Medical Coverage Policy

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Cardiac Omnibus Codes

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Related Coverage Resources

INSTRUCTIONS FOR USE

The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Each coverage request should be reviewed on its own merits. Medical directors are expected to exercise clinical judgment where appropriate and have discretion in making individual coverage determinations. Where coverage for care or services does not depend on specific circumstances, reimbursement will only be provided if a requested service(s) is submitted in accordance with the relevant criteria outlined in the applicable Coverage Policy, including covered diagnosis and/or procedure code(s). Reimbursement is not allowed for services when billed for conditions or diagnoses that are not covered under this Coverage Policy (see "Coding Information" below). When billing, providers must use the most appropriate codes as of the effective date of the submission. Claims submitted

for services that are not accompanied by covered code(s) under the applicable Coverage Policy will be denied as not covered. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Overview

This Coverage Policy addresses multiple cardiac-related devices and procedures, including:

- Carotid sinus baroreflex activation device (i.e., BAROSTIM™ NEO® System)
- Pulmonary artery pressure sensor (e.g., CardioMEMS™ HF system, Cordella™ Pulmonary Artery Sensor System)
- Cardiac contractility modulation (CCM®) therapy (i.e., OPTIMIZER Smart System)
- Coronary Intravascular Lithotripsy (IVL) (i.e., Shockwave C2 Coronary IVL System)

Coverage Policy

Carotid Sinus Baroreflex Activation Device
Carotid sinus baroreflex activation device (CPT® 0266T, 0268T and HCPCS code C1825) is considered experimental, investigational or unproven.

Pulmonary Artery Pressure Sensor
Implantation and monitoring of a pulmonary artery pressure sensor (CPT® 33289 and HCPCS C2624) is considered experimental, investigational or unproven.

Cardiac Contractility Modulation Therapy
The use of cardiac contractility modulation therapy (CPT® 0408T and HCPCS C1824) is considered experimental, investigational or unproven.

Coronary Intravascular Lithotripsy
Coronary intravascular lithotripsy (HCPCS code C1761) is considered experimental, investigational or unproven.

Health Equity Considerations

Health equity is the highest level of health for all people; health inequity is the avoidable difference in health status or distribution of health resources due to the social conditions in which people are born, grow, live, work, and age.

Social determinants of health are the conditions in the environment that affect a wide range of health, functioning, and quality of life outcomes and risks. Examples include safe housing, transportation, and neighborhoods; racism, discrimination and violence; education, job opportunities and income; access to nutritious foods and physical activity opportunities; access to clean air and water; and language and literacy skills.

Blacks have a higher incidence of HF and disproportionately have poor outcomes related to HF compared with whites. These racial differences in HF outcomes are caused, in part, by the higher prevalence of clinical risk factors for HF such as uncontrolled hypertension, endothelial dysfunction, and deleterious genetic polymorphisms among nonwhites. Before 50 years of age, HF

is more common among Blacks than whites. This higher risk is considered to be the result of differences in the prevalence of hypertension, diabetes mellitus, and low socioeconomic status (SES). Women with HF report worse health-related quality of life than men with HF. Women differ from men in clinical symptoms and experience more morbidity, particularly decreased functional status and depression. Generally speaking, the treatment guidelines for men and women are the same, although women have been underrepresented in trials evaluating HF therapy (White-Williams, et al., 2020).

General Background

CAROTID SINUS BAROREFLEX ACTIVATION DEVICE

Baroreceptors are sensors located in the carotid sinus and in the aortic arch. The carotid sinus baroreceptors are sensitive to pressure changes in the arterial blood pressure and relay the information to the brain. This response brings appropriate changes to maintain heart rate and blood pressure in normal physiological limits, which is known as 'carotid sinus baroreflex'.

Baroreflex activation therapy (BAT) is a device-based approach that consists of an implanted pulse generator (implanted in the pectoral region), external programming system, and leads placed adjacent to the carotid sinus to deliver electrical pulses to the carotid baroreceptors. Electrical stimulation of the carotid baroreceptors results in activation of the baroreflex system.

U.S. Food and Drug Administration (FDA): The BAROSTIM™ NEO® System (CVRx, Inc.) received FDA Premarket Approval Application (PMA) approval on August 16, 2019 (P180050). The BAROSTIM™ NEO® System is indicated for the improvement of symptoms of heart failure – quality of life, six-minute hall walk and functional status, for patients who remain symptomatic despite treatment with guideline-directed medical therapy, are NYHA Class III or Class II (who had a recent history of Class III), have a left ventricular ejection fraction ≤ 35%, a NT-proBNP < 1600 pg/ml and excluding patients indicated for Cardiac Resynchronization Therapy (CRT) according to AHA/ACC/ESC guidelines.

Patients are contraindicated if they have:

- Been assessed to have bilateral carotid bifurcations located above the level of the mandible
- Baroreflex failure or autonomic neuropathy
- Uncontrolled, symptomatic cardiac bradyarrhythmias
- Carotid atherosclerosis that is determined by ultrasound or angiographic evaluation greater than 50%
- Ulcerative plaques in the carotid artery as determined by ultrasound or angiographic evaluation
- Known allergy to silicone or titanium

Professional Societies/Organizations: The 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure (Heidenreich, et al., 2022) states:

> 7.4.2. Other Implantable Electrical Interventions
> Trials of device stimulation of the vagus nerve, spinal cord, and baroreceptors have had mixed responses.

Literature Review: Baroreflex activation therapy (BAT) is an emerging device-based therapy for heart failure (HF). It is also being studied for off-label uses including resistant hypertension. More data from large, comparative trials are needed to establish the efficacy of BAT on long term health outcomes such as hospitalizations and mortality.

In a multinational RCT (HOPE4HF), Abraham et al. (2015) assessed the safety and efficacy of carotid baroreflex activation therapy (BAT) in advanced HF.

- Patients with New York Heart Association (NYHA) functional class III HF and ejection fractions ≤35% on chronic stable guideline-directed medical therapy (GDMT) were enrolled at 45 centers in the United States, Canada, and Europe. They were randomly assigned to receive ongoing GDMT alone (control group) or ongoing GDMT plus BAT (treatment group) for 6 months. The primary safety end point was system- and procedure-related major adverse neurological and cardiovascular events. The primary efficacy end points were changes in NYHA functional class, quality-of-life score, and 6-minute hall walk distance.
- Of the 69 patients assigned to the control group who reached their activation dates, 15 did not complete 6 months of follow-up: 4 patients died, 5 withdrew consent, 3 were lost to follow-up, and 3 missed the visit.
- Of the 71 patients who received the BAT system and reached their activation date, 7 did not complete 6 months of follow-up: 5 died and 2 withdrew consent. At 6 months, statistically significant improvements were observed in NYHA functional class, MLWHFQ QoL score, and 6MHW distance in BAT patients compared with control patients ($p = 0.002$, $p < 0.001$, and $p = 0.004$, respectively). NT-proBNP was reduced in the treatment group and increased in the control group, with a significant between-group difference ($p=0.02$).

Weaver et al. (2016) reported on a total of 101 HOPE4HF trial patients who completed 12 months of follow-up (57 BAT+GDMT, 44 GDMT). Significant beneficial treatment effects in SBP, NT-proBNP, 6MHW, QOL, and NYHA Class observed at 6 months were sustained through 12 months, both for the study population as a whole as well as the no-CRT cohort. In the no-CRT cohort, improvement in NYHA Class for BAT+GDMT reached statistical significance, a finding not observed in the 6-month analysis.

Zile et al. (2015) conducted a study to define the differences in treatment effect produced by BAT in two protocol prespecified groups of patients: those with vs. those without cardiac resynchronization therapy (CRT) present. Some data was collected retrospectively, some prospectively.

- NYHA Class III chronic HF patients with an LVEF ≤35% were randomized to receive ongoing GDMT alone (control group) or ongoing GDMT plus BAT (BAT group).
- The CRT vs. no-CRT groups were similar with respect to baseline characteristics, except for the following characteristics: the no-CRT patients were younger, more frequently had hypertension noted in their medical history, and had a shorter QRS.
- Of the 69 patients assigned to the control group who reached their activation date, 21 had a CRT, 48 did not have a CRT. In the CRT control group patients, four did not complete 6 months of follow-up: two patients died, one withdrew consent, and one missed the visit. In the no-CRT control group patients 11 did not complete 6 months of follow-up: two patients died, four withdrew consent, three were lost to follow-up, and two missed the visit.
- Of the 71 patients implanted with the BAT system reaching their activation date 24 had a CRT and 47 did not. In the CRT BAT group patients two did not complete 6 months of follow-up (owing to death). In the no-CRT BAT group patients, five did not complete 6 months of follow-up: three patients died and two withdrew consent.
- MANCE-free rate at 6 months was 100% in CRT and 96% in no-CRT group. The difference was statistically significant in QoL score ($P = 0.04$), 6MHWD ($P = 0.01$), and LVEF ($P=0.02$), marginally significant in NYHA and HF hospitalization days, and not significant in NT proBNP and number of HF hospitalizations. Limitations of this study include small sample size and retrospective data collection.

The Baroreflex Activation Therapy for Heart Failure trial (BeAT-HF, NCT02627196) (Zile, et al., 2020) was a multicenter RCT conducted to the safety and effectiveness of baroreflex activation therapy (BAT) in 408 patients with heart failure with reduced ejection fraction (HFrEF). Patients

were randomized to receive either BAT plus optimal medical management (BAT group) or optimal medical management alone (control group).

- The three primary effectiveness endpoints included 6-min hall walk distance (6MHW), Minnesota Living with HF Questionnaire quality-of-life (QOL) score, and N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels. The single safety endpoint was major adverse neurological or cardiovascular system or procedure-related event-free rate (MANCE).
- During the 6-month follow-up, there was a significant difference in medical management between the 2 arms, with a disproportionately higher number of medications added in the control group.
- BAT improved the EuroQol-5 Dimensions (EQ-5D) index by a net difference of $\Delta=0.10$ ($p < 0.001$). BAT improved NYHA functional class (78 [65%] in the BAT group vs. 39 [31%] in the control group; $\Delta=34\%$; $p < 0.001$) statistically significant).
- Cardiovascular serious adverse events (non-heart failure-related events or non-cardiovascular death) were 0.101 events per patient-year in the BAT group vs. 0.206 in the control group; p= 0.023 (statistically significant); 51% reduction with BAT.
- In the 144 of 408 randomized patients that had a NT-proBNP >1,600 pg/ml, BAT did not have a statistically significant improvement on 6MHW distance or NT-proBNP but did improve QOL score compared with that in the control group.
- The authors concluded that BAT is safe, improved the patient-centered symptomatic endpoints of QOL score, exercise capacity, and functional status, and significantly decreased NTproBNP in patients with NYHA functional class III (or patients with NYHA functional class II who had a recent history of NYHA functional class III), EF ≤35%, NT-proBNP <1,600 pg/ml, and who did not have a Class I indication for CRT.

Zile et al. (2024) reported analyses that included follow-ups for all BeAT-HF trial patients from randomization until last patient visit. Overall, 323 patients had 332 primary events, with a median of 3.6 years of follow-up/patient. The primary endpoint was a composite of the rate of cardiovascular mortality and HF morbidity. BAT did not result in a significant difference in the composite primary endpoint, CV mortality and HF morbidity, or the individual components of the primary endpoints compared with control.

Coats et al. (2022) conducted an individual patient data (IPD) meta-analysis from all patients enrolled in Abraham et al. (2015) and Zile et al. (2020). A total of 554 randomized patients were included.

- In all patients, BAT provided significant improvement in 6MHW distance of 49m, MLWHF QoL of −13 points, and 3.4 higher odds of improving at least one NYHA class when comparing from baseline to 6 months. These improvements were similar, or better, in patients who had baseline NT-proBNP <1600 pg/ml, regardless of the cardiac resynchronization therapy indication status. NT-proBNP levels appeared to improve in all patients, but only reached statistical significance in the cohorts that excluded patients with NT-proBNP >1600 pg/ml.

Blanco et al. (2023) retrospectively reported on 30 patients with chronic heart failure with reduced ejection fraction (HFrEF) who received baroreflex activation therapy (BAT) with the Barostim Neo™ device at a single center in Germany. Most patients (83%) had previous heart failure hospitalization (HFH).

- Median follow-up time for clinical events defined as death or HF hospitalization was 16 (10–33) months. During this time, a total of 10 patients died [2 HF, 3 not related to HF (sepsis, renal failure, and malignancy), and 5 unexplained]. Mortality at 1 and 3 years was 20% and 33.3%.
- A total of 14 patients were hospitalized due to HF during follow-up. One of those patients was hospitalized twice for this reason, resulting in an event rate of 15.

- The LVEF improved from 25.5 (20.0–30.5) % at baseline to 30.0 (25.0–36.0) % at 12 months (P = 0.014). NYHA functional class significantly improved between baseline and 12-month follow-up (P < 0.001).
- Limitations of the study include small sample size and retrospective nature of the study.

IMPLANTATION AND MONITORING OF A PULMONARY ARTERY PRESSURE SENSOR

Heart failure (HF) is a complex clinical syndrome identified by presence of current or prior characteristic symptoms, such as dyspnea and fatigue, and evidence of cardiac dysfunction as a cause of these symptoms (e.g., abnormal left ventricular [LV] and/or right ventricular [RV] filling and elevated filling pressures). The functional status of patients with HF is often described using the New York Heart Association (NYHA). The NYHA classification, with severity of disability ranging from I to IV is the classification system that is most commonly used to quantify the degree of functional limitation imposed by HF is one first developed by the NYHA. This system assigns patients to one of four functional classes, depending on the degree of effort needed to elicit symptoms:

- Class I – Patients with heart disease without resulting limitation of physical activity. Ordinary physical activity does not cause HF symptoms such as fatigue or dyspnea.
- Class II – Patients with heart disease resulting in slight limitation of physical activity. Symptoms of HF develop with ordinary activity but there are no symptoms at rest.
- Class III – Patients with heart disease resulting in marked limitation of physical activity. Symptoms of HF develop with less than ordinary physical activity but there are no symptoms at rest.
- Class IV – Patients with heart disease resulting in inability to carry on any physical activity without discomfort. Symptoms of HF may occur even at rest.

Methods for obtaining pulmonary artery pressure (PAP) in patients with chronic heart failure include a right heart catheterization (RHC) procedure or PAP monitoring with an implantable hemodynamic monitoring system which also gets implanted via a RHC. A RHC is a procedure during which a catheter is inserted through a large vein in the neck or groin and subsequently advanced into the pulmonary artery. There are significant risks in undergoing a RHC, whether for repeated direct measurements or for the implantation of a PAP monitoring medical device.

U.S. Food and Drug Administration (FDA): The CardioMEMS™ HF system received FDA approval on May 28, 2014 (Abbotts, formerly St. Jude Medical, Inc., St. Paul, MN) (PMA P100045). The CardioMEMS HF System includes the CM2000 implantable PA Sensor/Monitor and transvenous catheter delivery system, the CM1000 Patient Electronics System (GSM), the CM1010 Patient Electronics System (GSM), and CM3000 Hospital Electronics System.

- According to the PMA, the device is indicated for wirelessly measuring and monitoring pulmonary artery (PA) pressure and heart rate in patients with New York Heart Association (NYHA) Class III HF who have been hospitalized for HF in the previous year.
- In February 2022, the FDA approved a PMA supplement for the CardioMEMs HF System (St. Jude Medical [Abbott]) for expanding the indications to include NYHA Class II patients (P100045/S056). The Feb 18, 2022 approval letter states: "The CardioMEMS HF System is indicated for wirelessly measuring and monitoring pulmonary artery pressure and heart rate in NYHA Class II or III heart failure patients who either have been hospitalized for heart failure in the previous year and/or have elevated natriuretic peptides. The hemodynamic data are used by physicians for heart failure management with the goal of controlling pulmonary artery pressures and reducing heart failure hospitalizations."

The Cordella™ Pulmonary Artery Sensor System (CorPASS) (Endotronix, Inc.) received FDA PMA approval on 06/20/2024 (P230040).

- Indications for Use: The Cordella Pulmonary Artery Sensor System is intended to measure, record and transmit pulmonary artery pressure (PAP) data from NYHA Class III heart failure patients who are at home on diuretics and guideline-directed medical therapy (GDMT) as well as have been stable for 30 days on GDMT. The device output is meant to aid clinicians in the assessment and management of heart failure, with the goal of reducing heart failure hospitalizations.
- Contraindications: The Cordella Pulmonary Artery Sensor System is contraindicated for patients with an inability to take dual antiplatelet or anticoagulants for one month post implant.
- Device description: The Cordella PA Sensor System is designed to be used with the Cordella Heart Failure System to better connect healthcare professionals and patients with tools for heart failure management. The Cordella PA Sensor is an implantable blood pressure monitor that permanently resides in the patient's pulmonary artery. With this Sensor, PA pressure can be wirelessly measured from the patient's home on demand. Active management of a patient using PA pressure data from the Cordella Sensor and vital signs and patient-reported symptoms data from Cordella HF System may improve long-term outcomes in patients with NYHA Class III heart failure. The Cordella PA Sensor System is comprised of the following subsystems:
  - Cordella PA Sensor
  - Cordella Delivery System
  - myCordella Handheld Patient Reader (including Dock)
  - Cordella Calibration Equipment (CalEQ)
  - Cordella Data Analysis Platform (CDAP)

The study reviewed for Cordella PMA approval has not yet been published in the peer-reviewed scientific literature.

- Guichard et al. (2023) states that "The PROACTIVE-HF study was originally approved in 2018 as a prospective, randomized, controlled, single-blind, multicenter trial to evaluate the safety and effectiveness of the Cordella pulmonary artery pressure (PAP) Sensor in patients with HF and with New York Heart Association (NYHA) functional class III symptoms. Since then, robust clinical evidence supporting PAP-guided HF management has emerged, making clinical equipoise and enrolling patients into a standard-of-care control arm challenging. Therefore, PROACTIVE-HF was changed to a single-arm trial in 2021 with prespecified safety and effectiveness endpoints to provide evidence for a similar risk/benefit profile as the CardioMEMS HF System. Conclusion: The single-arm PROACTIVE-HF trial is expected to further demonstrate the benefits of PAP-guided HF management of patients with NYHA class III HF. The addition of vital signs, patient engagement and self-reported symptoms may provide new insights into remote guideline-directed medical therapy (GDMT) titration and congestion management."
- The FDA stated that "The data in this [PMA] application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use. The primary and secondary safety and efficacy endpoints of PROACTIVE-HF were met. The safety profile showed 99.2% freedom from device- or system-related complications (DSRC) and 99.8% freedom from pressure sensor failure, with a 3.0% rate of all cause hemoptysis which was numerically higher than prior studies completed to date with similar PAP-measuring devices. In terms of effectiveness, the 6-month incidence of heart failure hospitalization and mortality were low across all populations analyzed. The incidence rate of 0.1589 [95% CI: 0.1200, 0.2106] events per patient 6-month met all criteria for primary endpoint success. While the PROACTIVE-HF aimed to enroll NYHA class III HF patients, the final event rate for the primary effectiveness endpoint (0.1589) was numerically much lower than the average event rate derived from published results from

clinically relevant, contemporary studies of NYHA class III HF subjects (as evidenced by an historical performance goal originally set at 0.43). This unexpected finding may warrant further evaluation in future studies. A post-approval study will address any remaining uncertainty in the overall benefit profile of the device.
There was an improvement in quality of life by five points and 6-minute walk test (6MWT) through 6 months. There was high compliance in both subject transmission of daily data and clinician acknowledgement of those transmissions. Of note, these secondary analyses are purely exploratory, not powered and not adjusted for multiple comparisons" (FDA, Summary of Safety and Effectiveness Data).

Professional Societies/Organizations: The ACC/AHA/Heart Failure Society of America (HFSA) 2022 Guideline for the Management of Heart Failure Section 4.6. Wearables and Remote Monitoring (Including Telemonitoring and Device Monitoring), notes the following:

- In selected adult patients with NYHA class III HF and history of a HF hospitalization in the past year or elevated natriuretic peptide levels, on maximally tolerated stable doses of GDMT with optimal device therapy, the usefulness of wireless monitoring of PA pressure by an implanted hemodynamic monitor to reduce the risk of subsequent HF hospitalizations is uncertain (2b B-R*).
- In patients with NYHA class III HF with a HF hospitalization within the previous year, wireless monitoring of the PA pressure by an implanted hemodynamic monitor provides uncertain value. (Value Statement: Uncertain Value, B-NR) (Heidenreich, et al., 2022).
*See Appendix for ACC/AHA Class of Recommendation and Level of Evidence

A 2023 Journal of the American College of Cardiology (JACC) Scientific Statement on Remote Monitoring for Heart Failure Management at Home (Stevenson, et al., 2023) summarized "To manage HF at home, signals need to be accurate and actionable, with response kinetics for early relooks after intervention. The major target for decreasing HFH and improving quality of life is relief and prevention of congestion, for which tracking of cardiac filling pressures or lung water content has shown most benefit thus far. Algorithms need to be personalized with more precision for signal thresholds and for levels of intervention, some of which should be automated for direct patient access. For patients at lower risk of HF events, multiparameter scores from implanted rhythm devices have identified patient trends for which clinical evaluation may be warranted." Highlights:

- Remote monitoring coupled with a system of care that engages, informs, and empowers patients is essential for effective home management of HF to control symptoms, avoid hospitalization, and ameliorate the patient's perception of illness.
- Effective remote monitoring requires an accurate, reliable signal that is actionable through personalized algorithms.
- Evolving digital health care must address the digital divide and deep gaps in access to HF management (Stevenson, et al., 2023).

Literature Review: Sharif et al. (2024) conducted a prospective, multi-centre, open-label, single-arm trial (SIRONA 2) evaluating the safety and efficacy of the Cordella PAP sensor and Cordella HF system in NYHA class III HF patients in Europe with HF hospitalizations (HFH) and/or an increase in natriuretic peptides in the previous 12 months. The primary efficacy endpoint was the accuracy of the PA sensor mean PAP (mPAP) measurement compared with the fluid-filled catheter during right heart catheterization (RHC) at 90 days.

- Inclusion criteria: Participants included were men or women over 18 years of age with a diagnosis of NYHA class III HF with reduced ejection fraction (HFrEF) or HF with preserved ejection fraction (HFpEF) for at least 6 months treated for a minimum of 3 months and stable for at least 1 month prior to enrolment. Patients had to have at least one HF-related hospitalization, HF treatment in a hospital day-care setting, or unplanned outpatient clinic HF visit within 12 months prior to consent and/or increase of brain natriuretic peptide

(BNP) or N-terminal pro-BNP at time of screening. Twenty-two (31.4%) had a preexisting implantable cardioverter-defibrillator device, and 13 (18.6%) had a cardiac resynchronization therapy (CRT) or CRT-defibrillator device. Twenty (28.6%) patients had left ventricular ejection fraction (LVEF) ≥ 50%.

- Results: A total of 70 patients were implanted with the Cordella PA Sensor System, 68 who were still in the study 12 months post-implant.
  - PAP sensor accuracy at the 12 month follow-up visit was assessed in 48 of the 70 implanted subjects via concurrent Cordella and fluid-filled RHC measurements. Tests of PA sensor accuracy indicated agreement between Cordella PA Sensor System and RHC PAP measurements at 12 months.
  - Fourteen patients (20.0%) experienced 18 HFH events (defined as in-hospital, hospital day-care setting, or urgent outpatient clinic HF visits) through 12 months. This translated into an event per patient year (EPPY) of 0.27. When examining the composite HFH plus death (N = 5 deaths), there were 23 events with an 0.33 EPPY.
- Study limitations: First, the major methodological limitation is the lack of a control group under standard HF care management. Second, comparison between HFHs prior to sensor implant and after sensor implant may be affected by a lack of robust study definition of HFH prior to sensor implant. Finally, nine months after SIRONA 2 began enrolment, the COVID-19 pandemic began.
- Author conclusion: Cordella wireless implantable PAP sensor system, incorporating comprehensive vital signs and PAP monitoring, along with high levels of patient engagement, enables long-term safe and accurate monitoring of HF status in NYHA class III HF patients (Sharif, et al., 2024).

Urban et al. (2024) conducted a meta-analysis examining the efficacy of pulmonary artery pressure (PAP) monitoring devices (CardioMEMS and Chronicle [not FDA-approved]) in preventing adverse outcomes in HF patients, addressing gaps in prior randomized controlled trials (RCTs). Five RCTs (2572 participants) were systematically reviewed.

- PAP monitoring significantly reduced HF-related hospitalizations ($p = 0.0006$) and HF events ($p = 0.03$), with no impact on all-cause or cardiovascular mortality. The risk of bias was generally high, with evidence certainty ranging from low to moderate. PAP monitoring devices exhibit promise in diminishing HF hospitalizations and events, especially in CardioMEMS and blinded studies. However, their influence on mortality remains inconclusive.
- Further research, considering diverse patient populations and intervention strategies with extended follow-up, is crucial for elucidating the optimal role of PAP monitoring in HF management.

Brugts et al. (2023) conducted an open-label, randomized trial (MONITOR-HF) done in 25 centers in the Netherlands. A total of 348 patients with chronic heart failure of New York Heart Association class III and a previous heart failure hospitalization were randomly assigned to:

1. CardioMEMS-HF group (n=176) (heart failure management with guideline-directed medical therapy [GDMT] and diuretics with the addition of hemodynamic monitoring by a pulmonary artery pressure sensor); or
2. standard care group (n=172) (heart failure management with GDMT and diuretics).

CardioMEMS-HF participants:

- Of the 176, 168 received treatment (8 did not receive intervention because 5 withdrew informed consent, 1 met exclusion criteria, 2 died before implantation).
- Of the 168, 49 discontinued treatments (7 withdrew informed consent, 40 died, and 2 stopped active monitoring [1 non-compliance, 1 sensor failure]).
- 176 included in intention-to-treat (ITT) analysis

Standard care participants:

- 172 received treatment

- 50 discontinued treatments (5 withdrew informed consent, and 45 died)
- 172 included in intention-to-treat (ITT) analysis

The primary endpoint was the mean difference in the Kansas City Cardiomyopathy Questionnaire (KCCQ) overall summary score at 12 months. The mean follow-up time was 1.8 years.

- The mean change in KCCQ overall summary scores between baseline and 12 months among patients in the CardioMEMS-HF group was +7.05 (p=0.0014), compared with -0.08 points among those in the standard care group (p=0.97).
- The total number of heart failure hospitalizations was 117 in the CardioMEMS-HF group and 212 in the control group.
- The median NT-proBNP was significantly reduced from 2377 pg/mL at baseline to 1708 pg/mL (p=0.013) at 12 months in the CardioMEMS-HF group. In the standard care group, there was non-significant difference in NT-proBNP (1907 pg/mL to 1607 pg/mL, p=0.81) at 12 months.

There was no difference on CV/all-cause mortality in patients with CardioMEMS or standard of care. The authors summarized that this MONITOR-HF study showed that hemodynamic monitoring and subsequent individualized adjustment of diuretics and GDMT significantly improved QOL and reduced the number of heart failure hospitalizations. The authors noted a study limitation is the open-label design, as well as the absence of a device (or sham) in controls, which can be prone to bias in the QOL endpoint by unmasking. Another study limitation is the large percentage of treatments that were discontinued, in both groups, for various reasons including death.

The hemodynamic-GUIDEed management of Heart Failure trial (GUIDE-HF) included a randomized arm (n=1000, completed) and a single-arm, observational study (n=2600, ongoing). The single arm of the trial is an observational arm in which NYHA class III patients (n = 2,600) with either a previous heart failure hospitalization (HFH) or elevated natriuretic peptides (but no recent HFH) will be implanted with a PA pressure sensor and observed for occurrence of the primary composite end point of cumulative HF events and mortality at 12 months.

- The randomized arm was a multicenter, single-blind study at 118 centers in the USA and Canada. The study enrolled 1022 patients with NYHA functional class II–IV heart failure, regardless of left ventricular ejection fraction, with a heart failure hospitalization within the 12 months before study consent or elevated natriuretic peptides (B-type natriuretic peptide [BNP] or N-terminal pro-BNP [NT-proBNP]) within 30 days before study consent. A total of 22 patients had unsuccessful implants. This left 1000 participants receiving an implantable PA pressure sensor (CardioMEMS HF System) who were then randomly assigned (1:1) to either hemodynamic-guided heart failure management based on pulmonary artery pressure (n=497) or a usual care (control) group (n=503). Patients were masked to their study group assignment. Investigators were aware of treatment assignment but did not have access to pulmonary artery pressure data for control patients. The primary study end point is the composite of cumulative HF events and all-cause mortality at 12 months. Secondary end points include quality-of-life and functional assessments. A total of 25 treatment group patients and 44 control group patients withdrew from the study before 12 months.
- The authors reported that hemodynamic-guided management did not reduce the combined endpoint of all-cause mortality, heart failure hospitalizations, and urgent heart failure hospital visits despite significant reductions in pulmonary artery pressure during study follow-up compared with the control group. They found no significant between-group differences in the prespecified secondary endpoints of total heart failure events, health related quality of life (KCCQ-12 and EQ-5D-5L), or functional capacity (6MHW). The authors stated that the COVID-19 pandemic had an important effect on the trial. A pre-COVID-19 impact analysis indicated a possible benefit of hemodynamic-guided management on the primary outcome in the pre-COVID-19 period, primarily driven by a lower heart failure hospitalization rate compared with the control group (Lindenfeld, et al., 2019; Lindenfeld, et al., 2021).

Shavelle et al. (2020) conducted a multi-center, prospective, open-label, observational, single-arm trial to assess the efficacy and safety of PA pressure-guided therapy in routine clinical practice with special focus on subgroups defined by sex, race, and ejection fraction (one-year outcomes from the CardioMEMS Post-Approval Study [PAS]).

- The study included 1,200 patients with New York Heart Association class III heart failure (HF) and a prior heart failure hospitalization (HFH) within 12 months and evaluated patients undergoing PA pressure sensor implantation between September 1, 2014, and October 11, 2017. The primary efficacy outcome was the difference between rates of adjudicated HFH one year after compared with the one year before sensor implantation. Safety end points were freedom from device- or system-related complications at two years and freedom from pressure sensor failure at two years. The mean age was 69 years, 37.7% were women, 17.2% were non-White, and 46.8% had preserved ejection fraction (37.7% women; Black 14.3%; Asian 1%; Other 1.5%).
- For the duration of year after sensor implantation, the mean rate of daily pressure transmission was 76±24% and PA pressures declined significantly. The rate of HFH was significantly lower at one year compared with the year before implantation (P<0.0001). The rate of all-cause hospitalization was also lower following sensor implantation (P<0.0001). Results were consistent across subgroups defined by ejection fraction, sex, race, cause of cardiomyopathy, presence/absence of implantable cardiac defibrillator or cardiac resynchronization therapy and ejection fraction. Freedom from device- or system-related complications was 99.6%, and freedom from pressure sensor failure was 99.9% at 1 year. The authors found that both HF hospitalizations and all-cause hospitalizations were significantly lower in the year following implantation of a PA pressure sensor to guide HF management. The magnitude of decrease in PA pressures was related to baseline PA pressures, with greatest reductions in those with the highest pressures at baseline. Reductions in HF hospitalization were consistent across sex and race, across all EF ranges and in addition to best medical and rhythm device therapy.

DeFilippis et al. (2021) reported on a cohort of the above CardioMEMS Post-Approval Study (PAS) study (Shavelle, et al., 2020) to examine sex differences in response to ambulatory hemodynamic monitoring in clinical practice. Four hundred fifty-two women (38% of total) enrolled in the PAS were less likely to be White (78% versus 86%) and more likely to have non-ischemic cardiomyopathy (44% versus 34%) and had significantly higher systolic blood pressure (132 versus 124 mm Hg), mean ejection fraction (44% versus 36%), and pulmonary vascular resistance (3.2 versus 2.6 WU) than men (P<0.001 for all). Both sexes experienced significant decreases in heart failure hospitalizations (HFH) over 12 months. In adjusted models, there were no significant differences in change in HFH between men and women (interaction P=0.13) or all-cause mortality at one year.

Angermann et al. (2020) reported on a prospective, non-randomized, multicenter study (CardioMEMS European Monitoring Study for Heart Failure [MEMS-HF]) to evaluate the safety, feasibility, and performance of CardioMEMS™ HF system in Germany, The Netherlands, and Ireland. The study noted that previously, the findings have not been replicated in health systems outside the United States.

- The study included 234 NYHA class III patients (68 ± 11 years, 22% female, ≥1 HFH in the preceding year) from 31 centers that were implanted with a CardioMEMS sensor and underwent pulmonary artery pressure (PAP)-guided heart failure (HF) management.
- The co-primary outcomes were one-year rates of freedom from device- or system-related complications and from sensor failure and the results were 98.3% [95% confidence interval (CI) 95.8-100.0] and 99.6% (95% CI 97.6-100.0), respectively. Survival rate was 86.2%.
- The secondary endpoints was annualized HFH rate during 12 months after vs.12 months before implant and additional endpoints included: 12-month all-cause death rate; PAP change from baseline; changes in the KCCQ clinical and overall summary scores (CSS, OSS), 20 PHQ-9 sum score, 21 and EQ-VAS score 22 at six and 12 months; changes in HF

medications and NYHA class at six and 12months; patient compliance with taking PAP readings, and healthcare provider compliance for weekly PAP readings.
- For the 12 months post- vs. pre-implant, HF hospitalizations (HFH) decreased by 62% (0.60 vs. 1.55 events/patient-year; hazard ratio 0.38, 95% CI 0.31-0.48; P < 0.0001). After 12 months, mean PAP decreased by 5.1 ± 7.4 mmHg, Kansas City Cardiomyopathy Questionnaire (KCCQ) overall/clinical summary scores increased (P < 0.0001), and the 9-item Patient Health Questionnaire sum score improved (P < 0.0001). The study is limited by the lack of randomization, and a control group, and use of within-patient comparisons.

Abraham et al. (2011) reported results of a randomized controlled trial (RCT): the CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Heart Failure Patients (CHAMPION) trial. The outcomes of this trial were reviewed by the FDA for premarket approval of this device.

- Eligible patients underwent implantation of a wireless pulmonary artery (PA) sensor monitoring system (i.e., CardioMEMS). Five hundred fifty individuals were implanted and randomized to the treatment group (n=270, standard of care HF treatment, plus PA pressure readings) or to the control group (n=280), standard of care HF treatment). Daily PA pressure readings were taken at home by patients in each group and sent to a secure website. In the treatment group clinicians had access to these readings; in the control group clinicians were unable to access pressure readings. Assessment at one, three and six months, and every six-months thereafter included a physical examination, assessment of New York Heart Association class and quality-of-life assessment by use of the 21-question Minnesota Living with Heart Failure questionnaire and review of drugs.
- The primary efficacy endpoint was the rate of heart failure-related hospitalizations during the six months after insertion of the pressure sensor in the treatment group versus the control group. The two primary safety endpoints were device-related or system-related complications. The mean follow-up was 15 months.
- At six months 83 heart-failure-related hospitalizations were reported in the treatment group compared with 120 in the control group (p<0.0001). During the entire follow-up (mean 15 months) the treatment group had a 39% reduction in heart-failure-related hospitalization compared with the control group (p<0.0001). Eight patients had device- or system-related complications (DSRC). Overall freedom from DSRC was 98.6%. Overall freedom from pressure-sensor failures was 100%. Survival rates in the treatment and control groups at six months were similar (p=0·45). Fifteen serious adverse events (AE) were reported, including, infection, bleeding, thrombosis, cardiac arrhythmias, one patient with cardiogenic shock, one atypical chest pain, and one delivery-system failure that required a snare to remove the delivery system.
- Data in this single clinical trial suggest improved short-term outcomes; however, additional large blinded RCTs replicating these findings are required before use of a wireless pulmonary artery sensor monitoring system (e.g., CardioMEMS HF system) is incorporated into routine clinical practice.

Abraham et al. (2016) examined the results of the above CHAMPION study (Abraham, et al., 2011) over 18 months of randomized follow-up and the clinical effect of open access to pressure information for an additional 13 months in patients formerly in the control group.

- The primary outcome was the rate of hospital admissions between the treatment group and control group in both the randomized access and open access periods. Analyses were by intention to treat. The study included 550 patients that were randomly assigned to either the treatment group (n=270) or to the control group (n=280). 347 patients (177 in the former treatment group and 170 in the former control group) completed the randomized access period and transitioned to the open access period.
- Over the randomized access period, rates of admissions to hospital for heart failure were reduced in the treatment group by 33% (hazard ratio [HR] 0·67 [95% CI 0·55-0·80];

p<0·0001) compared with the control group. After pulmonary artery pressure information became available to guide therapy during open access (mean 13 months), rates of admissions to hospital for heart failure in the former control group were reduced by 48% (HR 0·52 [95% CI 0·40-0·69]; p<0·0001) compared with rates of admissions in the control group during randomized access. Eight (1%) device-related or system related complications and seven (1%) procedure-related adverse events were reported.
- The reduction in the need for admission to hospital, both all-cause and heart failure related, seen during the first six months was maintained during longer randomized access follow-up and subsequently during open access in which adjustment of therapy was no longer monitored by study staff protocol.

In a subgroup analysis of the CHAMPION trial, Krahnke et al. (2015) compared HF and respiratory hospitalization rates in the entire CHAMPION cohort with the rates observed within the COPD and non-COPD subgroups. A total of 187 subjects met criteria for classification into the COPD subgroup.

- In the entire cohort, the treatment group had a 37% reduction in HF hospitalization rates (P<.0001) and a 49% reduction in respiratory hospitalization rates (P=.0061). In the COPD subgroup, the treatment group had a 41% reduction in HF hospitalization rates (P=.0009) and a 62% reduction in respiratory hospitalization rates (P=.0023). The rate of respiratory hospitalizations in subjects without COPD was not statistically different (P=.76).
- The authors stated that HF management incorporating hemodynamic information from an implantable PA pressure monitor significantly reduces HF and respiratory hospitalizations in HF subjects with comorbid COPD compared with standard care. The authors noted a limitation of this study was that pulmonary function test data were not available in this study and were not part of the COPD classification criteria.

CARDIAC CONTRACTILITY MODULATION THERAPY

CCM® is the brand name for cardiac contractility modulation (CCM), the non-excitatory electrical pulses delivered by the implantable Optimzer device proposed for the treatment of chronic heart failure with reduced and midrange ejection fractions (EFs). The Optimizer Smart System (Impulse Dynamics, Orangeburg, New York) is a CCM device that is proposed for the treatment of moderate to severe heart failure. The system comprised of programmable OPTIMIZER Smart Implantable Pulse Generator (IPG), Model CCM X10; port plug, #2 torque wrench for securing the implanted leads

- OMNI Smart Programmer, model OMNI™ II (with OMNI Smart Software)
- OPTIMIZER Smart Charger, model Mini Charger
- Implantable leads: 2 ventricular leads and 1 atrial lead.

CCM® is the brand name for cardiac contractility modulation, the non-excitatory electrical pulses delivered by the implantable Optimzer device. Unlike a pacemaker or a defibrillator, the OPTIMIZER system is designed to control the strength of contraction of the heart muscle rather than the rhythm.

According to the manufacturer's website, the Optimizer system is a device-based treatment option for the approximately seventy percent of CHF patients with advanced symptoms that have normal QRS duration and are not suitable for Cardiac Resynchronization Therapy (CRT). It is a minimally invasive implantable device designed to treat Chronic Heart Failure (CHF) in patients that are symptomatic despite appropriate medical treatment. The device is based on novel Cardiac Contractility Modulation technology and delivers non-excitatory electric pulses. CCM signals are nonexcitatory electrical signals applied during the cardiac absolute refractory period that enhance the strength of cardiac muscular contraction (Abraham, et al., 2018).

U.S. Food and Drug Administration (FDA): The OPTIMIZER Smart System received FDA premarket approval (PMA) March 2019. The device, which delivers Cardiac Contractility Modulation therapy, is indicated to improve 6-minute hall walk distance, quality of life, and functional status of New York Heart Association (NYHA) Class III heart failure patients who remain symptomatic despite guideline directed medical therapy, who are in normal sinus rhythm, are not indicated for Cardiac Resynchronization Therapy, and have a left ventricular ejection fraction ranging from 25% to 45%. On 07/30/2021, the FDA gave approval for commercial distribution of the OPTIMIZER SMART Mini System (P180036/S007).

On October 6, 2021, the FDA approved a modification of labeling for the Optimizer Smart medical device, giving approval for removing the Indications for Use requirement for patients to be in normal sinus rhythm (P180036/S008).

Professional Societies/Organizations: The AHA/ACC/HFSA Guideline for the Management of Heart Failure (Heidenreich, et al., 2022) states:

> 7.4.2. Other Implantable Electrical Interventions
> Cardiac contractility modulation (CCM), a device-based therapy that involves applying relatively high-voltage, long duration electric signals to the RV septal wall during the absolute myocardial refractory period, has been associated with augmentation of LV contractile performance. CCM is FDA-approved for patients with NYHA class III with LVEF of 25% to 45% who are not candidates for CRT. Four RCTs have shown benefits in exercise capacity and QOL but, as of yet, no benefits in death or hospitalizations (Abraham, et al., 2018; Kadish et al., 2011; Borggrefe, et al., 2008; Neelagaru, et al., 2006). Most patients in these trials were class III CHF.

Literature Review: Long-term RCT data are lacking to demonstrate the impact of using the Optimizer Smart System on morbidity/mortality. Studies fail to demonstrate if cardiac contractility modulation-guided therapy impacts long-term outcomes/survival.

According to Clinicaltrials.gov:

- Arrhythmia Burden in Patients With Impulse Dynamics Optimizer Cardiac Contractility Modulation (CCM) Device Implantation: Retrospective and Prospective Evaluation (NCT05704426) is recruiting.
- Assessment of Implantable CCM in the Heart Failure Group With Higher Ejection Fraction (AIM HIGHer trial, NCT05064709) is recruiting.
- Assessment of the Safety and Efficacy of a Combined Cardiac Contractility Modulation and Implantable Cardioverter Defibrillator Device for Subjects With Heart Failure and Reduced Ejection Fraction (INTEGRA-D trial, NCT05855135) is recruiting.

Linde et al. (2022) conducted a prospective, multicenter, single-arm pilot study to evaluate the efficacy and safety of CCM (Optimizer device) in heart failure patients with preserved ejection fraction (HFpEF).

- Some of the inclusion criteria included:
  - Baseline ejection fraction ≥50% (echocardiogram, as assessed by the site within 30 days of enrolment and confirmed by the core lab).
  - NYHA class II or III symptoms despite receiving stable optimal medical therapya for at least 30 days based on patient's medical records (chronic stable, not transient or crescendo HF or angina pectoris).
  - Stable optimal medical therapy for HF for 3 months.
- There were 47 individuals who met all the eligibility criteria and were implanted at 17 sites in Europe and Australia and completed the 24-week follow-up study. No patient was lost to follow-up.

- Reported results include a significant improvement in the Kansas City Cardiomyopathy Questionnaire (KCCQ) overall summary score from baseline to 24 weeks (18.0±16.6 points, p<0.001) (represents a 37% improvement from baseline). There were three procedure-related complications reported in three patients: two lead dislodgements and one worsening tricuspid regurgitation.
- The authors stated, "The current results are subject to the customary limitations of a pilot study: small sample size, single-arm design with no control group, and hence a potential role of placebo effect for the primary endpoint".

Akhtar et al. (2022) conducted a meta-analysis to review the effect of heart failure therapies on improvement in 6-minute walk distance (6MWD), which was analyzed across randomized controlled trials (RCTs) of drug-based therapy, device-based therapy, autonomic modulation, and exercise in patients with heart failure with reduced ejection fraction (HFrEF).

- The primary outcome was improvement in 6-minute walk distance (6MWD) at follow-up. A total of 4 studies with 847 patients with device-based intervention were identified. Included studies compared cardiac resynchronization therapy (CRT) and cardiac contractility modulation (CCM) with the control. Follow-up duration was six months, and the studies reported change in 6MWD. Overall results showed that device-based therapy (cardiac resynchronization therapy and cardiac contractility modulation), autonomic modulation, and exercise training programs are associated with improvement in 6MWD in patients with HFrEF.

Linde et al. (2022) conducted a prospective, multicenter study to assess the potential benefits of CCM in 47 patients with HF with preserved left ventricular (LV) EF (HFpEF). After CCM device implantation, patients were followed for 24 weeks. The primary efficacy endpoint, mean change in the Kansas City Cardiomyopathy Questionnaire (KCCQ) overall score, improved by 18.0 ± 16.6 points (p<0.001). This study is limited by small sample size and lack of comparison.

Fastner et al. (2021) published a retrospective analysis on 174 consecutive patients with chronic heart failure and CCM device implantation between 2002 and 2019, to compare the long-term therapeutic effects of CCM therapy in patients with ischemic (ICM) versus non-ischemic cardiomyopathy (NICM). Authors used data from the MAnnheim cardIac coNtracTility modulAtIoN obsErvational study (MAINTAINED) study in order to test for such differences in patients with ICM versus NICM. MAINTAINED is a single-center, observational study that retrospectively enrolled all patients with CCM device implantation. Before 2016, 3-lead Optimizer® II, III, or IVs systems were implanted; at later dates, 2-lead Optimizer® Smart devices were implanted.

- Baseline characteristics: 170 (61%) had ICM whereas 67 patients (39%) had NICM. Patients generally had advanced symptoms, with 77% having NYHA class III, 13% having NYHA class IV and 11% having NYHA class II (p = 0.45 between groups).
- There was loss to follow-up: 129 patients were available at 3 years and 84 patients available at 5 years. LVEF improved significantly in both groups (each p < 0.01), while the comparison of changes yielded no statistically significant difference (p = 0.83). There was a mortality rate of 28 (NYHA II group) vs. 35% (NYHA III/IV group) in the overall follow-up period (p = 0.54).
- Reported results include that LVEF was significantly higher in NICM patients after 3 years of CCM therapy (p = 0.0211), and after 5 years, also tricuspid annular plane systolic excursion (TAPSE) of NICM patients was significantly higher (p = 0.0437). There were no differences in other effectiveness parameters.
- Over the entire follow-up period, 35% of all patients died (p = 0.81); only in ICM patients, mortality was lower than predicted at 3 years (35 vs. 43%, p = 0.0395). The authors concluded that NICM patients can expect greater functional improvement in response to CCM therapy than ICM patients. Study limitations include retrospective design, change in number of leads, small sample size, with loss to follow-up.

Giallauria et al. (2020) performed an individual patient data meta-analysis of prospective trials of CCM that have measured functional capacity and/or quality of life questionnaires in patients with HF. Primary outcomes of interest were peak oxygen consumption (peak VO2), 6 min walk test distance, and quality of life (from established survey).

- Five trials were identified, four randomized studies enrolling 801 participants for all endpoints of interest, and for peak VO_2 alone (n = 60), there was an additional single arm non-randomized trial (FIX-HF-5C2) with a prospective comparison of its 24 week peak VO_2 data compared with the control group of the FIX-HF-5C control patients.
- Pooled analysis showed that, compared with control, CCM significantly improved peak VO_2 ($P < 0.00001$), 6 min walk test distance ($P = 0.005$), and quality of life measured by MLWHFQ ($P < 0.00001$). The authors noted study limitations include that the studies analyzed differed in study design limiting our ability to define representative results across different patient subgroups. They also noted that study cohorts are relatively young and predominantly male; therefore, future data would be needed in older individuals and in more women.

Kuschyk et al. (2020) a prospective registry study to assess long-term effects of cardiac contractility modulation delivered by the Optimizer Smart system on quality of life, left ventricular ejection fraction (LVEF), mortality and heart failure and cardiovascular hospitalizations. The study included 503 patients.

- Effects were evaluated in three groupings of LVEF (≤25%, 26–34% and ≥35%) and in patients with atrial fibrillation (AF) and normal sinus rhythm (NSR). Hospitalization rates were compared using a chi-square test. Changes in functional parameters of New York Heart Association (NYHA) class, Minnesota Living with Heart Failure Questionnaire (MLWHFQ) and LVEF were assessed with Wilcoxon signed-rank test, and event-free survival by Kaplan–Meier analysis.
- For the entire cohort and each subgroup, NYHA class and MLWHFQ improved at 6, 12, 18 and 24 months ($P < 0.0001$). At 24 months, NYHA class, MLWHFQ and LVEF showed an average improvement of 0.6 ± 0.7, 10 ± 21 and 5.6 ± 8.4%, respectively (all $P < 0.001$). LVEF improved in the entire cohort and in the LVEF ≤25% subgroup with AF and NSR. In the overall cohort, heart failure hospitalizations decreased from 0.74 [95% confidence interval (CI) 0.66–0.82] prior to enrolment to 0.25 (95% CI 0.21–0.28) events per patient-year during 2-year follow-up ($P < 0.0001$).
- Cardiovascular hospitalizations decreased from 1.04 (95% CI 0.95–1.13) events per patient-year prior to enrolment to 0.39 (95% CI 0.35–0.44) events per patient-year during 2-year follow-up ($P < 0.0001$). Similar reductions of hospitalization rates were observed in the LVEF, AF and NSR subgroups.
- Estimated survival was significantly better than predicted by the Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC) risk score which predicted mortality at one and three years in the entire cohort and in the LVEF 26–34% and ≥35% subgroups. The study is limited by the lack of randomization and a control group.

Wiegn et al. (2020) conducted a prospective, multicenter, single-arm study (FIX-HF-5C2 study) to test the performance, safety, and clinical effects of the 2-lead Optimizer Smart System.

- A total of 60 patients were enrolled. Major criteria included:
  - adult subjects with LVEF ≥25% and ≤45% by echocardiography (assessed by core laboratory)
  - NYHA III or ambulatory IV symptoms despite 90 days of guideline-directed heart failure medical therapy (including implantable cardioverter defibrillator when indicated) that was stable for 30 days before enrollment
  - and, not indicated for cardiac resynchronization therapy

- Subjects were evaluated at baseline and again at 12 and 24 weeks after implant. The primary effectiveness end point was an assessment of exercise tolerance measured by peak volume rate of oxygen (VO_2) obtained on cardiopulmonary stress testing (CPX). Changes in peak VO2 from baseline to 24-week follow-up in subjects implanted with the 2-lead system were compared to the changes observed in control group subjects of the prior FIX-HF-5C study (Abraham, et al., 2018).
- A total of 55 subjects (91.7%) completed the 24-week CPX test. In addition, four 24-week CPX tests were deemed inadequate by the core laboratory for which the patients declined requests to repeat testing, resulting in 52 tests for the primary end point analysis. However, to ensure robustness of findings, an additional analysis was performed that included these inadequate tests.
- Report results included that baseline characteristics were similar between FIX-HF-5C and FIX-HF-5C2 subjects except that 15% of FIX-HF-5C2 subjects had permanent atrial fibrillation versus 0% in FIX-HF-5C. CCM delivery did not differ significantly between 2- and 3-lead systems. The change of peak VO2 from baseline to 24 weeks was 1.72 mL/kg per minute greater in the 2-lead device group versus controls. 83.1% of 2-lead subjects compared with 42.7% of controls experienced ≥1 class New York Heart Association improvement (P<0.001). There were decreased Optimizer-related adverse events with the 2-lead system compared with the 3-lead system (0% versus 8%; P=0.03).
- Study limitations include small sample size, loss to follow-up, lack of randomization, and use of a historical control group.

Mando et al. (2019) performed a meta-analysis of the randomized clinical trials (RCTs) to assess the efficacy and safety of CCM therapy. Outcomes of interest were peak oxygen consumption (peak VO2), 6-Minute Walk Distance (6MWD), Minnesota Living with Heart Failure Questionnaire (MLHFQ), HF hospitalizations, cardiac arrhythmias, pacemaker/ICD malfunctioning, all-cause hospitalizations, and mortality. Data were expressed as standardized mean difference (SMD) or odds ratio (OR).

- Four RCTs including 801 patients (CCM n = 394) were available for analysis. The mean age was 59.63 ± 0.84 years, mean ejection fraction was 29.14 ± 1.22%, and mean QRS duration was 106.23 ± 1.65 msec. Mean follow-up duration was six months.
- CCM was associated with improved MLWHFQ (p = 0.0008). There were no differences in HF hospitalizations (p = 0.12), 6MWD (p = 0.10), arrhythmias (p = 0.14), pacemaker/ICD malfunction/sensing defect (p = 0.06), all-cause hospitalizations (p = 0.33), or all-cause mortality (p = 0.92) between the CCM and non-CCM groups.
- The authors concluded that short-term treatment with CCM may improve MLFHQ without significant difference in 6MWD, arrhythmic events, HF hospitalizations, all-cause hospitalizations, and all-cause mortality and that there is a trend towards increased pacemaker/ICD device malfunction. They noted that larger RCTs may be needed to determine if the CCM therapy will be beneficial with longer follow-up.

Anker et al. (2019) conducted prospective registry study with the aim to assess the longer-term impact of cardiac contractility modulation (CCM) on hospitalizations and mortality in real-world experience.

- The study included 140 patients with 25% ≤ left ventricular ejection fraction (LVEF) ≤ 45% receiving CCM therapy (CCM-REG25-45) for clinical indications. Cardiovascular and heart failure (HF) hospitalizations, Minnesota Living with Heart Failure Questionnaire (MLHFQ) and NYHA class were assessed over 2 years. Mortality was tracked through 3 years and compared with predictions by the Seattle Heart Failure Model (SHFM). Separate analysis was performed on patients with 35% ≤ LVEF ≤ 45% (CCM-REG35-45) and 25% ≤ LVEF < 35% (CCM-REG25-34).
- Hospitalizations decreased by 75% (from 1.2/patient-year the year before, to 0.35/patient-year during the 2 years following CCM, P<0.0001) in CCM-REG25-45 and by a similar

amount in CCM-REG35-45 (P<0.0001) and CCM-REG25-34. MLHFQ and NYHA class improved in all three cohorts, with progressive improvements over time (P<0.002).
- Three-year survival in CCM-REG25-45 (82.8%) and CCM-REG24-34 (79.4%) were similar to those predicted by SHFM (76.7%, P = 0.16; 78.0%, P = 0.81, respectively) and was better than predicted in CCM-REG35-45 (88.0% vs. 74.7%, P = 0.046). The limitations of the study include lack of randomization and no separate control group.

Abraham et al. (2018) conducted a randomized controlled study (the FIX-HF-5C study) to confirm a subgroup analysis of the prior FIX-HF-5 (Evaluate Safety and Efficacy of the OPTIMIZER System in Subjects With Moderate-to-Severe Heart Failure) study to evaluate that cardiac contractility modulation (CCM) improved exercise tolerance (ET) and quality of life in patients with ejection fractions between 25% and 45%.
- The study included 160 patients with NYHA functional class III or IV symptoms, QRS duration <130 ms, and ejection fraction ≥25% and ≤45% that were randomized to continued medical therapy (control, n=86) or CCM (treatment, n=74; 68 underwent device implantation) unblinded for 24 weeks. Peak rate of oxygen consumption (peak Vo_2) (primary endpoint), Minnesota Living With Heart Failure questionnaire, NYHA functional class, and 6-min hall walk were measured at baseline and at 12 and 24 weeks.
- The difference in peak Vo_2 between groups was 0.84 ml O_2/kg/min. Minnesota Living With Heart Failure questionnaire (p < 0.001), NYHA functional class (p < 0.001), and 6-min hall walk (p = 0.02) were all better in the treatment versus control group. There were seven device-related events, yielding a lower bound of 80% of patients free of events. The composite of cardiovascular death and HF hospitalizations was reduced from 10.8% to 2.9% (p = 0.048). Limitation of the study include limited follow-up duration of the current study which limits the ability to evaluate the long-term effects of CCM on mortality and hospitalizations.

Müller et al. (2017) reported on a prospective, two-year, multi-site evaluation of CCM in patients with heart failure.
- The study included 143 subjects with heart failure and reduced ejection fraction that were followed via clinical registry for 24 months recording NYHA class, Minnesota living with heart failure questionnaire (MLWHFQ) score, 6 min walk distance, LVEF, and peak VO2 at baseline and 6-month intervals as clinically indicated. Serious adverse events, and all cause as well as cardiovascular mortality were recorded. Data are presented stratified by LVEF (all subjects, LVEF <35%, LVEF ≥35%).
- One hundred and six subjects from 24 sites completed the 24-month follow-up. Baseline parameters were similar among LVEF groups. NYHA and MLWHFQ improved in all three groups at each time point. LVEF in the entire cohort improved 2.5, 2.9, 5.0, and 4.9% at 6, 12, 18, and 24 months, respectively. Insufficient numbers of subjects had follow-up data for 6 min walk or peak VO2 assessment, precluding comparative analysis. Serious adverse events (n = 193) were observed in 91 subjects and similarly distributed between groups with LVEF <35% and LVEF ≥35%, and similar to other device trials for heart failure.
- There were 18 deaths (seven cardiovascular related) over two years. Overall survival at two years was 86.4% (95% confidence intervals: 79.3, 91.2%). The study is limited by the lack of randomization and control group.

Röger et al. (2017) conducted a prospective blinded randomized trial including 48 patients to compare the efficacy and safety of CCM when the signal is delivered through one vs. two ventricular leads.
- Patients had symptomatic heart failure (NYHA Classes II–III) and reduced left ventricular ejection fraction. All patients received a CCM system with two ventricular leads and were randomized to CCM active through both or just one ventricular lead; 25 patients were randomized to receive signal delivery through two leads (Group A) and 23 patients to

signal delivery through one lead (Group B). The study compared the mean changes from baseline to 6 months follow-up in peakVO_2, NYHA classification, and quality of life (by MLWHFQ).
- The efficacy and safety of CCM in this study were similar when the signal was delivered through either one or two ventricular leads. The authors noted their results support the potential use of a single ventricular lead for delivery of CCM.

Kadish et al. (2011) conducted a randomized controlled trial (FIX-HF-5 trial) to test the longer-term safety and efficacy of CCM treatment.
- The study tested CCM in 428 New York Heart Association class III or IV, narrow QRS heart failure patients with ejection fraction (EF) ≤ 35% randomized to optimal medical therapy (OMT) plus CCM (n = 215) versus OMT alone (n = 213). Efficacy was assessed by ventilatory anaerobic threshold (VAT), primary end point, peak Vo_2 (pVo_2), and Minnesota Living with Heart Failure Questionnaire (MLWFQ) at six months. The primary safety end point was a test of non-inferiority between groups at 12 months for the composite of all-cause mortality and hospitalizations (12.5% allowable delta). The groups were comparable for age, EF, pVo_2 and other characteristics.
- While VAT did not improve at six months, CCM significantly improved pVo_2 and MLWHFQ [P = .024] and [P < .0001], respectively) over OMT. Forty-eight percent of OMT and 52% of CCM patients experienced a safety end point, which satisfied non-inferiority criterion (P = .03). Post hoc, hypothesis-generating analysis identified a subgroup (characterized by baseline EF ≥ 25% and New York Heart Association class III symptoms) in which all parameters were improved by CCM.
- The authors noted that based on the prespecified primary end point, CCM efficacy was not demonstrated, and further studies will be required to determine the role of CCM in the treatment of patients with medically refractory heart failure.

CORONARY INTRAVASCULAR LITHOTRIPSY

Debulking techniques are often necessary for successful lesion preparation in percutaneous coronary intervention (PCI). Rotational atherectomy (RA) is the current gold-standard treatment for severely calcified lesions. Coronary intravascular lithotripsy (IVL) has been proposed for vessel preparation in the presence of coronary artery calcification prior to stent delivery to open the coronary arteries that are narrowed or blocked due to calcification. IVL uses acoustic (sound) pressure shockwaves to break up calcifications. In contrast to ultrasound technologies which are characterized by low amplitude but very high frequency waveforms, an acoustic pressure shockwave has a very high amplitude but low frequency.

U.S. Food and Drug Administration (FDA): February 2021, the FDA granted premarket approval (PMA) for Shockwave Intravascular Lithotripsy (IVL) System with the Shockwave C2 Coronary Intravascular Lithotripsy (IVL) Catheter (Shockwave Medical, Inc., Santa Clara, CA / acquired by Johnson & Johnson MedTech May 2024). The device is indicated for lithotripsy-enabled, low-pressure balloon dilatation of severely calcified, stenotic de novo coronary arteries prior to stenting.

Contraindications for Use:
The Shockwave C2 Coronary IVL System is contraindicated for the following:
- This device is not intended for stent delivery.
- This device is not intended for use in carotid or cerebrovascular arteries.

The Shockwave Intravascular Lithotripsy (IVL) System consists of the Shockwave C2 Coronary IVL Catheter, the IVL Generator, the IVL Connector Cable, and its accessories. The Shockwave C2

Coronary IVL Catheter is used exclusively with these other components. The IVL Connector Cable is a remote actuator which connects the IVL Generator to the IVL Catheter and is used to activate the lithotripsy therapy from the IVL Generator.

Since FDA regulatory approval of coronary IVL, application of this technology beyond the confines of labeled indications (off label) has occurred, specifically in the clinical scenarios of left main coronary disease, in-stent restenosis (ISR) associated with stent under-expansion due to calcium, and IVL prior to drug coated balloon only percutaneous coronary intervention (PCI) (Visinoni, et al., 2024).

Professional Societies/Organizations: The 2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization includes two 'Recommendations for the Treatment of Calcified Lesions':

- In patients with fibrotic or heavily calcified lesions, plaque modification with rotational atherectomy can be useful to improve procedural success (2a B-R*).
- In patients with fibrotic or heavily calcified lesions, plaque modification with orbital atherectomy, balloon atherotomy, laser angioplasty, or intracoronary lithotripsy may be considered to improve procedural success (2b B-NR).

In the Background, the ACC states that lesions can be modified by using rotational atherectomy, orbital atherectomy, cutting balloon atherotomy, intracoronary lithotripsy, or excimer laser angioplasty. Despite promising results from hundreds of small mechanistic studies, dozens of large, randomized trials have shown that the routine use of atheroablative devices does not improve clinical or angiographic outcomes. However, the use of atheroablative devices may enhance procedural success in specific circumstances (ACC, 2021).

*See Appendix for ACC/AHA Class of Recommendation and Level of Evidence

The Society for Cardiovascular Angiography and Interventions (SCAI) published an Expert Consensus Statement on the Management of Calcified Coronary Lesions (Jan 2024).

- This publication includes a workflow graphic 'Treatment algorithm for calcified CAD'. The SCAI notes that "When deciding on the specific modality to use for calcium modification, consider the length of the calcified segment. Atherectomy may best address long, diffusely calcified lesions, whereas focal lesions may be amenable to treatment with specialty balloons. Consider IVL for concentric, eccentric, and CN lesions and in settings where atherectomy may be relatively contraindicated."
- Their Consensus Tips for Intravascular Lithotripsy state:
  - IVL is best for modifying circumferential calcium in balloon-crossable lesions. Although data show effectiveness of IVL therapy in eccentric and nodular calcium, more pulse delivery may be required in these lesions.
  - IVL can be used synergistically with atherectomy devices, especially in longer lesions where there is often more heterogeneity in vessel size and pattern of calcification.88
  - Longer rest periods between therapy may help prevent hemodynamic compromise when performing IVL in areas that subtend large myocardial distributions (eg, left main lesions).
  - IVL can be used with multiple guide wires in place (eg, bifurcation lesions).
  - Intravascular imaging can be useful in longer lesions to help determine where pulses are best used. This is also true after atherectomy because atherectomy may modify calcium in smaller diameter vessel segments but is less likely to do so in larger vessel segments.
- Under 'Emerging trials and therapies' section, the SCAI notes that several studies are underway.

- The Short-Cut (Shockwave Lithoplasty Compared to Cutting Balloon Treatment in Calcified Coronary Disease Trial; NCT06089135) trial aims to randomize 410 patients with calcified lesions to IVL vs CB in 2 cohorts—those prepared with or without RA.
- The DECALCIFY (Prospective, Randomized, Controlled, Multicenter Study for the Treatment of Calcified Coronary Artery Lesions With Rotational Atherectomy vs. Intravascular LithotripsY; NCT04960319) trial will randomize 100 patients to IVL vs RA and assess in-hospital MACEand stent expansion by OCT.
- The SONAR (Shockwave Balloon or Atherectomy With Rotablation in Calcified Coronary Artery Lesions; NCT05208749) multicenter RCT of 170 patients will randomize to IVL or RA and assess postprocedural myocardial infarction.
- The BALI (Balloon Lithoplasty for Preparation of Severely Calcified Coronary Lesions Before Stent Implantation; NCT04253171) RCT will compare IVL with the standard of care (which can include plain balloon angioplasty, CB/scoring balloons, and RA) in 200 patients with the primary end point being strategy failure (failed stent delivery, residual stenosis of ≥20%, or TVF).
- The VICTORY (Value of IVL Compared to OPN Noncompliant Balloons for Treatment of Refractory Coronary Lesions; NCT05346068) trial is a noninferiority RCT to compare the impact of IVL with that of very high–pressure balloon on final stent expansion assessed by OCT in 280 patients with calcified lesions.
- Intravascular Balloon Lithotripsy in Left Main Stem Percutaneous Coronary Intervention (NCT04319666) aims to follow 50 patients undergoing PCI for intravascular imaging–defined calcified left main disease.
- EMPOWERCAD (Equity in modifying plaque of women with undertreated calcified CAD; NCT05755711) is a post-market, multicenter, single-arm observational study to generate real-world clinical evidence associated with IVL in female patients.
- NCT05552131, a prospective, single-arm study evaluating the device success rate of a T-wave IVL catheter system (Suzhou Zhonghui Medical Technology; NCT05552131) in 190 patients
- The ACTIVE study (Safety and Efficacy Study of the SoundBite Crossing System With ACTIVE Wire in Coronary CTOs; NCT03521804) evaluating a novel guide wire (Soundbite Medical Solutions) that can penetrate calcium using pressure pulses characterized by high amplitude, rapid rise time, and short duration. Few studies compare multiple calcium modification devices.
- The ROLLING-STONE study (IVL and/or Mechanical Debulking for Severely Calcified Coronary Artery Lesions; NCT05016726) aims to prospectively follow 400 patients undergoing PCI for calcified disease treated with IVL or atherectomy
- The ROLLERCOASTR trial (Rotational Atherectomy, Lithotripsy, or Laser for the Treatment of Calcified Stenosis; NCT04181268) is one of the few randomized studies aimed at enrolling 150 participants undergoing PCI with RA, IVL, or ELCA for calcified disease (Society for Cardiovascular Angiography and Interventions, 2024).

Literature Review: There is a lack of large, randomized trials comparing long term outcomes of IVL versus standard rotational atherectomy (RA). The Rota.shock and EXIT-CALC trials are randomized but have very small IVL sample size (28 and 19, respectively). The DISRUPT CAD trials are not randomized.

<u>ROTA.shock Trial</u>
The ROTA.shock study (Blachutzik, et al., 2023) is a randomized, prospective, multicenter trial designed to compare the performance of the Shockwave™ coronary IVL system versus rotational atherectomy (RA), performed before percutaneous coronary intervention of severely calcified coronary lesions. The primary endpoint is the minimal stent area (MSA) at the end of the procedure.

- The primary endpoint analysis included 61 patients (RA = 33 and IVL = 28).

- The main inclusion criteria were clinically relevant coronary stenosis with proven myocardial ischemia and severe calcification defined by coronary angiography as radiopacities noted without cardiac motion before contrast injection generally compromising both sides of the arterial lumen as assessed by the operator. Additional inclusion criteria were an angiographic reference vessel diameter between 2.5 and 4.0 mm, and a patient age > 18 years. The main exclusion criteria were cardiogenic shock and bifurcation lesions requiring two-stent strategies. Additional exclusion criteria were chronic total occlusions and in-stent restenoses.
- In two of the 35 patients randomized to IVL, a cross-over to RA was necessary, because neither the IVL balloon nor an NC balloon for predilatation could be advanced into the lesion.
- Post-discharge follow-up assessments were conducted 1 and 6 months after the index procedure by standardized telephone interview. Final OCT scans for primary endpoint analysis were available from 28 patients (85%) out of the IVL group and from 33 patients out of the RA group (89%).
- The final MSA after the procedure was smaller but non-inferior in the IVL (mean: 6.10mm^2, 95% CI: 5.32–6.87mm^2) compared with the RA group (mean: 6.60mm^2, 95% CI: 5.66–7.54mm^2). During the 6-month follow-up, there was one case of TLF and TLR in the IVL group due to angiographical in-stent restenosis (RA: 0/33 vs. IVL 1/28) being treated by balloon angioplasty and drug-eluting balloon application. Repeat PCI for nontarget vessel revascularization was performed in four patients of the RA group and in two patients of the IVL group.
- Limitations include: the threshold for non-inferiority was lower than originally intended (with the pre-assumed MSA of 5.0 ± 1.4mm^2 for RA and the MSA of 6.1 ± 1.7mm^2 calculated from a preliminary case series for IVL); loss to follow up as only 61 of 70 patients were finally analyzed; and overall small patient population.

Blachutzik et al. (2024) conducted a retrospective analysis of data from the ROTA.shock trial to compare the effects of rotational atherectomy (RA) and intravascular lithotripsy (IVL) on coronary calcified nodules (CNs) as determined by OCT. In 19 of the patients out of this study CNs were detected by OCT in the target lesion and were treated by either IVL or RA. The authors determined that treatment of CNs by RA or IVL does not result in a significant reduction of the plaque mass of the CNs, and PCI using RA or IVL leads to a significant reduction in CN thickness.

Sardella et al. (2023) conducted a prospective, multicenter, observational study (ROTA.Shock registry) to evaluate the efficacy and safety of coronary IVL AFTER rotational atherectomy (RA) in consecutive lesions with severe coronary artery calcification (CAC).

- Primary efficacy end point was procedural success, defined as final diameter stenosis <30% by quantitative coronary angiography. Primary safety endpoint was freedom from serious angiographic complications. Clinical follow-up was limited to in-hospital outcomes.
- A total of 160 patients were enrolled with the primary efficacy end point was observed in 155 patients (96.9%). The primary safety end point occurred in 145 cases (90.6%).
- The authors concluded the following: more than a half of patients underwent IVL after RA failure, IVL as elective or bail-out strategy after RA was found to be effective in terms of procedural success, considering the complexity of lesions treated, the incidence of serious angiographic complications was generally low, with excellent in-hospital outcomes, and the incidence of in-hospital MACCE was low.
- This study has several limitations including that clinical follow-up was limited to in-hospital events, a small sample size, absence of a control group, and a primary efficacy endpoint of procedural success alone.

EXIT-CALC trial
Oomens et al. (2023) conducted a small, single-center RCT (EXpansion of stents after intravascular lithoTripsy versus conventional predilatation in CALCified coronary arteries, (EXIT-

CALC trial) to investigate if pre-treatment with IVL in severely calcified lesions increases stent expansion, assessed by optical coherence tomography (OCT), when compared to predilatation with conventional angioplasty balloons (scoring- / high pressure- / cutting balloons).

- A total of 40 patients were randomized to the IVL group (n = 19) and the conventional group (n=21). The inclusion criteria were: 1) indication for PCI of a calcified lesion in a native coronary artery; 2) optical coherence tomography (OCT)- derived calcium score of 4, defined as a maximum calcium angle of >180◦, maximum calcium thickness > 0.5 mm, and a minimal calcium length of 5 mm, as measured at the target lesion); 3) target vessel reference diameter between 2.5 and 4.0 mm (by visual estimation).
- Primary endpoint was stent expansion assessed by OCT. Secondary endpoints were the occurrence of peri-procedural events and major adverse cardiac events (MACE) in hospital and during follow-up. Patients were contacted by telephone at 30-days, 1-year and 2-years after randomization.
- However, true follow-up timeframes are unclear. OCT was performed after pre-treatment and was successful in 38 patients; in both groups 1 OCT run was insufficient for analysis.
- The authors reported found no significant difference in minimal stent expansion after plaque modification using IVL or conventional predilatation, in patients with prespecified severe coronary artery disease assessed by OCT. No peri-procedural, in-hospital and 30-day follow-up MACE were reported.
- Limitations of this study include unclear follow-up timeframes and small sample size.

DISRUPT CAD Trials

The Disrupt CAD IV trial was designed to obtain regulatory approval for the use of IVL in Japan. It did not include randomization or a control group. The intention to treat cohort included 64 patients at 8 centers. The primary endpoints were the same as the prior Disrupt CAD trials – freedom from MACE at 30 days post-IVL and procedural success (stent delivery with residual stenosis <50 % without in hospital MACE). Angiographic success was a secondary endpoint, defined as stent delivery with residual stenosis <50 % and no serious angiographic complications. All enrollees had severe CAC with a target lesion length ≤ 40 mm.

- Saito et al. (2022) reported on a total of 64 patients who were available for one year follow up.
- The cumulative incidence of events through 1 year of follow-up was 9.4% for MACE, 6.3% for TLF, 4.7% for TVR, and 1.6% for ID-TLR, all of which occurred in 6 patients. No death or stent thrombosis events occurred at 1 year and no MI events occurred after discharge because all 4 MI events were in hospital. The authors concluded favorable safety and effectiveness was observed with coronary IVL through 30 days are durably maintained over 1 year. This was evident by an absence of post-discharge MI, death, or stent thrombosis through 1 year, only 3 (4.7%) TVR procedures through 1 year, and complete resolution of angina in approximately 90% of patients.
- Limitations noted by the authors include a lack of comparison of IVL to other modalities for vessel preparation, such as atherectomy, in prospective trials, which may complicate the interpretation of comparative results. Furthermore, the adjunctive use of atherectomy in conjunction with coronary IVL was not evaluated in the present study. Complementary use of IVL with atherectomy to treat specific complex coronary lesions warrants further investigation.

The objective of the Disrupt CAD III trial was to evaluate the safety and efficacy of IVL in a larger patient population for US FDA regulatory approval. It did not include randomization or a control group. The trial included a total of 431 patients (47 "roll-in" and 384 intention-to-treat patients) from 47 sites across 4 countries. More than half of the patients were from the United States.

- All patients had severe CAC with lesion lengths ≤40 mm. Patients with acute MI or complex lesions (severe tortuosity, lesions at bifurcations, ostial lesions, or unprotected left main lesions) were excluded.

- The trial's primary endpoint was freedom from MACE at 30 days and the primary effectiveness endpoint was procedural success, defined as successful stent delivery with a residual stenosis <50 % by core laboratory assessment without in hospital MACE.
- According to Kereiakes et al. (2022), 47 patients reported 30-day results (Hill et al. 2020) and follow-up through one year was completed in 97.1% of patients (n=373). There were 384 patients in the intention-to-treat dataset for the primary and secondary endpoint analyses. The primary safety endpoint (freedom from 30-day MACE) was achieved in 92.2% of patients (Hill et al. 2020). The primary effectiveness endpoint (stent delivery with a residual stenosis <50% without in-hospital MACE) was achieved in 92.4% of patients. MACE and target lesion failure (TLF) through 30 days occurred in 7.8% and 7.6% of patients, respectively, and was primarily driven by target vessel MI.
- At 1 year, Kereiakes et al. (2022) reported MACE occurred in 13.8% of patients (cardiac death: 1.1%, MI: 10.5%, ischemia-driven target vessel revascularization: 6.0%) and target lesion failure occurred in 11.9% (ID-TLR: 4.3%), both driven by non-Q-wave MI (9.2%). Stent thrombosis (definite or probable) occurred in 1.1% of patients (including 1 event [0.3%] beyond 30 days).
- The study limitations include the lack of randomization and a control group. The author state that randomized studies would be required to compare the impact of IVL treatment versus other calcium-modifying technologies on longer term outcomes. Second, multiple angiographic and patient demographic subsets were excluded per protocol which limits broader generalization of the observations to a "real-world," all-comers population. These groups include biomarker-positive acute coronary syndromes, severe renal insufficiency, extreme target vessel tortuosity, or unprotected left main, ostial, and saphenous vein bypass graft target lesions.
- Of note, the one-year results (Kereiakes et. al., 2022) are not listed in PubMed. Additionally, the two-year results (Kereiakes et. al., 2023) are not available in a full text, peer-reviewed publication, but only in abstract form.

Ali et al. (2019) conducted a prospective multicenter, single-arm post-approval study to confirm the safety and effectiveness of IVL for modification of severe coronary artery calcification (CAC) (Disrupt CAD II study). This study was nonrandomized and lacked a control group. The study included 120 patients with severe CAC with a clinical indication for revascularization who underwent vessel preparation for stent implantation with IVL.

- The primary end point of in-hospital major adverse cardiac events (MACE, cardiac death, myocardial infarction, or target vessel revascularization) occurred in 5.8% of patients, consisting of 7 non-Q-wave myocardial infarctions.
- The authors concluded that in patients with severe CAC who require coronary revascularization, IVL was safely performed with high procedural success and minimal complications and resulted in substantial calcific plaque fracture in most lesions, procedural success with low MACE rates in severely calcified lesions in a Japanese population. The study was limited by lack of randomization and lack of a concurrent control group.

Meta-analysis

Sagris et al. (2024) conducted a meta-analysis that included meta-analysis to evaluate the safety and effectiveness of IVL in preparing highly calcified plaques in coronary arteries before stenting, by examining periprocedural and in-hospital/30-day outcomes. The meta-analysis included 38 studies including 2977 patients with heavily calcified coronary lesions.

- Considering the IVL use in coronary arteries, the overall clinical success rate was 93% and the procedural success 97%. A significant increase in the vessel diameter was observed. On the other hand, there was a reduction in diameter stenosis when IVL was performed, compared to pre-IVL. Additionally, our results showed that immediately after the IVL application, there was a mean acute luminal gain of 1.27 ± 0.6mm which increased to 1.94 ± 1.1mm after the implantation of a DES.

- Following the primary endpoints, our secondary endpoints met with the in-hospital and 30-days incidence of MACE calculated at 8%, while MI and death were 5% and 2%, respectively. Periprocedural complications such as perforations 1%, dissections 2%, slow flow 0%, or no-reflow phenomena 0% were uncommon, with only a few occurrences reported.
- The authors noted that limitations include there were no studies to compare IVL with the other techniques and to test its long-term effectiveness, and, the location and the nature of the lesions, therapy, and duration of treatment among the studies were heterogeneous as well as follow-up of the studies.
- The authors state that "Future prospective cohorts will be required to validate our findings and expand the use of IVL in patients with burdened atherosclerotic profile in the following recommendations".

Caminiti et al. (2023) conducted a meta-analysis analysis to evaluate the procedural success, complication rate, and major adverse cardiovascular events (MACEs) of the IVL treatment of stent underexpansion (SU) because of calcified coronary plaque (CCP). The meta-analysis included 13 studies with 354 patients.

- The mean follow-up time was 2.6 months. The primary end point was IVL 'strategy success', defined as the adequate expansion of the underexpanded stent. 'Strategy success' was seen in 88.7% (95% CI 82.3 to 95.1) of patients. The mean minimal stent area was reported in 6 studies, the pre-IVL value was 3.4 mm^2, and the post-IVL value was 6.9 mm^2. The mean diameter stenosis (percentage) was reported in 7 studies, the pre-IVL value was 69.4%, and the post-IVL value was 14.6%. The rate of intraprocedural complications was 1.6% (95% CI 0.3 to 2.9).
- A limitation of the analysis of note is the low quality of the studies. Also, the types of included studies (e.g., retrospective registries, prospective observational) are not specified. Furthermore, there is a wide heterogeneity in the length of follow-ups between the studies.

Mhanna et al. (2021/2022) conducted a meta-analysis of studies to evaluate the utility of adjunctive intravascular lithotripsy (IVL). The primary outcomes were the clinical success, defined as the ability of IVL to produce residual diameter stenosis <50% (RDS < 50%) after stenting with no evidence of in-hospital major adverse cardiac events, and the angiographic success, defined as success in facilitating stent delivery with RDS < 50% and without serious angiographic complications. The secondary outcomes included post-IVL and post-stenting changes in lumen area, calcium angle, and the maximum calcium thickness.

- The review included eight single-arm observational studies, with 980 patients (1011 lesions) (6 prospective, 2 retrospective). Acute coronary syndrome was present in 48.8% of the patients and severe calcifications were present in 97% of lesions.
- Clinical success was achieved in 95.4% of patients. Angiographic success was achieved in 97% of patients. There was an overall increase in postprocedural lumen area as well as significant reduction of calcium angle and maximum calcium thickness.
- The authors concluded that while IVL seems to have efficacy and safety in the management of calcified coronary lesions, adequately powered RCTs are needed to evaluate IVL compared to other calcium/plaque modifying techniques.

Leick et al (2023) reported on a prospective, observational study based on an all-comers registry that included consecutive patients with moderate or severe coronary calcification. The authors compared the effectiveness and safety of intravascular lithotripsy (IVL) (n = 86) (Shockwave C2) to that of modified balloon angioplasty (MB) (n = 92) (WOLVERINETM Cutting Balloon™).

- This all-comers registry included consecutive patients with moderate or severe coronary calcification.

- The primary endpoint was strategy success (<20% residual stenosis). The secondary endpoint was long-term safety outcomes [cardiac death, acute myocardial infarction (AMI), target lesion failure/ revascularization (TVR)].
- Quantitative coronary angiography (QCA) was performed in all patients. The presence of acute coronary syndrome at the time of admission was less frequent in the IVL group (p = 0.023). In-stent restenosis (ISR) lesions were less frequent in patients treated with IVL (p = 0.001).
- One patient was lost to follow-up. For all other patients, a follow-up period of at least 450 days was available. The primary endpoint was reached in 152 patients (85.4%) (IVL: 94.2% vs. MB 77.2%; p = 0.001). Five (5.8%) patients in the IVL group had residual stenosis vs. 21 (22.8%) in the MB group (p = 0.001) in quantitative coronary angiography (QCA).
- The authors concluded that lesion preparation with IVL resulted in a significantly lower rate of residual stenosis than MB angioplasty. During the follow-up period (450 days) there was no difference in cardiovascular mortality rate. The authors noted that randomized trials, which can overcome the selection bias inherent in all-comers registries are needed to compare different lesion preparation methods with IVL.

Honton et al. (2022) reported on a prospective multicenter observational study including 202 consecutive patients (220 lesions). Most patients presented de-novo calcified coronary lesions (DNL) (n = 170; 77.3%) whereas intra-stent restenosis (ISR) related to device underexpansion represented the other 50 patients of the cohort (22.7%).

- The primary effectiveness endpoint was procedural success, defined as <30% residual stenosis without severe angiographic complications and one-year outcomes.
- On the overall cohort of 202 patient, 7 (3.4%) patients were lost at 12 months follow-up. The rate of MACE-free survival at 1 year was 86.6% in the overall cohort. Rates of target vessel (TVR) and lesion (TLR) revascularization were 6.4% and 2.5%, respectively. The 1-year MACE rate was 91.5% in DNL group and 83.8% in ISR group. Procedural success was achieved in 95.5% of patients (DNL group: 96.5%; ISR group: 92.0%). In-hospital MACE occurred in 6.4% of cases, mainly driven by periprocedural infarctions.
- The authors noted that there was no comparative arm and that further studies will be needed comparing IVL with other devices dedicated to plaque preparation.

Cubero-Gallego et al. (2020) reported on a prospective, multicenter registry study that reports the initial experience of treatment of calcified lesions with coronary lithoplasty (CL) in an unselected and high-risk population.

- The study included 57 (66 lesions) patients that were all consecutive cases with calcified coronary lesions that underwent CL between August 2018 and August, 2019. The exclusion criteria consisted of a target lesion located in a small vessel (< 2.5mm) and the presence of dissection prior to CL. Quantitative coronary angiography and intravascular ultrasound/optical coherence tomography analysis were completed by an independent central core laboratory. The population was elderly (72.6±9.4 years) with high proportions of patients with diabetes (56%), chronic kidney disease (35%), and multivessel disease (84%). All lesions were classified as type B/C.
- More than 75% of lesions were predilated with noncompliant/semicompliant balloons or cutting-balloon. Rotablator was used in 5 lesions (7.6%) prelithoplasty. On average, CL required 1.17 balloons delivering a mean of 60 pulses. Successful CL was achieved in 98%. In 13% of cases, lithoplasty balloon was broken during therapy. There were few procedural complications.
- The authors concluded that the study supports the feasibility, safety, and short-term efficacy of PCI for calcified coronary lesions using CL in an unselected and high-risk population with promising results. The authors notes that this is an observational study, not a randomized controlled study, with the sample size was relatively small, with a short

follow-up time, absence of a comparison group, with heterogeneity of lesions included and with self-reporting of events and that larger multicenter registries with long-term follow-up are required to clarify the role of plaque modification using CL.

Retrospective
Basavarajaiah et al. (2022) reported 23-month results from a retrospective registry of 273 patients from eight European centers. Patients with significant coronary stenosis (>70% on angiography or hemodynamically significant on invasive pressure wire assessment) underwent IVL; 43% had previous PCI.

- Use of any adjuvant equipment to prepare the lesions (scoring/cutting balloons and/or rotational atherectomy) was at the discretion of the operator, as was subsequent treatment with drug-eluting stents (DES) or drug-coated balloons (DCB). Intravascular imaging was used in 33% (n = 90) of patients. An upfront IVL strategy was adopted in 34% (n = 92), while the rest were bailout procedures. Adjuvant rotational atherectomy ("RotaTripsy") was required in 11% (n = 31) of cases. The procedural success was 99%.
- The median follow-up was 687 days (22.9 months) (interquartile range: 549–787).
- Cardiac death occurred in 5% (n = 14), TVMI in 3% (n = 8), TLR in 6% (n = 16), and MACE rate was 11% (n = 30). Study limitations include lack of prospective design, lack of a comparator with standard of care.

El Jattari et al. (2022) reported on a prospective registry of observational data obtained from five Belgium facilities. However, follow-up was performed by retrospective medical record review. The purpose was to gain insight into the treatment of heavily calcified lesions in a real-world setting, including its use for in-stent restenosis (ISR), which is considered off-label use.

- The registry included 134 IVL procedures. The indications for coronary angiography (CAG) were diverse (stable angina in 44%, acute coronary syndrome in 33.6%, and silent ischemia in 22.4% of cases). IVL was used to treat de novo lesions in 70.1% of cases and to treat in-stent (re)stenosis in 29.9% of cases.
- The primary endpoint was final overall procedural success, which was obtained in 88.1% of cases, an aggregate of 92.6% in de novo lesions and 77.5% in stent underexpansion or in-stent restenosis (ISR). The 1-month major adverse cardiovascular event (MACE) rate was 4 deaths (3%), including 2 cardiovascular deaths (1 in-stent thrombosis and 1 coronary artery perforation).
- This study had small patient enrollment and lacked long term outcomes.

Rola et al. (2023) reported on a retrospective registry including 131 consecutive patients from two centers who underwent IVL. The two main inclusion criteria the presence of: calcified, resistant lesion (defined by an inadequate non-complaint balloon catheter inflation) or a significantly under-expanded stent (more than 20% of reference diameter).

- The study had two primary endpoints - successful clinical outcome and safety concerns. Clinical success was defined as effective stent deployment or optimization of a previously under-expanded stent (with less than <20% in-stent residual stenosis).
- At the 6-month-follow-up, the major adverse cardiac and cerebrovascular events (MACCE) rate was 7.9% with a concomitant target lesion revascularization (TLR) rate of 3.8%. The author noted that if they exclude patients who underwent IVL procedure for post-stenting optimization, the TLR would decrease to 2%.
- The authors conclude that their mid-term data confirms an acceptable safety and efficacy of intravascular lithotripsy as a valuable strategy for lesion preparation and stent optimization in an all-comers cohort with severely calcified coronary lesions.
- Limitations of this study include short follow-up, small sample size, and its retrospective method.

Takahashi et al. (2023) retrospectively reported on 109 consecutive patients who underwent IVL at two US facilities to evaluate the complementary utility and safety of IVL with atheroablative devices for the treatment of severely calcified lesions in contemporary, real-world practice.

- A total of 33 patients (30.3%) were treated with both IVL and atherectomy and had higher risk features. Patients had severely calcified de novo lesions as well as calcific under-expanded stents. High prevalence of previous revascularization (58.7%) and LVEF ≤50% (41.3%) was observed, with two-thirds of the included patients presenting with acute coronary syndrome. IVL patients were divided into 2 groups based on the combination of different tools: (1) patients treated with the combined use of IVL and atherectomy; and (2) those treated with non-atherectomy approaches (ie, IVL and balloon angioplasty).
- Clinical outcomes through 30 days were available in 104 patients (95.4%). The cumulative incidence of MACE at 30 days was 4.8% (5 patients) including 3 deaths in the combined group (2 cardiac and 1 non-cardiac deaths) and 1 cardiac death and 1 MI in the non-atherectomy group. There was no TVR within 30 days after the index procedure.
- The authors concluded that procedural success and complications were similar in patients undergoing IVL with and without atherectomy when treating calcified de novo lesions. Those who required a combined approach represented a high-risk population with high mortality, suggesting that a multidisciplinary approach is needed to optimize case selection and care beyond PCI.
- Two limitations of this study include its retrospective design as well as short follow-up period.

Medicare Coverage Determinations

	Contractor	Determination Name/Number	Revision Effective Date
NCD	National	No Determination found.	
LCD		No Determination found	

Note: Please review the current Medicare Policy for the most up-to-date information.
(NCD = National Coverage Determination; LCD = Local Coverage Determination)

Appendix

*Applying ACC/AHA Class of Recommendation and Level of Evidence to Clinical Strategies, Interventions, Treatments, or Diagnostic Testing in Patient Care

The Class (Strength) of Recommendation (COR) indicates the strength of recommendation, encompassing the estimated magnitude and certainty of benefit in proportion to risk.

Class I – Strong (is recommended)
Class 2a – Moderate (is reasonable)
Class 2b – Weak (may/might be reasonable)
Class 3 – No benefit (Moderate) (is not recommended)
Class 3 – Harm (Strong) (potentially harmful)

The Level (Quality) of Evidence (LOE) rates the quality of scientific evidence supporting the intervention on the basis of the type, quantity, and consistency of data from clinical trials and other sources.

Level A – High quality evidence from more than one randomized clinical trial, Meta-analyses of high-quality randomized clinical trials, One or more randomized clinical trials corroborated by high-quality registry.

Level B-R – Randomized. Moderate quality evidence from one or more randomized clinical trials, Meta-analyses of moderate-quality randomized clinical trials.
Level B-NR – Non-randomized. Moderate quality evidence from one or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies, Meta-analyses of such studies.
Level C-LD – Limited data. Randomized or nonrandomized observational or registry studies with limitations of design or execution, Meta-analyses of such studies, Physiological or mechanistic studies of human subjects.
Level C-EO – Expert Opinion. Consensus expert opinion based on the clinical experience

Coding Information

Notes:

1. This list of codes may not be all-inclusive since the American Medical Association (AMA) and Centers for Medicare & Medicaid Services (CMS) code updates may occur more frequently than policy updates.
2. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Considered Experimental/Investigational/Unproven:

CPT®* Codes	Description
33289	Transcatheter implantation of wireless pulmonary artery pressure sensor for long-term hemodynamic monitoring, including deployment and calibration of the sensor, right heart catheterization, selective pulmonary catheterization, radiological supervision and interpretation, and pulmonary artery angiography, when performed
0266T	Implantation or replacement of carotid sinus baroreflex activation device; total system (includes generator placement, unilateral or bilateral lead placement, intra-operative interrogation, programming, and repositioning, when performed)
0268T	Implantation or replacement of carotid sinus baroreflex activation device; pulse generator only (includes intra-operative interrogation, programming, and repositioning, when performed)
0408T	Insertion or replacement of permanent cardiac contractility modulation system, including contractility evaluation when performed, and programming of sensing and therapeutic parameters; pulse generator with transvenous electrodes

HCPCS Codes	Description
C1761	Catheter, transluminal intravascular lithotripsy, coronary
C1824	Generator, cardiac contractility modulation (implantable)
C1825	Generator, neurostimulator (implantable), nonrechargeable with carotid sinus baroreceptor stimulation lead(s)
C2624	Implantable wireless pulmonary artery pressure sensor with delivery catheter, including all system components

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Revision Details

Type of Revision	Summary of Changes	Date
Focused review	• Removed content for: Endovascular repair of iliac artery at the time of aorto-iliac artery endograft placement by deployment of an iliac branched endograft (i.e., GORE® EXCLUDER® Iliac Branch Endoprosthesis [IBE] device	11/01/2024
New Coverage Policy topic and Annual Review of four cardiac topics previously located in CP 0504 Omnibus Codes.	• Added new policy statement for carotid sinus baroreflex activation device (i.e., BAROSTIM™ NEO® System) (New topic) • No clinical policy statement changes from CP 0504 Omnibus Codes: ➢ Endovascular repair of iliac artery at the time of aorto-iliac artery endograft placement by deployment of an iliac branched endograft (i.e., GORE®	10/15/2024

	EXCLUDER® Iliac Branch Endoprosthesis [IBE] device ➢ Pulmonary artery pressure sensor (e.g., CardioMEMS™ HF system, Cordella™ Pulmonary Artery Sensor System) ➢ Cardiac contractility modulation (CCM®) therapy (i.e., OPTIMIZER Smart System) ➢ Coronary Intravascular Lithotripsy (IVL) (i.e., Shockwave C2 Coronary IVL System)	