FORWARD PAD IDE

Forward-Shifted Intravascular Lithotripsy (IVL) Technology in a Prospective, Multicenter, Single-arm Investigational Device Exemption (IDE) Study (FORWARD PAD IDE Study)

Statistical Analysis Plan Version 4.0

08 July 2024

NCT05858905

Statistical Analysis Plan (SAP)
Rev 04

July 08, 2024

Protocol Title: Statistical Analysis Plan for the pooled Mini S Australia and New Zealand Study and FORWARD IDE Study

Protocol Number(s): CP67398 & CP65324

Study Device: Shockwave Medical Peripheral IVL System with JAVELIN IVL Catheter

Study Sponsor Name and Address: Shockwave Medical, Inc.
5403 Betsy Ross Drive
Santa Clara, CA 95054

APPROVALS

The undersigned have reviewed this document and agree with its contents.

[redacted]

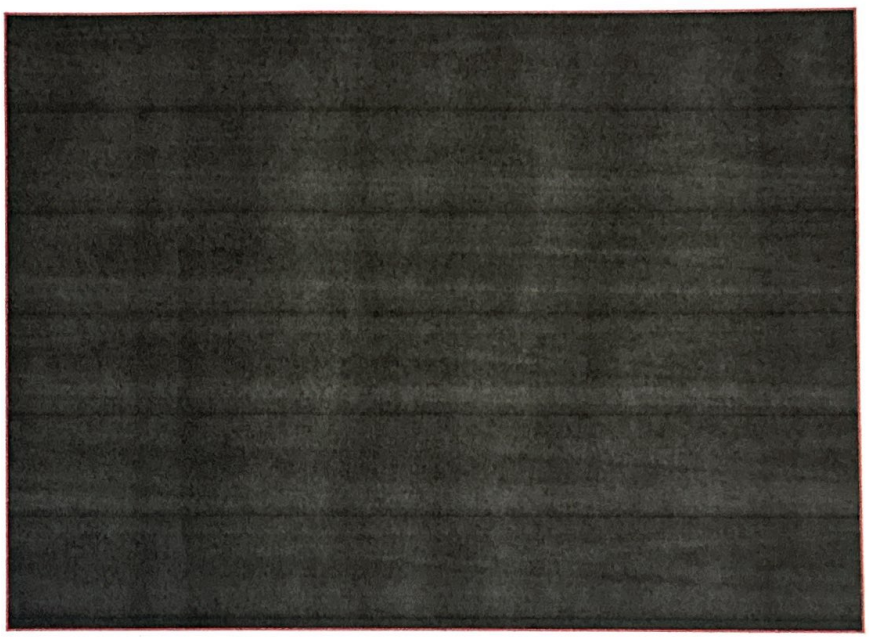


TABLE OF CONTENTS

1. INTRODUCTION

This statistical analysis plan (SAP) outlines the data and procedures used for assessing the safety and effectiveness of the Shockwave Medical JAVELIN Peripheral IVL Catheter over pooled data from two studies: the Mini S Australia and New Zealand Study (CP65324) and the FORWARD IDE Study (CP67398).

Data from subjects enrolled under the IDE protocol will be pooled with data from the Mini S Australia and New Zealand Study to form a pooled primary analysis cohort of 90 subjects. Results of the first 90 consecutively enrolled subjects with evaluable data across both studies (with a minimum of 50% of patients from the US) will comprise the primary analysis cohort and will be submitted to FDA to support a Premarket Notification 510(k) application for the JAVELIN IVL Catheter. Results of the full cohort from both studies in up to 125 subjects will be provided to FDA in annual progress reports.

2. STUDY OBJECTIVE

The objective of this Clinical Proposal is to use the data that Shockwave Medical is currently collecting from the two clinical studies described above to demonstrate the safety and effectiveness of the Shockwave Medical JAVELIN Peripheral IVL Catheter compared to pre-defined performance goals. This document may modify and supersede the statistical plans outlined in the respective study protocols.

3. STUDY DESIGN

The ongoing Mini S Australia and New Zealand Study is a prospective, multi-center, single-arm study. The FORWARD IDE Study is also a prospective, multi-center, single-arm study. Results of the first 90 consecutively enrolled analyzable subjects across both studies (with a minimum of 50% of patients from the US) will comprise the pooled primary analysis cohort and will be submitted to support a Premarket Notification 510(k) submission for the Mini S IVL Catheter.

4. STUDY ENDPOINTS

The primary and secondary endpoints for the pooled cohort are presented below. To reduce bias and ensure poolability of data, all endpoints for both studies will be adjudicated by the same independent Clinical Events Committee as well as the same angiographic and ultrasound core labs.

4.1. Primary Safety Endpoint

The primary safety endpoint for the pooled cohort is Major Adverse Events (MAE) at 30 days defined as a composite of:

- Cardiovascular death
- Unplanned target limb major amputation (above the ankle)
- Clinically-driven target lesion revascularization (CD-TLR)

4.2. Primary Effectiveness Endpoint

The primary effectiveness endpoint is **Technical Success** defined as final residual stenosis ≤50% without flow-limiting dissection (≥ Grade D) of the target lesion by angiographic core lab.

4.3. Secondary Endpoints

- **Serious angiographic complications** defined as flow-limiting dissection (≥ grade D), perforation, distal embolization, or acute vessel closure as assessed by the angiographic core lab.
- **IVL Technical Success (post-dil)** defined as *post-dilatation* residual stenosis ≤50% without flow-limiting dissection (≥ Grade D) of the target lesion by angiographic core lab (measured immediately following mandatory post-dilatation).
- **IVL Device Success** defined as the ability to deliver, advance across the target lesion, pressurize, pulse, flush and retrieve the JAVELIN IVL Catheter.
- **Technical Success (final)** defined as *final* residual stenosis ≤30% without flow-limiting dissection (≥ Grade D) of the target lesion by angiographic core lab.
- **MAE** at 6 and 12 months (as a composite and individual components)
- **Primary Patency** at 12 months defined as:
  - Above the knee lesions: freedom from ≥50% restenosis as determined by Duplex Ultrasound (DUS) and freedom from Clinically-Driven Target Lesion Revascularization (CD-TLR)
  - Below the knee lesions: freedom from both total occlusion (100% diameter stenosis by DUS) in all of the target lesions in a flow pathway, as well as a CD-Revascularization (CD-TLR).

5. DETERMINATION OF PERFORMANCE GOALS

The primary endpoints and associated performance goals (PGs) were developed after consulting FDA and are based on predicate submissions for the Shockwave Peripheral IVL System and supported by results of a recent meta-analysis on peripheral IVL and benchmark devices.

Specifically, prior FDA review of the original Peripheral IVL System 510(k) K161384 (cleared September 14, 2016) and predicate device Shockwave S4 510(k) K180454 (cleared June 27, 2018) was taken into consideration. K161384 included a pooled analysis of the Disrupt PAD I & II studies used to support substantial equivalence, and K180454 provided confirmatory clinical data from Disrupt BTK related to modifications to the cleared device.

As part of an ongoing clinical evaluation process, periodic literature searches are conducted to assess the ongoing benefit risk profile of the device. The most recent literature search and associated meta-analyses provide additional justification for the PGs for the pooled primary

analysis cohort. For details on the methodology used to conduct the meta-analyses on the relevant literature sources identified in the search, refer to Appendix B.

5.1. Performance Goal for Safety

As noted in Section 4.1, the primary safety endpoint for the pooled analysis cohort is MAE at 30 days. This is consistent with the pooled PAD I & II analysis and the Disrupt PAD BTK study, previously submitted to FDA in K161384 and K180454, respectively. MAE is a clinically relevant composite endpoint frequently used in peripheral vascular research [1-4]. Composites generated by the combination of individual endpoints provide additional statistical power to detect potentially meaningful differences between treatments [5].

In the pooled PAD I/II analysis, the PG for 30-day MAE was 8.7%. For the pooled primary safety hypothesis, a conservative 2.5% non-inferiority adjustment was applied to account for a more complex patient population in the JAVELIN studies including Rutherford Classification 5, dialysis patients, smaller diameter vessels, infrapopliteal lesions, and a higher rate of chronic total occlusions (CTOs). As a result, the primary safety endpoint PG for 30-day MAE is 11.2%.

The primary safety endpoint PG is further supported by the clinical literature for benchmark plaque-modifying devices designed to treat PAD. The literature review -described above identified 16 unique sources with at least 50 subjects and published within the last 10 years, representing 3,207 subjects, with complete data available for 30-day MAE (see Appendix B for details). Sample sizes ranged from 50 to 800, and the reported 30-day MAE rates ranged from 0.0% - 14.0% with associated 95% upper confidence limits ranging from 2.2 - 22.3%. The meta-analysis random effects model estimated a mean 30-day MAE rate of 2.8% (95% CI: 1.6-4.9).

As noted in Section 6.1 below, with a PG of 11.2% and 90 subjects, rejection of the null hypothesis would demonstrate an expected true population 30-Day MAE rate of 2.0% with an upper 2-sided 95% CI of less than or equal to 11.2% which are clinically and regulatory appropriate estimates based on prior investigations of peripheral IVL [1-3] and also consistent with the broader contemporary peripheral literature sources and meta-analysis (Appendix B).

5.2. Performance Goal for Effectiveness

As noted in Section 4.2, the primary effectiveness endpoint for the pooled analysis cohort is Technical Success defined as final residual stenosis ≤50% without flow-limiting dissection (≥ Grade D) of the target lesion by angiographic core lab. The stenosis threshold used in this definition (≤ 50%) is consistent with the effectiveness endpoints used in the Disrupt PAD I & II (K161384) pooled analysis and the Disrupt PAD BTK study (K180454). Technical Success is a clinically relevant outcome given the highly stenotic lesions targeted in the Mini S studies and is supported by published standards for clinical trial endpoints [9]. Consensus definitions from the Peripheral Academic Research Consortium (PARC) note that acute technical success for peripheral revascularization is defined as the achievement of a final residual diameter stenosis < 30% for stent and < 50% for angioplasty or atherectomy by angiography at the end of the procedure (and without flow-limiting arterial dissection or hemodynamically significant

translesional pressure gradient < 10 mm Hg) for endovascular revascularization [9]. Clinical evidence from the Disrupt PAD studies demonstrates a dramatic reduction in the need for bailout stents and justifies the 50% threshold [10].

In the pooled PAD I/II analysis, the PG for the effectiveness endpoint was 89.3%. For the pooled JAVELIN primary effectiveness hypothesis, a 5% non-inferiority adjustment was applied to account for a more complex patient population in JAVELIN studies including small vessel diameters, infrapopliteal vessels and a higher rate of CTOs. As a result, the primary effectiveness PG for the JAVELIN program is 85.0% for Technical Success.

The primary effectiveness endpoint PG is further supported by the clinical literature for benchmark plaque-modifying devices designed to treat PAD. The literature review -described in Section 5 identified 9 unique sources, with at least 50 subjects and published since 2013, representing 2129 total subjects, that reported the percentage of cases with final residual stenosis <50% (see Appendix B). Sample sizes ranged from 52 to 733, and the reported rates ranged from 83.2% - 100% with associated 95% lower confidence limits ranging from 76.2 – 94.9%. The meta-analysis random effects model based on these studies estimated a mean rate of 92.5% (95% CI: 88.5-95.2).

As noted in Section 6.2 below, with a PG of 85.0% and 90 subjects, rejection of the null hypothesis would demonstrate an expected true population rate of 97.0% with a lower 2-sided 95% CI of greater than or equal to 85% which are a clinically and regulatory appropriate estimates based on prior investigations of peripheral IVL [1-3] and -also consistent with the broader contemporary peripheral literature sources and meta-analysis. (Appendix B).

6. HYPOTHESES AND SAMPLE SIZE CONSIDERATIONS

The following hypotheses and associated PGs for the primary safety and effectiveness endpoints are both clinically and statistically relevant to demonstrate study success and supported by the results of the meta-analysis (Appendix B).

6.1. Primary Safety Hypothesis

The primary safety hypothesis is:

$$H_0: \Pi_S > PG_S \quad \text{vs.} \quad H_A: \Pi_S \leq PG_S$$

where Π_S is the proportion of patients who experience a MAE within 30 days of procedure and PG_S is the Safety Performance Goal.

All subjects in whom a Mini S IVL catheter was introduced into the vasculature will be included in the analysis (i.e., it is an intent-to-treat analysis). The hypothesis will be tested using a one-sided Exact Binomial Test at α=0.025.

The assumptions for the sample size calculations are listed below.

- Expected 30-day MAE rate of 2.0% = Π_S
- Performance goal of 11.2% = PG_S
- One-sided statistical significance level of 0.025 = α
- The hypothesis will be tested using a one-sided Exact Binomial Test.
- Statistical power of 96.5%

6.2. Primary Effectiveness Hypothesis

The primary effectiveness hypothesis is:

$$H_0: \Pi_E \leq PG_E \quad \text{vs.} \quad H_A: \Pi_E > PG_E$$

where Π_E is the proportion of target lesions with technical success and PG is the effectiveness Performance Goal.

The assumptions for the sample size calculations are listed below.

- Expected Technical Success rate of 97.0% = Π_E
- Performance goal of 85.0% = PG_E
- One-sided statistical significance level of 0.025 = α
- The hypothesis will be tested using a one-sided Exact Binomial Test.
- Statistical power of 98.1%.

6.3. Sample Size Justification

The study will be deemed a success if both the primary safety and effectiveness endpoints are met. To provide at least 80% power study-wide, each endpoint was powered to at least 90%. A one-tailed scenario was used to assess the minimum sample size needed to detect a difference in the assumed true rate of safety (2%) versus the safety performance goal of 11.2%. The same calculation was done for the assumed true rate of effectiveness (97%) versus the performance effectiveness goal of 85%. A sample size of 90 subjects provides a study-wide power of 94.7% to meet both the safety and effectiveness endpoints. No adjustments for multiplicity are needed.

7. POOLABILITY

Results for the first 90 consecutively enrolled evaluable subjects across both studies (with a minimum of 50% of patients from the US) will comprise the primary analysis cohort and will be submitted to support a Premarket Notification 510(k) submission.

Justification of poolability is based on the following: The Mini S Australia and New Zealand and the FORWARD IDE Study protocols share the same eligibility criteria, data collection requirements, and IVL treatment algorithm and patient follow-up procedures. Both studies utilize the same electronic data capture system, are monitored with 100% source document

verification, include independent angiographic and duplex core labs, independent clinical events committee (CEC) for endpoint adjudication of MAE, and data safety monitor (DSM). Both studies use the standard and flex configurations of the JAVELIN IVL Catheter.

Primary endpoints will be analyzed using a logistic regression model including an intercept term and fixed effect for geographical region to determine whether any significant differences exist. The tests will be performed at a 15% level of significance level. A significant result will require further inspection of the by-region results to assess the reasons for differences and to evaluate whether pooling across geographies is appropriate.

8. ANALYSIS SET

The primary analysis cohort will be the first 90 consecutively enrolled evaluable subjects across both studies (with a minimum of 50% of patients from the US), which will be submitted to support a Premarket Notification 510(k) application.

9. STATISTICAL METHODS OF ANALYSES

9.1. General Considerations

Descriptive statistics will be provided in this clinical study. Analyses will be reported on at pre-specified time points including 30 days, 6, and 12 months.

Categorical variables will be summarized by the number of non-missing observations, and the frequency and percentage for each category. Unless otherwise noted, missing data will be excluded from the denominator.

Continuous variables will be summarized by the mean, standard deviation, median, IQR, minimum, and maximum.

Statistical analyses will be performed using SAS System® Version 9.4 or higher.

9.2. Baseline Characteristics

The following will be carried out for all subjects: demographic, medical history and other clinically relevant baseline variables will be summarized using the appropriate descriptive statistics as described above.

9.3. Handling of Dropouts and Missing Data

No imputation of or adjustments for missing data will be performed for the primary analyses. All available data will be presented. For time to event analyses, subjects who do not experience the event in question will be censored at their last known follow-up.

For the primary safety endpoint analysis, the denominator for each parameter in the safety measures will be the number of subjects who had sufficient follow up (at least 23 days for 30-day visit) plus any subjects who had an event prior to the milestone visit.

10. ADDITIONAL DATA SUMMARIES / SUPPLEMENTAL ANALYSES

10.1. Subgroup Analyses

Analyses to examine the consistency of results across different subgroups will be performed for the primary safety and effectiveness endpoints for the following subgroups, and results will be reported using descriptive statistics:

- Geography (US, OUS)
- Above the knee (ATK) lesions vs below the knee (BTK) lesions

To support the subgroup analyses, a minimum of 15 subjects with BTK lesions, and a minimum of 15 subjects in each geography will be included. No formal hypothesis testing for subgroup analyses is pre-specified. However, to examine the consistency of results across different subgroups, the primary safety and effectiveness endpoints will be compared between subgroups using a logistic regression model including an intercept term and fixed effect for the subgroup, with corresponding 95% confidence interval and p-value presented. Additional analyses of group differences will be completed if the subgroup term in the model has a p-value of ≤ 0.15.

10.2. Data Screening and Acceptance

All data involved in the determination of endpoints will be screened for missing and unusual values. Any missing data affecting the ability to determine or analyze any endpoint will be queried by Data Management for confirmation of irretrievability. Unusual values, such as outliers, are also to be queried, and if confirmed, will be used as recorded.

10.3. Glossary of Terms and Abbreviations

The Clinical Protocols provide a current Glossary of Terms and Abbreviations.

11. REFERENCES

1. Roberts, D., et al., *Effective endovascular treatment of calcified femoropopliteal disease with directional atherectomy and distal embolic protection: final results of the DEFINITIVE Ca(+)(+) trial.* Catheter Cardiovasc Interv, 2014. **84**(2): p. 236-44.
2. Dave, R.M., et al., *Excimer laser recanalization of femoropopliteal lesions and 1-year patency: results of the CELLO registry.* J Endovasc Ther, 2009. **16**(6): p. 665-75.
3. Gray, W.A., et al., *Jetstream Atherectomy System treatment of femoropopliteal arteries: Results of the post-market JET Registry.* Cardiovasc Revasc Med, 2018. **19**(5 Pt A): p. 506-511.
4. Rocha-Singh, K.J., et al., *Directional atherectomy before paclitaxel coated balloon angioplasty in complex femoropopliteal disease: The VIVA REALITY study.* Catheter Cardiovasc Interv, 2021.
5. Gomez, G., M. Gomez-Mateu, and U. Dafni, *Informed choice of composite end points in cardiovascular trials.* Circ Cardiovasc Qual Outcomes, 2014. **7**(1): p. 170-8.
6. Brinton, T.J., et al., *Feasibility of Shockwave Coronary Intravascular Lithotripsy for the Treatment of Calcified Coronary Stenoses: First Description.* Circulation, 2019. **139**(6): p. 834-836.
7. Brodmann, M., A. Holden, and T. Zeller, *Safety and Feasibility of Intravascular Lithotripsy for Treatment of Below-the-Knee Arterial Stenoses.* J Endovasc Ther, 2018. **25**(4): p. 499-503.
8. Brodmann, M., et al., *Primary outcomes and mechanism of action of intravascular lithotripsy in calcified, femoropopliteal lesions: Results of Disrupt PAD II.* Catheter Cardiovasc Interv, 2019. **93**(2): p. 335-342.
9. Patel, M.R., et al., *Evaluation and treatment of patients with lower extremity peripheral artery disease: consensus definitions from Peripheral Academic Research Consortium (PARC).* J Am Coll Cardiol, 2015. **65**(9): p. 931-41.
10. Tepe, G., et al., *Intravascular Lithotripsy for Peripheral Artery Calcification: Mid-term Outcomes From the Randomized Disrupt PAD III Trial.* Journal of the Society for Cardiovascular Angiography & Interventions, 2022.
11. *FDA Guidance Document: Multiple Endpoints in Clinical Trials.* https://www.fda.gov/regulatory-information/search-fda-guidance-documents/multiple-endpoints-clinical-trials-guidance-industry, 2022.
12. DerSimonian, R. and N. Laird, *Meta-analysis in clinical trials.* Control Clin Trials, 1986. **7**(3): p. 177-88.

APPENDIX A – DATA HANDLING AND ANALYSIS

This appendix provides additional details on the data handling and analysis of the study data.

Incomplete Data

If a date needed for calculation (e.g., date of birth for age) is an incomplete date (e.g., **112006 or ****2006) it will be completed as follows:

For incomplete event dates '01' or '0101' will be entered, respectively (worst case).

However, if an imputed event date is before the date of procedure, the date of event will be set equal to the date of procedure.

For all other incomplete dates '15' or '0107' will be entered, respectively (less far from correct date). If the missing month is known to be between July and December, the month September will be used.

If the entire start date of an event or a medication is missing, the procedure date will be imputed. Imputed dates will be limited to date of birth, AE start date, and medication start and end dates.

General Analysis Definitions

Assessments will be presented chronologically by study day, which is defined in the following:

Study day= assessment day – date of index-procedure.

Index-procedure day = 0. Events occurring on the day of the index-procedure will be considered day 0.

Events occurring on the day of discharge will be considered in-hospital.

Time of follow-up = date of last contact – date of index procedure. Where date of last contact is date of death or the latest of: date of last adverse event, date of last procedure, or date of last-follow-up visit.

Events will be reported as days elapsed since index procedure, or Event Day = event start date – index procedure date. Partial or missing dates will be imputed based on the rules described above. This approach avoids bias that increases with time since index procedure, as well as any confusion that may occur during event adjudication. For analysis at each time point, subjects will be censored at the time point or time to follow-up as defined above, whichever is earlier.

For all the clinical endpoints, the denominator will include subjects who either have an adjudicated event (e.g., death, revascularization) before the time of interest, or have a contact beyond the lower window of the follow-up.

Specific Reporting Conventions

Two types of endpoints will be reported – Clinical/safety endpoints and Core lab endpoints.

A. Clinical/Safety Endpoints

Clinical endpoints include repeat revascularization procedures on target lesions/vessels, death, target limb amputations, and safety endpoints including Major Adverse Events, that occur within a specific time period. For each reporting period, the event rate will be defined as the number of subjects experiencing the event divided by the number of evaluable subjects. A subject will be considered evaluable for a reporting period if the study day of last contact is at or after the lower limit of the reporting window on the snapshot date. Acceptable study contacts include a study visit, adverse event, CEC adjudicated event date, image date, or other verifiable event that occurs during the active follow-up of a subject. Active follow-up ends when a subject completes the study, withdraws consent, or is considered lost to follow-up.

B. Core Lab Endpoints

Core lab endpoints include the endpoints that are determined by core lab assessment (duplex ultrasound or angiography), such as restenosis measured by duplex ultrasound or residual stenosis by angiography. Core lab endpoints rely on the actual evaluable assessment. If the scheduled assessment is not completed or the data are not evaluable (i.e., not readable or non-diagnostic), it will be treated as missing value and excluded from the analysis. Data will be used for subjects who have an evaluable (readable or diagnostic) scheduled duplex ultrasound.

C. Determination of Primary Patency Composite Effectiveness Endpoint

Primary patency contains both core lab endpoint (by visit) and clinical/safety endpoint (by cut-off days); the event of the individual component will be determined first, and the composite endpoint will then be determined.

APPENDIX B – LITERATURE REVIEW & META-ANALYSIS METHODOLOGY

Literature Review: Overview

As part of ongoing clinical evaluation of the Shockwave Peripheral IVL System, periodic literature reviews are conducted to continually assess the benefit risk profile of the device. The most recent review was a comprehensive literature search which spanned 21 years from January 2000 through Q3 2022 and included an appraisal of peripheral IVL and benchmark devices including atherectomy catheters (orbital/rotational/laser) and cutting/scoring balloons.

For each objective, publications representing unique sources were reviewed to determine which sources reported on the parameter being analyzed including 30-day MAE-and final residual stenosis <50%. In response to study design considerations from FDA, data sources were limited to reports with at least 50 subjects and published within the last 10 years. Case studies, editorials, and literature reviews were not included in the meta-analyses, nor were sources reporting on only one component of MAE. Data from the relevant publications for each safety and effectiveness endpoint were extracted and tabulated for analysis.

Meta-Analysis: Statistical Methods

A meta-analysis was performed for the safety and effectiveness endpoints from the literature review. Two initial models were constructed for each meta-analysis, a common (or fixed) effect model and a random effects model (using the DerSimonian and Laird method [12]). Both models use a weighted average of the outcome, in which the weights are the inverse of the total variance for that study.

The common (or fixed) effect model assumes there is no variation in the true rate between studies (between-study variance equal to 0 with a single intercept), so any observed heterogeneity is assumed to be due to sampling error only. In practice, the studies that are part of the meta-analysis would need to be nearly identical in the composition of their samples for the assumptions of the fixed effect model to hold. The random effects model considers within-study and between-study variance (with a varying intercept value). This is a more realistic characterization of the sample of studies summarized in this meta-analysis. Therefore, the results from random effects models is the basis for these analyses.

Literature Review: Data Extraction Results

A total of 18 articles had outcome data available for at least one performance goal. **Table B1** below lists each article used in the meta-analyses; see bibliography in Appendix C for complete citations. For studies with multiple device cohorts (e.g., orbital and rotational atherectomy), each cohort was treated as an independent data source; as such, these publications may be listed more than once in the table. Each source was given a unique reference ID for the meta-analysis.

Table B1. Source Articles Used in Meta-Analyses

Meta-Analysis ID	Article Short Label	30-day MAE	RS<50%
9	Adams 2021 [9] (IVL)		Yes
11	Stavroulakis 2022 [11] (IVL)	Yes	
17	Rocha-Singh 2021 [17] (Atherectomy)	Yes	
19	Rundback 2019 [19] (Atherectomy)	Yes	
23A	Iida 2022 [23A] (Atherectomy)	Yes	
31A	Mustapha 2019 [31A] (Atherectomy)	Yes	Yes
31B	Mustapha 2019 [31B] (Atherectomy)	Yes	Yes
31C	Mustapha 2019 [31C] (Atherectomy)	Yes	Yes
34	Shammas 2018 [34] (Atherectomy)	Yes	
35	Davis 2017 [35] (Atherectomy)	Yes	Yes
38	Gandini 2020 [38] (Atherectomy)		Yes
41	Shammas 2020 [41] (Atherectomy)	Yes	
43	Gray 2018 [43] (Atherectomy)	Yes	
47	Ponukumati 2020 [47] (Atherectomy)	Yes	
48	McKinsey 2014 [48] (Atherectomy)	Yes	
49	Roberts 2014 [49] (Atherectomy)	Yes	Yes
78	Disrupt PAD I/II 2014 [78] (IVL)	Yes	Yes
79	Distrupt PAD III RCT 2021 [79] (IVL)	Yes	Yes

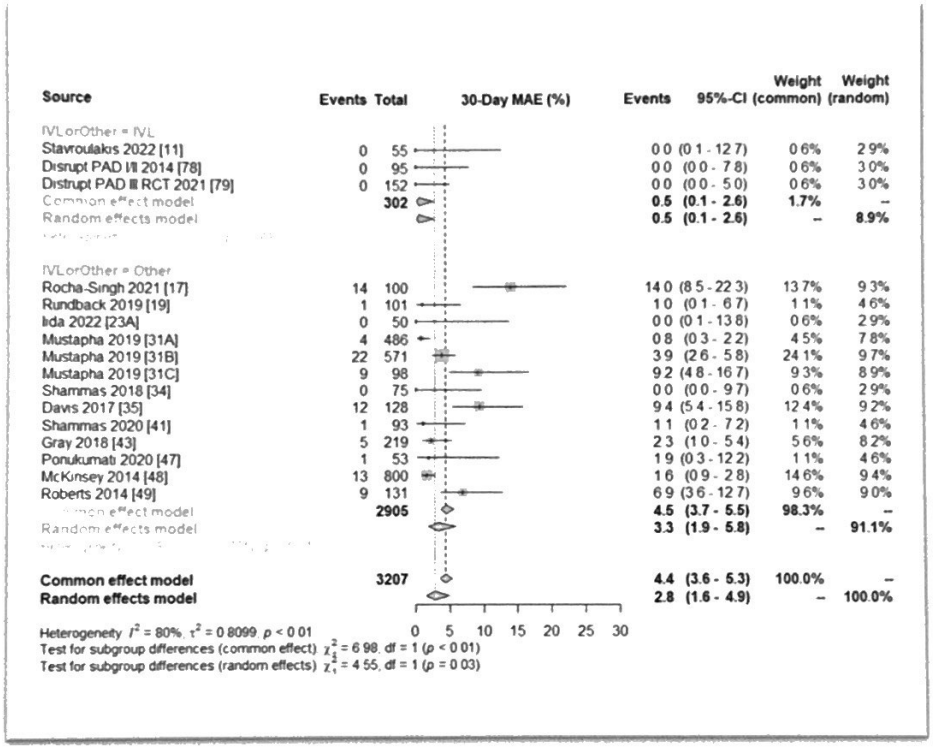
*Meta-Analysis re-run 05JAN2023, excluding sources **ten** or more years old **(i.e. 2013 – Q3 2022)** and excluding sources with less than 50 subjects. IVL and Benchmark literature sources were included.

Literature Review: 30-Day MAE

The literature review identified 16 unique sources, representing 3,207 total subjects, with complete data available for 30-day MAE (see **Figure B1.** Meta-Analysis Forest Plot for 30-Day MAE). Sample sizes ranged from 50 to 800 and the reported 30-day MAE rates ranged from 0.0% - 14.0%. In the meta-analysis, the common effect model estimated 30-day MAE at 4.4% (95% CI:

3.6-5.3), and the random effects model estimated 2.8% (95% CI: 6-4.9). Residual heterogeneity was considered high with $I^2 = 80\%$.

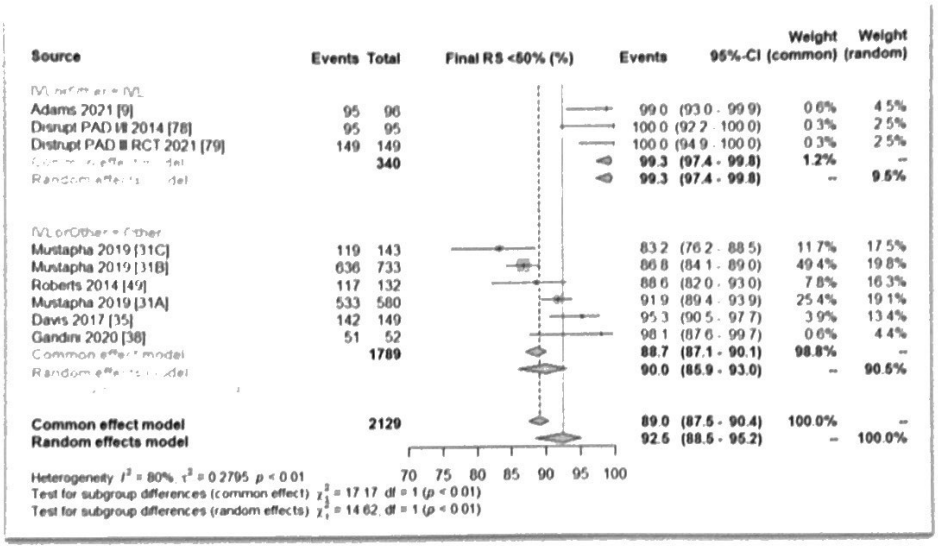
Figure B1. Meta-Analysis Forest Plot for 30-Day MAE



Literature Review: Final Residual Stenosis <50%

The literature review identified 9 unique sources, representing 2129 total subjects, that reported the percentage of cases with final residual stenosis <50% (see **Figure B2**). Sample sizes ranged from 52 to 733, and the reported rates ranged from 83.2% - 100%. In the meta-analysis, the common effects model estimated final residual stenosis <50% at 89.0% (95% CI: 87.5-90.4), and the random effects model estimated a rate of 92.5% (95% CI: 88.5-95.2). Residual heterogeneity was considered high with $I^2 = 80\%$.

Figure B2. Forest Plot for Final Residual Stenosis < 50%



Meta-Analysis Discussion

Substantial residual heterogeneity was observed in both analyses, represented by I2 values greater than 70% and p-values associated with the I2 of <0.01. The I2 value represents the percentage of all observed heterogeneity that is attributed to between-study variance in the true population proportion, and a significant p-value indicates that the null hypothesis of a single true population proportion (Π) has been rejected, and thus the point estimate represents a range of true population proportions. A high I2 value indicates that, while the point estimate of the range of true population proportions is accurate, it will be less precise than is optimal for a performance goal that will be applied across a range of studies. The study hypotheses take these findings into consideration.

With a PG of 11.2% and 90 subjects, rejection of the null hypothesis would demonstrate an expected true population 30-Day MAE rate of 0.0-4.4% with an upper 2-sided 95% CI of less than or equal to 11.2% and with a PG of 85.0%. Rejection of the null effectiveness hypothesis would demonstrate an expected true population rate of 93.3 - 100.0% with a lower 2-sided 95% CI of greater than or equal to 85%. These results are clinically and regulatory appropriate estimates based on prior investigations of peripheral IVL [1-3] and are also consistent with the broader contemporary peripheral literature sources and meta-analysis.

APPENDIX C – BIBLIOGRAPHY OF PUBLICATIONS USED IN META-ANALYSES

Ardita, V., et al., Jetstream Atherectomy System for Treatment of Femoropopliteal Artery Disease: A Single Center Experience and Mid-term Outcomes. Ann Vasc Surg, 2020. 62: p. 365-374.

Brodmann, M., et al. (2017). "Safety and Performance of Lithoplasty for Treatment of Calcified Peripheral Artery Lesions." J Am Coll Cardiol 70(7): 908-910.

Brodmann, M., et al. (2019). "Primary outcomes and mechanism of action of intravascular lithotripsy in calcified, femoropopliteal lesions: Results of Disrupt PAD II." Catheter Cardiovasc Interv 93(2): 335-342.

Davis, T., et al., Safety and effectiveness of the Phoenix Atherectomy System in lower extremity arteries: Early and midterm outcomes from the prospective multicenter EASE study. Vascular, 2017. 25(6): p. 563-575.

Gandini, R., et al., A Single-Center Experience With Phoenix Atherectomy System in Patients With Moderate to Heavily Calcified Femoropopliteal Lesions. Cardiovasc Revasc Med, 2020. 21(5): p. 676-681.

Gray, W.A., et al., Jetstream Atherectomy System treatment of femoropopliteal arteries: Results of the post-market JET Registry. Cardiovasc Revasc Med, 2018. 19(5 Pt A): p. 506-511.

Iida, O., et al., Clinical Safety and Efficacy of Rotational Atherectomy in Japanese Patients with Peripheral Arterial Disease Presenting Femoropopliteal Lesions: The J-SUPREME and J-SUPREME II Trials. J Endovasc Ther, 2022. 29(2): p. 240-247.

Kokkinidis, D.G., et al., Two-Year Outcomes of Orbital Atherectomy Combined With Drug-Coated Balloon Angioplasty for Treatment of Heavily Calcified Femoropopliteal Lesions. J Endovasc Ther, 2020. 27(3): p. 492-501.

Maehara, A., et al., Intravascular ultrasound evaluation of JETSTREAM atherectomy removal of superficial calcium in peripheral arteries. EuroIntervention, 2015. 11(1): p. 96-103.

McKinsey, J.F., et al., Lower extremity revascularization using directional atherectomy: 12-month prospective results of the DEFINITIVE LE study. JACC Cardiovasc Interv, 2014. 7(8): p. 923-33.

Mustapha, J., et al., One-Year Results of the LIBERTY 360 Study: Evaluation of Acute and Midterm Clinical Outcomes of Peripheral Endovascular Device Interventions. J Endovasc Ther, 2019. 26(2): p. 143-154.

Ponukumati, A.S., et al., Outcomes of rotational atherectomy in complex lesions of the superficial femoral artery. J Vasc Surg, 2020. S0741-5214: p. 30594-2.

Roberts, D., et al., Effective endovascular treatment of calcified femoropopliteal disease with directional atherectomy and distal embolic protection: final results of the DEFINITIVE Ca(+)(+) trial. Catheter Cardiovasc Interv, 2014. 84(2): p. 236-44.

Rocha-Singh, K.J., et al., Directional atherectomy before paclitaxel coated balloon angioplasty in complex femoropopliteal disease: The VIVA REALITY study. Catheter Cardiovasc Interv, 2021. 98(3): p. 549-558.

Rundback, J., et al., Novel laser-based catheter for peripheral atherectomy: 6-month results from the Eximo Medical B-Laser IDE study. Catheter Cardiovasc Interv, 2019. 94(7): p. 1010-1017.

Shammas, N.W., et al., Long-term outcomes with Jetstream atherectomy with or without drug coated balloons in treating femoropopliteal arteries: A single center experience (JET-SCE). Cardiovasc Revasc Med, 2018. 19(7 Pt A): p. 771-777.

Shammas, N.W., et al., Acute and 30-Day Safety and Effectiveness Evaluation of Eximo Medical's B-Laser, a Novel Atherectomy Device, in Subjects Affected With Infrainguinal Peripheral Arterial Disease: Results of the EX-PAD-03 Trial. Cardiovasc Revasc Med, 2020. 21(1): p. 86-92.

Stavroulakis, K., et al. (2022). "Intravascular Lithotripsy and Drug-Coated Balloon Angioplasty for Severely Calcified Femoropopliteal Arterial Disease." J Endovasc Ther: 15266028221075563.

Tepe, G., et al (2021). "Intravascular Lithotripsy for Peripheral Artery Calcification: 30-Day Outcomes From the Randomized Disrupt PAD III Trial." J Am Coll Cardiol 14(12).

Yamamoto, Y., et al., Effects of high-speed rotational atherectomy in peripheral artery disease patients with calcified lesions: a retrospective multicenter registry. Cardiovasc Interv Ther, 2020. 35(4): p. 393-397.

Zeller, T., et al., Directional Atherectomy Followed by a Paclitaxel-Coated Balloon to Inhibit Restenosis and Maintain Vessel Patency: Twelve-Month Results of the DEFINITIVE AR Study. Circ Cardiovasc Interv, 2017. 10(9).

Document History: