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Original Research

Intravascular Lithotripsy for Peripheral Artery Calcification: Mid-term Outcomes From the Randomized Disrupt PAD III Trial

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A B S T R A C T

Background: Endovascular treatment of calcified peripheral artery lesions may be associated with suboptimal vessel expansion, increased complication risk, and reduced long-term patency. The primary endpoint from the Disrupt PAD III randomized controlled trial (RCT) demonstrated superior procedural success in patients treated with intravascular lithotripsy (IVL) vs percutaneous transluminal angioplasty (PTA). The present study evaluates primary patency after 1 and 2 years in this randomized population.

Methods: The Disrupt PAD III RCT enrolled 306 patients with moderately-to-severely calcified femoropopliteal arteries treated with IVL ($n = 153$) or PTA ($n = 153$) prior to DCB treatment or stenting. The powered secondary effectiveness endpoint was primary patency at 1 year, defined as freedom from clinically driven target lesion revascularization *plus* freedom from restenosis determined by duplex ultrasound. Acute PTA failure requiring stent placement during the index procedure was prespecified as a loss of primary patency.

Results: Primary patency at 1 year was significantly greater in the IVL arm (80.5% vs 68.0%, $P = .017$). The requirement for provisional stenting was significantly lower in the IVL group (4.6% vs 18.3%, $P < .0001$). Freedom from clinically driven target lesion revascularization (IVL: 95.7% vs PTA: 98.3%, $P = .94$) and restenosis rates (IVL: 90.0% vs PTA: 88.8%, $P = .48$) were similar between the 2 groups at 1 year. At 2 years, primary patency remained significantly greater in the IVL arm (70.3% vs 51.3%, $P = .003$).

Conclusions: The Disrupt PAD III RCT secondary endpoint of superior 1-year primary patency was achieved, confirming the consistent safety and effectiveness of IVL followed by DCB treatment to facilitate a durable approach for patients with heavily calcified femoropopliteal arteries largely without stent requirement.

Introduction

Endovascular revascularization has gained acceptance as a primary treatment strategy in patients with femoropopliteal peripheral artery disease (PAD).[1] However, the presence of vascular calcification may interfere with the delivery of endovascular therapies, where it is responsible for suboptimal vessel expansion and increased risk of vascular complications including dissection and perforation, resulting in higher provisional stent rates and increased risk of suboptimal stent-related restenosis.[2-5] Furthermore, vascular calcification portends

Abbreviations: BTK, Below-the-Knee; CD-TLR, clinically driven target lesion revascularization; CTO, chronic total occlusion; DCB, drug-coated balloon; EQ-5D, EuroQol-5 Dimension; IVL, intravascular lithotripsy; MAE, major adverse event; PAD, peripheral artery disease; PARC, Peripheral Academic Research Consortium; PTA, percutaneous transluminal angioplasty; WIQ, Walking Impairment Questionnaire.

Keywords: Calcification; drug-coated balloon; femoropopliteal artery; intravascular lithotripsy; peripheral artery disease.

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a poor prognosis and is independently associated with increased cardiovascular mortality and morbidity risk, limiting the durability of minimally invasive procedures.[5-8] While randomized controlled trials have established the effectiveness of paclitaxel drug-coated balloon (DCB) treatment in reducing revascularization rates when compared with percutaneous transluminal angioplasty (PTA) alone, those studies primarily evaluated lesions with less severe calcification. Results from the few single-arm studies evaluating DCB effectiveness in heavily calcified lesions have demonstrated reduced long-term patency, suggesting that the presence of vascular calcium may serve as a barrier to drug uptake and therefore may limit the effectiveness of DCBs in complex calcified PAD.[5,8]

Intravascular lithotripsy (IVL) utilizes multiple emitters mounted on a traditional angioplasty balloon catheter that provide pulsatile acoustic pressure energy to fracture superficial and deep calcium without affecting local soft tissues or liberating emboli, thereby serving as a novel vessel preparation option to improve luminal compliance and facilitate definitive endovascular treatment.[9] The Disrupt PAD III randomized controlled trial compared the outcomes of vessel preparation using IVL or PTA followed by DCB treatment in heavily calcified femoropopliteal lesions. As previously reported, the primary endpoint of procedural success (residual stenosis ≤30% without flow-limiting dissection) in Disrupt PAD III was superior following vessel preparation with IVL compared with PTA prior to DCB treatment or stent placement. In addition, significantly lower rates of severe dissection and provisional stent placement were also observed in the IVL arm than in the PTA arm.[10] While short-term results have been reported, longer term follow-up is required to determine the durability of early clinical benefit of IVL compared with PTA as the vessel preparation strategy for the treatment of calcified femoropopliteal arteries prior to DCB treatment and/or stent placement. In the current study, we report the powered secondary endpoint of 1-year primary patency and primary patency at 2 years from the Disrupt PAD III randomized controlled trial.

Methods

Trial design and oversight

The present report represents the prespecified 1-year analysis and primary patency at 2 years from the Disrupt PAD III randomized controlled trial. Disrupt PAD III (NCT02923193) is a global, single-blind randomized controlled trial designed to assess the safety and effectiveness of IVL vs PTA as a vessel preparation strategy prior to definitive treatment with DCB and/or stent in patients with calcified femoropopliteal lesions. Major inclusion and exclusion criteria, endpoints, definitions, and 30-day results have been previously described in detail.[10] The trial was approved by local ethics review boards, and all participants provided written informed consent.

Study patients

Eligible patients were randomly allocated to vessel preparation with IVL ($n = 153$) or PTA ($n = 153$) followed by definitive treatment with a DCB or provisional stenting in case of failed vessel preparation prior to DCB at 45 centers in Austria, Germany, New Zealand, and the United States.[10] Complete patient inclusion and exclusion criteria were previously reported.[10] Briefly, patients presenting with symptomatic leg claudication and/or rest pain (Rutherford class 2-4) and angiographic evidence of ≥70% stenosis within the superficial femoral and/or popliteal artery, lesion length up to 180 mm (up to 100 mm for chronic total occlusion [CTO]), reference vessel diameter 4-7 mm, and moderate or severe calcification were eligible for enrollment. Calcification was graded using the Peripheral Academic Research Consortium (PARC) criteria.[11]

Study device and procedure

Following angiographic confirmation of study eligibility and successful guidewire passage through the target lesion, 306 patients were randomly allocated (1:1) to receive IVL or PTA prior to treatment with DCB and/or provisional stenting. Randomized group assignments were provided to investigators using an interactive voice response system or via a secure website (Bioclinica). All randomized patients were included in the intent-to-treat analysis and remained blinded through completion of the study. Vessel predilatation was allowed in the trial to facilitate catheter delivery in the IVL treatment arm when necessary.

The IVL system and peripheral IVL catheter and their technique for use have been described previously.[10,12,13] Patients allocated to IVL received vessel preparation with a low-pressure lithotripsy balloon (Shockwave Medical Inc). The IVL system consists of a generator, a connector cable, and a catheter that incorporates an array of 5 lithotripsy emitters enclosed in an integrated balloon. The Shockwave M^5 IVL balloon used in the study measures 60 mm in length and is available at diameters between 3.5 and 7.0 mm with 0.5-mm increments. The calcified arterial lesion was crossed with a 0.014-inch guidewire, and the Shockwave M^5 IVL catheter, sized at 1.1:1 relative to reference vessel diameter, was then advanced across the lesion and positioned using radiopaque markers. The lithotripsy balloon was inflated to 4 atm using a 1:1 diluted contrast/saline solution, and the generator was activated producing pulsatile acoustic pressure waves delivered from the lithotripsy emitters at 1 pulse per second that travel safely through soft tissue and facilitate superficial and deep calcium disruption.[9] Patients allocated to PTA were treated with a standard PTA balloon of the physician's choice sized at 1:1 relative to the reference vessel diameter. After vessel preparation with IVL or PTA, post-dilatation with a standard PTA balloon was required *per protocol* as necessary for a residual stenosis ≥30% or flow-limiting dissection (≥type D) and a translesion gradient >10 mm Hg. An angiographic acquisition was obtained to evaluate procedural success, after which provisional bare-metal or drug-eluting stent placement was mandated *per protocol* for a residual stenosis ≥50% or flow-limiting dissection and a translesion gradient >10 mm Hg. Patients who did not receive a provisional stent received treatment with a DCB (IN.PACT DCB; Medtronic) as indicated in the IN.PACT DCB instructions for use. Final angiography with distal runoff to the foot was then performed to assess the target lesion and identify potential distal embolization or thrombus. Patients received dual antiplatelet therapy according to individual site protocols.

Study endpoints

The primary effectiveness endpoint of the trial was procedural success, determined by the angiographic core laboratory as residual stenosis ≤30% without flow-limiting dissection (≥type D) following the randomized treatment and prior to DCB treatment and/or provisional stent placement. The powered secondary endpoint was primary patency at 1 year, defined as freedom from clinically driven target lesion revascularization (CD-TLR) and freedom from restenosis as determined by duplex ultrasound (DUS) or angiogram ≥50% stenosis. DUS-derived freedom from restenosis was defined as a peak systolic velocity ratio ≤2.4. As prespecified *per protocol*, acute PTA failure requiring a stent at any time during the index procedure was considered a loss of primary patency. To maximize DUS core lab assessments at the 1-year visit, observations beyond the 1-year analysis window were allowed. Eligible patients through 2 years were also assessed for primary patency. Additional secondary endpoints at 1 year included ankle-brachial index, EuroQol-5 Dimension (EQ-5D) questionnaire, Walking Impairment Questionnaire (WIQ), and major adverse events (MAEs), defined as unplanned surgical revascularization or major (above ankle) amputation of the target limb, symptomatic thrombus or embolus requiring treatment, and perforation requiring provisional stent placement or other treatment.

Data quality

Trial data were regularly reviewed for accuracy and completeness by independent monitors (NAMSA). Independent core laboratories analyzed duplex ultrasonography (VasCore) and angiography (Yale Cardiovascular Research Group). MAEs and target vessel revascularization procedures were adjudicated by an independent clinical events committee (Yale Cardiovascular Research Group). Study participants, DUS core laboratory readers, and the clinical events committee were blinded to treatment allocation. Investigators and research staff were not blinded to treatment assignment due to obvious differences in the study devices.

Statistical analysis

The trial was powered to demonstrate superiority of IVL over PTA for both the primary and secondary endpoints of procedural success and 1-year primary patency. The composite of primary patency was assessed hierarchically such that patients who had provisional stenting were excluded from the freedom from CD-TLR and restenosis analysis (since stenting has demonstrable effects on patency), and patients with CD-TLR events were likewise excluded from the freedom from restenosis analysis. The alternative hypothesis of the study was superior primary patency rate at 1 year in the IVL arm compared to the PTA arm. Therefore, a 1-sided Fisher exact test was prespecified with a conservative alpha of 0.025 for primary patency at 1 year. Since there were 2 hypothesized primary and powered secondary endpoints of procedural success and primary patency at 1 year, an alpha of 0.025 maintained a study-wise type 1 error probability of <0.05. Kaplan-Meier survival analysis was used for the evaluation of primary patency for patients with evaluable 2-year follow-up, with no prespecified formal hypothesis testing for primary patency at 2 years. A *post hoc* analysis was also performed to assess primary patency defined as freedom from CD-TLR and freedom from restenosis as determined by DUS or angiogram $\geq$50% stenosis, without provisional stent placement counted as a failure of primary patency. The independent predictors of primary patency at 1 year were determined by multivariate logistic regression using stepwise selection with a $P < .2$ threshold for entry into the model and a $P < .1$ level of significance to stay in the final model. Candidate variables included baseline and demographic characteristics and treatment group (IVL or PTA).

All analyses followed intention-to-treat principles where patients were analyzed according to the allocated randomization group. Continuous variables are presented as mean ± standard deviation. Group comparisons of secondary endpoints were explored using 2-sided t test for continuous data and chi-square test for categorical data. Statistical significance was set at $P < .05$ for all comparisons. All analyses were performed using SAS v9.4 (SAS Institute).

Results

Patients and procedures

Between February 2017 and May 2020, 306 patients were randomly allocated to vessel preparation with IVL ($n = 153$) or PTA ($n = 153$) followed by definitive treatment with a DCB and/or provisional stenting. Baseline patient and lesion characteristics have been previously reported[10] and were well matched with demographics typical of a PAD patient population (Supplemental Table S1). The only baseline variable for which a statistically significant difference was observed was lesion location where popliteal artery involvement was more prevalent in the IVL group (18.3% vs 9.8%, $P = .03$). A patient flow diagram depicting assessment for primary patency is shown in Figure 1. As previously reported, the primary effectiveness endpoint of procedural success was superior in the IVL arm (65.8% vs 50.4%, $P = .0065$). Superior procedural success in the IVL arm was accompanied by lower use of embolic protection, post-dilatation, lower maximum balloon inflation pressure, and lower need for provisional stenting (Central Illustration).[10]

Primary patency

Primary patency at 1 year was superior in the IVL group compared to the PTA group (80.5% vs 68.0%, $P = .017$, Table 1). The difference in primary patency was driven by the freedom from provisional stent placement rate, which was significantly greater in the IVL group (95.4% vs 81.7%, $P < .0001$). Freedom from the individual endpoints of CD-TLR and restenosis at 1 year were similar between the 2 groups (Table 1). Predictors of primary patency at 1 year are shown in Table 2, with univariate analysis results shown in Supplemental Table S2. By multivariable logistic regression, lesion preparation with IVL, age >75 years, and non-CTO lesions were independent predictors of successful primary patency at 1 year. Primary patency remained greater in the IVL arm at 2 years (Figure 2). A *post hoc* Kaplan-Meier analysis of primary patency modeled without defining provisional stenting as a failure demonstrated similar 2-year primary patency rates between the 2 groups (IVL: 79.2% vs PTA: 75.6%, $P = .70$). Of the combined 35 patients who received provisional stenting during the index procedure (IVL $n = 7$, PTA $n = 28$) and evaluable for primary patency at 2 years, only 2 patients in the PTA arm and no patients in the IVL arm experienced restenosis during the 2-year follow-up period. Similarly, a *post hoc* Kaplan-Meier analysis of non-stented patients demonstrated similar 2-year primary patency rates between the 2 groups (IVL: 78.6% vs PTA: 72.7%, $P = .48$).

Secondary outcomes

The MAE rate at 1 year was similar in both groups (IVL: 0.0% vs PTA: 1.4%, $P = .15$). The 2 clinical events committee-adjudicated MAEs occurred in the PTA group during the index procedure (distal embolization and perforation) with no further events through 1 year. While both groups demonstrated marked clinical improvement in ankle-brachial index, WIQ, EQ-5D, and Rutherford category, there were no differences in the change from baseline to 1 year between the 2 groups (Table 3).

Discussion

Patients with severely calcified PAD are often excluded from adequately powered randomized clinical trials due to the challenge of safe and effective treatment of these complex lesions.[14-16] The Disrupt PAD III randomized controlled trial sought to address this evidence gap, resulting in the largest published level I evidence to date, guiding endovascular treatment for patients with heavily calcified femoropopliteal artery lesions. The key findings from this study are as follows: (1) IVL followed by DCB therapy enables safe and effective treatment in this heavily calcified lesion cohort demonstrating superior procedural success compared to PTA driven by a significantly lower rate of major dissections and need for provisional stent placement; (2) the powered secondary endpoint of superior primary patency at 1 year following IVL treatment was achieved, confirming the consistent safety and effectiveness of IVL followed by DCB treatment to facilitate a durable treatment for patients with heavily calcified femoropopliteal arteries; (3) the independent predictors of primary patency at 1 year were treatment with IVL, age >75 years, and non-CTO lesions; and (4) freedom from CD-TLR and restenosis as well as the improvement in WIQ, EQ-5D, and Rutherford classification were comparable between the 2 groups at 1 year demonstrating the effectiveness of DCBs in heavily calcified femoropopliteal arteries.

The powered primary and secondary endpoints of superior procedural success and primary patency at 1 year with IVL followed by DCB treatment were achieved, confirming the atraumatic procedural experience with IVL is associated with durable clinical benefits. Superior procedural success was achieved with IVL despite greater procedural effort in the PTA arm as demonstrated by significantly greater maximum balloon inflation pressure and protocol-driven post-dilatation with balloon angioplasty (Central Illustration). These results underscore the different mechanisms of action between IVL and PTA in the treatment of

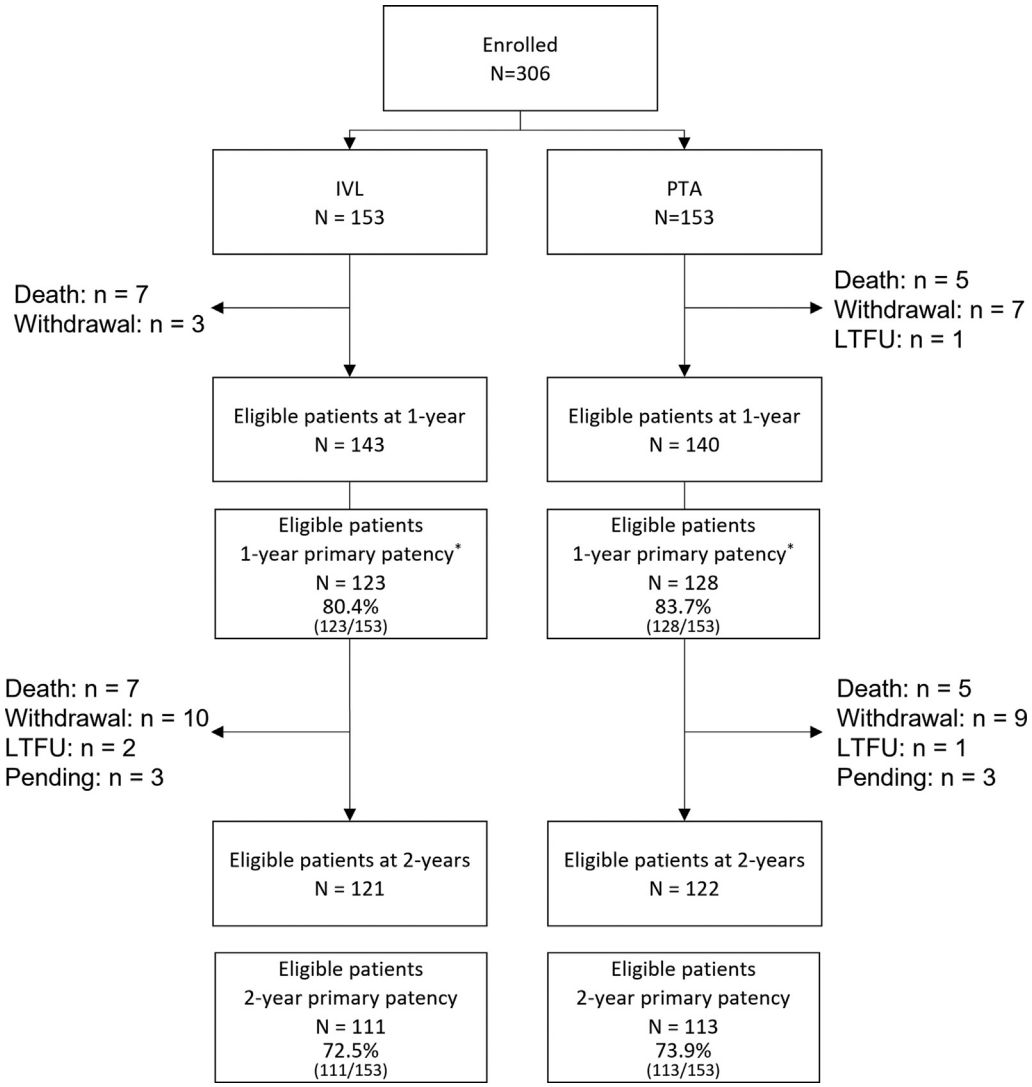


Figure 1. Study patient flow diagram. Patients were analyzed for the secondary effectiveness endpoint of primary patency at 1 year if a provisional stent was placed, a CD-TLR event occurred within the first 365 days after the index procedure, or a diagnostic DUS was available ≥335 days after the index procedure. *Powered secondary effectiveness endpoint. CD-TLR, clinically driven target lesion revascularization; DUS, duplex ultrasound; IVL, intravascular lithotripsy; LTFU, lost to follow-up; PTA, percutaneous transluminal angioplasty.

complex calcified PAD. The mechanism of IVL action utilizes acoustic pressure waves, delivered at a low balloon pressure of 4 atm, that travel circumferentially through soft tissue without any effect to safely modify superficial and deep calcium leading to improved vascular compliance.[9] Conversely, endovascular revascularization with high-pressure balloon angioplasty involves arterial wall disruption and vessel wall stretching causing permanent deformation with subsequent remodeling, often resulting in severe dissection requiring bailout stenting when treating complex lesions.[17,18]

Superior 1-year primary patency was demonstrated in the IVL arm, driven by the significantly lower rate of provisional stent placement in the IVL arm due to the lower rate of flow-limiting dissections (1.4% vs 6.8%, $P = .03$) and greater rate of posttreatment balloon residual stenosis ≤30% by core lab assessment (66.4% vs 51.9%, $P = .02$). Primary patency remained superior in the IVL arm at 2 years. Although freedom from restenosis remained statistically similar between the 2 groups at 2 years, the difference in restenosis rates appeared to increase over time. Longer term follow-up beyond 2 years as conducted in Disrupt PAD III is needed to evaluate this trend. When primary patency was assessed without defining provisional stenting as a failure, the IVL and PTA arms demonstrated 2-year Kaplan-Meier primary patency rates of 79.2% and 75.6%, respectively. Interestingly, the mid-term primary patency results from Disrupt PAD III, achieved in heavily calcified PAD, are comparable to primary patency rates reported in landmark studies evaluating DCBs in markedly less calcified femoropopliteal arteries.[19-22]

The outcomes achieved in the current clinical trial are consistent with recent "real-world" IVL studies demonstrating consistent procedural safety and effectiveness with IVL in both above-the-knee and below-the-knee calcified peripheral vascular territories[12,13,23,24] as well as durable 1-year primary patency in calcified femoropopliteal arteries,[25] suggesting that the IVL results observed in Disrupt PAD III are generalizable to clinical use in "real-world" settings. Stavroulakis et al[25] recently reported their single-center experience with IVL followed by DCB to treat heavily calcified femoropopliteal arteries ($N = 55$ patients/71 lesions with 78% peripheral artery calcification scoring system 3 and 4 calcification). The flow-limiting dissection and bailout stenting rates were 3% and 7%, respectively, resulting in a 1-year primary patency rate (defined as freedom from restenosis or any reintervention) of 81% and freedom from TLR rate of 92%. The results of this "real-world" study, of which 56% of patients presented with critical limb ischemia (Rutherford class 4-6), are comparable to the results achieved in the IVL arm of the current study.

Conversely, the low CD-TLR and restenosis rates observed at 1 year in the PTA arm are contrary to prior reports of increased late lumen loss following PTA and DCB treatment in lesions with increased calcium severity, which suggested that the presence of vascular calcium may serve as a barrier to drug absorption from PTA and definitive DCB treatment.[5,8] It remains unclear if aggressive vessel preparation with PTA in the clinical trial setting of Disrupt PAD III contributed to improved DCB effectiveness and optimal stent placement in heavily calcified lesions compared to prior published results in the "real-world" setting.

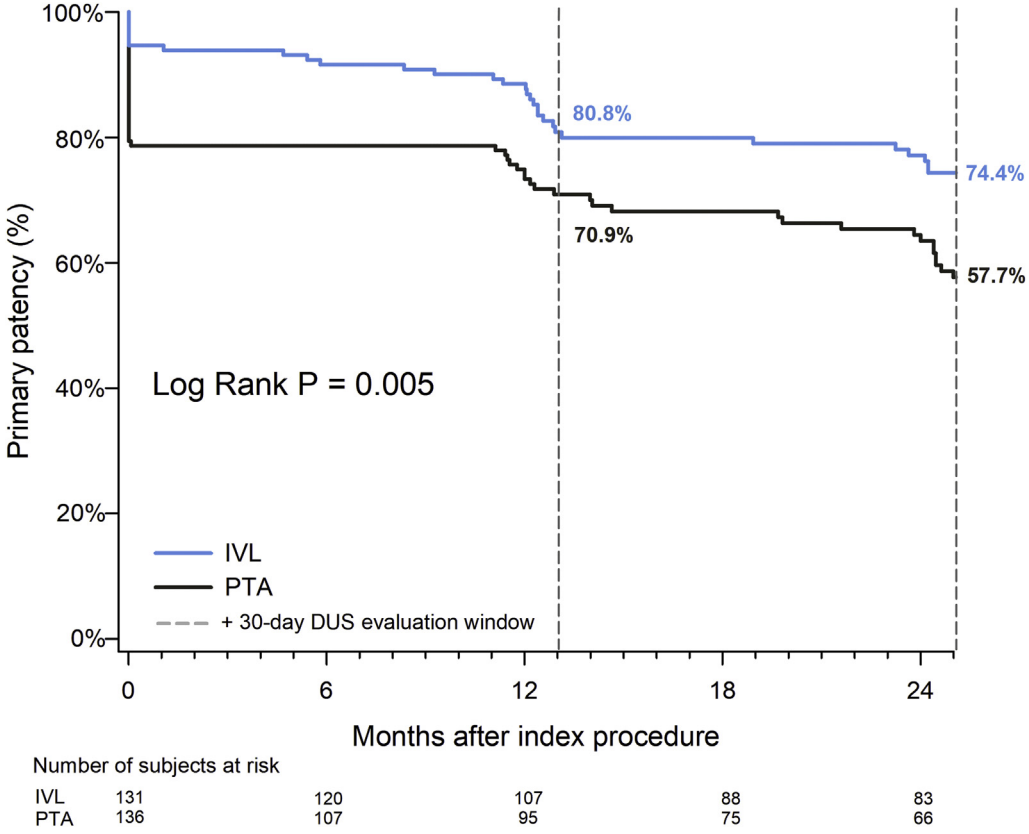


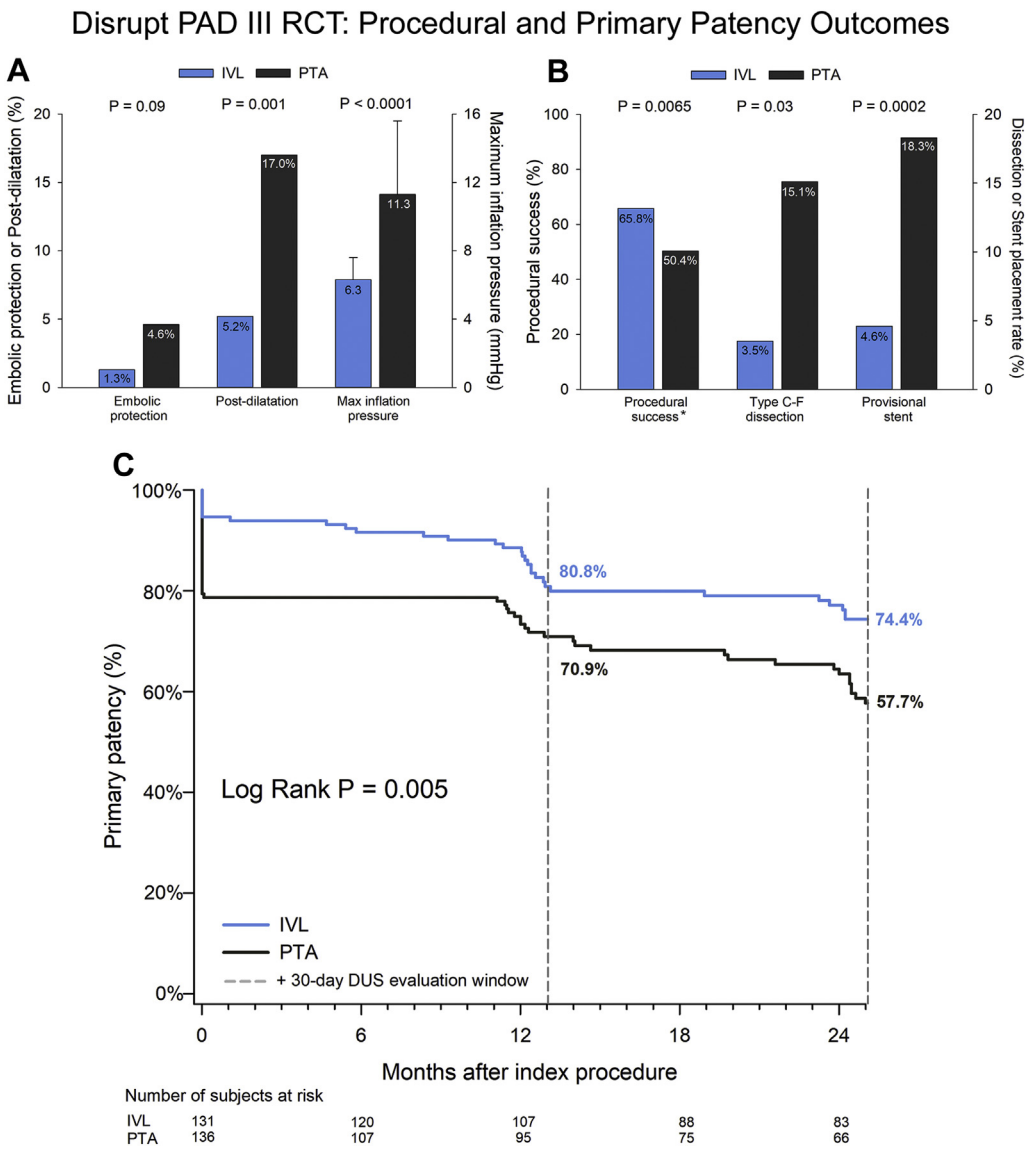
Figure 2. Kaplan-Meier estimate of primary patency through 2 years. Primary patency was significantly greater in the group receiving IVL treatment for lesion preparation than in the PTA group. Primary patency was defined as freedom from CD-TLR and freedom from restenosis by duplex ultrasound. Acute PTA failure requiring provisional stenting at any time during the procedure was counted as a loss of primary patency. CD-TLR, clinically driven target lesion revascularization; DUS, duplex ultrasound; IVL, intravascular lithotripsy; PTA, percutaneous transluminal angioplasty.

Indeed, control arm outcomes in the setting of clinical trials often surpass those achieved in "real-world" historical comparisons suggesting that careful attention to procedural details is commonly seen in the clinical trial setting.[20,26] The current study was not designed to specifically assess drug uptake in the presence of calcium since not all patients received drug-eluting therapy in the event of bare-metal stent placement prior to DCB treatment. Furthermore, while 99% of lesions were determined to be moderately to severely calcified in both groups using the PARC criteria, the inherent limitation of angiographic assessment precludes granular assessment of calcium morphologies that may affect drug uptake such as circumferential calcium angle and thickness.[27] Additional studies are needed to specifically evaluate the potential effects of vascular modification with IVL or PTA on drug uptake following DCB treatment in these complex lesions. Additionally, low CD-TLR and restenosis rates were observed following provisional stent placement in both arms in the current study. Acceptable longer term outcomes in noncalcified or mildly calcified PAD have been reported when optimal stent deployment is achieved.[20,28,29] However, stent placement in heavily calcified PAD is often associated with poor long-term outcomes, likely due to suboptimal stent deployment,[7] adding to procedural burden given the increased dependence on bailout stenting with increasing lesion complexity.[21,30] Again, it may be that optimal PTA vessel preparation in the setting of the Disrupt PAD III clinical trial facilitated optimal stent deployment resulting in good longer term patency not previously reported in prior studies. Nevertheless, avoidance of stent placement in claudicants with calcified femoropopliteal PAD allows treatment options to remain open, which is important given the progressive nature of calcific PAD, and avoids the known long-term risk of adverse clinical events such as stent fracture and restenosis.[31]

Although not evaluated in Disrupt PAD III, the use of atherectomy to treat calcified PAD has been reported in small randomized and single-arm studies.[15,16,32-35] Atheroablative technologies can be effective in debulking vascular calcium and improving luminal area, but procedural complications remain a concern. The recent REALITY single-arm study (N = 102 patients) reported on the safety and effectiveness of directional atherectomy followed by DCB therapy to treat long, severely calcified femoropopliteal PAD.[33] Although the primary patency rate at 1 year was 76.7% in this challenging lesion cohort, the rates of angiographic complications remained high (major dissection: 14.3%; perforation: 3.1%; distal embolization despite the use of embolic protection: 12.8%; bailout stenting: 8.8%). Cross-trial comparisons to the Disrupt PAD III are difficult, and randomized trials are needed to assess the comparative outcomes between IVL and atherectomy in the treatment of calcified PAD. Nevertheless, IVL combines consistent safety and effectiveness with durable long-term patency in these challenging calcified PAD lesions, without the need or the additional cost of distal embolic protection.

Limitations

There are several limitations of this study. First, IVL was compared to PTA for vessel preparation, and therefore, the comparative effectiveness of IVL vs other calcium-modifying strategies such as atherectomy remains unclear. Meaningful cross-trial direct comparisons between Disrupt PAD III and trials involving other calcium-modifying technologies are not possible given the differences in trial parameters.[15,32,33] Randomized trials comparing IVL and atherectomy (rotational, orbital, or directional) are required to define the relative safety and effectiveness of these devices. Second, these results may not be generalizable to patients with chronic limb threatening ischemia due to calcified, stenotic infrapopliteal lesions owing to the prespecified trial eligibility criteria. However, outcomes following IVL treatment of calcified infrapopliteal lesions have been reported in the Disrupt Below-the-Knee (BTK) trial[36] and more recently from the PAD III Observational Study using the Shockwave S^4 IVL catheter.[23] The Disrupt BTK II study (NCT05007925) is currently enrolling and will evaluate up to 250 patients with calcified BTK lesions treated with IVL with follow-up through 2 years. Furthermore, a recent single-center



Central Illustration. IVL demonstrates a safe and effective vessel preparation strategy with durable primary patency results in patients with calcified femoropopliteal arteries. The Disrupt PAD III randomized controlled trial demonstrated (**A**) greater procedural effort with PTA to treat heavily calcified PAD (99.3% moderate-severe calcification in both groups using the PARC definition of calcification by core lab assessment, $P = .23$); (**B**) superior procedural success with IVL vessel preparation with lower rates of major dissections and stent placement; and (**C**) superior primary patency[†] in patients followed through 2 years driven by the need for greater provisional stent placement in the PTA arm. The number at risk represents patients with evaluable DUS imaging at 1 or 2 years with an additional 30 days allowed for DUS evaluation. *Procedural success, the primary endpoint of the study, was defined as residual stenosis ≤30% without flow-limiting dissection (≥grade D) prior to DCB and/or stenting by angiographic core lab assessment. [†]Primary patency was defined as freedom from CD-TLR and freedom from restenosis as determined by DUS or angiogram ≥50% stenosis. As prespecified by protocol, acute PTA failure requiring a stent at any time during the index procedure was counted as a loss of primary patency. CD-TLR, clinically driven target lesion revascularization; DCB, drug-coated balloon; DUS, duplex ultrasound; IVL, intravascular lithotripsy; PARC, Peripheral Academic Research Consortium; PTA, percutaneous transluminal angioplasty.

Table 1. Mid-term primary patency.

Outcome	IVL	PTA	*P* value
Primary patency at 1 y[a]	80.5% (99/123)	68.0% (87/128)	.017
Freedom from provisional stenting at index procedure	95.4% (146/153)	81.7% (125/153)	<.0001
Freedom from CD-TLR at 1 y	95.7% (132/138)	98.3% (114/116)	.94
Freedom from restenosis at 1 y	90.0% (99/110)	88.8% (87/98)	.48
Primary patency at 2 y	70.3% (78/111)	51.3% (58/113)	.003
Freedom from provisional stenting at index procedure	95.4% (146/153)	81.7% (125/153)	<.0001
Freedom from CD-TLR at 2 y	91.5% (108/118)	91.2% (93/102)	.56
Freedom from restenosis at 2 y	83.0% (78/94)	76.3% (58/76)	.19

CD-TLR, clinically driven target lesion revascularization; IVL, intravascular lithotripsy; PTA, percutaneous transluminal angioplasty.

[a] Powered secondary endpoint. Values are % (*n*/*N*). Primary patency was defined as freedom provisional stenting at the index procedure, freedom from clinically driven target lesion revascularization, and freedom from restenosis determined by duplex ultrasound. By protocol, acute PTA failure requiring provisional stent placement was considered as a failure of primary patency. Patients with provisional stent placement were excluded from CD-TLR and restenosis composite, and patients with CD-TLR were excluded from restenosis composite.

study by Stavroulakis et al[25] included a majority of patients with chronic limb threatening ischemia, which demonstrated consistent 1-year primary patency outcomes following IVL treatment. Third, while IVL has demonstrated consistent results across clinical trial and "real-world" settings, the results achieved in the PTA arm in Disrupt PAD III may not be generalizable to the "real-world" clinical setting. Poorer outcomes relative to those achieved in the current study have been previously reported following PTA and DCB treatment in calcified PAD. It remains to be seen if low rates of revascularization and restenosis can be achieved outside the clinical trial setting. Lastly, this study was not designed to specifically evaluate calcium as a barrier to drug uptake following vessel preparation with IVL or PTA and definitive treatment with DCB. Specific studies designed to evaluate vascular micromorphologic changes following vessel preparation with calcium-modifying technologies and associated drug absorption are needed to address this important question. In addition, while core laboratory angiographic assessment was used to evaluate calcium severity using the well-established PARC criteria, there are inherent limitations of angiography in determining specific calcium morphologies (ie, concentric, eccentric, superficial, deep). Intravascular imaging studies are needed for further evaluation of these calcific lesion subtypes.

Table 2. Independent predictors of primary patency at 1 year.

Outcome	OR (95% CI)	*P* value
Treatment group (IVL vs PTA)	2.05 (1.11-3.77)	.021
Age <75 y (yes vs no)	0.46 (0.24-0.90)	.023
CTO (yes vs no)	0.51 (0.27-0.95)	.034

The independent predictors of primary patency at 1 year were determined by multivariable logistic regression using stepwise selection with a $P < .2$ univariate threshold for entry and a $P < .01$ level of significance to stay in the final model. Primary patency was defined as freedom provisional stenting at index procedure, freedom from clinically driven target lesion revascularization, and freedom from restenosis determined by duplex ultrasound. The following variables were entered into the model: treatment group (IVL vs PTA), age (75 years), sex, diabetes, eGFR (<60 mL/min/1.73 m^2), RVD (<5.3 mm, dichotomized at medial value), lesion location (SFA vs popliteal), calcium severity (PARC-defined moderate vs severe), and calcium eccentricity (eccentric vs concentric calcium).
CI, confidence interval; CTO, chronic total occlusion; eGFR, estimated glomerular filtration rate; IVL, intravascular lithotripsy; OR, odds ratio; PARC, Peripheral Academic Research Consortium; PTA, percutaneous transluminal angioplasty; RVD, reference vessel diameter; SFA, superficial femoral artery.

Conclusions

Disrupt PAD III is the largest randomized trial to evaluate endovascular treatment of heavily calcified PAD and is the first statistically powered level I evidence to guide treatment strategies in this challenging patient cohort. The IVL treatment arm demonstrated superior procedural success and primary patency compared to the PTA arm, achieving success for the powered primary and secondary endpoints of the study. When treating heavily calcified PAD, vessel preparation with IVL offers a more safe and predictable procedure than PTA while providing durable longer term vascular patency results with significantly reduced need for provisional stenting.

Declaration of competing interest

Dr Tepe is on the advisory board for BBraun, BSC, and Medtonic and received study support from Bayer Health Care, BBraun, Biotronic, Bard, BSC, Gore, Medtronic, Verian, and Shockwave Medical. Dr Brodmann is on the advisory board for Medtronic, BD Bard, Philipps Spectranetics, Intact Vascular, Boston Scientific, Biotronik, Shockwave Medical, Cagent, Profusa, and Bayer Healthcare. Dr Bachinsky received research grant support from and is a consultant for Abbott Vascular, Boston Scientific, BD Bard Vascular, Medtronic, and Shockwave Medical. Dr Holden is on the advisory board for Medtronic, Boston Scientific, Gore Medical, Philips, Shockwave Medical, Abbott, Intact Vascular, and Cagent and is a clinical investigator for Reflow Medical, LimFlow, Surmodics, and Shape Memory. Dr Zeller received honoraria from Abbott Vascular, BIBA Medical, Biotronik, Boston Scientific Corp, Cook Medical, Efemoral Medical, Gore & Associates, Medtronic, Philips-Spectranetics, Shockwave, and Veryan. He consulted for Boston Scientific Corp, CSI, Gore & Associates, Medtronic, Veryan, Intact Vascular, Shockwave, Bayer, and Vesper Medical. His institution received research, clinical trial, or drug study funds from Bard Peripheral Vascular, Veryan, Biotronik, Cook Medical, Gore & Associates, Medtronic, Philips, Terumo, TriReme, Shockwave, Med Alliance, Intact Vascular, B. Braun, CSI, Boston Scientific, University of Jena, Pluristem, Philips, and PQ Bypass. He holds common stock from QT Medical. Dr Mangalmurti is a consultant for Shockwave Medical, Philips, Cardiovascular Systems Inc, and Medtronic. Dr Nolte-Ernsting has received honoraria from Medtronic, Biotronik, and Penumbra and has served on advisory boards of Shockwave Medical, Medtronic, and Gore & Associates. Dr Virmani reports grant/research/clinical trial support from NIH, Leducq Foundation Grant, 480 Biomedical 4C Medical, 4Tech, Abbott, Accumedical, Amgen, Biosensors, Boston Scientific, Canon USA, Cardiac Implants, Celonova, Claret Medical, Concept Medical, Cook, CSI, DuNing, Inc, Edwards LifeScience, Emboline, Endotronix, Envision Scientific, Lutonix/Bard, Gateway, Lifetech, Limflo, MedAlliance, Medtronic, Mercator, Merrill, Microport Medical, Microvention, Mitralign, Mitra assist, NAMSA, Nanova, Neovasc, NIPRO, Novogate, Occulotech, OrbusNeich Medical, Phenox, Profusa, Protembis, Qool, ReCor Medical, Inc, Senseonics, Shockwave, Sinomed, Spectranetics, Surmodies, Terumo, Vesper, W.L. Gore, and Xeltis and is a consultant for Abbott Vascular, Boston Scientific, Celenova, Cook Medical, CSI, Edwards LifeScience, Bard BD, Medtronic, OrbusNeich Medical, ReCor Medical, SinoMedical Technology, Surmodics, Terumo Corporation, W.L. Gore, and Xeltis. Dr Parikh receives institutional research support from Abbott Vascular, Boston Scientific, Shockwave, SurModics, TriReme, and Veryan Medical; is a consultant to Abiomed, Canon, Inari Medical, Penumbra, and Terumo; and serves on the advisory boards of Abbott Vascular, Boston Scientific, Cordis, Janssen, Medtronic, and Philips. Dr Gray is a consultant to Shockwave Medical and has received institutional research support from Shockwave Medical.

Table 3. Secondary endpoints at 1 year.

Outcome	IVL ($n = 153$)	PTA ($n = 153$)	*P* value[a]
Major adverse events	0.0% (0/143)	1.4% (2/140)	.15
Ankle-brachial index			
Baseline	0.74 ± 0.19	0.78 ± 0.24	.21
1 y	0.94 ± 0.18	1.00 ± 0.25	.02
Change from baseline	0.19 ± 0.20	0.23 ± 0.24	.25
WIQ overall score			
Baseline	25.9 ± 20.9	26.5 ± 22.0	.83
1 y	52.9 ± 32.2	55.0 ± 30.1	.59
Change from baseline	25.9 ± 29.4	26.8 ± 28.9	.80
EQ-5D summary index			
Baseline	0.74 ± 0.19	0.74 ± 0.18	.96
1 y	0.84 ± 0.18	0.82 ± 0.20	.44
Change from baseline	0.09 ± 0.20	0.07 ± 0.21	.54
Change in Rutherford category			.76
−5	0.0% (0/134)	0.0% (0/130)	
−4	3.7% (5/134)	3.8% (5/130)	
−3	48.5% (65/134)	51.5% (67/130)	
−2	26.1% (35/134)	26.9% (35/130)	
−1	9.7% (13/134)	10.0% (13/130)	
0	11.9% (16/134)	6.9% (9/130)	
1	0.0% (0/134)	0.0% (0/130)	
2	0.0% (0/134)	0.8% (1/130)	
3	0.0% (0/134)	0.0% (0/130)	
4	0.0% (0/134)	0.0% (0/130)	
5	0.0% (0/134)	0.0% (0/130)	

Values are % (*n/N*) or mean ± standard deviation.
EQ-5D, European Quality of Life 5 Dimension; IVL, intravascular lithotripsy; PTA, percutaneous transluminal angioplasty; WIQ, Walking Impairment Questionnaire.
[a] *t* Test for continuous variables, and chi-square for discrete variables.

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Ethics statement

The trial was approved by local ethics review boards, and all participants provided written informed consent.

Supplementary material

To access the supplementary material accompanying this article, visit the online version of the *Journal of the Society for Cardiovascular Angiography & Interventions* at https://doi.org/10.1016/j.jscai.2022.100341.

Peer review statement

Given his role as Associate Editor, Sahil A. Parikh had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to Alexandra Lansky.

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