Nu de geometrie in kaart gebracht is kan ook gekeken worden naar de eventuele invloed van de ruimtes tussen de stents en de vaatwand op de bloedstroom. Hiervoor zijn de in vitro modellen geplaatst in een opstelling waarmee de bloedsomloop gesimuleerd kan worden. Door gebruik te maken van lasers en hogesnelheidscamera's kan de stroming rond de stents met hoge resolutie (zowel in plaats als tijd) in beeld worden gebracht. Hieruit is naar voren gekomen dat de ruimtes tussen de stent en vaatwand zorgen voor recirculaties aan de instroom gedurende de gehele hartcyclus in het geval van covered kissing stents. Van deze recirculaties is bekend dat ze de kans op trombose verhogen en daarnaast ook de wandschuifspanning van het bloed op de vaatwand verlagen. Hierdoor is een reactie van de vaatwand te verwachten via atherosclerotische en neoplastische processen. Bij de bare metal kissing stents treedt stase van bloed op tussen de anatomische bifurcatie en neobifurcatie. Dit zorgt mogelijk voor een verhoogde kans op trombosevorming. In een casestudie van Saker et al. (2000) wordt de vorming van trombus en neoplastisch weefsel beschreven op deze locatie bij een geëxplanteerde bare metal kissing stent configuratie². In geval van de CERAB zijn er geen recirculaties zichtbaar bij de instroom en is de wandschuifspanning gelijk aan het controlemodel. Op het punt waar de trechter en de pootjes aansluiten zijn recirculaties zichtbaar, maar in mindere mate dan bij de gecoverde stents. Ook hier zijn de wandschuifspanningen gelijk aan het controlemodel.

In een vervolgstudie is de uitstroom van de CERAB verder onderzocht. In een aantal gevallen ontstaat er een restenose of occlusie, mogelijk door de aanwezigheid van distale stenoses. In de uitstroom van de CERAB wordt, onafhankelijk van een distale stenose, een wandschuifspanning gemeten die twee maal lager is dan het controlemodel. De wandschuifspanning die gemeten wordt bij een significante stenose is, in vergelijking met het controlemodel, drie keer lager. Ondanks de gunstige instroom van bloed in het proximale gedeelte van de CERAB is het belangrijk om het uitstroom gedeelte tijdens controles goed te monitoren, afgaand op de klinische en hemodynamische resultaten.

Naast een goed beeld van de lokale invloed van de stents op de bloedstroom is het ook belangrijk om patiënten met een CERAB-stent te (blijven) volgen. In het laatste hoofdstuk van dit proefschrift zijn alle patiënten welke behandeld zijn met de CERAB-stent in het Rijnstate ziekenhuis Arnhem en het Ziekenhuis Netwerk Antwerpen gevolgd. Hieruit blijkt dat de primaire patency van de CERAB-stents drie jaar na plaatsing 82,1 % is, de secundaire patency is 97 % na drie jaar. Deze resultaten zijn veelbelovend, zeker gezien het feit dat vooral complexe laesies behandeld zijn met de CERAB-techniek (type TASC C en D). In vergelijking met de kissing stent techniek wordt hier een winst behaald van 5,5 % na 36 maanden follow-up (76,6 % vs. 82,1 %). De complicatie percentages van de CERAB-techniek zijn daarbij niet hoger dan de kissing stent technieken die worden toegepast voor de behandeling van AISV.

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Addenda

ABBREVIATIONS

ABFB	Aorto-bi-femoral bypass	HT	Hypertension
ABI	Ankle-brachial index	IC	Intermittent claudication
AIOD	Aortoiliac occlusive disease	ICC	Intra-class correlation
ASA	Acetylsalicylic acid	ICU	Intensive care unit
BE	Balloon-expandable	IIA	Internal iliac artery
BMF	Bloodmimicking fluid	IMA	Inferior mesenteric artery
BMK	Bare metal kissing	IPD	Individual patient data
CAD	Computer aided design	IRB	Institutional review board
CD-TLR	Clinically driven target lesion revascularization	KM	Kaplan–Meier
CERAB	Covered endovascular reconstruction of the aortic bifurcation	KS	Kissing stents
CFA	Common femoral artery	LMWH	Lowmolecular-weight heparin
CFD	Computational fluid dynamics	MOF	Multi organ failure
CI	Confidence interval	OR	Odds ratio
CIA	Common iliac artery	OSI	Oscillatory shear index
CK	Covered kissing	PA	Popliteal artery
CLI	Critical limb ischemia	PAD	Peripheral arterial disease
CLL	Centre lumen line	PAP	Primary assisted patency
CT	Computed tomography	PBA	Plain balloon angiography
CT-A	Computed tomographic angiography	PIV	Particle image velocimetry
CVD	Cardiovascular disease	PP	Primary patency
DM	Diabetes mellitus	PRISMA	Preferred items for systematic reviews and meta-analysis
echoPIV	Contrast-enhanced, high-frame rate, ultrasound	PSV	Peak systolic velocity
EIA	External iliac artery	QoL	Quality of life
ePTFE	Expanded polytetrafluoroethylene	R	Retrospective
ESV	End-systolic velocity	ROI	Region of interest
fps	Frames per second	SE	Self-expandable
FR	Flow reversal	S.E.	Standard error
FU	Follow-up	SFA	Superficial femoral artery
GFR	Glomerular filtration rate.	SP	Secondary patency
HD	Hemodynamic	TASC	Transatlantic inter-society consensus
HL	Hyperlipidemia	TAWSS	Time-averaged wall shear stress
		WSS	Wall shear stress

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BIOGRAPHY

Erik Groot Jebbink was born on the first of October 1987 in Deventer, The Netherlands. In 2006 he graduated from the Etty Hillesum Lyceum in Deventer.

Thereafter he studied Technical Medicine between 2006 and 2013. During this period he also joined the organizing committee of the Batavierenrace, an annual relay race between Nijmegen and Enschede.

Erik performed his graduation project at the Rijnstate hospital Arnhem, department of surgery. Thereafter he

joined the study program of Technical Medicine at the University of Twente, lecturing in the fields of surgical skills and medical ultrasound. Parallel to this Erik started to work on his PhD project, also in collaboration with the department of surgery of the Rijnstate hospital.

After obtaining his PhD degree Erik will continue to work on blood flow quantification in relation with stent patency and patient outcome at the University of Twente and the Rijnstate hospital.

DANKWOORD

Voordat ik begon aan het schrijven van het dankwoord, voelde ik een lichte aarzeling. Dat kan komen door het feit dat dit echt het laatste onderdeel van mijn proefschrift is, waarna ik dus een mooie periode definitief afsluit of omdat dit het meest gelezen hoofdstuk van mijn proefschrift zal zijn. Dat is ook niet zonder reden; het laat namelijk zien wie allemaal een bijdrage hebben geleverd. Op de omslag staat alleen mijn naam en ik ben zeker niet de enige die veel energie in dit project heeft gestoken. Alle mensen die hierbij betrokken zijn geweest, wil ik dan ook graag bedanken.

De afgelopen vier jaar heb ik mogen werken in een combinatie tussen onderwijs & onderzoek en daarnaast ook in een combinatie tussen de Universiteit Twente en het Rijnstate ziekenhuis. Op beide plekken heb ik met een team mogen werken wat zich richt op verbetering en vooruitgang van de zorg. Dit was de perfecte voedingsbodem om dit proefschrift te kunnen afronden.

Michel, inmiddels werken we al een hele tijd onafgebroken met elkaar samen. De start was mijn derde M2 stage. Je opmerking 'stage moet vooral leuk zijn' staat in mijn geheugen gegrift. We hebben daarna altijd contact gehouden en zo is onze samenwerking en de omvang van de projecten steeds verder gegroeid. Je niet aflatende enthousiasme en drive tot innovatie zijn een inspiratie voor mij. Toch verlies je nooit de zakelijke kant uit het oog: voor niets komt de zon op! Dank voor je toewijding om dit project te ondersteunen, tot in de kleinste details.

Michel, na een kleine omzwerving op de Universiteit Twente heb ik bij jou de kennis en ondersteuning gevonden die aansloot bij de experimenten en studies die ik uitgevoerd heb. Voorafgaand aan onze afspraken had ik altijd ruim de tijd om mijn resultaten nog even door te nemen op de bank bij je kantoor. Desondanks had je altijd nog een niet aflatende hoeveelheid kritische vragen en nieuwe ideeën, altijd als doel om tot een beter eindresultaat te komen, dank daarvoor! Los van je vakkennis heb je mij veel inzicht gegeven in de 'universiteitspolitiek' en hoe daarmee om te gaan.

Voor de totstandkoming van dit proefschrift heb ik mogen samenwerken met een aantal zeer gewaardeerde collega's.

Suzanne, ons overleg op maandagochtend was altijd een mooi moment voor mij om mijn vragen en resultaten uit de klinische studies met je te delen. Aan het eind van dit overleg had ik altijd weer een lijst van punten om verder uit te pluizen.

Kees, je bent vanaf de start betrokken geweest bij mijn opleiding. Wanneer ik even vast zat of een frisse blik op de zaak wilde kon ik altijd bij jou terecht. Je humor en houding tegenover het leven en de wetenschap hebben voor mij veel zaken gerelativeerd.

Henny, zonder jouw vindingrijkheid en technisch inzicht hadden we alle ideeën nooit in de praktijk kunnen brengen en hadden alle opstellingen met plakband aan elkaar gehangen. Ik ben je enorm veel dank verschuldigd.

Jorrit, Varghese, Simon, Lennart en Guillaume: lab partners in crime! Zonder jullie had ik de resultaten in dit proefschrift nooit zo fraai kunnen presenteren.

Bob, Peter, Jean-Paul, Frederike, Jacques, Jan-Willem, Luuk en Steven. In dit proefschrift is veel tijd besteed aan het uitwerken van modelstudies. Het gevaar is altijd dat de experimenten alle connectie met de realiteit verliezen. Door jullie input hebben we er samen voor gezorgd dat we altijd één been in de kliniek hadden en één been in het lab.

Hans, Nico, Rik, Jason en Frank. Dit proefschrift roept natuurlijk weer meer nieuwe vragen op dan het antwoorden geeft. Ik ben blij dat we met jullie expertise al een start hebben kunnen maken aan het oplossen daarvan.

Collega's en SA's van het ECTM en de opleiding TG: bij jullie voel ik mij thuis. De afgelopen vier jaar was het erg fijn om met jullie samen te werken, zowel voor onderwijs als onderzoek.

Collega-onderzoekers van de chirurgie uit het Rijnstate. Sinds we ons eigen kantoor hebben, zijn er al veel serieuze en minder serieuze momenten geweest. Ik kom elke maandag met veel plezier naar Arnhem toe!

Voor u ligt een prachtig opgemaakt proefschrift. Vanaf het moment dat de vormgeving belangrijk werd, heb ik dat samen kunnen oplossen met Arthur. Het opmaken van tekst en de vormgeving zijn echt jouw terrein, Arthur. Ik heb weer veel van je geleerd en wil je ontzettend bedanken voor alle tijd en moeite die je hebt genomen om elke ondertitel, punt en komma de juiste nuance te geven.

Lieve paranimfen, Anique en Stefan. De afgelopen jaren heb ik met jullie lief en leed gedeeld, bij jullie kon ik altijd even stoom afblazen. Jullie bleven dan kritisch en wezen mij ook op andere invalshoeken om e.e.a. te nuanceren. Daarom ben ik ook heel blij dat jullie mij op 1 december bijstaan in het verdedigen van mijn proefschrift.

Bram, Bram, Mark en Wim. Na een week hard werken kijk ik er altijd naar uit om met jullie gezellig een biertje te drinken in de stad en over zinnige en minder zinnige dingen in het leven te praten.

Pap, mam, bij jullie kan ik altijd terecht voor raad en support. Natuurlijk niet alleen de afgelopen vier jaar, maar al mijn hele leven. Manon, wanneer de werkdag weer voorbij is en ik (al dan niet) voldaan op weg naar huis ga is het zo fijn om bij jou thuis te komen en sinds enkele maanden is daar nog een reden bijgekomen (welkom lieve Jet!). Samen zijn jullie een onmisbaar onderdeel van mijn leven!