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Medicare Evidence Development and Coverage Advisory Committee: Health Outcomes in Studies for Heart Failure Treatment Technologies
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The American Heart Association (AHA) is pleased to provide comments to the Medicare Evidence Development and Coverage Advisory Committee (MEDCAC) on health outcomes in studies for heart failure treatment technologies.

AHA is the nation's largest voluntary health organization with over 22.5 million volunteers and supporters. Since 1924, AHA has dedicated itself to building healthier lives free of cardiovascular disease and stroke – the #1 and #4 leading causes of death in the United States – through research, education, community-based programs, and advocacy. AHA supports the efforts of the Centers for Medicare & Medicaid Services (CMS) and MEDCAC to examine the ideal health outcomes in research studies of heart failure treatment technologies and the appropriate follow-up duration to ensure transparency of National Coverage Analyses (NCA).

Heart failure has reached epidemic proportions worldwide and is associated with substantial public and personal burden as evidence by the enormous costs of caring for these patients. Heart failure affects 2.4% of the adult population or approximately 5.7 million Americans. Among adults age 65 and older, the incidence of heart failure approaches 10 per 1,000 individuals and increases to 11% of the population above age 80. Patients benefit from the availability of new and innovative medical products and medical technologies, but access should not be at the expense of patient safety. The AHA applauds MEDCAC panel's decision to examine the growing challenges associated with the decreased level of evidence generated prior to market authorization of new and innovative technologies.

Standalone Primary Health Outcomes

How confident are you that the following are standalone, meaningful primary health outcomes in research studies of heart failure treatment technologies?

a) Heart failure hospitalization

Heart failure hospitalization is an important endpoint in research studies, but it is not sufficient as a standalone outcome. While HF hospitalization will likely be responsive to effective therapies, only certain technologies act by a mechanism predicted to affect hospitalization. HF hospitalizations have been well validated as an endpoint for worsening heart failure and denote a significant change in the prognostic trajectory of the disease process. Avoidance of hospitalization in the sickest HF patients is essential to evaluate. Patients with HF are highly motivated to avoid hospitalization so many live with unwelcome symptoms without being hospitalized. Therefore, investigation of functional endpoints is warranted in many trials as well.

In any research study of a new technology, the purpose and goal of that technology should be an essential part of determining the proper primary health outcome of interest. This is particularly critical as therapies for heart failure with preserved ejection fraction (HFpEF) are evaluated because these patients carry a very high symptom burden, but many are hospitalized less often. A composite of death or HF hospitalization would be a better index. Almost all large pharmacological trials in heart failure have used heart failure hospitalization along with CV death as either the primary composite endpoint or as a key secondary endpoint

b) Heart failure hospitalization or heart failure hospitalization equivalent events (i.e., outpatient IV therapy for heart failure)

Heart failure hospitalization admissions or heart failure hospitalization is an important endpoint, but it is not sufficient as a standalone outcome. Because hospitalization is a publicly reported metric, there is an incentive among hospitals and providers to avoid HF hospitalization. There are no agreed upon admission criteria for HF. As a result, admission is subjective and varies depending on the setting in which the patient is treated. Capturing these events is difficult, but is increasingly important as the healthcare landscape is changing away from inpatient care of HF. will miss important episodes of worsening disease.

While administration of IV diuretics in non-inpatient settings is a less well-accepted primary health outcome, there is considerable and growing literature that heart failure patients who require outpatient intravenous diuretics have comparably poor outcomes who are hospitalized. This may directly result from the aforementioned de-escalation of care setting given fiscal, policy and reporting constraints. However, provider variability for the same degree of worsening heart failure may lead to escalating oral combination diuretic regimen rather than administration of intravenous medication, in the absence of uniform guidelines. We may soon be administering IV diuretics in the "medical homes" of our patients. Most recent clinical trials have started to include these hospitalization equivalents in trial design, and continued evolution and sophistication in measurement of such events will be necessary as dictated by the reimbursement landscape.

c) Total Hospitalizations

Total hospitalizations are important for safety, efficacy, and high risk interventions, but it is not adequate as a standalone outcome. Total hospitalizations over a fixed period of time includes all admissions and readmissions, regardless of cause. It is significant to patients and serves as an indicator of resource use. In trials of HFpEF, total hospitalizations appear more responsive to therapeutic intervention than time to readmission. Furthermore, this metric gives a complete picture of the efficacy and safety of novel therapies and it quantifies patient burden more accurately. Generally, mortality should always be combined with or presented in parallel with hospitalization metrics because if patients die they are not eligible for hospitalization events. Without the inclusion of mortality, the data would be skewed.

The potential benefit of the technology must always be considered when making determinations about outcomes. The timeframe for examining outcomes will vary depending on the nature of an intervention and the way the assessment will be used. For example, the benefits of interventions like beta-blockers and valve interventions may take months. In contrast, the benefits of transitional care interventions following discharge may present early results. New technology may make it easier to live with severe disease, reduce the number of face-to-face visits with providers, or transition from aggressive to palliative pathways more quickly and appropriately. If this were to happen, understanding the impact of technology on these important outcomes for purposes of safety and risk-benefit analyses is would remain critical. However, examination of mortality and hospitalizations may not be the optimal primary outcomes for such technologies.

Surrogate and Intermediate Endpoints

How confident are you that surrogate and intermediate endpoints are predictive of standalone, meaningful primary health outcomes (e.g., reduction in mitral regurgitation, cardiac remodeling, ejection fraction, or biomarkers) in clinical research studies of heart failure treatment technologies for:

a) Heart failure with preserved ejection fraction;

In heart failure with preserved ejection fraction, surrogate and intermediate endpoints are not adequately predictive of standalone meaningful primary health outcomes. Understanding, defining, treating, and following patients with heart failure with preserved ejection fraction (HFpEF) has been more challenging than patients with heart failure with reduced ejection fraction (HFrEF) because HFpEF physiology is less understood. Parameters of cardiac remodeling and their association with outcomes are less clear for HFpEF than for HFrEF. Natriuretic peptides increase less in HFpEF for similar degrees of symptoms. While they still confer prognostic information for these patients, decision-making based on natriuretic peptides is far more difficult in HFpEF. In addition, biomarkers in general have shown a less reliable association with disease activity and outcomes in HFpEF than in HFrEF. Thus, HFpEF studies and metrics must be particularly vigilant in defining the disease and how patients are followed. Given that HFpEF patients tend to be older with many comorbidities, both the mechanism of the technology and the patients' desired results should be considered when choosing outcomes to measure. Few patients report that changes in biomarkers are of

importance, but nearly all will report that changes in exercise capacity, health-related quality of life, or hospitalizations are important. Biomarker outcomes should be paired with patient-centered meaningful outcomes.

b) Heart failure secondary to mitral regurgitation where the focus of therapy is mitral valve repair/replacement;

In heart failure secondary to mitral regurgitation, surrogate and intermediate endpoints are not adequately predictive of standalone meaningful primary health outcomes. Treatment of mitral regurgitation in heart failure creates particularly challenging assessments using many surrogate markers. Treatment of the valve lesion acutely changes ventricular volumes and, as a result, LVEF. Long-term benefits may not be apparent early after intervention. Thus, assessment of hard outcomes (hospitalization, mortality) for more than a year are likely necessary to characterize interventions for mitral regurgitation. There are significant data that LV volumes and natriuretic peptides are strongly linked with more important clinical outcomes in HFrEF. Patient-centered outcomes, including quality of life and exercise capacity, are critical metrics following this treatment, when there may be drops in both regurgitant volume and ejection fraction following an intervention, and overall efficacy may be difficult to predict based on a single parameter.

c) Heart failure with reduced ejection fraction (e.g., cardiac remodeling, ejection fraction)?

In heart failure with reduced ejection fraction, surrogate and intermediate endpoints are not adequately predictive of standalone meaningful primary health outcomes. Hard endpoints may include novel outcomes such as "days alive and out of hospital." In the very elderly with less invasive technological interventions, even "days able to leave home" or "days able to perform self care" may be meaningful, but not often captured. Additional surrogate endpoints will be necessary to show improvements in the heart failure syndrome that are technology and disease-specific. A tailored approach is necessary when selecting surrogates with the understanding that devices must be safe with low procedural risk. Effects on mortality should be tracked by registries over the long term.

Quality of Life Measures

How confident are you that quality of life measures [e.g., Kansas City Cardiomyopathy Questionnaire (KCCQ), Minnesota Living With Heart Failure Questionnaire (MLWHFQ):

a) Are adequate measures which reflect the patient experience?

These measures reflect the patient experience when they are well designed, as they capture what is meaningful to patients. The KCCQ has been extensively validated in over 20 years of work and is known to be inclusive of the primary symptoms and impacts of heart failure from patients' perspectives. It has also been shown to be similarly valid, reliable, sensitive to change, prognostic of mortality/readmissions/costs and interpretable in all etiologies of HF – including HFrEF and HFpEF. Importantly, it maintains validity even in the presence of significant comorbidity. A change in score of 5 points on the KCCQ has been shown to be associated with changes in clinical status and physical functioning, and is agreed to be of clinical significance. The KCCQ has been shown to be more sensitive to clinical change

than the MLHF questionnaire. KCCQ also comes in a 12-item version to ease implementation and reduce burden on providers and patients. Quality of life is secondary to survival for most patients, but it is important to understand that a significant minority of patients will trade some survival for improvement in quality of life. Thus, both quantity and quality of life measures are important.

Ultimately, approval of a new technology should not require a positive impact on mortality if other benefits on patient-centered outcomes are clear and demonstrable. A comprehensive understanding of the trade-offs in terms of of risk and benefit is the most critical factor in decision-making for a HF patient. Our community has become familiar with this in our experience with ventricular assist device technologies. A general health status measure may better integrate benefits and side effects of interventions with off target side effects. LVAD, for example, may improve HF symptoms, but creates several other burdens and adverse events that may not be directly HF related. While some individuals find this trade-off worth it, others do not. Assistance in helping patients understand and apply these complex decisions is a critical accompaniment to new technology development.

b) *Should be included as the standalone, meaningful primary health outcomes in research studies?*

It would absolutely be reasonable for the QOL measures to be included as the standalone, meaningful primary health outcomes in some research studies, providing safety of the intervention is also known or assessed. In fact symptoms and functional capacity issues have been standalone outcomes for other cardiovascular disease like angina, peripheral vascular disease, and pulmonary hypertension. This is especially important for HFpEF as this is largely a disease of elderly in mid 70s or over 80 years of age. These patients have many competing risks for mortality so even if a treatment is unable to prolong life, improving quality of life of these patients is a worthy goal.

c) *Should be include as composite standalone, meaningful primary health outcomes in research studies?*

Failure to include any measure of patient QOL could be seen as a failure to comprehensively study an intervention. This is particularly true with technology, as the response of different patients to technological interventions can be variable and unpredictable. It is critical that when included QOL measures not be part of composite endpoints, as they are qualitatively different from less subjective endpoints such as hospitalization or death. We are obligated to understand the impact of new technology on patients lives, not just on their disease manifestations and symptoms. We would strongly support a requirement for some assessment of impact on QOL as an adjunct to other endpoints in design of technology trials.

Functional Assessments

How confident are you that functional assessments [e.g., 6 min walk test (6MWT), VO2max, ventilator threshold]:

a) Are adequate measures which reflect the patient experience?

These measures are well-established and clinically meaningful outcomes and have been extensively used in trials and in early phase studies. Functional assessments correlate with disease severity and functionality as a domain of health status. In general, simpler measures of functional capacity that can be performed accurately and reproducibly in multiple settings are superior to complex, operator dependent functional assessments. As a standalone outcome, any measure of functional capacity should be based on validated data, have relevance to patients, with known parameters regarding the degree of improvement that has clinical relevance and for which data can be obtained reliably and reproducibly. It is also important that when functional capacity is used to assess a HF intervention, one is confident that HF is the primary limitation and not another disease processes, e.g. arthritis.

b) Should be included as the standalone, meaningful primary health outcomes in research studies?

These measures are reasonable in some situations with the caveats discussed above.

c) Should be included as a composite standalone, meaningful primary health outcomes in research studies?

These measures are a critical piece of most composite endpoints, as information about functional capacity is critical to determine the impact of a new technology on overall patient-centered outcomes. Although the example of ICD therapy tells us that a therapy that impacts mortality with no effect on functional capacity can be important and accepted, the impact on functional capacity becomes increasingly critical in older HF patients. In all situations the purpose of the technology being studied, how these endpoints are combined with other outcomes, how they will be assessed, will they be used as continuous measure or categorized, and how to evaluate the data if the components of a composite endpoint trend in discordant directions are important factors to consider prior to initiation of study. Safety must always be assessed in parallel, particularly with more invasive technologies.

Discussion

• " *Please discuss whether additional patient-reported measurement [e.g., Short Form-36 (SF-36), EuroQol five dimensions' questionnaire (EQ5D)] should be considered to capture burdens associated with the heart failure therapy under study.*

There is little evidence that other questionnaires improve understanding of therapeutic burden associated with HF and HF therapies beyond what is found in KCCQ. Although there is a theoretical concern that collateral impact of treatment on QOL issues not directly related to HF may be missed, little data support this in HF populations since the HF condition tends to dominate QOL issues. Depending on the therapy, adjunctive surveys may be of interest to explore outcomes of interest in more detail such as depression, social engagement, caregiver burden, and mobility. These outcomes should be incorporated on a case by case basis and in addition to disease-specific measures.

• " *Please discuss the appropriate length of follow-up post-heart failure intervention for assessing patient-reported measurements.*

Often benefits in quality of life are realized quickly particularly if major surgical procedures are not necessary. QOL benefits appear to plateau for many therapies, as seen in

resynchronization pacemakers and ventricular assist devices. Collecting additional QOL data after this plateau is not worthwhile, and may be contaminated by ongoing processes not impacted by the technology, diluting the efficacy signal. Ideally, early phase studies will provide clues to the pace of QOL improvement, but 6-12 months is reasonable for most technology interventions.

- " *Please discuss the impact of unblinded study participants on patient-reported measurements and functional assessments.*

Blinding is important in patient-reported outcomes and essential for accurate interpretation of the impact of a new intervention. Lack of blinding is particularly problematic with technology based interventions because there is usually a belief in the technology among those willing to participate in such studies. This has been shown to potentially enhance the placebo effect significantly. Such placebo effects require a blinded study for evaluation. This has been seen repeatedly in HF trials, where significant improvement is predictably seen in the placebo arm. Approval of a technology-based therapy should require a blinded study unless absolutely impossible.

- " *Please discuss how to best consider the impact of adverse events associated with heart failure technologies while balancing the potential for improvements to meaningful health outcomes.*

It is ideal, when interpreting results of research in which benefit is not unequivocal or universal, to understand the impact of the technology on domains of most interest to the patient. In HF patients, different patients have different goals, and these goals change as patients age, live with disease, and develop other limiting comorbidities. No decision is right for every heart failure patient. The ideally designed study will inform shared decision making by improving estimates of benefit and harm, while more clearly defining the type and severity of these outcomes. Such data can then be used by patients and providers in shared-decision making about pursuing additional therapies.

- *Please discuss how to balance the benefits and harms of therapies which may improve near-term patient-reported health outcome assessments or clinical measurements (e.g., 6 MWT or symptoms) but may decrease length of life.*

In a therapy in which benefits are clear, but harm is also present, the best course appears to develop tools, to the extent possible, to characterize risks for individual patients and allow informed and shared decision making. Providers do this routinely with anticoagulant therapy for atrial fibrillation, where there is a risk benefit equation for each patient. Similarly, with decisions to use bare metal or drug eluting stents. At the end of a trial, we should have detailed information about benefit and harm that will enable discussions with patients.

Additional Discussion Topics

- *Please discuss health outcomes of interest and appropriate follow-up duration in studies of technologies designed for diagnosis of acute decompensation of heart failure.*

Patients with acute decompensated heart failure have particularly poor outcomes and therefore a 3-6-month time frame may be enough for assessment; certainly by 12 months if there is benefit to be had, it will emerge. Outcomes of interest include health status over time,

rates of return to former levels of health and function or better, recurrent heart failure hospitalizations, survival, and resource utilization.

- *With the health outcomes and information that we have discussed today, how confident are you that there will be enough accurate information provided to patients for them to make informed decisions?*

Ideally patients need to understand how different options will affect the range of outcomes important to them. This requires collecting comprehensive information on risks and benefits, including survival and health status information. It also requires that such information be delivered in a way that is easiest for the patients to understand. Formal patient decision aids are one way to facilitate such information transfer and encourage appropriate discussions between patients, families, and clinicians.

- *Please discuss how studies can be designed to accurately capture patient preferences and how their preferences can best be considered and operationalized once the study has concluded.*

While there is a significant literature on this topic, there is no perfect answer. Prospective serial assessment of ranked preferences for outcomes, satisfaction scores, decisional conflict and decision regret have been developed and employed for this purpose. HF patients have been documented to change their minds frequently about outcomes of importance to them, increasing the complexity of analyzing this important parameter in an accurate way. This is an incredibly important issue and the PCORI is actively working on these issues.

Thank you again for the opportunity to share our comments on these issues related to the health outcomes for heart failure treatment technologies. If you have any questions, please feel free to contact Stephanie Curtis at stephanie.curtis@heart.org or 202-785-7931.

Sincerely,

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President