Efficacy and safety of intravascular lithotripsy for the treatment of peripheral arterial disease: An individual patient-level pooled data analysis

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Abstract

Background: Peripheral arterial disease (PAD) is one of the most common manifestations of atherosclerotic disease worldwide. Peripheral arterial calcification reduces acute success and long-term patency of endovascular therapy for PAD. Several calcium modification devices are available for use in peripheral interventions. Outcomes after peripheral intravascular lithotripsy (IVL), a novel approach using pulsatile sonic waves to treat luminal and medial calcium in patients with PAD, have not been extensively characterized. Therefore, we sought to perform an individual patient-level data (IPD) pooled analysis of available studies to evaluate the efficacy and safety of IVL in the treatment of PAD.

Methods and results: We pooled IPD, including baseline and procedural variables, from five prospective studies which assessed IVL in the treatment of patients with extensive peripheral artery calcification. Final post-procedural percent diameter stenosis (%DS) and procedural angiographic complications were assessed by independent core laboratory. Efficacy endpoints were analyzed using linear mixed effects models and safety endpoints were tabulated overall and by vascular bed. Among 336 patients who underwent endovascular revascularization with use of IVL, there was a significant reduction between pre-procedural and final %DS of 55.1% (95% confidence interval 53.3–57.0%, p < .0001). Core-laboratory assessed lesion-level complications, including flow-limiting dissections (Types D–F), vessel perforation, distal embolization, thrombus, abrupt closure, and no reflow, occurred in 4/328 (1.22%) of treated lesions.

Conclusions: The present IPD of five prospective studies, marking the largest analysis to date evaluating the use of IVL in significantly calcified PAD lesions, demonstrates this treatment strategy to be both effective and safe.
Peripheral arterial disease (PAD) impacts more than 200 million people worldwide.\(^1\) Vascular calcification is common in PAD and is associated with increased risk for acute vessel complications and reduced long-term patency following endovascular treatment.\(^2\) Intimal peripheral artery calcification is typically the result of atherosclerotic disease whereas medial calcification is most often associated with renal disease, diabetes, and aging.\(^3\)–\(^4\) Both forms of calcification pose distinct challenges for the treatment of obstructive PAD. Although a number of tools such as atherectomy and specialty balloons such as focal force, scoring, and cutting balloons have been developed to modify the calcific plaque thereby allowing effective change in arterial compliance and therefore vessel dilation. These modalities are often associated with elevated risk for periprocedural complications and have limited randomized trial data to support their use. Moreover, these methods of lesion modification primarily affect intimal calcification rather than medial calcification. Intravascular lithotripsy (IVL), which uses pulsatile sonic waves to fracture intimal and medial vascular calcium, has emerged as a novel endovascular therapy. Representative case images before and after IVL therapy in a severely calcified right superficial femoral artery lesion are presented (Figure 1). However, to date, this device has only been evaluated in small-to-intermediate sized nonrandomized studies.\(^5\)–\(^9\) Therefore, we sought to perform an individual patient-level data (IPD) pooled meta-analysis of available IVL trials to assess the efficacy and safety of this technique in the treatment of moderately-to-severely calcified PAD lesions.

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**FIGURE 1** Representative images before and after IVL. Significant occlusion in right superficial femoral artery with baseline RVD of 5.1 mm, 100% diameter stenosis, severe PARC calcification (a), lesion treatment with intra-vascular lithotripsy (b), post-IVL catheter angiographic assessment demonstrates 22.6% diameter stenosis and acute gain of 4.2 mm (c), and final angiographic assessment demonstrates 23.1% diameter stenosis, acute gain of 3.9 mm, and no evidence of complications (d). PARC, Peripheral Academic Research Consortium; RVD, reference vessel diameter.
the present analysis are DISRUPT PAD I, II, III, BTK, and CFA.5–9 IPD for these studies were provided by the study sponsor (Shockwave Medical). Databases were pooled by an independent biostatistician at a leading academic research organization in cardiovascular clinical trials (Cardiovascular Research Foundation, New York, NY). Included studies were approved by the governing regulations of participating sites, and all patients provided written informed consent. Anonymized patient- and lesion-level data were pooled, and consistent definitions were applied across studies. An independent core laboratory (Yale Angiographic Core Laboratory, New Haven, CT) conducted angiographic analysis for all studies included in this IPD. Trials included in this analysis are summarized in Table S1. A modified PRISMA IPD flow chart with database search strategies is included as Figure S1.

Data regarding baseline patient characteristics, procedural and intervention information, acute procedural success, and clinical events were compared with published reports when available. The study sponsor was contacted for clarification in the event of any inconsistencies. Patients included in these studies may have received peripheral IVL as standalone therapy or in conjunction with other therapies, including balloon angioplasty, specialty balloons, drug-coated balloons, atherectomy, as well as peripheral stenting.

2.3 | Objectives and endpoints

The primary objective of the current analysis was to study the acute procedural success and short-term clinical outcomes in patients who underwent treatment of PAD with IVL. Final postprocedural percent diameter stenosis (%DS) was considered as the primary efficacy endpoint. Percent DS immediately post-IVL (when available), final %DS <50%, final acute gain, and final acute gain indexed to baseline reference vessel diameter (RVD; i.e., net gain index)10 were assessed as secondary efficacy endpoints. The primary safety endpoints included the following angiographic-defined complications assessed during final measurements after intervention: flow limiting dissection (Types D through F), vessel perforation, abrupt closure, thrombus, distal embolization, and no reflow. Efficacy and safety endpoints were compared in patients who received IVL only versus IVL with adjunctive therapies. Secondary clinical endpoints included ankle brachial index (ABI), Rutherford classification, emergency target limb revascularization, and emergency amputation of target limb prior to discharge from index hospitalization, when available.

2.4 | Statistical analysis

Continuous data are presented as mean ± standard deviation and categorical variables are presented as percentage and frequency. The number of studies and observations with available data are also reported. Primary and secondary efficacy endpoints were analyzed longitudinally using linear mixed effects regression models, including time (baseline, post-IVL, and final) as a fixed effect and a random effect for lesions nested within patients. Primary safety endpoints are tabulated overall and summarized graphically by vascular bed. ABI and Rutherford classifications are compared between baseline and discharge using a paired t test and Wilcoxon signed-rank test, respectively. All statistical tests were two-sided and a p < .05 is considered statistically significant. Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC) and figures were generated using R version 3.6.1 (R Foundation).

3 | RESULTS

3.1 | Patient characteristics

This IPD included 336 patients from five different IVL trials. Baseline patient characteristics are presented in Tables 1 and S1. Mean patient age was 72.9 ± 8.8 years. Most patients included in this analysis were men (75.6%), and cardiovascular risk factors were common, including history of coronary artery disease (61.8%), diabetes mellitus (49.8%),

| TABLE 1 | Baseline patient characteristics |
|------------------|---------------------------|
| Number of studies | All patients (N = 336) |
| Age (years) | 72.9 ± 8.8 |
| Male sex | 75.6% (254/336) |
| White race (vs. other) | 96.5% (300/313) |
| Coronary artery disease | 61.8% (191/309) |
| Diabetes mellitus | 49.8% (156/313) |
| Hypertension | 95.8% (300/313) |
| Hyperlipidemia | 84.6% (264/312) |
| History of smoking | |
| Current (within the last 3 months) | 20.2% (63/312) |
| Former (stopped >3 months ago) | 57.4% (179/312) |
| Renal insufficiency | 21.5% (67/311) |
| History of CVA or TIA | 12.2% (38/311) |
| Respiratory or pulmonary disease | 32.4% (101/312) |
| PAD measures | |
| Baseline ABI | 0.71 ± 0.28 (n = 251) |
| Baseline walking impairment score | 29 ± 23 (n = 95) |
| Rutherford category | |
| 0 | 0.0% (0/328) |
| 1 | 0.6% (2/328) |
| 2 | 16.2% (53/328) |
| 3 | 58.5% (192/328) |
| 4 | 8.2% (27/328) |
| 5 | 14.9% (49/328) |
| 6 | 1.5% (5/328) |

Note: Data are presented as mean ± SD (n) or % (n/N). Abbreviations: ABI, ankle brachial index; CVA, cerebrovascular accident; PAD, peripheral arterial disease; TIA, transient ischemic attack.
hypertension (95.8%), hyperlipidemia (84.6%), current (20.2%) or former smoking (57.4%), and renal insufficiency (21.5%). Clinical information regarding baseline ABI, walking impairment questionnaire score, and Rutherford classification are presented when available. The majority of patients were Rutherford class III (58.5%) prior to intervention, and 24.7% of patients presented with chronic limb threatening ischemia (i.e., Rutherford 4–6).

3.2 | Patient-level procedural data

Information regarding patient-level procedural characteristics are presented in Tables 2 and S2. The mean number of lesions per patient was 1.1 ± 0.3, and mean number of IVL pulses was 174.9 ± 113.4. IVL was successfully delivered in 335/336 patients (99.7%) included in this analysis. Patients in the PAD III and CFA studies may have received adjunctive lesion modification therapies, including atherectomy (19.8% of PAD III and 4.8% of CFA), specialty balloons (6.1% of PAD III), and drug-coated balloon therapy (77.7% of PAD III and 28.6% of CFA) in addition to IVL prior to final angiographic assessment. A total of 62 (18.6%) patients received stent placement. Figure 2 demonstrates significant improvements in ABI and Rutherford classification categories after IVL treatment in the subset of patients with discharge measurements available (p < .0001 for both). Changes in Rutherford classification on discharge are also highlighted in the shift table presented in Table S5. Mean hospital stay was 1.1 ± 0.8 days in the 115 patients for which these data were available.

3.3 | Lesion-level procedural data

Pre-procedural lesion-level angiographic characteristics for 358 lesions are presented in Tables 3 and S3. Patients underwent intervention for iliac artery (9.0%), common femoral artery (13.4%), superficial femoral artery (54.1%), popliteal (16.5%), and infrapopliteal (7.0%) lesions. Mean lesion length across these various vascular beds was 87.4 ± 63.3 mm with mean RVD of 5.45 ± 1.46 mm. Mean pre-procedural minimal luminal diameter was 1.15 ± 1.00 mm with baseline %DS of 78.8 ± 16.6. The majority of lesions were considered severely calcified whether assessed by Yale core laboratory criteria (68.2%) or Peripheral Academic Research Consortium (PARC) criteria (81.0%). Most lesions (63.7%) had at least two-vessel runoff prior to intervention. Other pre-procedural lesion characteristics such as presence of eccentric calcification, chronic total occlusions (CTOs), thrombus, and aneurysmal segments are also presented in Tables 3 and S3.

Post-IVL and final angiographic characteristics are presented in Tables 3 and S3. Post IVL %DS measurement was available in 246 lesions (and not available in all studies), and final %DS measurement was available in 328 lesions. Percent DS was 28.6 ± 11.8 after IVL and 23.7 ± 8.6 on final assessment after intervention. Longitudinal linear mixed effects regression models which compared %DS values at baseline, after IVL, and postprocedurally (final) are presented with 95% confidence intervals in Figure 3a. The primary efficacy endpoint of final %DS was significantly improved compared with pre-procedural measurements (78.8 [95% CI 77.1–80.5] vs. 23.6 [95% CI 22.7–24.6], difference 55.1 [95% CI 53.3–57.0], p < .0001). Additionally, when comparing %DS immediately after IVL therapy to baseline measurements (available for most lesions except for those in PAD II), there was a significant reduction in %DS (78.8 [95% CI 77.1–80.5] vs. 28.9 [95% CI 27.4–30.3], difference 49.9 [95% CI 47.9–51.9], p < .0001). The difference in %DS between post-IVL and final measurements was 5.2 (95% CI 3.9–6.6), p < .0001. A total of 95.9% (236/246) and 98.8% (323/327) lesions were measured to have DS < 50% after IVL and during final measurements after completed intervention, respectively.

In the subgroup of severely calcified lesions by PARC criteria, there were significant reductions in %DS on final postprocedural assessment (difference 55.2 [95% CI 53.2–57.3], p < .0001) and also immediately after
IVL therapy (difference 48.9 [95% CI 46.6–51.3], p < .0001) by longitudinal linear mixed effects regression models. Figure 3b demonstrates no significant differences in final %DS by study when adjusted for baseline measurements (p = .63). Additionally, as demonstrated in Figure 3c, there were no significant differences in final %DS by advanced age, diabetes mellitus, renal insufficiency, presence of CTO, degree of peripheral arterial calcification (by PARC), presence of concentric versus eccentric calcification, vascular territory, poor distal runoff (≤ 1 vessel), or chronic limb threatening ischemia (Rutherford categories 4–6) when adjusted for baseline measurements. Notably, there was also no difference in final %DS appreciated in the subset of patients who received IVL as standalone therapy versus IVL and other adjunctive lesion modification devices when adjusted for baseline measurements (24.0 [95% CI 22.6–25.4] vs. 23.2 [95% CI 21.7–24.8], p = .46). The subgroup of women appeared to derive greater benefit in improvement in %DS from IVL compared with men.

With regards to secondary effectiveness endpoints, mean final acute gain was measured to be 3.1 ± 1.2 mm. By longitudinal linear mixed effects regression models, acute gain was noted to be 3.17 [95% CI 3.04–3.30] on final assessment and 2.73 [95% CI 2.61–2.86] after IVL, and net gain index values were found to be 0.59 [95% CI 0.57–0.61] on final assessment and 0.51 [95% CI 0.49–0.53] after IVL. Similar values were noted in the subset of lesions with severe peripheral calcification by PARC criteria. Additionally, by subgroup analysis, no statistically significant differences in final acute gain were noted by the degree of peripheral calcification whether assessed by PARC (none/mild: 2.89 [95% CI 2.33–3.45] vs. moderate: 3.44 [95% CI 3.04–3.83] vs. severe: 3.25 [95% CI 3.10–3.41], p = .27) or Yale criteria (none/mild: 3.19 [95% CI 2.14–4.23] vs. moderate: 2.94 [95% CI 2.68–3.20] vs. severe: 3.23 [95% CI 3.06–3.39], p = .18). Moreover, there were no statistically significant differences in net gain index by PARC (p = .09) or Yale (p = .89) criteria. While acute gain was numerically but not statistically significantly improved (3.20 [95% CI 3.04–3.35] vs. 2.85 [95% CI 2.49–3.20], p = .08), there was a significant trend for improved net gain index (0.60 [95% CI 0.58–0.63] vs. 0.48 [95% CI 0.43–0.52], p < .0001) in lesions with concentric (vs. eccentric) calcification. Postprocedural vessel runoff was at least two-vessel in 66.7% of lesions and importantly, there was no noted reduction in the number of postprocedure runoff vessels to suggest embolization.
TABLE 3  Patient lesion characteristics (lesion-level)

| Number of studies | All lesions(N = 358) |
|-------------------|----------------------|
| Lesion location (%) |                      |
| Illac             | 9.0% (32/357)        |
| CFA               | 13.4% (48/357)       |
| SFA               | 54.1% (193/357)      |
| Popliteal         | 16.5% (59/357)       |
| Infraopliteal     | 7.0% (25/357)        |
| Calcium length (mm) | 5                   |
| Lesion length (mm) | 87.4 ± 63.3 (n = 354) |
| Calcium length (mm) | 5                   |
| Calcification (Yale)^a (%) | 5               |
| Moderate           | 29.6% (106/358)      |
| Severe             | 68.2% (244/358)      |
| Calcification (PARC)^b (%) | 3               |
| Moderate           | 14.6% (46/316)       |
| Severe             | 81.0% (256/316)      |
| Eccentric calcification^c (%) | 5             |
| Moderate           | 17.3% (62/358)       |
| Severe             | 72.7% (256/358)      |
| Chronic total occlusion (%) | 5            |
| Thrombus (%)       | 0.6% (2/355)         |
| Pre-intervention   |                      |
| Diameter stenosis (%) | 5                |
| Reference vessel diameter (mm) | 5              |
| Minimal lumen diameter (mm) | 5           |
| Runoff vessels     | 5                    |
| Absent             | 5.7% (20/353)        |
| 1 vessel           | 18.1% (64/353)       |
| ≥2 vessels         | 63.7% (225/353)      |
| Not assessable     | 12.5% (44/353)       |
| Post-IVL therapy   |                      |
| Diameter stenosis (%) | 4                |
| Minimal lumen diameter (mm) | 4          |
| Acute gain (mm)    | 4                    |
| Final              |                      |
| Diameter stenosis (%) | 5                |
| Diameter stenosis <50% | 5             |
| Minimal lumen diameter (mm) | 5          |
| Runoff vessels     | 5                    |
| Absent             | 0.6% (2/321)         |
| 1 vessel           | 14.3% (46/321)       |
| ≥2 vessels         | 66.7% (214/321)      |
| Not assessable     | 18.4% (59/321)       |

Note: Data are presented as mean ± SD (n) or % (n/N).
Abbreviations: CFA, common femoral artery; PARC, Peripheral Academic Research Consortium; SFA, superficial femoral artery.

^aModerate calcification defined as densities noted prior to contrast injection and severe calcification defined as densities noted prior to contrast injection generally involving both sides of arterial wall.

^bModerate calcification defined as densities ≥180° and less than one-half total lesion length and severe calcification defined as ≥180° and greater than one half of the total lesion length.23

^cEccentricity defined as a stenotic lesion that has one of its luminal edges in the outer one-quarter of apparent normal vessel lumen.

3.4 | Procedural complications

Tables 4 and S4 present rates of the primary safety endpoints, and angiographically defined procedural complications assessed at the completion of index intervention. On final angiographic assessment, the majority of lesions were free of flow-limiting dissections (Types D–F) (99.1%) and perforation (99.7%). Of note, this single perforation event occurred after drug-coated balloon inflation. Rates of dissections grouped by vascular bed are presented in Figure 3d. There were no lesions with abrupt closure, thrombus, distal embolization, or no reflow noted at the time of final measurement. The difference in rates of procedural complications in lesions which were treated with IVL as standalone therapy versus IVL and other adjunctive lesion modification therapy did not meet statistical significance (0.65 vs. 2.01%, odds ratio 0.32 [95% CI 0.03−3.09], p = .32).

4 | DISCUSSION

The present IPD of 336 patients from five prospective studies marks the largest such analysis to date to evaluate the efficacy and safety of IVL for endovascular treatment of moderately-to-severely calcified PAD lesions. The principle findings from this manuscript are as follows: (a) %DS significantly improved after IVL therapy compared with baseline measurements; (b) this benefit of IVL with regards to improvement of percent diameter stenosis extended to a number of high-risk subgroups which are frequently difficult to adequately dilate and are therefore high risk for restenosis, including severely and concentrically calcified lesions; (c) acute gain and net gain index significantly improved after IVL therapy; (d) rates of procedural complications were very low across all vascular beds despite most lesions containing severe calcification, supporting the excellent safety profile of IVL; and (e) significant improvements in clinical markers including extent of PAD, ABI, and Rutherford class were noted after treatment with IVL.

4.1 | Efficacy of treatment

Endovascular therapy in patients with significantly calcified PAD remains a challenge as these lesions render balloon and stent expansion difficult and increase the risk for flow limiting dissection and other peri-procedural complications.11 Moreover, the fact that patients included in these trials all had significant peripheral artery calcification and would have likely been excluded from clinical studies of other technologies suggests the critical need for further investigation to optimize treatments and outcomes in this high-risk patient population. In the present report, the majority of patients had calcified PAD with almost all of the patients (96%) classified as moderately-to-severely calcified, as assessed by the PARC definition. With regards to acute relief of occlusive PAD with IVL therapy in these patients, the primary efficacy endpoint of final %DS significantly improved compared with baseline measurements in all major peripheral vascular
 territorial, with an overall mean final %DS of 23.7%; essentially 99% of all lesions treated were noted to have <50% DS on final angiographic assessment. Additionally, when compared to baseline measurements, the majority of the reduction in %DS was achieved post-IVL. While a proportion of patients from the PAD III and CFA studies included in this analysis did receive other adjunctive lesion modification therapies, 51.1% patients received standalone IVL treatment (i.e., no additional therapy beyond IVL). Notably, there was no significant difference in final %DS in patients who received these adjunctive therapies in addition to IVL compared with IVL alone (p = .46). In other words, most of the "work" of lesion expansion and vessel dilation was accomplished by IVL as opposed to the composite of techniques such as atherectomy followed by balloon angioplasty. Moreover, while prior studies have demonstrated that orbital and rotational atherectomy devices resulted in similar relief in %DS as was achieved with IVL therapy in this analysis, it is important to note that the majority of those studies did not employ core laboratory assessment of peripheral angiograms and included far fewer patients with severely calcified PAD.

Furthermore, we demonstrate that significant reductions in final %DS were achievable in number of patient subgroups at high-risk for restenosis after IVL therapy, as identified in ACC/AHA and TASC II guidelines. It has been well described that vascular calcification can contribute to worse acute and long-term outcomes, including higher rates of restenosis. In the current analysis, the efficacy of IVL as measured by final %DS did not differ significantly in the subgroups of advanced age, diabetes mellitus, renal dysfunction, CTOs, vascular territory, poor distal runoff, or concern for chronic limb threatening ischemia (Rutherford category 4–6). Women, who are typically at higher risk for suboptimal outcomes and restenosis after peripheral revascularization, experienced a greater acute benefit with IVL compared with men. Additionally, no significant differences in final %DS were noted by core laboratory-assessed degree of calcification by PARC criteria or by distribution of calcium, eccentric or concentric. There were also no significant differences noted in final %DS between the five studies included in this analysis. Key secondary efficacy endpoints including final acute gain and net gain index were similar between the overall cohort and the subgroup of severely calcified PAD.

**FIGURE 3** Efficacy and safety of IVL therapy. Longitudinal linear mixed effect regression models comparing baseline, post-IVL, and final percent diameter stenosis measurements are presented in panel (a). Final percent diameter stenosis by study and pooled estimate values are presented in panel (b). Final percent diameter stenosis by key clinical subgroups, including age, sex, diabetes mellitus, renal insufficiency, chronic total occlusion, severe calcification by Yale and PARC definitions, calcium distribution, vascular bed, poor distal runoff (≤1 vessel), high-risk Rutherford categories 4-6, and use of adjunctive lesion modification therapies are presented in panel (c). Rates of dissection by vascular bed (iliac, common femoral, superficial femoral, popliteal, infrapopliteal) after intervention are presented in panel (d). CI, confidence interval; DS, diameter stenosis; PARC, Peripheral Academic Research Consortium.
lesions by PARC criteria. Interestingly, while efficacious in both lesion subsets, there was a numeric trend toward improved acute gain and statistically significant trend for improved net gain index in lesions which were concentrically rather than eccentrically calcified. While early angioplasty studies described the utility of net gain index in assessing efficacy of coronary revascularization, to the best of our knowledge, the present analysis is the first to describe the use of this parameter to allow for the normalization of acute gain to the RVD in a cohort with lesions in different peripheral vascular territories. Thus, not only do these data suggest that the benefit of this therapy likely extends to a number of vascular beds, complex patient populations and challenging lesion subtypes, but also that the mode of action of using ultrasound waves which can penetrate severely calcified lesions in the intimal and medial spaces may be even more efficacious in difficult-to-treat lesions compared with atheroablative strategies.

### 4.2 Safety of treatment

The present IPD analysis also demonstrates IVL to be safe and associated with low rates of peri-procedural complications after treatment of moderately-to-severely calcified lesions. Rates of perforation, thrombus, distal embolization, no reflow, and abrupt closure were virtually nonexistent. Rates of dissection were also low, with any dissection occurring in 14.6% of patients and flow-limiting dissections (Types D–F) evident in only 0.9% of lesions. Moreover, there were no emergent revascularizations or amputations of target limbs in patients with this data available prior to discharge (N=115), speaking to the excellent safety profile of IVL catheter-based therapy. Significant calcium deposition has been shown to increase the risk for vascular dissections and poor acute and long-term revascularization success rates after angioplasty alone. In comparison with other lesion modification devices, this, the present data compare favorably to the core-lab assessed Liberty 360 study of orbital atherectomy in which rates of perforation (1.0–1.8%), abrupt closure (0.7–2.0%), and distal embolization (4.5–5.6%) were demonstrated to be similar in lesions across Rutherford categories in a cohort of 1,204 patients, of which 58.5% had calcified lesions. Rates of severe dissection were noted to occur in 2.2–4.7% lesions in Liberty 360; however, varying rates of any dissection have been reported after orbital atherectomy in other studies which did not have core-lab assessment, ranging from 2 to 11%. Thus, the overall safety profile for IVL appears to be comparable if not favorable to available endovascular techniques for treatment of calcified PAD.

### 4.3 Clinical surrogates of disease

Patients with symptomatic PAD are known to be at-risk for poor quality of life and functional status. Prior reports have demonstrated that ABI is associated with poor quality of life scores, especially physical functioning metrics. In the current analysis, we demonstrate that ABI and Rutherford category significantly improved on discharge after IVL therapy compared with baseline values in patients with these data collected. Thus, these data demonstrate that IVL is associated with improvements in key clinical surrogates for PAD. While these acute improvements are encouraging, longer-term follow-up will be needed to verify the potential for improved quality of life metrics after revascularization with in calcified lesions.

### 4.4 Limitations

There are several limitations which must be acknowledged with this analysis. The trials included in this analysis are single-arm studies with no comparators, and so we are unable to effectively compare the efficacy and safety of IVL with other endovascular PAD treatment devices. It is also important to note that a proportion of patients received adjunctive device therapy (~12% received atherectomy), and so isolating the benefits of IVL in this specific patient subset is challenging. However, we performed separate analyses to evaluate improvements in vascular dimensions and safety profiles in patients who received standalone IVL therapy with IVL and other adjunctive treatments and found no differences in final %DS or procedural complication rates between these groups. Given the varying dimensions of the vascular beds included in this analysis, there is a need for improved endpoints and parameters which have applicability in these different therapeutic settings. We present net gain index as one potential measure of efficacy, which may allow for assessment and
comparison of procedural success across different vascular territories. To fully understand the comparative effectiveness of these therapies, head-to-head strategy trials ideally with the use of intravascular imaging would need to be conducted to better appreciate mechanisms of action. Given the limited number of patients available to study in each of the described key clinical subgroups (including a limited number of patients with chronic limb threatening ischemia), larger cohorts will need to be studied to verify these observations. Lastly, discharge and follow-up clinical assessment and outcomes data were not systematically collected in several of the studies included in this analysis, making it challenging to draw robust conclusions regarding the long-term risks and benefits of treatment with IVL, with or without other calcium modification therapies. Future studies should aim to address these limitations.

4.5 Conclusions

The present patient-level pooled analysis demonstrates that IVL treatment of significantly calcified lesions in patients with PAD is both effective and safe across multiple vessel beds, in high-risk patient cohorts, and in the setting of either eccentric or concentric calcium. These data support the need for prospective randomized trials comparing IVL to non-IVL approaches for the treatment of PAD, such as the ongoing DISRUPt PAD III randomized controlled trial. Further studies are required to determine optimal treatment strategies for PAD in this vulnerable patient population.

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CONFLICT OF INTEREST

Dr Mena-Hurtado is a consultant for Abbott, Boston Scientific, Cardinal Health, Cook, Medtronic, and Bard. Dr Garcia reports grants/research support from Abbott and Covidien/Medtronic; Nonfinancial consulting relationships with Covidien/Medtronic, Boston Scientific, and Abbott; Equity in Arsenal, Primacée, TissueGen, CV Ingenuity, Spirox, Scion Cardiovascular, Syntervention, Essential Medical, Transit Medical, and Orchestra Medical; and Ownership/Founder of Innovation Vascular Partners. Dr Parikh reports institutional grants/research support from Abbott Vascular, Shockwave Medical, TriReme Medical, Sumodics, Silk Road, Medical, and the NIH; consulting fees from Terumo and Abiomed; and Advisory Board participation for Abbott, Medtronic, Boston Scientific, CSI, and Philips. The other authors have nothing to disclose.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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