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RE: CAG-00469N Cardiac Contractility Modulation for Heart Failure

The American College of Cardiology, Heart Rhythm Society, and Heart Failure Society of America represent the physicians and healthcare professionals dedicated to the care of heart failure (HF) patients undergoing cardiac contractility modulation (CCM). These societies strongly support a National Coverage Determination (NCD) for CCM in HF under coverage with evidence development (CED). We appreciate the opportunity to comment on the national coverage analysis (NCA).

CCM is a device-based therapy that delivers relatively high-voltage, long-duration electrical signals to the right ventricular (RV) septal wall during the absolute myocardial refractory period. CCM therapy has shown significant benefits in the management of HF. One of the key mechanisms by which CCM operates is by increasing intracellular systolic calcium, which acutely improves myocyte inotropy (Burkhoff et al., Am J Physiol, 2005). This enhancement in contractility occurs without a corresponding increase in myocyte oxygen consumption, making it an efficient therapeutic option (Lawo et al., JACC, 2005). Importantly, CCM therapy has been demonstrated to be safe and not proarrhythmic, addressing a critical concern in HF treatments (Neelagaru et al., Heart Rhythm, 2006).

Beyond its immediate effects, CCM also induces modifications in gene expression and surface proteins implicated in HF. These changes occur both locally and, after several weeks, in areas remote from the site of CCM therapy (Imai et al., JACC, 2007; Butter, JACC, 2008). In patients with an ejection fraction (EF) between 25% and 45%, CCM has been shown to improve the Minnesota Living with Heart Failure (MLWHF) score, NYHA Class, EF, ventilatory anaerobic threshold (VAT), and 6-minute walk test (6MWT) distance (Abraham et al., Am Heart J, 2008). Further studies have demonstrated that CCM improves VO2 and significantly reduces cardiovascular death and HF hospitalizations by 50% in this patient group (Kadish et al., Am Heart J, 2011; Abraham, JACC HF,

2018). These clinical trial findings have been repeated in a registry study, which showed similar outcomes: improvements in NYHA Class, MLWHF score, and EF (Kuschyk et al., Eur J Heart Fail. 2021; Yucel G, Pacing Clin Electrophysiol, 2022).CCM therapy has similar effects in patients with both ischemic and non-ischemic cardiomyopathy (Fastner, Int J Cardiol, 2021). It also improves cardiac diastolic function and promotes weight loss in HF patients (Deak et al., Interv Card Electrophysiol, 2024). Long-term studies indicate that, unlike the typical decline seen in HF patients, renal function remains stable in those receiving CCM (Yuecel et al., Cardiorenal Med, 2024).Additionally, in HF patients with prolonged QRS duration (120-149 msec), CCM improves NYHA Class, reduces HF hospitalizations, and enhances EF and MLWHF score to a similar degree as in those with a QRS duration of less than 120 msec (Fastner et al., Heart Rhythm, 2024). These findings collectively underscore the efficacy and safety of CCM therapy in improving clinical outcomes for HF patients, making it a valuable addition to the therapeutic arsenal for this condition.

Patient Criteria

The Optimizer Smart Mini system is currently the sole CCM device approved by the U.S Food & Drug Administration (FDA). The Optimizer is indicated to improve 6-minute hall walk distance, quality of life, and functional status of NYHA Class III heart failure patients who remain symptomatic despite guideline directed medical therapy, are not receiving Cardiac Resynchronization Therapy (CRT), and have a left ventricular ejection fraction ranging from 25% to 45%. The Societies broadly supports applying the FDA-approved indications to the patient coverage criteria.

NYHA Class III:
Typically, NYHA Class is determined through clinical history, which has been widely accepted for decisions regarding defibrillator implants and CRT candidacy. While advanced testing such as 6MWT or Cardiopulmonary Exercise Testing (CPET) could provide more precise differentiation of symptoms, these tests may not be widely available and could pose an obstacle to accessing beneficial therapy due to their cost and availability.

Left Ventricular Ejection Fraction 25-45%:
Current FDA approval for CCM does not specify the method of EF assessment. Transthoracic echocardiogram is generally accepted for EF assessment. Although the FDA has approved CCM for patients with an EF of 25-45%, data from Europe suggests that patients with EF <25% benefit similarly to those with EF >25% (Kuschyk et al., Eur J Heart Fail. 2021; Yucel et al., Pacing Clin Electrophysiol, 2022). Coverage could be extended to patients with EF <25% if FDA approval is obtained.

On Guideline-Directed Medical Therapy:
This requirement is prevalent across nearly all criteria for advanced HF therapies, and all data on CCM is in patients who are on guideline-directed medical therapy (GDMT).

Not Candidates for CRT:
It is crucial that the patient coverage criteria use more specific language than "not receiving CRT." The prior FDA criteria, "not candidates for CRT" was clearer. The current language, "not receiving

CRT", may allow for simply turning off CRT before a CCM implant and then reactivating it afterward. We ask for clarification, although not necessarily limitation. For example, there is some evidence which suggests that CRT non-responders may benefit from CCM, though more investigation is necessary (Kuschyk et al., Int J Cardiol. 2019). As CRT non-responders may have no other options for symptom palliation, CCM may be appropriate to use. Additionally, the data suggests that CCM benefits patients who are not suitable for CRT and may provide similar advantages to CRT (Yuecel et al., ESC Heart Fail. 2024). This supports the idea that we should strive to make CCM accessible to all patients who could benefit from it. However, more investigation is needed to understand the effect of CCM in CRT non-responders. As more robust research becomes available, CMS should consider updating the patient criteria.

Institution & Operator Criteria

CCM implant procedures closely resemble those for pacemakers, so the institutional requirements for CCM can be aligned with those for pacemaker implants. Physicians who are qualified to implant cardiac pacemakers and implantable cardiac defibrillators should also be deemed capable of implanting CCM devices, as they possess the necessary technical skills and experience to manage the more complex cases typically seen in sicker HF patients. However, specific considerations must be taken into account. For patients with concomitant defibrillators, it is appropriate to require training or licensure in Cardiac Electrophysiology, as assessing any interaction between the CCM device and the Implantable Cardioverter Defibrillator (ICD) during the procedure is necessary.

It is necessary to awaken the patient mid-procedure to assess for pain with active CCM therapy, which may not be feasible with "conscious sedation" alone. Therefore, CCM placement may need to be performed with local anesthesia only or at hospitals where short-acting drip medications can be used for sedation.

Health Disparities and Equity

Health disparities and equity are critical considerations in the implementation of CCM therapy. As with all therapeutic opportunities, obstacles to qualification—such as the need for more testing and additional visits—disproportionately affect patients with lower socioeconomic status and those in underserved areas. These barriers can limit access to CCM for the very patients who might benefit the most. HF symptoms are extremely severe, similar to those experienced by patients on dialysis and with major depressive disorder (Juenger et al., Heart, 2002). With an average survival rate of only 50% at five years (Taylor et al., Brit Med J, 2019), it is crucial to ensure that CCM therapy is accessible to our sickest patients, whose time remaining is the most valuable because of limited longevity. Moreover, the timing of CCM implantation is essential for achieving optimal outcomes. Evidence from cardiac resynchronization therapy (CRT) shows that earlier implantation after meeting criteria is associated with better mortality rates and reduced HF hospitalizations (Leyva et al., EP Europace, 2023). Therefore, any obstacles to qualification and coverage that delay CCM implantation could significantly mitigate its benefits. Addressing these disparities and ensuring equitable access to CCM is vital for improving outcomes and quality of life for HF patients.

Essential Conditions for CCM Success and Urgent Research Priorities

To achieve the outcomes demonstrated in clinical studies for CCM, specific treatment conditions must be met. Patient selection is paramount, as excluding patients with comorbidities that would negate improvements from CCM is critical. While improving systolic function theoretically enhances mortality, this benefit should not be assumed in the absence of symptom improvement. For instance, a patient with morbid obesity might experience an improvement in EF but still remain short of breath. Until more definitive data demonstrates a mortality benefit from CCM, it would be premature to recommend it solely for mortality improvement without symptom relief. The CCM-REG study suggested that patients with an EF between 25% and 45% had better-than-expected mortality rates compared to the MAGGIC score, but this finding has not been conclusively determined (Kuschyk et al., Eur J of Heart Fail, 2019).

Future research should urgently address several key questions. One area of investigation is whether single-lead CCM can achieve similar outcomes to two-lead CCM. A small study indicated this might be true, which could alleviate concerns about tricuspid regurgitation caused by multiple leads across the tricuspid valve. If single-lead CCM proves equally effective, it could reduce morbidity related to infections and device extraction in the future (Röger et al., J Cardiol, 2017). Another critical area is the timing of CCM implantation. It has been shown that the timing of cardiac resynchronization therapy (CRT) affects outcomes, and similar investigations are needed for CCM to determine if earlier or later implantation influences patient results (Leyva et al., EP Europace, 2023). Additionally, in a population already vulnerable to both atrial and ventricular arrhythmias, it is essential to explore whether CCM reduces the burden of arrhythmias, including the risk of defibrillator therapies such as anti-tachycardia pacing and shocks. Addressing these questions with urgency will help optimize CCM therapy and improve outcomes for heart failure patients.

There is also an ongoing study evaluating a combined CCM and ICD device. This device aims to provide both therapies in a single implant, potentially reducing the number of procedures patients with heart failure may require. Given the potential benefits of this combined device, it may be necessary to establish specific qualifications for future Medicare coverage. These qualifications could ensure that patients who would benefit most from this "higher use" device—those at high risk for both heart failure symptoms and sudden cardiac death—have access to it. By doing so, we can limit the total number of procedures these patients may need, improving their overall quality of care and reducing healthcare costs.

CED Requirements

Coverage with Evidence Development (CED) is an extremely powerful mechanism offering significant value to payers, clinicians, and patients. CED has been demonstrated to be an ingenious technique allowing the diffusion of diverse innovative cardiovascular technologies and services into the marketplace while simultaneously promoting timely clinical safety and effectiveness evaluations. The societies support the use of CED to provide Medicare beneficiaries with prompt access to

newer technologies and services when early evidence suggests, but does not yet convincingly demonstrate, a net benefit for beneficiaries.

Registry Participation

The societies recommend that the heart team and hospital participate in a prospective, national, audited registry. The success of the National Cardiovascular Data Registry (NCDR) is well-established. It is recommended that reporting to the NCDR EP Device Implant Registry™ under CED will facilitate understanding of patient selection, post-market surveillance, outcome measurement, and comparative effectiveness research for this emerging technology. The existing EP Device Implant Registry is accepting data on CCM procedures as of January 2025.

Participation in society-run registries is essential for several reasons:

1. Real-World Insights: These registries capture data from routine clinical practice, providing insights into how treatments and interventions perform outside the controlled environment of clinical trials. This real-world relevance is vital for understanding the practical effectiveness of medical procedures and treatments.
2. Longitudinal Data: Society-run registries often track patients over time, allowing for the collection of longitudinal data. This data reveals trends, which are valuable for assessing the effectiveness and safety of treatments over time, as well as determining if a treatment is reasonable and necessary.
3. Breadth of Data: By including data from a wide range of institutions and patient populations, the NCDR provides a comprehensive picture of how treatments work across different demographics and clinical settings. This variety ensures that the findings are applicable to a broad spectrum of patients and hospitals.

The societies support Medicare coverage of CCM therapy for HF and appreciate the opportunity to provide feedback on the NCA. Please direct any questions or concerns to Amanda Stirling, Regulatory Affairs Associate, at 202-375-6553 or astirling@acc.org.

Sincerely,

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