

➤ **Original Article** ➤

Catheter-Directed Thrombolysis in the Treatment of Acute Ischemia in Lower Extremities Is Safe and Effective, Especially with Concomitant Endovascular Treatment

Lærke Urbak, MD,¹ Louise de la Motte, MD, PhD,¹ Peter Rørdam, MD,¹
Aamir Siddiqi, MD,² and Henrik Sillesen, MD, DMSc¹

Objective: To evaluate the influence of pre-procedural characteristics on immediate and late results as well as the safety of catheter-directed thrombolysis (CDT) in acute ischemia of the lower extremity.

Materials and Methods: A retrospective study comprising 249 patients treated by CDT from January 2006 to December 2012. Outcomes were primary patency, haemorrhagic complications, amputation and mortality.

Results: Primary patency for CDT alone was 68%, for CDT plus endovascular treatment 87% and for successful CDT with supplementary surgery 62% giving an overall primary patency of 76%. Two (0.8%) patients suffered from cerebral haemorrhage during CDT. We found a significant correlation between 30 day amputation rate and no visual distal run-off at CDT start (OR 2.31; CI95% 1.09–4.91; p-value=0.02) and onset of symptoms to CDT start of 8–14 days (OR 4.09; CI95% 1.42–11.81; p-value=0.01). Lack of visualized distal run-off was also associated with a significant risk of 30 day mortality (OR 5.84; CI95% 1.26–27.00; p-value=0.02).

Conclusion: Our results show that CDT is a feasible and safe treatment option especially when combined with angioplasty +/- stent. However, no distal run-off at primary angiography is associated with higher rates of amputation during follow-up and 30 day mortality.

Keywords: thrombolysis, acute ischemia, lower extremities, CDT, limb ischemia

Introduction

Acute limb ischemia is a severe condition that carries a high risk of limb loss when left untreated. In addition, the systemic impact from local ischemia can lead to high morbidity and mortality.¹⁾

Traditionally, treatment of acute limb ischemia has been open surgical intervention, although associated with relatively high perioperative morbidity and mortality.²⁾ During the past decades catheter-directed thrombolysis (CDT) has proven equally efficient with respect to revascularization rates and the risk of amputation and/or death.³⁾ Therefore CDT has become part of the treatment options for acute limb ischemia in patients where primary open surgical revascularisation alone may give suboptimal results. CDT has its limitations, since the affected limb must tolerate the time needed to dissolve the thrombus. Furthermore, it may result in incomplete revascularization due to chronic atherosclerotic obstruction or because thrombolysis may need to be stopped early due to complications. Finally, CDT has been associated with serious haemorrhagic complications.⁴⁾

We undertook a retrospective analysis of our experience in order to evaluate the influence of pre-procedural characteristics on immediate and late results of CDT in a 7-year period after the procedure had been routine practice at our institution for some time.

Methods

Data collection

Patients treated with CDT for acute limb ischemia of the lower extremities at our institution during the period from January 1st 2006 to December 31st 2012 were identified in the Danish Vascular Registry⁵⁾ using current Nordic Classifications of Surgical Procedures codes (Fig. 1). Follow-up ended by September 1st 2013.

Demographic and peri-procedural data were obtained

¹ Department of Vascular Surgery, Rigshospitalet and University of Copenhagen, Copenhagen, Denmark

² Department of Vascular Interventional Radiology, Rigshospitalet, Copenhagen, Denmark

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Corresponding author: Lærke Urbak, MD. Department of Vascular Surgery, Rigshospitalet and University of Copenhagen, Blegdamsvej 9, 2100 Copenhagen, Denmark
Tel: +45-35-45-24-07, Fax: +45-35-45-23-03
E-mail: laerke.urbak.01@regionh.dk



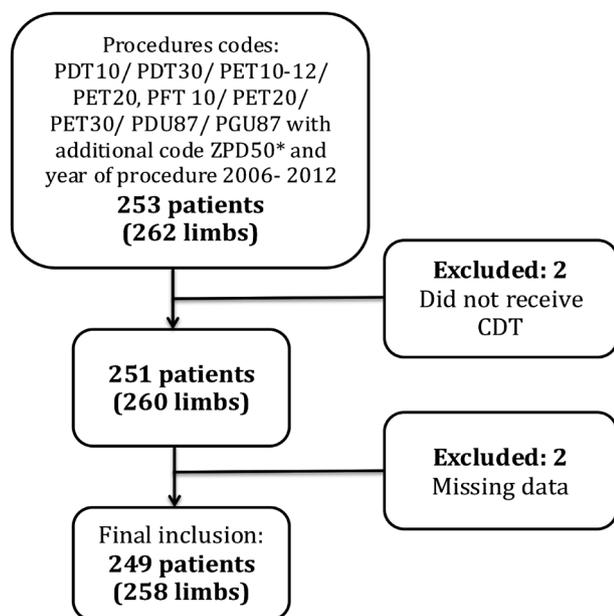


Fig. 1 Patient flowchart. Procedural codes according to the Nordic Classification of Surgical Procedures. PDT10 injection of medication in the aorta, PDT30 injection of medication in an iliac artery, PET10 injection of medication in the femoral artery, PET11 injection of medication in the profunda femoral artery, PET12 injection of medication in the superficial femoral artery, PET20 injection of medication in a femoral-popliteal bypass, PFT10 injection of medication in the popliteal artery, PFT20 injection of medication in a bypass from the femoral or popliteal artery, PFT30 injection of medication in the lower leg, PDU87 injection of medication in an aortic or iliac bypass, PGU87 injection of medication in an extra-anatomical bypass. ZPD50 thrombolytic agent. In 9 patients both limbs were treated with thrombolysis during the relevant period. And in 4 cases both limbs were treated at the same time.

retrospectively through review of patient records. Severity of ischemic symptoms at admission was classified according to the Rutherford classification.¹⁾

An experienced interventional radiologist evaluated angiograms and endovascular procedures retrospectively.

Data on mortality and amputation were obtained from patient records and the Danish National Patient Registry,⁶⁾ in which all patients in contact with the Danish healthcare system are registered according to their social security number. Approval of data collection was obtained from the Danish Data Protection Agency (no. 02861).

Patients

In the Danish Vascular Registry⁵⁾ we identified 253 patients (262 limbs) with acute lower limb ischemia treated by CDT at our institution from January 1st 2006 until December 31st 2012. Only patients who received CDT as primary treatment were included. Four patients were

excluded as 2 did not receive CDT and 2 patient records could not be obtained (Fig. 1). For six of the patients all demographic data were not registered in the medical file, but since the remaining data were present these patients were not excluded. During the study period, 9 patients had both limbs treated with CDT. Of these, 4 patients had both limbs treated at the same time and 5 had the two limbs treated at different times.

For patients with both limbs treated during the study period the limb with poorest distal run-off before CDT and/or the worse outcome was chosen for statistical analyses.

According to our local protocol, CDT is indicated in cases with relatively recent (<4 weeks) arterial thrombosis, if the thrombolysis catheter can be placed near or in the thrombosis, if the patient is inoperable (no visible run-off vessels) or if CDT may optimize the distal run-off. Patients were screened for the presence of any absolute or relative contraindications to CDT. The contraindications being: surgical procedure or greater trauma within the past 10 days, critical acute ischemia with signs of potential irreversible alterations, haemorrhagic diathesis, potential haemorrhagic focus such as duodenal ulcer or previous cerebral haemorrhage, stroke within the past 6 months, lack of treatment compliance, intractable hypertension (systolic blood pressure >160 mmHg) or pregnancy.

Definitions

Acute limb ischemia was defined as relatively recent (<4 weeks) onset or worsening of ischemic manifestations of the lower extremities due to arterial thrombosis or embolism.

Cerebrovascular disease was defined as a history of stroke or transient ischemic attack. Cardiac disease was defined as a history of previous myocardial infarction, angina pectoris, cardiac arrhythmia, percutaneous coronary intervention or coronary artery bypass grafting. Hypertension, chronic obstructive pulmonary disease (COPD) and diabetes mellitus were registered according to patient files. Renal disease was defined as known decreased renal function or a creatinine >120 $\mu\text{mol/L}$. Smoking was defined as ever smoked, and alcohol as an intake of ≥ 36 gram alcohol/day. Previous vascular intervention was defined as previous endovascular procedures (including previous CDT) or open surgery (e.g., thrombectomy, embolectomy, bypass, thromboendarterectomy) of the lower extremities. Bypass included both autologous graft and prosthetic bypass.

Patients were divided into 4 groups according to duration of symptoms: ≤ 24 h, 2–7 days, 8–14 days and >14 days.

Complications to CDT included minor bleeding, defined as mucosal bleeding, hematoma and bleeding from the

access site. Major bleeding was defined as bleeding where surgical intervention were needed, gastrointestinal bleeding with symptoms of hematemesis, melena or haematochezia and cerebral haemorrhage verified by a Computed Tomography scan.

Amputation included any amputation above the ankle joint. Outcomes were registered as occurring ≤ 30 days and/or during follow-up.

Primary patency was defined as resolution of the thrombosis by CDT treatment (including angioplasty during CDT and supplemental surgery to successful CDT) without re-thrombosis, amputation or mortality within 30 days.

CDT treatment

An interventional radiologist performed all procedures. Patients were heparinized with 3-10.000IE Heparin (LEO Pharma Nordic, Malmö, Sweden) intravenously. Preferably contralateral vessel access was obtained and prior to catheter placement a diagnostic arteriogram demonstrating the level of thrombosis was performed. CDT was performed using alteplase (Actilyse, Boehringer Ingerheim, Copenhagen, Denmark)⁷ which was infused continuously (80 mg/h) and was supplemented with a daily injection of 3500 IE Tinzaparin (Innohep, LEO Pharma Nordic, Malmö, Sweden) subcutaneously. When symptoms of improvement or deterioration were observed, angiographic control was performed in order to adjust catheter placement. Percutaneous transluminal angioplasty (PTA) (+/-stent) was performed before catheter withdrawal when a significant stenosis treatable by endovascular technique was observed following thrombolysis. Duration of CDT was defined as the total number of days a patient underwent thrombolysis.

Statistics

Data were analysed with IBM[®] SPSS Statistic, version 22. Univariate analyses of binary nominal and ordinal variables were conducted using cross-tabulations. Variables with a p-value ≤ 0.1 were used for comparative analyses and entered into a binary analysis for 30 days follow-up and cox-regression analysis for overall follow-up. The level of significance was set at $p < 0.05$. Significant associations were expressed in terms of odds ratio (OR) or hazard ratio (HR) according to statistical analysis, 95% confidence intervals (CI95%) and p-value. Continuous variables were registered as median and range.

Results

The analysis included 258 limbs in 249 patients (Fig. 1) with a median follow-up of 40 months (range 0–90 months). One hundred and sixty (65%) patients

Table 1 Demographics and comorbidity prior to CDT

	Total (n=249)
Male gender	151 (61%)
Age (years)	65 (21–94)
Smoking ^o	194 (84%)
Alcohol ⁺	49 (20%)
Hypertension [*]	87 (36%)
Diabetes [*]	42 (17%)
Cardiac disease [*]	76 (31%)
COPD [*]	18 (7%)
Cerebrovascular disease [*]	33 (14%)
Previous amputation [*]	7 (3%)
Previous clinical symptoms of PAD [*]	160 (65%)
≥ 1 previous vascular intervention [*]	105 (42%)

^{*}Nine patients had missing alcohol data. The percentage was calculated using 240 patients. Likewise, ^o17 patients have missing data resulting in a total of 232 patients, ^{*}6 patients have missing data resulting in 243 patients and ^{*}1 patient have missing data which resulted in a total of giving 248 patients. The total number of patients for each category was used to calculate the percentage. Data are given in number (percentage) and median (range).

Table 2 Pre-procedural status

	Total (n=249)
Duration of symptoms [*]	
<24 h	78 (32%)
2–7 days	106 (43%)
8–14 days	29 (12%)
> 14 days	30 (12%)
Status before CDT [*]	
Rutherford 0	0 (0%)
Rutherford I	85 (35%)
Rutherford II	138 (56%)
Rutherford III	14 (6%)
Location of occlusion [*]	
Aorto-iliac	39 (16%)
Femoro-popliteal	91 (37%)
Crural	26 (10%)
Graft	58 (23%)
Multilevel	28 (11%)
Distal run-off before CDT [*]	
0 distal run-off vessels	49 (20%)
1 distal run-off vessel	83 (33%)
2 distal run-off vessels	63 (25%)
3 distal run-off vessels	42 (17%)

^{*}6 patients have missing data for duration of symptoms, 12 have unknown Rutherford classifications and 7 for the location of the occlusion because of no or unclear notation in patient file. Distal run-off could not be retrospectively evaluated in 12 cases due to missing angiogram or pure quality. For the 9 patients with both lower limbs treated during the study period the limb with less visualized distal run-off and the worse outcome was chosen.

were known with peripheral artery disease (PAD), and of these 105 (42%) had vascular intervention performed previously (Table 1). On admission, 78 (32%) of the patients had shown symptoms of acute ischemia for less than 24h, 106 (43%) patients had symptoms for 2–7 days, 29 (12%) for 8–14 days and 30 (12%) patients for >14 days. For 6 patients the duration of symptoms was unknown (Table 2).

CDT procedure

The duration of CDT varied from 0–4 days with a median of 2 days. Due to minor bleeding complications 26 (10%) patients received a decreased dose of alteplase and 19 (7%) received a bolus because of increased pain or clinical deterioration.

Of the 249 patients treated with CDT 138 (55%) were initially treated with CDT alone, 97 (39%) with CDT and an endovascular procedure and 14 (6%) had a surgical intervention as supplement to successful CDT. These supplementary operations were five peripheral bypasses (three due to popliteal aneurysms), two thrombectomies, five revisions of existing bypasses, one thromboendarterectomy and one operation for pseudoaneurysm.

At 30 days, 95 (68%) of those treated with CDT alone remained patent as did 85 (87%) of those treated with CDT plus an endovascular procedure and 8 (62%) of those treated with CDT and adjunct surgery. This resulted in an overall 30 day primary patency of 76% (188 patients). We found a significant difference in one month patency between patients treated with CDT alone and patients treated with CDT plus an endovascular procedure (OR 3.66 CI95% 1.78–7.53; p-value <0.01).

Fifteen (6%) patients had a thrombectomy due to incomplete CDT. Of these 2 improved with CDT treatment but had persisting thrombosis after 3 days of thrombolysis, 4 had a thrombectomy due to aggravation in symptoms during CDT, 7 had a thrombectomy due to complications (1 had a thrombosis of the other limb, 4 developed compartment syndrome, 1 malignant hypertension and 1 patient suffered from gastrointestinal bleeding) and 2 were unknown. Four of the thrombectomies had no distal run-off prior to CDT (1 improved with CDT, 1 did not improve and 2 had complications to CDT treatment). Except for 2 of the 15 patients who received thrombectomy, all of the above including the ones with no distal run-off prior to CDT were known with prior PAD. One of the patients with aggravated symptoms, 2 of those with complications and 1 patient with unknown reason for thrombectomy were amputated within 1 month. The remaining 11 thrombectomies were successful.

Thirteen patients (5%) were operated due to lack of improvement from CDT. Of these 4 patients had a thrombectomy and are mentioned in the section above. One of these

patients had no distal run-off prior to CDT treatment. We found no significant correlation between pre-procedural characteristics and outcome for these patients. However, we did find an increased risk of operation within 30 days in patients known with cardiac disease (OR 0.38 CI95% 0.15–0.96; p-value=0.04) or symptom duration of 2–7 days (OR 2.20 CI95% 1.13–4.28; p-value=0.02).

Of the patients with no distal run-off prior to CDT 34 (69%) were treated with CDT alone, 13 (27%) with CDT and endovascular procedure and 2 (4%) with successful CDT and operation (1 thrombectomy and 1 peripheral bypass). During 30 day follow-up 4 more patients had a thrombectomy, 2 patients had a peripheral bypass, 2 patients a revision of existing bypass and 1 patient was operated for pseudoaneurysm. During the entire follow-up period, three more patients underwent operation.

Haemorrhagic complications

Forty-eight (19%) patients had haemorrhagic complications (Table 3), 19 (8%) of which required discontinuation of CDT including 2 (0.8%) with non-fatal cerebral haemorrhage. We found no risk factors for cerebral haemorrhage or major haemorrhagic complications. Patients receiving 3 days of CDT had a significantly higher risk of minor bleeding (OR 2.82 CI95% 1.05–7.54; p-value=0.04) as compared to patients receiving less or more than 3 days of CDT. In no cases did bleeding complications result directly in surgical intervention.

Amputation

30 day amputation rate was 8% (20 patients) and 16% (41 patients) during follow-up. We found a correlation

Table 3 CDT outcome

	Total (n=249)
Overall 30 days primary patency	188 (76%)
Surgery within 30 days	39 (16%)
Complications	
Cerebral haemorrhage	2 (0.8%)
Gastrointestinal bleeding	6 (2%)
Minor bleeding	40 (16%)
Surgery due to re-thrombosis within 30 days ^o	7 (3%)
Re-thrombolysis within 30 days	9 (4%)
Re-thrombolysis during follow-up	41 (17%)
Amputation within 30 days	20 (8%)
Amputation during follow-up	41 (16%)
Mortality within 30 days	7 (3%)
Mortality during follow-up	54 (22%)

No missing data. ^oOf the patients that primarily benefitted from CDT, 7 had re-thrombosis within the first month after CDT and were operated. Of these, 4 underwent thrombectomy, 2 bypass surgery and 1 was operated for a popliteal aneurysm.

Table 4 Analysis of pre-procedural characteristics, amputation and mortality within 1 month

	Amputation within 1 month	Mortality within 1 month
Smoking	14 (77.8%) p: 0.51	4 (80%) p: 1.00
Alcohol	3 (16.7%) p: 0.77	1 (14.3%) p: 1.00
Hypertension	5 (27.8%) p: 0.61	5 (71.4%) p: 0.10
Diabetes	4 (22.2%) p: 0.53	1 (14.3%) p: 1.00
Cardiac disease	6 (33.3%) p: 0.58	3 (42.9%) p: 0.39
COPD	2 (11.1%) p: 0.63	1 (14.3%) p: 0.42
Previous amputation	2 (11.1%) *p: 0.05 OR: 5.63	1 (14.3%) p: 0.18
Previous clinical symptoms of PAD	13 (72.2%) p: 0.62	4 (57.1%) p: 0.69
Previous vascular interventions	6 (33.3%) p: 0.47	2 (28.6%) p: 0.70
Duration of symptoms		
<24 h	5 (26.3%) p: 0.79	2 (28.6%) p: 1.00
2–7 days	7 (36.8%) p: 0.64	4 (57.1%) p: 0.47
8–14 days	6 (31.6%) *p: 0.01 OR: 4.09	1 (14.3%) p: 0.59
>14 days	1 (5.3%) p: 0.48	0 (0%)
Rutherford 0	0 (0%)	0 (0%)
Rutherford I	4 (21.1%) p: 0.32	2 (28.6%) p: 1.00
Rutherford II	13 (68.4%) p: 0.34	4 (57.1%) p: 1.00
Rutherford III	2 (10%) p: 0.29	1 (14.3%) p: 0.34
0 distal run-off vessels	8 (42.1%) *p: 0.02 OR: 2.31	4 (57.1%) *p: 0.02 OR: 5.84
1 distal run-off vessels	7 (36.8%) p: 0.80	1 (14.3%) p: 0.43
2 distal run-off vessels	1 (5.3%) *p: 0.07 OR: 0.15	2 (28.6%) p: 1.00
3 distal run-off vessels	1 (5.3%) p: 0.21	0 (0%)
Total	20 (8%)	7 (3%)

All calculations were done with cross-tabulations in SPSS. The number, percentage and p-values are noted in the table. Variables marked with * had a p-value <0.1 with cross-tabulation and were therefore entered into a binary analysis. It is the p-value and odds ratio (OR) from the last analysis that is shown here.

between duration of symptoms of 8–14 days and both 30 day amputation rate (OR 4.09; CI95% 1.42–11.81; p-value=0.01) and amputation rate during follow-up (HR 2.44; CI95% 1.12–5.33; p-value=0.03) (Table 4). We did not find any correlation between duration of symptoms <8 days or >14 days and amputation rate, respectively OR 1.28; CI95% 0.47–3.48; p-value=0.58 and OR 1.7; CI95% 0.53–5.47; p-value=0.37. No visualized distal run-off prior to CDT showed an increased risk of 30 day amputation (OR 2.31; CI95% 1.09–4.91; p-value=0.02) and amputation during follow-up (HR 2.72; CI95% 1.38–5.34; p-value=0.04). However, 67% improved the distal run-off to 1 vessel or more with CDT treatment. Resulting in an insignificant decreased risk in 30 days amputation and mortality compared to the group with no improvement in run-off (Table 5). We did not find any statistically significant correlations between any of the other pre-procedural characteristics and amputation.

Mortality

The mortality rate was 3% (7 patients) within the first 30 days and 22% (54 patients) during follow-up. The only pre-procedural characteristic that was statistically significantly correlated to 30 day mortality was no vi-

Table 5 Outcome for limbs with no visual distal run-off at CDT start

	No improvement (n=16)	Improved (n=33)	p-value
Surgery within 30 days	0	9 (27%)	0.08
Surgery during follow-up	0	13 (39%)	*1.00
Amputation within 30 days	4 (25%)	4 (12%)	0.68
Amputation during follow-up	8 (50%)	5 (15%)	0.16
Mortality within 30 days	2 (13%)	2 (6%)	1.00
Mortality during follow-up	5 (31%)	10 (30%)	0.50

No missing data. Numbers and percentage for each outcome are noted according to no improvement or improvement of the distal run-off with CDT treatment. P-values were calculated from cross-tabulation and binary regression if the p-value in cross-tabulation was ≤ 0.1 .*

visualized distal run-off (OR 5.84; CI95% 1.26–27.0; *p*-value = 0.02) (Table 4).

Discussion

Our results and patient material were comparable to those of other studies although the demographic data did not seem to affect outcome.^{3,8–11} In our population 65% of patients were known with PAD prior to hospitalization. This may explain the percentage of patients having endovascular (39%) and open vascular procedures performed (6%) adjunct to CDT. Overall primary patency with and without these adjunct procedures was 76% (we included adjunct procedures in primary patency as it was part of the primary treatment). We did not find that the need for adjunct endovascular procedures or surgery correlated with any pre-procedural characteristics including PAD. However, we did find a significantly better patency in patients treated with CDT and angioplasty +/- stent than in those treated with CDT alone. This suggests that supplementary angioplasty is indicated in a larger number of patients. The need for supplementary angioplasty was evaluated by the interventionist based on the angiogram, which suggests this visualization alone may be insufficient to determine whether a lesion needs supplementary treatment. Hence, this part of the treatment might benefit from a more active approach. For instance, a vulnerable, thrombogenic lesion does not necessarily need to be stenotic (>50% stenosis) and therefore may not be considered important to treat when judging the angiogram. However, covering such a lesion by a stent may prevent re-thrombosis. Supplementary techniques such as intravascular ultrasound to identify a potentially unstable lesion could also be considered. Also, treatment with double antiplatelet therapy for a period (e.g., 3–6 months) could most likely have improved our results, as this was not standard during the study period.

One of the known disadvantages of thrombolysis is the increased risk of haemorrhagic complications.^{3,10} The number of haemorrhagic complications in our study is similar to findings in previous reports ranging from 0.78% for cerebral haemorrhage to 13% for major bleeding.^{3,9,12–14} However, in our study we only observed 3% with major bleeding. Our low rate of major bleeding complications might be explained by a more restrictive inclusion to the treatment and a quick termination of CDT when bleeding was observed. Sixteen percent experienced minor bleeding and overall CDT seemed a safe treatment option in our institution. We found that minor bleeding correlated with 3 days of CDT treatment but did not find the same correlation with 4 days of CDT treatment probably due to the small numbers (10 patients (4%)).

Contrary to The Stile Trial¹⁰ we found that duration of

symptoms of 8–14 days increased the risk of amputation. This was not the case for patients with symptoms of > 14 days. It is possible that these patients had a well-developed collateral circulation permitting them to tolerate the occlusion better.

Our rates of amputation and mortality are similar to those found in previous studies.^{3,10,13} In our study lack of visualized distal run-off prior to CDT was the only pre-procedural characteristic that correlated with increased rates of amputation and mortality. This is in accordance with the findings of Løkse et al.¹² However, we found that 67% of the patients, with no visualized distal run-off improved their distal run-off during treatment and these patients had a 50% reduction in amputation rate and mortality compared to the patients with no improvement of distal run-off. This was not statistically significant probably due to the small numbers. These observations and the fact that there is no surgical solution for these patients, indicate that CDT does have a place in treating even those with the highest morbidity rate.

A weakness of this study is that it is retrospective with missing data that cannot be obtained. However, our study is one of the largest studies in the last 10 years and due to the Danish National Patient Register our follow-up is nearly 100% for amputation and mortality, thus improving its strength regarding these hard endpoints.

Conclusion

Our data confirms that CDT especially with supplementary angioplasty +/- stent is a relatively safe and efficient procedure for acute lower limb ischemia when no irreversible ischemic damage is present at CDT start. Furthermore our study indicates that CDT is a reasonable treatment option even in patients without distal run-off at the primary angiogram and even though no run-off predicts increased rates of amputation and mortality.

Disclosure Statement

The authors have no relevant conflicts of interest to declare.

Author Contributions

Study conception: LU, LM, PR, HS

Data collection: LU, AS

Analysis: LU

Investigation: LU, LM

Critical review and revision: all authors

Final approval of the article: all authors

Accountability for all aspects of the work: all authors

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