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The role of directional atherectomy in critical-limb ischemia

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Abstract

Background: Our aim was to review the current literature of the use of directional atherectomy (DA) in the treatment of lower extremity critical-limb ischemia.

Methods: A search for relevant literature was performed in PubMed and PubMed Central on 16 April 2020, sorted by best match. Three searches across two databases were performed. Articles were included that contained clinical and procedural data of DA interventions in lower extremity critical-limb ischemia patients. All studies that were systematic reviews were excluded.

Results: Eleven papers were included in this review. Papers were examined under several parameters: primary patency and secondary patency, limb salvage/amputation, technical/procedural success, complications/periprocedural events, and mean lesion length. Primary and secondary patency rates ranged from 56.3% to 95.0% and 76.4% to 100%, respectively. Limb salvage rates ranged from 69% to 100%. Lesion lengths were highly varied, representing a broad population, ranging from 30 ± 33 mm to 142.4 ± 107.9 mm.

Conclusions: DA may be a useful tool in the treatment of lower extremity critical-limb ischemia.

Keywords: Directional Atherectomy, Critical Limb Ischemia, Peripheral Artery Disease

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Introduction

Peripheral artery disease (PAD) is an atherosclerotic disease of the lower limbs that affects over 200 million people worldwide.[1–4] PAD is uncommon in younger populations but its prevalence rises sharply with increasing age to approximately 30% of men and 40% of women above the age of 80.[4] PAD has placed a considerable burden on the American healthcare system, which will only increase due to the rising proportion of the American population developing key risk factors for PAD such as diabetes mellitus, hypertension, dyslipidemia, and obesity.[1,3] The American healthcare system spent $4.37 billion on PAD-related treatment in 2001.[5] Many PAD patients are asymptomatic but symptomatic patients present with symptoms ranging from lifestyle-limiting claudication to critical-limb ischemia (CLI).[2,6,7]

CLI, defined clinically as ischemic rest pain, tissue loss, or gangrene in the presence of PAD and hypoperfusion of the lower extremity, is associated with significant mortality, morbidity, and increased use of healthcare resources.[8,9] CLI represents the most advanced form of PAD and currently encapsulates 1–3% of all PAD patients.[10] Left untreated, CLI patients can lose their limbs or suffer from complications such as gangrene and sepsis.[11] Across all patients with PAD, there is a 30–50% occurrence of cardiovascular events including myocardial infarction and stroke over a 5-year period.[12] Patients with CLI however, face the same risk over a 1-year period.[12] Additionally, the risk of major amputation at or above the ankle is less than 5% in claudicant patients over 5–10 years; it is 30–50% in the first year for CLI patients who are not revascularized.[12] The rate of primary amputation in CLI patients is 25%, increasing to 30% at 1 year.[13] Therefore, this subgroup of the PAD patient population will become increasingly relevant in the treatment and management of PAD.

Directional atherectomy (DA) has become a popular endovascular technique that is safe and effective in treating patient populations including both claudicants and CLI.[14] DA mechanically removes plaque and debulks vessels without leaving a stent within.[14] The advent of drug-coated balloons (DCBs) have propelled forward the 'leaving nothing behind' approach of treatment.[6] Additionally, DCBs have shown superior results compared with plain old balloon angioplasty (POBA) as demonstrated by various clinical trials such as the LEVANT I and II, IN.PACT SFA, and ILLUMENATE treating short- to intermediate-length lesions.[15–18]

In this systematic review, we aimed to evaluate the body of literature on the clinical outcomes of endovascular interventions utilizing DA in the CLI cohort of PAD patients.

Methods

By using the participant, interventions, comparisons, outcomes, and study design search strategy, an examination of relevant literature was performed in PubMed and PubMed Central (PMC) on 16 April 2020 sorted by best match. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist was followed to conduct a study-level systematic review; however, a review protocol did not exist for this specific topic. Detailed here are the specific keyword searches and criteria used to filter search results thereafter. The search terms are in square brackets with the Boolean relationship 'AND' or 'OR'. All searches excluded publications before the year 2000 and used filters for 'English,' 'Humans,' and 'Full Text' in PubMed. No specific filters were utilized for the type of publication such as 'Clinical Study' or 'Systematic Review' in an effort to include any relevant literature and additional references found therein.

Articles were included that contained clinical and procedural data of DA interventions in CLI patients in the lower extremities or DA used in a combination therapy in CLI patients in the lower extremities. There was no additional contact to authors for acquiring further information. All studies that were systematic reviews were excluded.

(1) **PubMed-Include:** [Directional Atherectomy AND Critical Limb Ischemia]; Directional Atherectomy; Critical Limb Ischemia
21 results

The purpose of this search before manual evaluation of article content was to perform a broad search on the current literature of DA in relation to CLI. Upon applying a set of filters ('English,' Humans,' 'Full Text,' and a time range of '01/01/2000–12/31/2020') 13 results remained to be independently evaluated. Articles were included if data of CLI patients being treated with DA were presented. This generated four references used in this literature review (Figure 1).

(2) **PubMed-Include:** [Directional Atherectomy AND Critical Limb Ischemia OR Critical Limb Threatening Ischemia]; Directional Atherectomy; Critical Limb Ischemia; Critical Limb Threatening Ischemia
323 results

The purpose of this search before manual evaluation of article content was to encapsulate articles that utilize the term 'critical-limb-threatening ischemia' (CLTI), another commonly used term in describing PAD patients with ischemic rest pain or tissue loss. Upon applying a set of filters ('English,' 'Humans,' 'Full Text,' and a time range of '01/01/2000–12/31/2020') 175 results remained to be independently evaluated. Articles were included if data of CLI or CLTI patients being treated with DA was presented. This generated one additional reference used in this literature review (Figure 1).

(3) **PMC-Include:** [Directional Atherectomy AND Critical Limb Ischemia]; Directional Atherectomy; Critical Limb Ischemia
111 results

The purpose of this search before manual evaluation of article content was to utilize an extension to the PubMed database to capture any references not found in the first search. Upon applying a time range of '01/01/2000–12/31/2020,' 109 results remained to be independently evaluated. Articles were included if data of CLI patients being treated with DA was presented. This

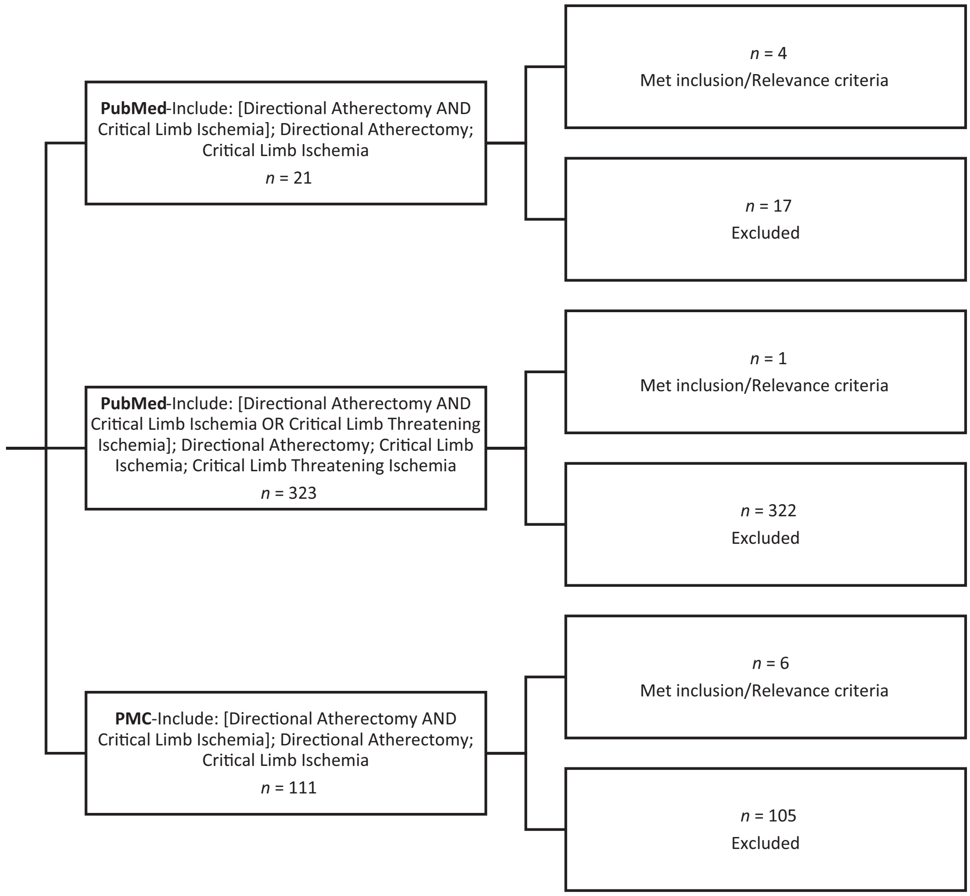

Figure 1. Flowchart of reference selection.

generated an additional six references used in this literature review (Figure 1) bringing the total number of references in this review to 11.

Once individual evaluation was complete, we separated each article's results according to the outcomes and follow-up period. The categories were as follows: primary and secondary patency, limb salvage/amputation, technical/procedural success, complication/periprocedural events, and mean lesion lengths. We compared each of these study outcomes at equivalent follow-up periods.

An analysis using the Cochrane ROBINS-I assessment tool[19] was also utilized to determine overall risk of bias for each article in this study (Table 1).

Results

Eleven references were selected for review and discussion from the search detailed in the methods section above. Three searches were performed for this literature review and findings from the references will be presented under the following headings in the results section: primary patency and secondary patency, limb salvage/amputation, technical/procedural success, complications/periprocedural events, and mean lesion length. Table 2 presents the study characteristics extracted from each article, as well as additional information that is relevant to this review.

Primary patency and secondary patency

One of the most critical parameters when evaluating the efficacy of endovascular intervention devices are the primary and secondary patency rates. Of the 11 papers reviewed, 10 discussed primary patency rates at 12 months. Two single-center, single-arm, prospective, non-randomized studies by Stavroulakis *et al.*[16] and Cioppa *et al.*[17] examined a combination therapy of DA with DCB in a cohort where patients presented with

Table 1. Risk bias analysis of articles.

Study	Pre-intervention			At intervention	Post-intervention			Overall risk of bias
First author	**Bias due to confounding**	**Bias in selection of participants into the study**	**Bias in classification of interventions**	**Bias due to deviations from intended interventions**	**Bias due to missing data**	**Bias in measurement of outcomes**	**Bias in selection of reported results**	**Low/moderate/ serious/critical**
Stavroulakis *et al.*[16]	Low	Moderate	N/A	Low	Low	Moderate	Low	Low
Cioppa *et al.*[17]	Low	Moderate	N/A	Low	Low	Low	Low	Low
Gallagher *et al.*[18]	Moderate	Moderate	N/A	Low	Moderate	Moderate	Low	Moderate
Mckinsey *et al.*[14]	Moderate	Low	N/A	Low	Low	Low	Low	Low
Zeller *et al.*[19]	Moderate	Moderate	N/A	Low	Low	Moderate	Low	Low/moderate
Semaan *et al.*[20]	Moderate	Moderate	N/A	Low	Low	Moderate	Moderate	Moderate
Bracale *et al.*[21]	Moderate	Moderate	N/A	Low	Low	Low	Low	Low
Loor *et al.*[22]	Moderate	Moderate	N/A	Low	Low	Low	Low	Low
Keeling *et al.*[23]	Moderate	Moderate	N/A	Low	Low	Low	Low	Low
Todd *et al.*[24]	Moderate	Moderate	N/A	Low	Low	Low	Moderate	Low/moderate
Tan *et al.*[25]	Moderate	Moderate	N/A	Low	Low	Moderate	Low	Low/moderate

N/A, not applicable.

either lifestyle-limiting claudication or CLI (18 lifestyle-limiting claudication + 3 CLI and 18 lifestyle-limiting claudication + 12 CLI, respectively).[20,21] The cohorts in both of these papers were very small, limiting any generalizability of their findings. In addition, only a small proportion of these already limited cohorts were CLI patients. Stavroulakis *et al.*[16] showed primary patency at 12 months in 19 out of 20 patients (1 patient died in follow up) and showed secondary patency in all patients throughout the study.[20] Cioppa *et al.*[17] showed primary patency in 27 of the 30 patients and secondary patency in all 30 at 12 months.[21] Unfortunately, only the overall primary patency rate was presented for the entire cohort. There was no distinction made between claudication and CLI patients. A largescale retrospective review of a prospectively maintained database by Gallagher *et al.*[18] examined 304 CLI patients who presented with superficial femoral artery (SFA) lesions.[22] Depending on the location of the lesion, primary patency rates at 12 months and 24 months for CLI patients ranged from 37.8% ± 7.1% to 56.3% ± 5.3% and 21.6% ± 6.5% to 49.3% ± 6.0%.[22] Secondary patency at 12 months and 24 months ranged from 70.2% ± 4.9% to 83.1% ± 6.9%, and 61.8% ± 7.5% to 73.9% ± 8.7%, respectively.[22] Out of the 799 included subjects in the DEFINITIVE LE trial by McKinsey *et al.*,[14] 201 were CLI patients. Depending on the lesion location, primary patency at 12 months ranged from 67% to 78%, and secondary patency at 12 months was 88%.[14] In a study by Zeller *et al.*,[20] 19 of the 36 subjects treated with DA had CLI and reported 12- and 24-month primary and secondary patency rates (67% and 91%; 60% and 80%, respectively).[23] Semaan *et al.*[21] conducted a retrospective review

Table 2. Characteristics of each study used in this review.

	Study population	Subjects with CLI (atherectomy)	Intervention	Outcomes	Study design	Follow up
Stavroulakis *et al.*[16]	21	3 (21)	DA + DCB	Primary patency, secondary patency	Single armed, single centered, prospective	6 and 12 months
Cioppa *et al.*[17]	30	12 (30)	DA + DCB	Primary patency, secondary patency, 12-month salvage rates	Single armed, single centered, prospective	12 months
Gallagher *et al.*[18]	1233	304 (194)	PTA, PTA + stent, or DA	Primary patency, secondary patency, 12-month salvage rates, reinterventions	Retrospective analysis	6, 12, 18, and 24 months
Mckinsey *et al.*[14]	799	279 (799)	DA	Primary patency, secondary patency, 12-month salvage rates	Single armed, single centered, prospective	30 days, 6, and 12 months
Zeller *et al.*[19]	36	19 (36)	DA	Primary patency, secondary patency, ABI	Single armed, single centered, prospective	12 and 24 months
Semaan *et al.*[20]	56	43 (18)	Angioplasty *versus* DA	Primary patency, secondary patency, 12 month salvage rates	Retrospective analysis	3, 6, and 12 months
Bracale *et al.*[21]	18	18 (18)	DA	Primary patency, secondary patency, ABI and Rutherford improvement	Single armed, single centered, prospective	12 and 24 months
Loor *et al.*[22]	99	(33)	DA *versus* Open bypass	Primary patency, secondary patency, 12-month salvage rates	Retrospective analysis	12 months
Keeling *et al.*[23]	60	12 (6)	DA	Primary patency, secondary patency	Single armed, single centered, prospective	1, 3, and 6 months, followed by yearly check ups
Todd *et al.*[24]	421	418 (79)	PTA or DA	Primary patency, secondary patency, 12-month salvage rates, reintervention date, survival	Retrospective analysis	1, 3, 6, and 12 months
Tan *et al.*[25]	35	17 (20)	Angioplasty or DA	6-month salvage rates	Retrospective analysis	6 months

ABI, Ankle Brachial Index; CLI, critical-limb ischemia; DA, directional atherectomy; DCB, drug-coated balloon; PTA, percutaneous transluminal angioplasty.

of 56 patients who received endovascular revascularization.[24] Of the 56, 18 received DA with 12 of those treated with DA presenting with CLI.[24] Among patients who were treated with DA there was a 75% 12-month primary patency rate.[24] A prospective study of 18 consecutive CLI patients from March 2012 to March 2013 by Bracale *et al.*[22] reported a 12-month primary and secondary patency rate of 83.3% and 94.4%, respectively.[25] Within a CLI subject cohort of 99

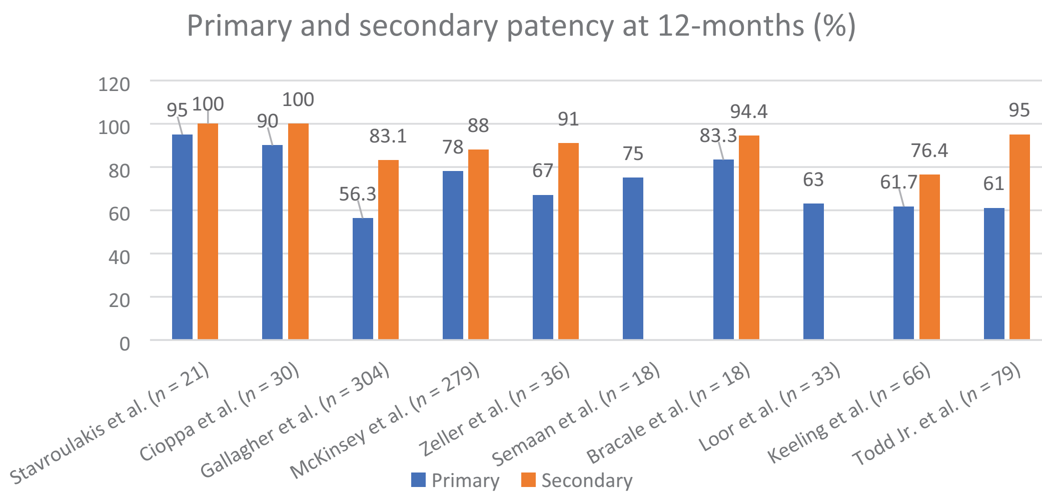

Figure 2. Comparison of primary and secondary patency rates at 12 months (%).

patients, Loor *et al.*[23] reported a 12-month primary patency rate of 63% in 33 subjects treated with DA.[26] Patients treated with DA from August 2004 to January 2006 were enrolled into a prospective database by Keeling *et al.*[24] that included 70 plaque excisions across 66 patients.[27] Twenty-five excisions occurred within a limb considered to be critically ischemic.[27] Across the entire cohort, 12-month primary and secondary patency rate was 61.7% and 76.4%, respectively.[27] Upon conducting a retrospective review of 480 tibial interventions across 421 patients, Todd *et al.*[25] examined 418 CLI interventions, of which 79 were treated with atherectomy, and 13 with DA specifically.[28] Primary and secondary patency rates are reported only for the atherectomy group as a whole (61% and 95%, respectively).[28] The primary and secondary patency rates at 12 months are detailed below in Figure 2.

Limb salvage/amputation

Preserving the integrity of the target limbs and preventing amputation in CLI patients is critical in attempting to treat and manage other systemic morbidities exacerbating their PAD. Stavroulakis *et al.*[16] reported no amputations in their CLI cohort (n=3) and did not report limb salvage rates.[20] Cioppa *et al.*[17] reported 12 month 100% (n=18) limb salvage and 3 minor below-ankle amputations in CLI patients.[21] Gallagher *et al.*[18] reported limb salvage rates at 12 and 24 months for SFA, popliteal, tibial, and multilevel lesions. In the SFA (n=76), 12- and 24-month limb salvage rates were 97.1% and 91.2%, respectively.[22] Popliteal (n=35) limb salvage rates were 87.0% and 78.3% at 12 and 24 months, respectively.[22] The tibial (n=121) 12- and 24-month limb salvage rates were 79.7% and 77.0%, respectively.[22] Although not significant, DA was superior to POBA or POBA and stenting in limb salvage rates.[22] Multilevel lesions (n=71) had limb salvage rates of 81.4% and 76.7% at 12 and 24 months, respectively.[22] McKinsey *et al.*[14] reported a 12-month limb salvage rate of 95% in CLI patients (n=201) and three unplanned amputations in the CLI group. In a comparison of DA (n=18) and angioplasty (n=38), Semaan *et al.*[21] reported no significant differences in limb salvage rates (87% and 97%, respectively).[24] In a similar comparison of DA (n=20) and angioplasty (n=15), Tan *et al.*[26] presented 6-month limb salvage rates of 88% and 78%, respectively.[29] The rates of limb salvage were similar between groups, and no statistical difference was found. Loor *et al.*[23] reported a significantly higher 12-month limb salvage rate in their surgical bypass group of subjects (n=59) compared with the DA group (n=33; 87% *versus* 69%).[26] In the atherectomy group of the CLI cohort (n=79) examined by Todd *et al.*[25] there was a 12-month limb salvage rate of 81%.[28] The available data have been tabulated in Figures 3 and 4.

Technical/procedural success

The technical and procedural success of devices is a key parameter in evaluating their safety. Stavroulakis *et al.*[16] reported a 90% technical success rate, and Cioppa *et al.*[17] reported a 100%

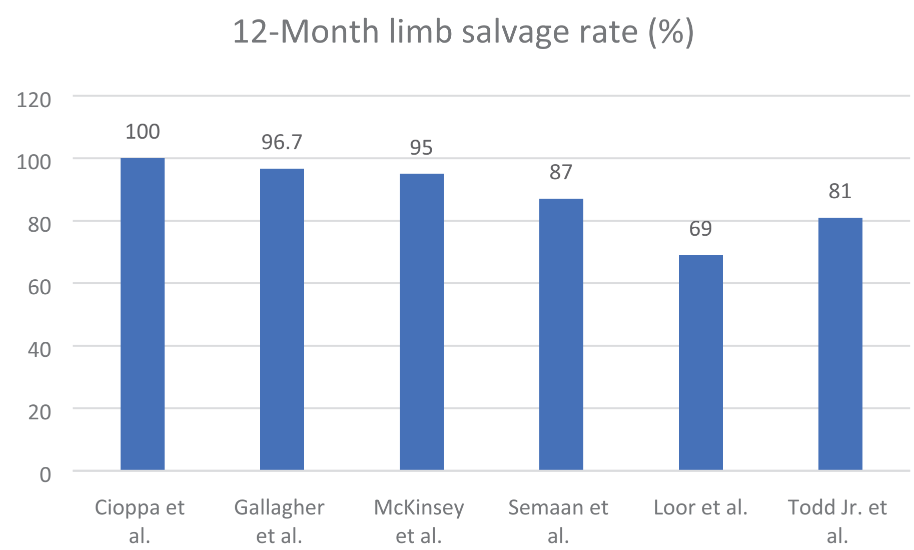

Figure 3. Limb salvage rates at 12 months (%).

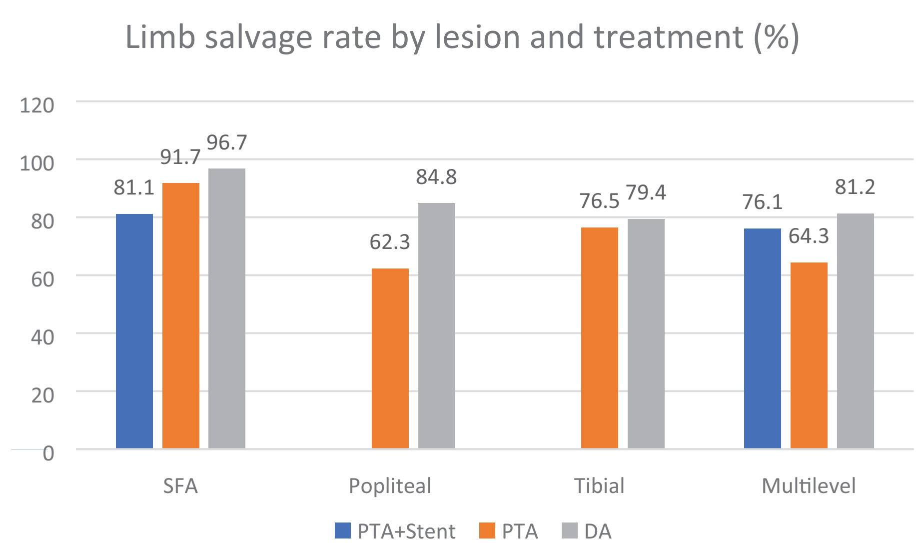

Figure 4. Limb salvage rates by lesion and treatment (Gallagher *et al.*[18])
DA, directional atherectomy; PTA, percutaneous transluminal angioplasty; SFA, superficial femoral artery.

procedural success rate.[20,21] McKinsey *et al.*[14] reported a procedural success rate of 83.0% in CLI patients within the DEFINITIVE LE trial. Semaan *et al.*[21] reported 94% technical success in DA patients.[24] Tan *et al.*[26] reported a collective technical success of 93% across DA and angioplasty patients.[29] Bracale *et al.*[22] reported 100% technical success.[25] Across the 70 plaque excisions presented by Keeling *et al.*[24] there was a technical success of 87.1%.[27] Todd *et al.*[25] saw a technical success rate of 98% in the atherectomy group.[28] Gallagher *et al.*,[18] Zeller *et al.*,[20] and Loor *et al.*[23] did not provide technical or procedural success rates.[22,23,26]

Complications/periprocedural events

In addition to technical and procedural success rates, the presence or absence of complications or periprocedural events acts as a valuable assessor of

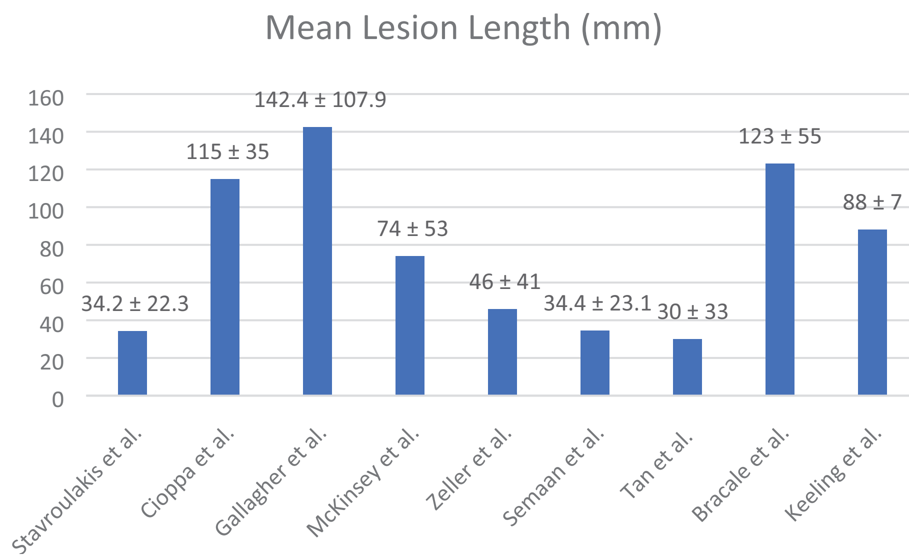

Figure 5. Comparison of mean lesion length (mm).

the safety of a device or technique being examined. Gallagher *et al.*[18] reported only an overall complication rate of 6.9% for both claudicant and CLI patients.[22] Stavroulakis *et al.*[16] reported periprocedural complications in 15% of the cohort.[20] Cioppa *et al.*[17] reported no complications or periprocedural events.[21] McKinsey *et al.*[14] reported periprocedural events in 12.9% of the CLI subgroup. Zeller *et al.*[20] reported a 3% complication rate.[23] Semaan *et al.*[21] reported thromboembolic events in 22% of the DA group.[24] Tan *et al.*[26] reported a complications/periprocedural event rate of 58.6% in the DA group;[29] Todd *et al.*[25] reported a 13% complication rate in their atherectomy group.[28]

Mean lesion length

The mean lesion lengths were reported in 9 of the 11 articles reviewed and have been tabulated in Figure 5. For clarity, it is important to note that McKinsey *et al.*,[14] Bracale *et al.*,[22] and Keeling *et al.*[24] were the only references to report mean lesion length specific to CLI patients.

Discussion

CLI continues to be classified as the most severe complication of PAD, with treatment modalities limited to either endovascular revascularization or open surgical revascularization. The former includes POBA, drug-eluting stents (DES), bare metal stents (BMS) and DCBs, which have all shown safety and efficacy in treating CLI.[27–31] However, the effectiveness for DA as an adjunctive or stand-alone treatment for CLI remains to be assessed.

From the current literature, DA as an adjunct to DCB shows positive effects for lower extremity lesions. Stavroulakis *et al.*[16] and Cioppa *et al.*[17] who both conducted prospective studies, found higher rates of 12-month primary and secondary patency amongst their patient populations, as well as a higher rate of 12-month limb salvage for subjects with CLI. Furthermore, Stavroulakis *et al.*[16] and Cioppa *et al.*[17] reported higher 12-month primary patency rates than the DEFINITIVE AR study (86.7%), which assessed DA as an adjunct to DCB among a population without CLI.[32] While these results may shine greater light on the use of DA with DCB, it is not without mention that both Stavroulakis *et al.*[16] and Cioppa *et al.*[17] utilized small study populations, with the former recruiting just three CLI patients.

The remaining nine studies assessed DA as its own treatment modality. Of these articles, Gallagher *et al.*,[18] Todd *et al.*,[25] and the DEFINITIVE LE trial by McKinsey *et al.*[14] had the largest participant pools. Each study also compared the outcomes with other groups, where Gallagher *et al.*[18] compared DA with percutaneous transluminal angioplasty (PTA) or PTA with stenting; McKinsey *et al.*[14] compared DA in claudicants with DA in CLI; and Todd *et al.*[25] compared DA with angioplasty.

While Gallagher *et al.*[18] did not notice a difference in first-year outcomes across treatment groups, CLI patients with SFA chronic total occlusions (CTOs) treated with DA had better 2-year outcomes than the angioplasty-alone group. In addition, McKinsey's DEFINITIVE LE trial determined that DA was safe and effective across in both patients with claudicants or CLI.[14] Only Todd *et al.*[25] claimed that DA did not provide benefit over angioplasty. While these opinions may differ, the strengths of the McKinsey *et al.*[14] and Gallagher *et al.*[18] studies are they analyzed far more patients undergoing atherectomy than Todd *et al.*[25] (799, 194, and 79, respectively). Additionally, the work by McKinsey *et al.*[14] is a prospective, single-armed trial that contains the largest cohort of CLI patients treated with DA, while the work by both Gallagher *et al.*[18] and Todd *et al.*[25] were retrospective analyses.

Of the remaining articles, each assessed the outcomes of DA in only a small number of CLI patients. Keeling *et al.*,[24] Zeller *et al.*,[20] Semaan *et al.*,[21] and Tan *et al.*[26] determined that DA was an effective method of treatment for endovascular therapy, but specific outcomes for the patients that had CLI were not discussed. Semaan *et al.*,[21] and Tan *et al.*[26] were also studies that compared DA with angioplasty, where they concluded both methods were viable PAD treatments. Bracale *et al.*[22] was a unique study in this review, as they assessed only CLI patients, arriving at the same conclusion previously stated where DA is an effective modality of treatment. Lastly, Loor *et al.*[23] was the only study that compared DA with bypass surgery, concluding that bypass may provide better outcomes for CLI patients than atherectomy.

With the current evidence, a greater number of studies lean towards the safety and efficacy of DA, but the specific relationship of this technique in regard to CLI requires further exploration. Six of the articles in this review were single-center, single-armed, prospective, non-randomized studies which limits the extent to which meaningful findings can be drawn from the results. The remaining studies were all retrospective analyses, which may contain an inferior level of evidence compared with prospective studies, along with an inherent bias as each investigator reviewed their databases. In addition, while McKinsey's DEFINITIVE LE trial contained the greatest study population, its non-randomized nature hampered the strength of the evidence provided.

Outside of the DEFINITE LE trial, there are no largescale clinical trials that have examined the efficacy and safety of DA use in treating CLI patients with comprehensive data on key outcomes for CLI patients such as limb salvage rates and amputations. Most studies examine cohorts comprising a combination of claudication and CLI patients, with the latter commonly consisting of fewer subjects. DA presents itself as a potentially useful tool in the treatment of lower extremity CLI; however, additional, focused studies of this cohort are needed.

Limitations

The limitations of this systematic review include inherent bias of the individual studies selected. Many were single-armed, prospective studies, which lacked comparison or control groups. The remaining studies were retrospective, and while they compared different interventions, there was a lack of any randomization. Additionally, different methodologies were followed by each study. Lastly, there was the potential of omitting relevant articles due to our search consisting of only the databases of PMC and PubMed.

Author contributions

All authors contributed in a significant manner to the conception, planning, writing and editing of this manuscript.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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