CardioMEMS™ HF System (St. Jude Medical, Inc.) and Sacubitril/Valsartan (Entresto™, Novartis AG) for Management of Congestive Heart Failure: Effectiveness, Value, and Value-Based Price Benchmarks

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The California Technology Assessment Forum (CTAF) – a core program of ICER – reviews evidence reports and provides a public venue in which the evidence on the effectiveness and value of health care services can be discussed with the input of all stakeholders. CTAF seeks to help patients, clinicians, insurers, and policymakers interpret and use evidence to improve the quality and value of health care.

The CTAF Panel is an independent committee of medical evidence experts from across California, with a mix of practicing clinicians, methodologists, and leaders in patient engagement and advocacy, all of whom meet strict conflict of interest guidelines, who are convened to evaluate evidence and vote on the comparative clinical effectiveness and value of medical interventions. More information about CTAF is available at http://www.ctaf.org

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List of Acronyms Used in this Report

ACE	Angiotensin-converting enzyme
AE	Adverse event
AHA	American Heart Association
AHRQ	Agency for Healthcare Research and Quality
ARB	Angiotensin II receptor blocker
BI	Budget impact
BID	Bis in die (twice daily)
BMI	Body mass index
CDC	Centers for Disease Control and Prevention
CHARM	Candesartan in Patients with Chronic Heart Failure
CHF	Congestive heart failure
CI	Confidence interval
CMS	Centers for Medicare & Medicaid Services
COPD	Chronic obstructive pulmonary disease
CPI	Consumer price index
CRT	Cardiac resynchronization therapy
CRT-D	Cardiac resynchronization therapy with defibrillator
CV	Cardiovascular
ED	Emergency department
EQ-5D	European Quality of Life-5 Dimensions
FDA	Food and Drug Administration
GDP	Gross domestic product
HFH	Heart Failure Hospitalization
HR	Hazard ratio
ICD	Implantable cardioverter-defibrillator
ICER	Incremental cost-effectiveness ratio
IHM	Implantable hemodynamic monitor
KCCQ	Kansas City Cardiomyopathy Questionnaire
LVEF	Left ventricular ejection fraction
MI	Myocardial infarction
MLHF	Minnesota Living with Heart Failure
NHE	National Health Expenditure
NNT	Number needed to treat
NYHA	New York Heart Association
PA	Pulmonary artery
PAP	Pulmonary artery pressure
PCI	Percutaneous coronary intervention
pEF	Preserved ejection fraction
PH	Pulmonary hypertension
PICOTS	Population(s), Intervention(s), Comparator(s), Outcome(s), Timing, Setting(s)
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QALY	Quality-adjusted life-year
RAAS	Renin-angiotensin-aldosterone system
RCT	Randomized controlled trial

rEF	Reduced ejection fraction
RHC	Right heart catheterization
RR	Relative risk
SAE	Serious adverse event
SG	Swan-Ganz (catheter)
USPSTF	United States Preventive Services Task Force
WAC	Wholesale acquisition cost
WHO	World Health Organization

Executive Summary

Background

Congestive heart failure (CHF) describes the condition of fluid build-up in the body as the heart inefficiently fills with or pumps out blood. CHF results from other conditions that weaken the heart muscle including coronary artery disease, myocardial infarction, cardiomyopathy, and hypertension, and is a major public health concern.

Two new interventions for CHF have received significant attention – a device and associated software for monitoring increases in pulmonary artery (PA) pressure (a key indicator of worsening CHF) known as the CardioMEMS™ HF System (St. Jude Medical), and a drug, Entresto™ (Novartis AG), a combination of the angiotensin II receptor blocker (ARB) valsartan and the neprilysin (nep-rĭ-lī-sin) inhibitor sacubitril. The objective of this report is to evaluate the accumulated evidence on these two new interventions, to understand the context around their potential use in clinical practice, and to assess their cost-effectiveness and budgetary impact.

Topic in Context

In summarizing the contextual considerations for appraisal of a health care intervention, we seek to highlight the four following specific issues:

- Is there a particularly high burden/severity of illness?
- Do other acceptable treatments exist?
- Are other equally or more effective treatments nearing introduction into practice?
- Would other societal values accord substantially more or less priority to providing access to this treatment for this patient population?

Congestive Heart Failure Morbidity and Management

CHF is associated with 1) substantial morbidity and mortality, with five-year mortality similar to that of many cancers; and 2) high rates of hospitalization and intensive outpatient care.[1,2] In the United States, the lifetime risk of developing CHF approaches 20%,[1] and the disease currently affects about 6.2 million individuals.[3]

The severity of CHF is often classified according to the New York Heart Association (NYHA) system of classification by patient functional status.[4] These classes commonly appear in treatment guidelines and as enrollment criteria for CHF clinical trials:

- Class I: Patients have no physical activity limitation.
- Class II: Patients have slight limitation of physical activity such that symptoms develop with ordinary activity but not at rest.
- Class III: Patients have marked limitation of physical activity such that symptoms develop with mild exertion but not at rest.
- Class IV: Patients are unable to carry on any physical activity without discomfort, and symptoms may occur at rest.

Management of CHF is guided by treating the underlying cause—often a chronic systemic disease process such as hypertension, diabetes, coronary artery disease, valvular heart disease, or myocarditis—and lifestyle improvements (e.g., diet, exercise, smoking cessation). Although a variety of evidence-based medical and device therapies for CHF are available, the morbidity, mortality, and costs associated with the condition remain high and no major advancements in treatment have occurred in well over a decade.

CardioMEMS

Fluid overload is one of the primary causes of CHF-related hospitalizations. Although regular monitoring of signs and symptoms of fluid overload, such as shortness of breath, swelling, fatigue, and weight gain, is a common component of CHF management, these signs and symptoms are not sensitive enough to reflect early pathophysiologic changes that increase the risk of decompensation.[5-9] Several studies have demonstrated that elevations in PA pressure closely correlate with worsening heart failure and may increase several days or weeks before signs and symptoms manifest.[7] These findings prompted the development of new implantable devices to assess cardiopulmonary filling pressures.

The CardioMEMS device is a small wireless sensor that is permanently implanted in the pulmonary artery via a catheter inserted through the femoral vein. The sensor measures PA pressure and is paired with a portable electronic transmitter. The system allows patients to wirelessly transmit pressure readings to a secure online database from which treating physicians can access the data. The price to Medicare for CardioMEMS is $17,750, which does not include costs associated with device implantation or monitoring.[10,11]

Entresto

Angiotensin converting enzyme (ACE) inhibitors have been the cornerstone of pharmacologic treatment for heart failure in patients with CHF due to reduced ejection fraction for more than two decades.[12] Over the same time period, researchers have explored strategies to bolster the effects of naturally occurring natriuretic peptides, a family of hormones the body releases to help maintain fluid balance.[13,14] Entresto was designed to combine the neprilysin inhibitor sacubitril with an ARB (i.e., angiotensin II receptor *blocker*) instead of an ACE inhibitor in order to reduce the risk of

angioedema.[15] Entresto is taken twice daily with an annual wholesale acquisition cost (WAC) of $4,560.[16]

CardioMEMS

Comparative Clinical Effectiveness

Results

Clinical Benefits

The literature search for CardioMEMS identified 23 potentially relevant references (see Appendix Figure A1) of which five publications concerning a single randomized controlled trial (RCT) (the CHAMPION trial) and one case series met our inclusion criteria. Details of the included studies are summarized in Appendix Table E1.

The CHAMPION trial was a single-blind RCT of 550 patients who met eligibility criteria of having NYHA Class III heart failure and a CHF-related hospitalization within the 12 months prior to screening.[17] All patients underwent implantation of a CardioMEMS device and took daily readings of PA pressure using a home electronic console. Clinicians received pressure readings from patients in the treatment group but did not have access to pressure data from the control group. The control group continued to receive standard of care management, which consisted of medication changes in response to patients' clinical signs and symptoms and routine clinic appointments. All patients remained blinded to their assigned groups until the last patient completed six months of follow-up, resulting in a mean duration of follow-up of 15 months for the entire patient population. The authors reported outcomes both at six months and over the entire duration of follow-up. In subsequent submission to FDA, the mean blinded follow-up period was cited as 17.6 months.[18]

The CHAMPION trial was powered to detect differences in CHF hospitalization. Mortality was assessed based on a secondary endpoint of time to first CHF hospitalization or death. Over the full follow-up period, a total of 107 patients in the treatment group either died or had a hospitalization for CHF versus 138 in the control group (hazard ratio [HR] 0.73; 95% confidence interval [CI]: 0.57-0.94, p=.0146). In addition, there was a statistically-significant, albeit modest, increase in the mean number of days alive outside of the hospital in the treatment group (174.4 vs. 172.1; p=0.02).

The CHAMPION trial also measured quality of life using the Minnesota Living with Heart Failure (MLHF) questionnaire. At six months, the treatment group had a statistically-significant, but clinically marginal, improvement in MLHF score vs. the control group (-10.6 vs. -7.4, p=0.04).[19]

Health Care Utilization Outcomes

In the first six months after device implantation, the treatment group had fewer CHF-related hospitalizations (84; 0.32 hospitalizations per patient) relative to the control group (120; 0.44 hospitalizations per patient; HR 0.72 [95% CI: 0.60-0.85]; p=0.0002). The treatment group also had a shorter average length of stay for CHF-related hospitalizations (2.2 days vs. 3.8 days; p=0.02). Over the entire 15-month follow-up period, the treatment group had a 37% reduction in CHF-related hospitalizations, with 158 and 254 hospitalizations in the treatment and control groups, respectively (HR 0.63; 95% CI: 0.52-0.77; p<0.0001). The authors calculated that during the first six months of follow-up, eight patients would need to be managed with CardioMEMS to prevent one additional hospitalization for CHF; this number decreased to four patients over the entire 15-month follow-up period.

Harms

In the CHAMPION trial, 98.6% of patients had no device- or system-related complications, and no pressure-sensor failures occurred. Fifteen serious adverse events (SAEs) occurred among the entire cohort of 550 patients, of which eight were related to the device or system and seven were related to the implant procedure. SAEs included four bleeding events, three hospitalizations related to anticoagulation treatment, two exacerbations of pre-existing atrial dysrhythmias during right heart catheterizations, two febrile illnesses, one pulmonary in-situ thrombus during right-heart catheterization, one cardiogenic shock, one atypical chest pain, and one delivery-system failure.

Controversies and Uncertainties

The Food and Drug Administration (FDA) Advisory Committee had several methodological concerns about the efficacy of the CardioMEMS device. One of the primary objections was that patients in the treatment arm of the CHAMPION trial received some form of study nurse involvement in addition to having their PA pressures sent to the treating clinician. These study nurses communicated information about the patient to the treating physicians in a way that was not completely mimicked in the control arm. The other key issues pertained to differences in outcomes between men and women and questions about why an independent survival benefit could not be detected given reductions in hospitalization rates.[20]

The Advisory Committee concluded that the bias introduced by the existence of nurse correspondence in the treatment arm was impossible to fully neutralize despite extended data collection and subsequent analyses. The Advisory Committee also noted that the lack of mortality benefit suggested the need for additional study. CardioMEMS ultimately received FDA approval on May 28, 2014 with the requirement that the manufacturer perform two post-approval prospective, multi-center, open-label US-based trials in order to 1) examine the device's safety and effectiveness among new recipients with enough sample size to detect gender differences, and 2) compare post-

market effectiveness to a subset of pre-market recipients with specific attention to certain subgroups (women vs. men, reduced ejection fraction [rEF] vs. preserved ejection fraction [pEF], ischemic vs. non-ischemic etiology, and implantable cardioverter-defibrillator [ICD] or cardiac resynchronization with defibrillator [CRT-D] vs. non-ICD/CRT-D).[21] Details of the ongoing trials are provided in Appendix D.

Alternative Management Strategies

Several RCTs, systematic reviews, and technology assessments have evaluated the effectiveness of programs of varying intensity for reducing readmissions of patients with heart failure after a first hospitalization.[2,22-26] Certain interventions have become common components of usual care, including education on symptoms, instruction on self-management, dietary advice, medication review, exercise recommendations, and weight monitoring; however, there is considerable heterogeneity in the content, intensity, duration, setting, personnel, and combination of components employed in CHF management across programs.[26] Given the risk of unknown confounders, great caution must be given to interpreting any comparison of results from individual treatment arms across different studies. With this caution in mind, systematic reviews have found that the rate of CHF hospitalizations among patients receiving non-pharmacologic interventions such as structured telephone support, multidisciplinary care, or patient education and self-management is similar to that among patients in the CHAMPION trial who were monitored with the CardioMEMS device; however, indirect comparison of CardioMEMS and telemonitoring suggests a relative benefit conferred by CardioMEMS.

Summary and Comment

For patients with Class III CHF with either reduced or preserved ejection fraction who have been hospitalized in the prior 12 months, we judge there to be moderate certainty of a small net benefit for the CardioMEMS HF System compared with usual monitoring of patients' signs and symptoms. There is moderate certainty because while the CHAMPION trial indicated that patients had fewer hospitalizations when care was informed by the CardioMEMS HF System, the results of the CHAMPION study are limited by concerns regarding the potential confounding influence of the study nurse on the superior outcomes in the treatment arm. In addition, while post-hoc analyses have been presented illustrating reductions in cardiovascular mortality with CardioMEMS, there have been no published data from trials powered to detect mortality differences. It seems reasonable to surmise that ongoing post-marketing trials evaluating the device may demonstrate a wide variety of outcomes, from substantial net health benefit to a small likelihood of overall "negative" benefit given the potential harms associated with device placement. Therefore, we judge the current body of evidence on CardioMEMS to be "promising but inconclusive" using the ICER Evidence Rating framework.

Other Benefits or Disadvantages

With CardioMEMS being an implanted device, there exist potential disadvantages to patients who must undergo a medical procedure, both with respect to minor anxiety over the procedure itself as well as over the understanding that it is a permanent device. The latter point may well serve as a benefit to some patients and their caregivers who may feel reassured by the continual monitoring offered by the device. We have not noted potential other benefits or disadvantages associated with CardioMEMS implantation and monitoring.

Incremental Costs per Outcomes Achieved

Cost–Effectiveness Model: *Overview*

We developed a Markov model of the natural history of chronic heart failure using event rates from the published literature.[17,18,27-36] For the CardioMEMS HF System, we specifically modeled the outcomes and costs based on its use in the CHAMPION trial cohort of NYHA Class III heart failure patients who had a heart failure hospitalization in the previous year, both in patients with rEF and pEF.[17] We compared the CardioMEMS device to routine care (i.e., treatment adjustments based on signs and symptoms).[17,18,29] We utilized the efficacy of the CardioMEMS device in the CHAMPION trial to estimate numbers of CHF hospitalizations, costs, deaths, life-years, and quality-adjusted life years (QALYs). These estimates were used to calculate the cost per QALY gained via the intervention. The costs of the CardioMEMS device were estimated from the Medicare price ($17,750); the model also included the costs of the implantation procedure, routine monitoring, and any device-based complications.[10,37]

Additional details on all model parameters and key assumptions can be found in the full report.

Cost–Effectiveness Model: *Results*

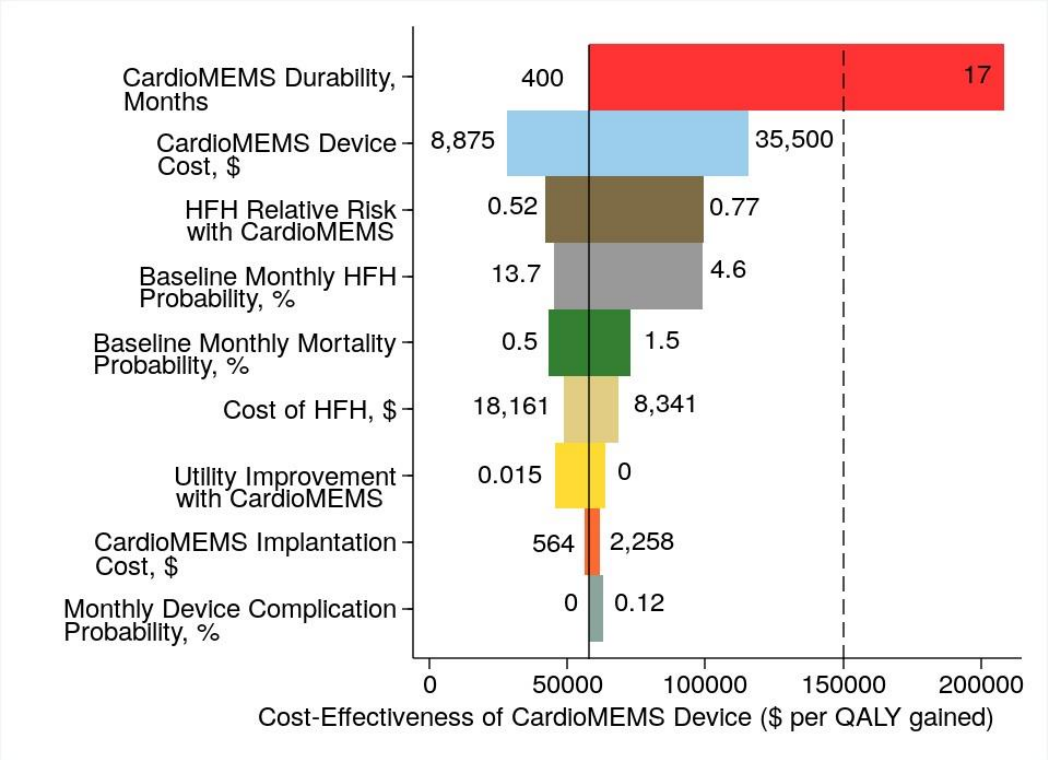
In the base case, the CardioMEMS arm experienced 2.19 CHF hospitalizations per patient compared to 3.18 in the routine care arm. The CardioMEMS arm had 5.72 life-years and 2.74 QALYs per patient compared to 5.28 life-years and 2.44 QALYs in the routine care arm. The total costs in the CardioMEMS arm were $174,037 per patient compared to $156,764 in the routine care arm. The CardioMEMS arm achieved its increased life expectancy of 0.44 years and 0.30 QALYs at an increased cost of $17,274. The resulting cost per QALY gained of the CardioMEMS intervention was $57,933.

Sensitivity Analyses

We performed sensitivity analyses on all input parameters (see Figure ES1). The model was most sensitive to the durability of the CardioMEMS device. In our base case we assumed a lifelong

benefit of the device (400 months) although the CHAMPION trial had a mean patient follow-up of 17 months, and the open access, non-randomized data submitted to the FDA had a follow-up duration of 25.5 months. If the device were no longer more effective than usual care after 17 months, the cost per QALY gained would be $208,545. The cost per QALY decreased with a longer duration of effectiveness; the incremental cost-effectiveness ratio was $100,000/QALY when the duration of effect was reduced to 56 months and was $150,000/QALY when the duration of effect was reduced further to 29 months duration.

Figure ES1. CardioMEMS Tornado Diagram: Series of One-way Sensitivity Analyses



Note: This figure demonstrates the model parameters that most affect the cost per QALY of CardioMEMS therapy. The solid black line represents the cost-effectiveness in the base case. Only the analysis of device durability crosses the $150,000 threshold (dashed black line).

Threshold Analyses

As shown in Table ES1, we also evaluated the device costs at which CardioMEMS would be considered cost-effective under conventional willingness-to-pay thresholds of $50,000/QALY, $100,000/QALY, and $150,000/QALY. The Medicare price for CardioMEMS of $17,750 is relatively close to the price of $15,400 at which the cost/QALY = $50,000 and far lower than the $30,293 price that the device could have if a willingness-to-pay threshold of $100,000/QALY is assumed.

Table ES1. Threshold Analyses: Device Cost at which CardioMEMS Would Be Cost-Effective under Varying Willingness-to-Pay Thresholds

	Willingness-to-Pay Threshold		
	$50,000/QALY	$100,000/QALY	$150,000/QALY
ALL SUBPOPULATIONS	$15,400	$30,293	$45,202

Potential Budget Impact

Overview

We also used the cost-effectiveness model to estimate the potential total budgetary impact of CardioMEMS with different uptake assumptions. We then combined consideration of the price range between cost-effectiveness thresholds of $100,000 to $150,000 per QALY with potential budget impact to calculate a value-based price benchmark.

Our calculations assume that utilization of new devices occurs without payer, provider group, or pharmacy benefit management controls in place in order to provide an estimate of "unmanaged" uptake by five years after launch. We assign a new device to one of four categories of unmanaged uptake patterns: 1) very high (75% uptake by year 5); 2) high (50% uptake by year 5); 3) intermediate (25% uptake by year 5); and 4) low (10% uptake by year 5). In this analysis, we assumed an "intermediate" uptake pattern for CardioMEMS given evidence of significant clinician interest in the device, moderated by potential patient reluctance to undergo the implantation procedure.

We then compare our estimates to a budget impact threshold that represents a potential trigger for policy mechanisms to improve affordability through changes to pricing, payment, or patient eligibility. As described in ICER's methods presentation (http://www.icer-review.org/wp-content/uploads/2014/01/Slides-on-value-framework-for-national-webinar1.pdf), this threshold is based on an underlying assumption that health care costs should not grow more than 1% faster than growth in the overall national economy. From this foundational assumption, our potential budget impact threshold is derived using an estimate of growth in US gross domestic product (GDP) +1%, the average number of new device approvals by the FDA each year, and the contribution of spending on devices to total health care spending. According to our calculations, for 2015-16, the five-year annualized potential budget impact threshold that should trigger policy actions to manage affordability totals approximately $603 million per year.

We combine consideration of the potential budget impact with the threshold prices presented above (i.e., prices based on incremental costs per outcomes achieved) to calculate a value-based price benchmark for each new drug or device. This price benchmark begins with the price range to

achieve cost-effectiveness ratios of $100,000-$150,000 per QALY for the population being considered, but it has an upper limit determined by the price at which the new drug or device would exceed the potential budget impact threshold (i.e., $603 million for devices). If the potential budget impact does not exceed these thresholds, then the value-based price benchmark remains the full price range determined from the analysis of incremental costs per outcomes achieved.

Results

Results for CardioMEMS indicate that the total budgetary impact at one year is similar to the annual average over five years; this is because nearly all CardioMEMS costs are incurred at the time of implantation, and ongoing monitoring and other costs are minimal ($27 per month). Because equal proportions of patients are assumed to receive the device each year, budget impact varies only according to these ongoing costs as well as the potential for cost offset (i.e., patients who receive the device earlier in the timeframe have more potential for offset). On an annualized basis, cost-offset (equally weighted by timing of device implant over the five-year time horizon) is estimated to be $2,265. Total budgetary impact of CardioMEMS is estimated to be approximately $5 billion, or $1 billion annually under our assumed pattern of uptake (~360,000 patients receiving the device by year 5) (see Table ES2). This is above the device budgetary impact threshold of $603 million per year. In order to not exceed this threshold, approximately 16% of the 287,000 Class III patients hospitalized each year could receive CardioMEMS.

Table ES2. Total Budget Impact (BI) of CardioMEMS Based on Assumed Pattern of Uptake

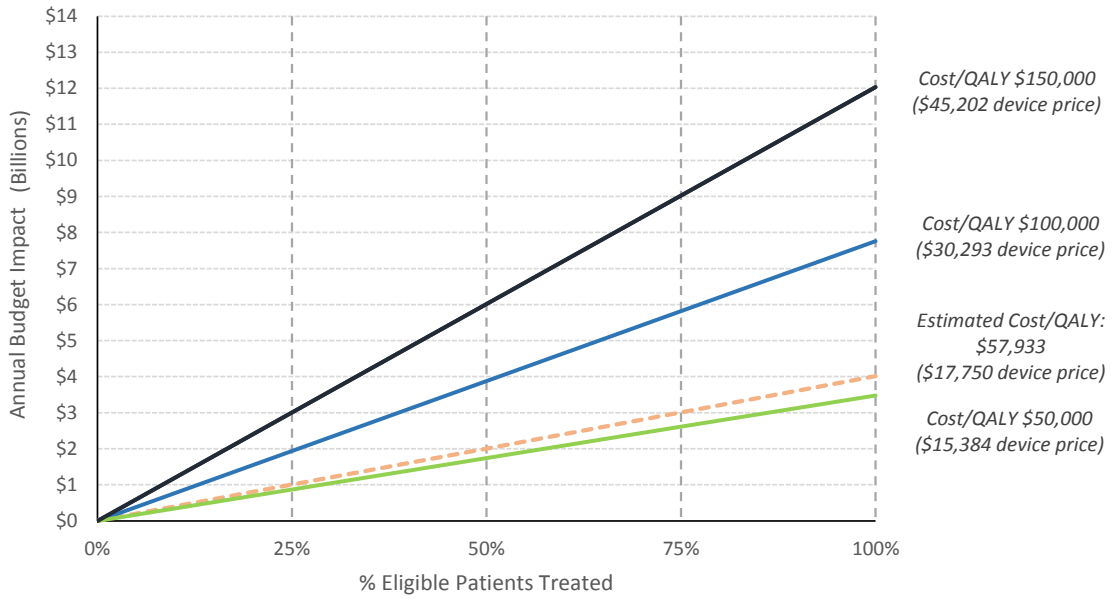
		Analytic Horizon = 1 Year			Analytic Horizon = 5 Years		
	Eligible Population (thousands)	Number Treated (thousands)	Weighted BI per Patient ($)*	Total BI (billions)	Number Treated (thousands)	Weighted BI per Patient ($)*	Total BI per year (billions)
CardioMEMS	1,435	72	$15,760	$1.1B	359	$13,988	$1.0B

*Weighted budget impact calculated by subtracting cost offsets from device costs for one-year horizon. For five-year horizon, device costs and cost offsets apportioned assuming 20% of patients in uptake target undergo device implantation each year. Those initiating in year 1 receive full device costs and cost offsets, those initiating in year 2 receive full device costs and 80% of cost offsets, etc.

Figure ES2 provides findings of multiple analyses that give perspective on the relationship between varying possible device prices, cost-effectiveness ratios, uptake patterns, and potential budget impact. The vertical axis shows the annualized budget impact, and the horizontal axis represents the percentage of eligible patients treated over a five-year period. The colored lines demonstrate how quickly the annual budget impact increases with increasing percentages of patients treated at four different prices: those at which the cost/QALY = $50,000, $100,000, and $150,000; and the Medicare price used in this analysis (i.e., $17,750 for the CardioMEMS device).

Even though the Medicare price for CardioMEMS is near the price at which it would achieve a relatively low cost/QALY of $50,000, at the level of uptake that we have estimated (25% by the end of the fifth year), the annualized budgetary impact for CardioMEMS exceeds the $603 million threshold for devices by approximately $400 million per year.

Figure ES2. ICER Five-Year Combined Cost-effectiveness and Potential Budget Impact Graph for CardioMEMS. Colored lines represent the annualized budget impact of different uptake patterns (eligible patients treated) at the actual Medicare price of the device (dashed line), and at device prices needed to achieve common incremental cost-effectiveness ratios.



Draft Value-Based Price Benchmark

We combine consideration of the potential budget impact with the threshold prices presented above (i.e., prices based on incremental costs per outcomes achieved) to calculate a value-based price benchmark for each new drug or device. This price benchmark begins with the price range to achieve cost-effectiveness ratios of $100,000-$150,000 per QALY for the population being considered, but it has an upper limit determined by the price at which the new drug or device would exceed the potential budget impact threshold (i.e., $603 million for devices). If the potential budget impact does not exceed these thresholds, then the value-based price benchmark remains the full price range determined from the analysis of incremental costs per outcomes achieved.

As shown in Table ES3, the $100,000-$150,000/QALY price range, what we term the “care value” price range, is much higher than the actual Medicare price for CardioMEMS. However, as noted

previously, at full Medicare price our estimated potential budgetary impact for CardioMEMS exceeds the threshold of $603 million per year when annualized over a five-year time horizon. The device price for CardioMEMS that would not exceed the $603 million annual device benchmark is $10,665.

Therefore, the draft ICER value-based price benchmark for CardioMEMS, with all the assumptions mentioned previously regarding five-year uptake patterns and cost offsets, is $10,665, which represents a 40% discount from the full Medicare price ($17,750).

Table ES3. Draft Value-based Price Benchmarks for CardioMEMS Device

Population	Price to Achieve $100K/QALY	Price to Achieve $150K/QALY	Max Price at Potential Budget Impact Threshold	Draft Value-Based Price Benchmark
n=358,738	$30,293	$45,202	$10,665	$10,665

Summary and Comment

The findings of our cost-effectiveness analysis indicate that CardioMEMS has the potential to provide clinical benefit over standard approaches to CHF management. The primary estimate for the cost-effectiveness of CardioMEMS is approximately $58,000 per QALY gained at an assumed device price of $17,750. The cost/QALY findings remained below commonly accepted cost-effectiveness thresholds in a variety of secondary analyses and additional sensitivity analyses.

However, when intervention costs and potential cost savings are evaluated on a population basis, and likely patterns of CardioMEMS uptake are considered, the annual costs of CardioMEMS exceed the potential budget impact threshold at which excessive cost burdens would be placed on the overall health care system. Our value-based price benchmark is therefore $10,665 for the CardioMEMS device.

Entresto

Comparative Clinical Effectiveness

Results

Clinical Benefits

The combined search results for Entresto identified 134 potentially relevant studies for this assessment (see Appendix Figure A2). After elimination of duplicate and non-relevant references, we identified seven reports containing information from two RCTs. Details of the included studies are summarized in Appendix Table E2.

The dominant study in the development of Entresto was the large PARADIGM-HF trial. In this double-blind Phase III trial, 8,442 patients (mean age 63.8; 78.2% male) with NYHA Class II-IV CHF and reduced ejection fraction (≤35%) were randomly assigned to Entresto (200 mg BID) or enalapril (10 mg BID) in addition to other recommended therapy. After a median duration of 27 months follow-up, the study's executive committee voted to stop the trial because the pre-specified boundary for an overwhelming benefit had been crossed.[38]

Over 27 months of follow-up in the PARADIGM-HF trial, the primary composite endpoint of death from cardiovascular causes or first hospitalization for worsening heart failure occurred in 21.8% of the Entresto group and 26.5% of the enalapril group (HR 0.80; 95% CI: 0.73-0.87; p<0.001); the number needed to treat (NNT) in order to avoid one event of either cardiovascular death or first CHF hospitalization was 21.

Investigators of the PARADIGM-HF trial also reported mortality and hospitalization outcomes separately (see the section on health care utilization for hospitalization outcomes). A total of 558 patients (13.3%) in the Entresto group and 693 patients (16.5%) in the enalapril group died from cardiovascular causes (HR 0.80; 95% CI: 0.72-0.89; p<0.001), with an NNT of 31 patients needing to be treated with Entresto to avoid one cardiovascular death. Death from any cause occurred in 711 (17.0%) patients in the Entresto group and 835 patients (19.8%) in the enalapril group (HR 0.84; 95% CI: 0.76-0.93; p<0.001); the NNT for death from any cause was 36 patients.[38,39]

Another patient-centered outcome of interest for this review was quality of life, which was assessed using the Kansas City Cardiomyopathy Questionnaire (KCCQ). The PARADIGM-HF trial reported a lower mean reduction in quality of life of 2.99 points in the Entresto group compared to 4.63 points in the enalapril group between baseline and month 8 (between-group difference 1.64 points; 95% CI: 0.63-2.65; p=0.001).[38,40]

Health Care Utilization Outcomes

Two publications from the PARADIGM-HF trial reported outcomes related to health care utilization.[41,42] Relative to patients in the enalapril arm, intensification of outpatient therapy related to worsening heart failure occurred in fewer patients in the Entresto group (520 [12.4%] vs. 604 [14.3%] for enalapril; HR 0.84; 95% CI: 0.74-0.94; p=0.003). Moreover, the authors reported a lower likelihood of first CHF-related hospitalization in the Entresto group (537 [12.8%]) compared to the enalapril group (658 [15.6%]; HR 0.79; 95% CI: 0.71-0.89; p<0.001), fewer emergency department (ED) visits (208 vs. 151; HR 0.70; 95% CI: 0.52-0.94; p=0.017), and fewer patients treated in the ED relative to the enalapril group (102 [2.4%] vs. 150 [3.6%]; HR 0.66; 95% CI: 0.52-0.85; p=0.001). In comparison with enalapril, patients treated with Entresto were significantly less likely to have repeat hospitalizations and were significantly less likely to have one ED visit for worsening heart failure.

Harms

In the PARADIGM-HF trial, 46.1% of the Entresto group and 50.7% of the enalapril group experienced at least one serious adverse event. The most commonly reported adverse events (AEs) were hypotension, cardiac failure, hyperkalemia, renal impairment, and cough. Discontinuation of study medication due to an adverse event occurred in 10.7% of the Entresto group and 12.3% of the enalapril group (p=0.03).

Controversies and Uncertainties

Criticisms of Entresto center on the PARADIGM-HF trial having compared the combination neprilysin inhibitor and ARB valsartan to the ACE inhibitor enalapril rather than to valsartan alone. Another critique relates to the fact that the pivotal trial was conducted only among patients who tolerated a "run-in" phase of treatment with enalapril followed by treatment with Entresto. There is also concern that neprilysin inhibition itself can potentiate angioedema. In fact, more patients in the treatment arm developed angioedema than did in the enalapril arm of the PARADIGM-HF trial (0.5% versus 0.2%). Further, investigators in the PARADIGM-HF trial gave patients in the control arm 10mg twice daily dosing of enalapril rather than 20mg twice daily dosing, which is the maximum (and goal) dose.

Neprilysin inhibition is an emerging practice, which means there is limited experience using drugs like sacubitril long-term, and the long-term risks that might be associated with it are unknown. There is a theoretical risk that neprilysin inhibition might potentiate dementia from accumulation of amyloid plaques in the brain. FDA has required Entresto's manufacturer to conduct a multi-center, randomized, double-blind, active-controlled trial to examine its effects compared to valsartan on cognitive function in patients with CHF and preserved ejection fraction. The argument for proceeding with drug approval before cognitive function studies are complete is that average life

expectancy in patients with CHF is much shorter than the amount of time it usually takes to develop dementia.[43]

Summary

We judge there to be moderate certainty of an incremental to substantial net benefit for Entresto compared to standard of care with ACE inhibitor treatment in patients with Class II-IV CHF and reduced ejection fraction. There is moderate certainty because the PARADIGM-HF trial was a large, good quality study in which Entresto produced significant reductions in cardiovascular and all-cause mortality as well as in heart failure specific hospitalization and ED visits in comparison to an agent that itself has demonstrated clinical benefits in these domains. Some uncertainties remain, however, including the relative contribution of sacubitril versus valsartan to these results, the expected tolerability of Entresto, its clinical performance in real-world practice, and its potential for harm in certain patient subgroups.

Given the entire body of evidence, our rating of comparative clinical effectiveness using the ICER Evidence Rating framework is B+ ("Incremental or better").

Other Benefits or Disadvantages

We have not identified potential other benefits or disadvantages associated with Entresto therapy compared to existing drug therapies.

Incremental Costs per Outcomes Achieved

Cost–Effectiveness Model: *Overview*

We developed a Markov model of the natural history of chronic heart failure using event rates from the published literature.[17,18,27-33,35,36] For Entresto, we modeled a cohort of NYHA Class II-IV heart failure patients with reduced ejection fraction based on the PARADIGM-HF trial and other published literature.[38,42,44,45] We compared Entresto with standard treatment with lisinopril and used this drug as the comparator instead of enalapril 10mg twice daily (the comparator in PARADIGM-HF) because it is less expensive and much more widely used.[16,46] We utilized the results from the PARADIGM-HF trial to estimate numbers of CHF hospitalizations, costs, deaths, life-years, and quality-adjusted life years (QALYs). These estimates were used to calculate the cost per QALY gained via the intervention, also known as the incremental cost-effectiveness ratio. Costs of drug treatments were estimated using wholesale acquisition prices from *The Red Book*, with Entresto assigned a monthly cost of $380.[16] Costs of medication intolerance and angioedema (a key side effect of interest for both Entresto and ACE inhibitors) were estimated using Medicare payment rates for office visits and hospitalization, respectively.

For Entresto treatment, we also conducted an analysis of risk-sharing purchasing models given the interest in alternative payment plans expressed by the manufacturer.[47] We modeled a risk-sharing approach in which payers do not pay for the drug for six months after any CHF hospitalization that occurred following treatment initiation. Additionally, if the patient dies of cardiovascular disease, any payments made in the previous six months are refunded.

Cost-Effectiveness Model: *Results*

Our model predicted 6.78 years of survival in the ACE inhibitor arm with 0.97 undiscounted CHF hospitalizations per patient. In the Entresto arm, it predicted an average of 8.98 years of survival with 0.90 undiscounted CHF hospitalizations. The ACE inhibitor arm had averages of 5.56 QALYs and total costs of $123,578. The Entresto arm had an additional 0.57 QALYs and an additional $29,138 in costs. This included an increase of $25,892 in treatment costs and a savings of $923 from reduction in CHF hospitalizations in the Entresto arm compared with the ACE inhibitor arm. The resulting cost per QALY gained with Entresto therapy was $50,915.

Value-Based Purchasing Analysis

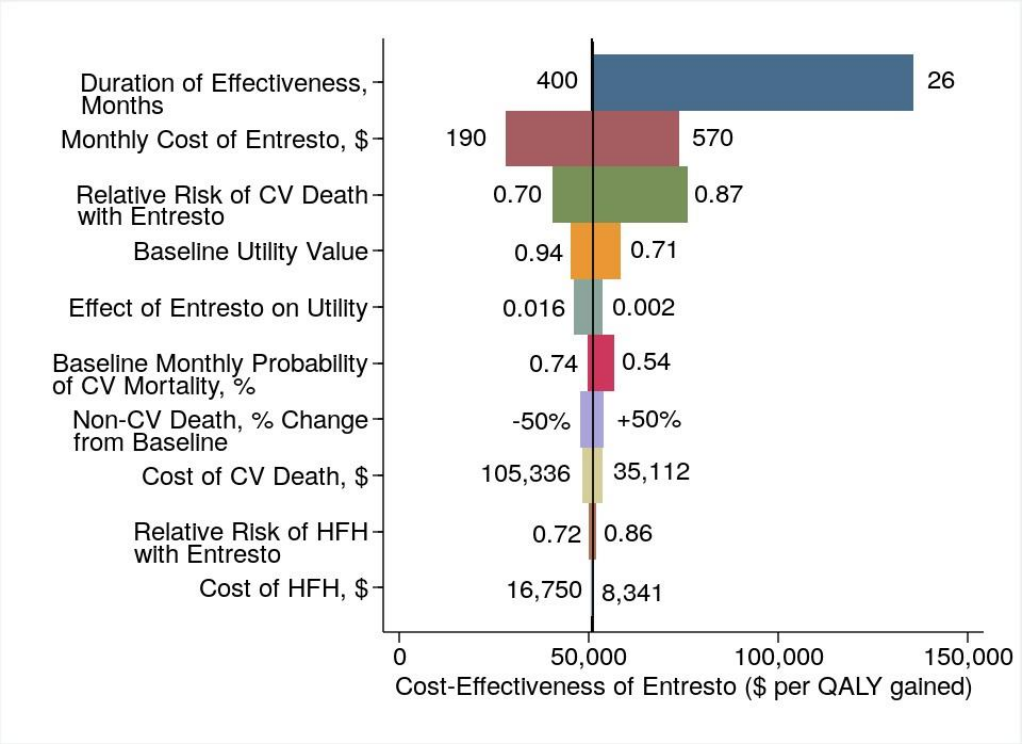
The risk-sharing model described above translated into an effective 8.6% discount on the drug price (i.e., $4,168 annually vs. $4,560), and a cost per QALY gained of $47,000.

Sensitivity Analyses

We performed sensitivity analyses on all input parameters (see Figure ES3). The model was most sensitive to the duration of effectiveness of the treatment. If the treatment was assumed to be effective only for the mean duration of the trial (26 months), the cost per QALY gained would increase to $135,815. The cost per QALY gained was less than $100,000 if the treatment was effective for at least 40 months.

We estimated a relative risk of cardiovascular mortality of 0.78 in the base case with a 95% confidence interval of 0.70-0.87. If the effectiveness in reducing cardiovascular death was increased to a relative risk of 0.87 (less effective than the base case), the incremental cost-effectiveness ratio of Entresto would increase to $76,129 per QALY gained. If the relative risk were decreased to 0.70 (more effective than the base case), the incremental cost-effectiveness ratio would decrease to $40,493 per QALY gained. Changes to other measures of treatment effectiveness, including the relative risk of CHF hospitalization, the relative risk of ED visits, and the incremental utility with Entresto do not change the cost per QALY substantially.

Figure ES3. Entresto Tornado Diagram: Series of One-way Sensitivity Analyses



Note: This figure represents a series of one-way sensitivity analyses for the parameters that have the largest influence on the cost per QALY gained with Entresto therapy. The vertical black line represents the cost-effectiveness in the base case analysis. None of the analyses lead to a cost per QALY gained greater than $150,000.

Threshold Analyses

As shown in Table ES4, we also evaluated the annual drug costs at which Entresto would be considered cost-effective under conventional willingness-to-pay thresholds of $50,000/QALY, $100,000/QALY, and $150,000/QALY. The price to achieve a $50,000/QALY threshold is very similar to the current list price ($4,464 vs. $4,560 respectively). This price could more than double and still remain under a cost-effectiveness threshold of $100,000/QALY.

Table ES4. Threshold Analyses: Annual Drug Cost at which Entresto Would Be Cost-Effective under varying Willingness-to-Pay Thresholds

	Willingness-to-Pay Threshold		
	$50,000/QALY	$100,000/QALY	$150,000/QALY
ALL SUBPOPULATIONS	$4,464/year	$9,480/year	$14,472/year

Potential Budget Impact

Overview

We also used the cost-effectiveness model to estimate the potential total budgetary impact of Entresto with different uptake assumptions. We then combined consideration of the price range between cost-effectiveness thresholds of $100,000 to $150,000 per QALY with potential budget impact to calculate a value-based price benchmark.

Our calculations assume that utilization of new drugs occurs without payer, provider group, or pharmacy benefit management controls in place in order to provide an estimate of "unmanaged" uptake by five years after launch. We assign a new drug to one of four categories of unmanaged uptake patterns: 1) very high (75% uptake by year 5); 2) high (50% uptake by year 5); 3) intermediate (25% uptake by year 5); and 4) low (10% uptake by year 5). In this analysis, we assumed a "very high" uptake pattern for Entresto given that it is the first agent in well over a decade to demonstrate both mortality and hospitalization benefit relative to an active comparator that represents the current standard of care.

We then compare our estimates to a budget impact threshold that represents a potential trigger for policy mechanisms to improve affordability through changes to pricing, payment, or patient eligibility. As described in ICER's methods presentation (http://www.icer-review.org/wp-content/uploads/2014/01/Slides-on-value-framework-for-national-webinar1.pdf), this threshold is based on an underlying assumption that health care costs should not grow more than 1% faster than growth in the overall national economy. From this foundational assumption, our potential budget impact threshold is derived using an estimate of growth in US gross domestic product (GDP) +1%, the average number of new drug approvals by the FDA each year, and the contribution of spending on drugs to total health care spending. According to our calculations, for 2015-16, the five-year annualized potential budget impact threshold that should trigger policy actions to manage affordability totals approximately $904 million per year.

We combine consideration of the potential budget impact with the threshold prices presented above (i.e., prices based on incremental costs per outcomes achieved) to calculate a value-based price benchmark for each new drug or device. This price benchmark begins with the price range to achieve cost-effectiveness ratios of $100,000-$150,000 per QALY for the population being considered, but it has an upper limit determined by the price at which the new drug or device would exceed the potential budget impact threshold (i.e., $904 million for drugs). If the potential budget impact does not exceed these thresholds, then the value-based price benchmark remains the full price range determined from the analysis of incremental costs per outcomes achieved.

Results

Results from the budget impact model showed that, with the uptake pattern assumptions mentioned above, 334,000 individuals would receive Entresto in the first year (see Table ES5). After one year of treatment, cost offsets due to reductions in the CHF hospitalization were $1,043 per patient, or approximately 25% of the drug cost. Including this cost offset, one-year budget impact is estimated to be approximately $1.2 billion.

Over the entire five-year time horizon, we estimate that "unmanaged" uptake would lead to approximately 1.7 million persons taking Entresto for one or more years. Across this timeframe, the weighted budgetary impact (i.e., adjusted for differing periods of drug utilization and associated cost-offsets) is slightly less than $9,000 per patient. Total budgetary impact over five years is approximately $15 billion, or approximately $3 billion in net cost growth per year, despite cost offsets that would average $1,462 per year of treatment. This annualized potential budget impact is well above the budget impact threshold of $904 million for a new drug. In order to not exceed this budget impact threshold, approximately 9% of eligible patients could be treated each year at the list price of $4,560 annually.

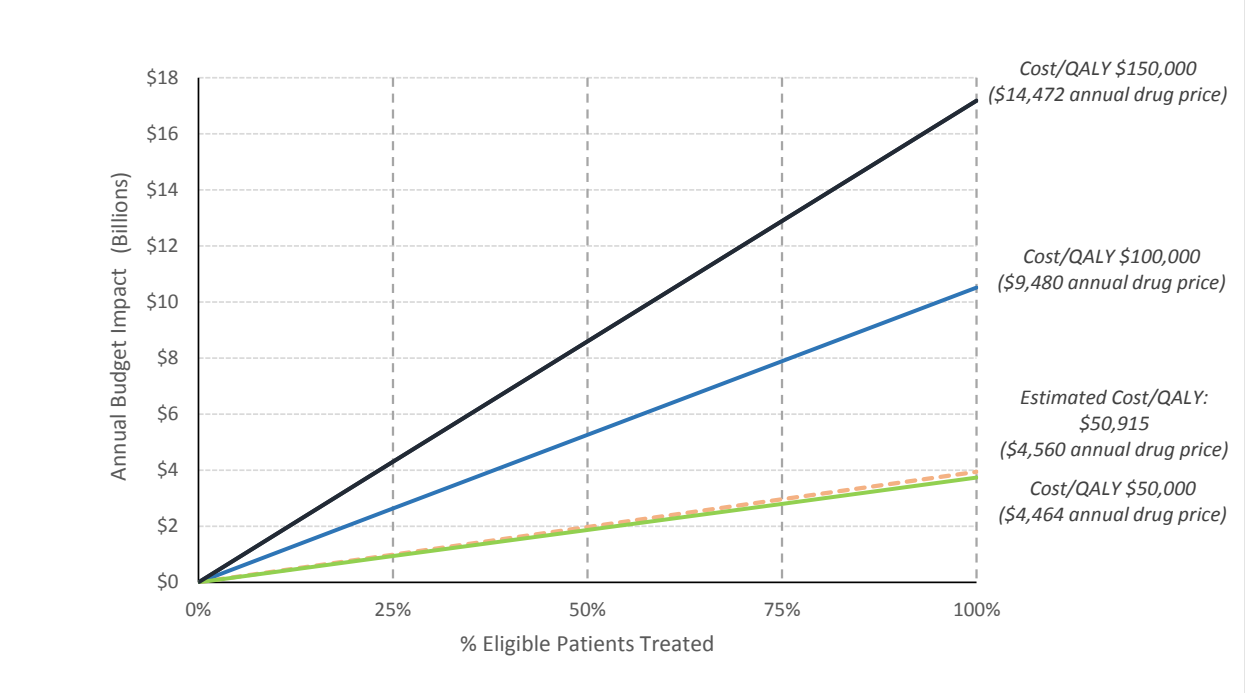
Table ES5. Total Budget Impact (BI) of Entresto Based on Assumed Pattern of Update

		Analytic Horizon = 1 Year			Analytic Horizon = 5 Years		
	Eligible Population (thousands)	Number Treated (thousands)	Weighted BI per Patient ($)*	Total BI (billions)	Number Treated (thousands)	Weighted BI per Patient ($)*	Total BI per year (billions)
Entresto	2,226	334	$3,481	$1.2B	1,669	$8,856	$3.0B

*Weighted budget impact calculated by subtracting cost offsets from drug costs for one-year horizon. For five-year horizon, drug costs and cost offsets apportioned assuming 20% of patients in uptake target initiate therapy each year. Those initiating in year 1 receive full drug costs and cost offsets, those initiating in year 2 receive 80% of drug costs and cost offsets, etc.

Figure ES4 provides findings of multiple analyses that give perspective on the relationship between varying possible drug prices, cost-effectiveness ratios, uptake patterns, and potential budget impact. The vertical axis shows the annualized budget impact, and the horizontal axis represents the percentage of eligible patients treated over a five-year period. The colored lines demonstrate how quickly the annual budget impact increases with increasing percentages of patients treated at four different prices: those at which the cost/QALY = $50,000, $100,000, and $150,000; and the list prices used in this analysis (i.e., $4,560 annually for Entresto).

Figure ES4. ICER Five-Year Combined Cost-effectiveness and Potential Budget Impact Graph for Entresto. Colored lines represent the annualized budget impact of different uptake patterns (eligible patients treated) at the actual list price of the drug (dashed line), and at drug prices needed to achieve common incremental cost-effectiveness ratios.



Draft Value-Based Price Benchmark

We combine consideration of the potential budget impact with the threshold prices presented above (i.e., prices based on incremental costs per outcomes achieved) to calculate a value-based price benchmark for each new drug or device. This price benchmark begins with the price range to achieve cost-effectiveness ratios of $100,000-$150,000 per QALY for the population being considered, but it has an upper limit determined by the price at which the new drug or device would exceed the potential budget impact threshold (i.e., $904 million for drugs). If the potential budget impact does not exceed these thresholds, then the value-based price benchmark remains the full price range determined from the analysis of incremental costs per outcomes achieved.

As shown in Table ES6, the $100,000-$150,000/QALY price range, what we term the “care value” price range, is much higher than the actual list price for Entresto. However, as noted previously, at full list price, our estimated potential budgetary impact for Entresto far exceeds the threshold of $904 million per year when annualized over a five-year time horizon. The annual price for Entresto that would not exceed the $904 million annual device benchmark is $4,168.

Therefore, the draft ICER value-based price benchmark for Entresto, with all the assumptions mentioned previously regarding five-year uptake patterns and cost offsets, is $4,168. This figure represents an approximate 9% discount from the full WAC assumed in our analysis ($4,560 annually). Note that the Entresto value-based price benchmark is coincidentally the same as the price arrived at in the risk-sharing analysis; it should be noted, however, that different assumptions and calculations were used in the risk-sharing and value-based price benchmark analyses.

Table ES6. Draft Value-based Price Benchmarks for Entresto Therapy

Population	Price to Achieve $100K/QALY	Price to Achieve $150K/QALY	Max Price at Potential Budget Impact Threshold	Draft Value-Based Price Benchmark
n=1,669,235	$9,480/year	$14,472/year	$4,168/year	$4,168/year

Summary and Comment

The findings of our cost-effectiveness analysis indicate that Entresto has the potential to provide clinical benefit over standard approaches to CHF management (i.e., use of ACE inhibitors). Our estimate of the cost-effectiveness of Entresto at its list price is approximately $51,000 per QALY gained versus ACE inhibitor treatment. The cost-effectiveness remained below generally-accepted thresholds for cost-effectiveness in sensitivity analyses testing a variety of ranges in model parameter inputs.

However, when intervention costs and potential cost savings are evaluated on a population basis, and likely patterns of intervention uptake are considered, the annual cost of Entresto exceeds the potential budget impact threshold at which excessive cost burdens would be placed on the overall health care system. Our value-based price benchmark is therefore $4,168 annually for Entresto.

CTAF Votes on Comparative Clinical Effectiveness and Value

During CTAF public meetings, the CTAF Panel deliberates and votes on key questions related to the systematic review of the clinical evidence, an economic analysis of the applications of the medical technologies or treatments under examination, and the supplementary information presented. Because any judgment of evidence is strengthened by real-life clinical and patient perspectives, subject matter experts are recruited for each meeting and provide input to the CTAF Panel, serve as a resource to the Panel during their deliberation, and help form recommendations with the Panel on ways the evidence can be applied to policy and practice. At each meeting, after the CTAF Panel votes, a policy roundtable discussion is held with the CTAF Panel, clinical experts, and representatives from provider groups, payers, and patient groups.

At the October 29, 2015 meeting, the CTAF Panel discussed issues regarding the application of the available evidence to help patients, providers, and payers address the important questions related to the management of congestive heart failure. Following the evidence presentation and public comments, the CTAF Panel voted on key questions concerning the comparative clinical effectiveness and comparative value of Entresto and, separately, of CardioMEMS.

In its deliberations and voting related to value, the CTAF Panel made use of a value assessment framework with four different components of *care value*, a concept which represents the long-term perspective, at the individual patient level, on patient benefits and the incremental costs to achieve those benefits. The four components of care value are comparative clinical effectiveness, incremental cost per outcomes achieved, additional benefits or disadvantages, and contextual considerations regarding the illness or therapy. Once they made an overall assessment of care value as low, intermediate, or high considering these four components, the CTAF Panel then explicitly considered the affordability of Entresto and of CardioMEMS in assessing *provisional* health system value as low, intermediate, or high, a judgment integrating consideration of the long-term care value of a new intervention with an analysis of its potential short-term budget impact if utilization is unmanaged (see Figure ES5 and Figure ES6, as well as the detailed explanation in section 7.1).

Figure ES5. Care Value Framework

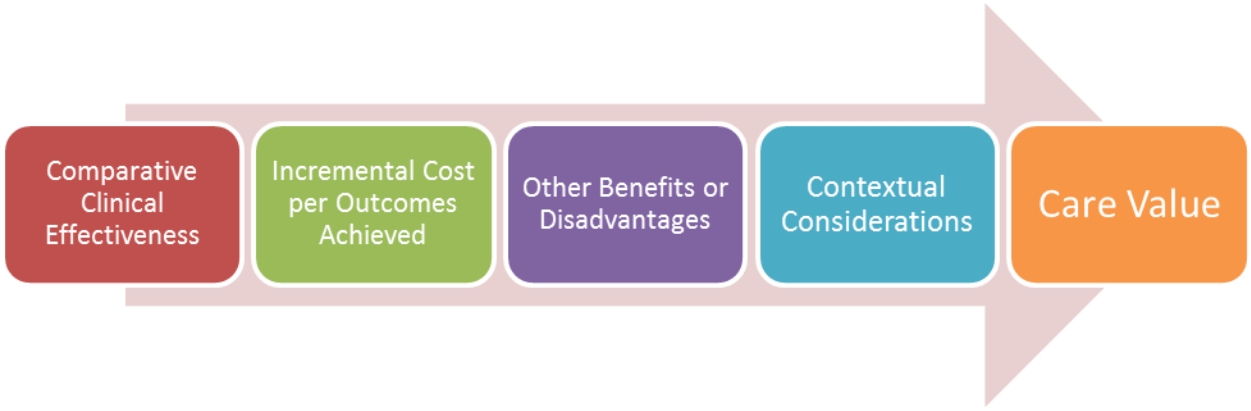
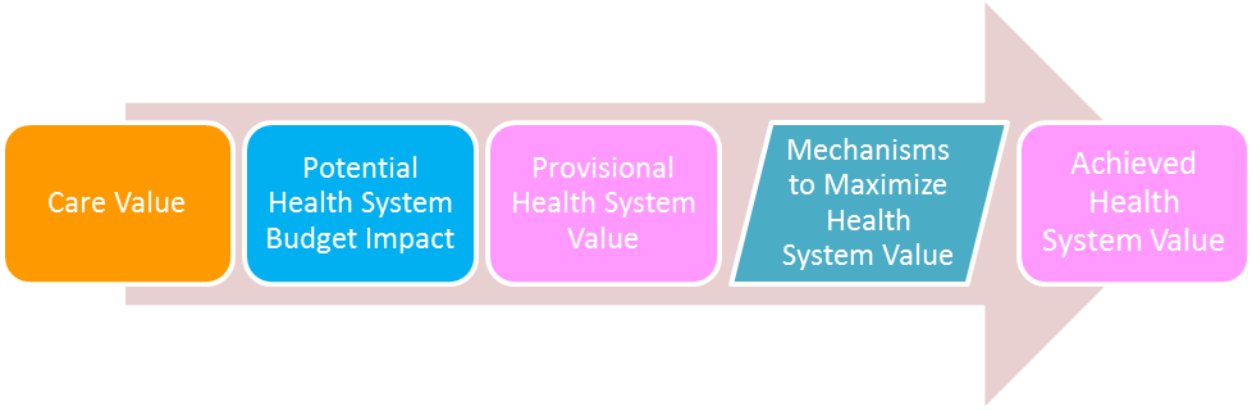


Figure ES6. Health System Value Framework



CTAF Panel Voting Results

Entresto

1. For patients with Class II-IV levels of CHF and reduced ejection fraction, is the evidence adequate to demonstrate that the net health benefit of Entresto is greater than that of usual care with ACE inhibitors?

   CTAF Panel Vote: 9 Yes (90%) 1 No (10%)

2. Given the available evidence for patients with Class II-IV CHF and reduced ejection fraction, what is the care value of Entresto vs. usual care with ACE inhibitors?[j]

   CTAF Panel Vote: a. 2 Low (22%) b. 5 Intermediate (56%) c. 2 High (22%)

3. Given the available evidence for patients with Class II-IV CHF and reduced ejection fraction, what is the provisional health system value of Entresto vs. usual care with ACE inhibitors?[a]

   CTAF Panel Vote: a. 7 Low (78%) b. 1 Intermediate (11%) c. 1 High (11%)

CardioMEMS

4. For patients with Class III CHF and a hospitalization in the prior 12 months, is the evidence adequate to demonstrate that the net health benefit of CardioMEMS is greater than that of usual care?

[a] Nine members of CTAF voted on questions relating to care value and provisional health system value, with one abstention. The panel member who abstained from voting on value questions provided input on the economic modeling section of the ICER report.

CTAF Panel Vote: 6 Yes (60%) 4 No (40%)

5. Given the available evidence for patients with Class III CHF and a hospitalization in the prior 12 months, what is the care value of CardioMEMS vs. usual care?[b]

   CTAF Panel Vote: a. 5 Low (56%) b. 2 Intermediate (22%) c. 2 High (22%)

6. Given the available evidence for patients with Class III CHF and a hospitalization in the prior 12 months, what is the provisional health system value of CardioMEMS vs. usual care?[k]

   CTAF Panel Vote: a. 7 Low (78%) b. 1 Intermediate (11%) c. 1 High (11%)

Policy Roundtable Discussion and Key Policy Recommendations

Entresto:

1. *Provider groups and payers may wish to limit prescribing of Entresto to cardiologists or, at a minimum, require other clinicians to prescribe in consultation with a cardiologist, due to the potential for side effects at initiation, importance of selecting appropriate patients, and relatively large expense when compared to generic ACE inhibitors or ARBs.*
2. *Based on the combination of its clinical benefits, pricing aligned with patient benefit, and short-term affordability, payers and purchasers should consider placing Entresto in the "preferred brand" category, especially if discounts can be obtained that bring the price in line with thresholds for health-system affordability.*
3. *Further research and real-world experience with Entresto are needed to help identify the most appropriate patients among those who have Class II-IV heart failure and reduced ejection fraction.*

CardioMEMS:

4. *Within the labeled indications, clinicians should carefully select patients for whom CardioMEMS would offer the best chance of clinical benefit and reduced costs.*
5. *Provider groups that are starting to use CardioMEMS should explore providing care within a Center of Excellence paradigm, as should payers that are considering covering it.*
6. *Further research into the benefits of CardioMEMS is needed to address some of the uncertainties that impact its adoption by clinicians and coverage by payers.*

[b] Nine members of CTAF voted on questions relating to care value and provisional health system value, with one abstention. The panel member who abstained from voting on value questions provided input on the economic modeling section of the ICER report.

Both Entresto and CardioMEMS:

7. *Manufacturers and payers should consider performance-based agreements (i.e., reduced costs or refunds) for both Entresto and CardioMEMS.*
8. *Clinicians and patients should work together to prevent and intensively manage health conditions that are a precursor to CHF, as this may improve patient outcomes including quality of life and reduce costs.*

The prevalence of CHF and the challenges of helping patients whose condition is not well controlled have created the need for new disease management and treatment options. The device and drug reviewed in this assessment are targeted to subsets of patients with CHF, and further research and real-world experience are needed to appropriately target the use of these interventions. The clinical evidence and the value recommendations summarized in this report should guide patients, payers, and clinicians, and policymakers in their efforts to treat CHF.

1. Background

1.1 Introduction

Congestive heart failure (CHF) describes the condition of fluid build-up in the body as the heart inefficiently fills with or pumps out blood. CHF results from other conditions that weaken the heart muscle including coronary artery disease, myocardial infarction, cardiomyopathy, and hypertension, and it is a major public health concern. In the United States, the lifetime risk of developing CHF approaches 20%,[1] and the disease currently affects about 6.2 million individuals.[3] CHF is associated with 1) substantial morbidity and mortality, with five-year mortality similar to that of many cancers; and 2) high rates of hospitalization and intensive outpatient care.[1,2] Growth in per capita medical spending and aging of the population are expected to contribute to substantial increases in the direct medical costs of treating CHF, with annual costs totaling nearly $80 billion by 2030.[48]

The management of CHF has seen no major breakthroughs in well over a decade, but two new interventions have the potential to markedly shift clinical practice – a system for monitoring increases in pulmonary artery (PA) pressure (a key indicator of worsening CHF) known as the CardioMEMS™ HF System (St. Jude Medical), and Entresto™ (Novartis AG), a combination of the angiotensin II receptor blocker (ARB) valsartan and the novel neprilysin (nep-rĭ-lĭ-sin) inhibitor sacubitril. The objective of this report is to evaluate the accumulated evidence on these two new interventions, to understand the context around their potential use in clinical practice, and to assess their cost-effectiveness and budgetary impact.

The scope for this assessment is described in the sections that follow using the PICOTS (Population, Interventions, Comparators, Outcomes, Timing, Settings) framework. We included evidence from comparative studies (Phase III randomized controlled trials [RCTs] and comparative cohort studies) as well as high-quality systematic reviews where available; Phase II RCTs were included only if they evaluated the same treatment dosage as in larger Phase III trials and reported on one or more of the outcomes of interest for this assessment. Evidence was also culled from case series that met certain quality criteria (e.g., sample retention, consecutive patients, clearly defined entry criteria). Grey literature, primarily from manufacturer submissions to the Food and Drug Administration (FDA) and FDA approval packages, was used to supplement peer-reviewed literature. **Of note, we considered each intervention of interest to address independent aspects of CHF management and therefore did not compare the health and economic outcomes of the two interventions to each other.** The analytic frameworks for both the drug- and device-based assessments are depicted in Figure 1.

Populations

The population of focus for the reviews of both interventions included adult individuals (age 18+) with moderate or severe heart failure (New York Heart Association [NYHA] Class II, III, or IV; see Section 2 of this report [Topic in Context] for definitions). While the indications for the interventions of focus have narrower specifications (e.g., the CardioMEMS HF System is indicated for NYHA Class III patients with a hospitalization in the previous 12 months), we also included studies of the interventions in patients who did not meet labeled indications. Of note, while the majority of patients evaluated in the key clinical studies of both interventions had reduced ejection fraction (i.e., left ventricular ejection fraction [LVEF] <40%), we also evaluated available evidence from studies including patients with preserved ejection fraction, as these individuals represent approximately 50% of incident cases of heart failure.[49] In addition, while Entresto has been evaluated in patients with hypertension, we focused exclusively on its effectiveness in patients with CHF.

Interventions

The interventions of interest included the CardioMEMS HF System™ and the combination drug sacubitril/valsartan (Entresto™).

Comparators

Comparators for the CardioMEMS HF System included usual CHF monitoring, which consists of treatment adjustments in response to reported or observed signs and symptoms. Of note, because defined programs of discharge planning and outpatient interventions have been developed to reduce the incidence of readmission in CHF patients, we also summarize the evidence on these programs as a separate form of treatment. The comparator treatment for Entresto was the current standard of care, angiotensin converting enzyme (ACE) inhibitors or ARB treatment with co-administration of beta blockers. The FDA approved another drug for heart failure, ivabradine (Corlanor®), in July 2015. We did not consider this drug as a comparator to Entresto because it is indicated for a small population of patients who meet specific parameters for ejection fraction, heart rate/rhythm, and beta-blocker use.

Outcomes

This review examined clinical and health care utilization outcomes related to both interventions. Listed below are the outcomes of interest:

- Mortality
- Worsening of CHF (i.e., reduced ejection fraction, fluid retention, other laboratory markers)
- CHF-related hospitalizations and readmissions
- Measures of CHF symptoms, functional status, and/or health-related quality of life

- Short- and long-term complications and adverse events of treatment/monitoring
- Costs, cost-effectiveness, and budget impact of CHF management

We assessed the evidence on an overall basis as well as stratified by important baseline characteristics (e.g., NYHA class, reduced vs. preserved ejection fraction, comorbidity burden).

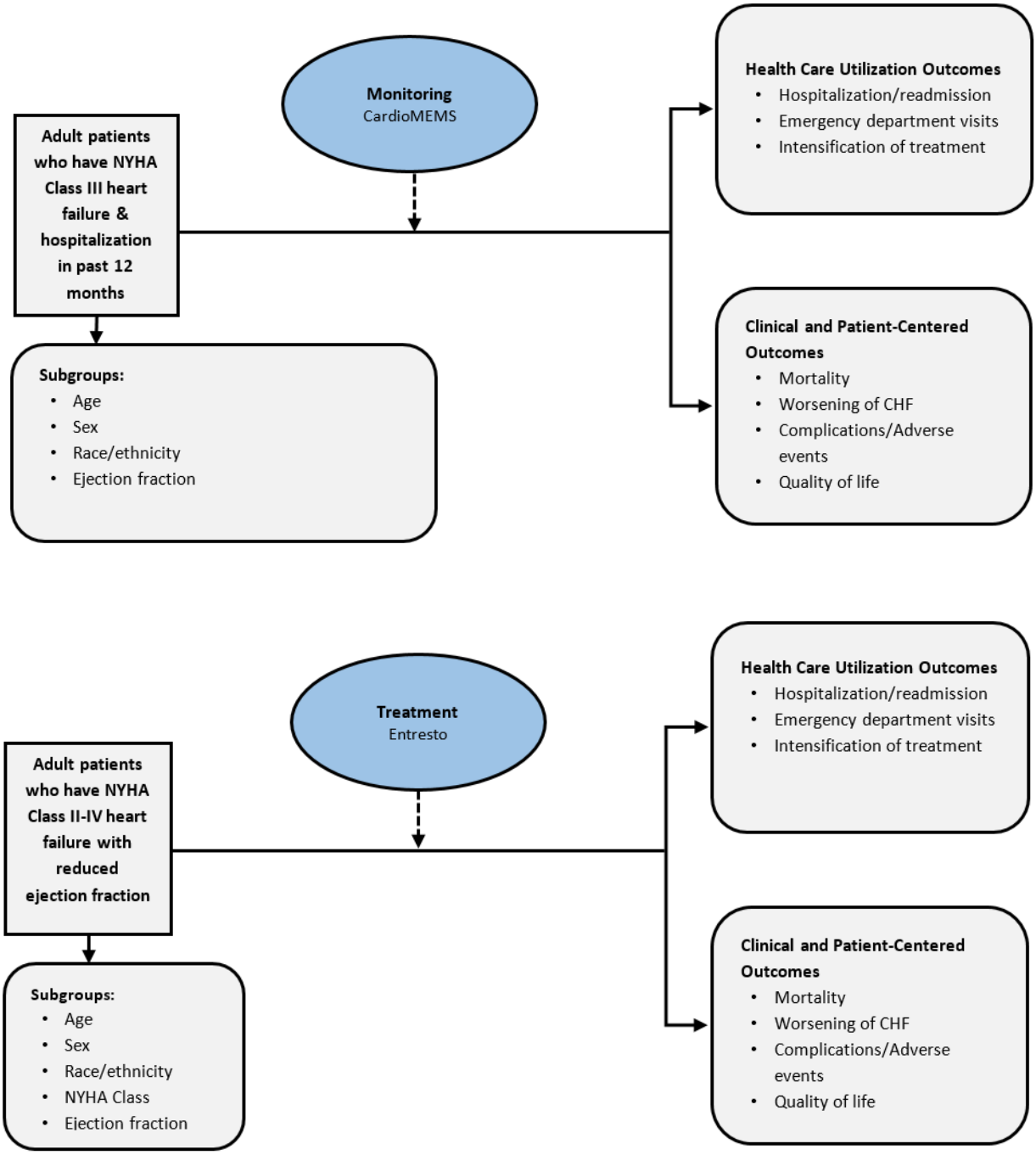
Timing

Evidence on intervention effectiveness and harms was derived from studies of any duration.

Settings

All relevant settings were considered, including inpatient, clinic, and outpatient settings.

Figure 1. Analytic Frameworks for Evaluation of CardioMEMS HF System and Entresto*



*Adapted from Feltner, et al., 2014

2. The Topic in Context

Heart failure is caused by conditions that damage or overwork the heart muscle, weakening its ability to pump and/or fill with blood. Patients are characterized as having either systolic heart failure (CHF with reduced ejection fraction) or diastolic heart failure (CHF with preserved ejection fraction). Ejection fraction is the percentage of blood that is pumped out of the left ventricle with each contraction. A normal healthy heart ejects 55-70% of its blood volume out of the left ventricle. Approximately half of patients with symptomatic CHF have heart failure with *reduced* ejection fraction (typically defined as <40% as measured by echocardiography or other means). Alternatively, ejection fraction may be *preserved* if the ventricles are stiff and allow less blood to fill the cavity, resulting in CHF despite a near normal percent ejection fraction.[50] Patients with reduced ejection fraction have benefitted from disease-modifying pharmacotherapies, fluid management, and implantable devices (i.e., cardiac resynchronization therapy [CRT] and implantable cardioverter-defibrillator [ICD])[c] that have improved the prognosis of CHF over the past three decades.[51] The availability of evidence-based therapies for those with preserved ejection fraction, however, is far more limited.[52]

The severity of CHF is often classified according to the NYHA system of classification by patient functional status.[4] These classes commonly appear in treatment guidelines and as enrollment criteria for CHF clinical trials:

- Class I: Patients have no physical activity limitation.
- Class II: Patients have slight limitation of physical activity such that symptoms develop with ordinary activity but not at rest.
- Class III: Patients have marked limitation of physical activity such that symptoms develop with mild exertion but not at rest.
- Class IV: Patients are unable to carry on any physical activity without discomfort, and symptoms may occur at rest.

Management of CHF is guided by treating the underlying cause—often a chronic systemic disease process such as hypertension, diabetes, coronary artery disease, valvular heart disease, fluid overload or myocarditis—and lifestyle improvements (e.g., diet, exercise, smoking cessation). Although a variety of evidence-based medical and device therapies for CHF are available, the morbidity, mortality, and costs associated with the condition remain high, and no major advancements in treatment have occurred in well over a decade.[5]

[c] An ICD is an implantable device that monitors heartbeat and delivers electric shocks to restore normal rhythm when dangerously fast heartbeats are detected. CRT devices simultaneously stimulate the left and right ventricles to restore a synchronous pattern of pumping blood to the body.

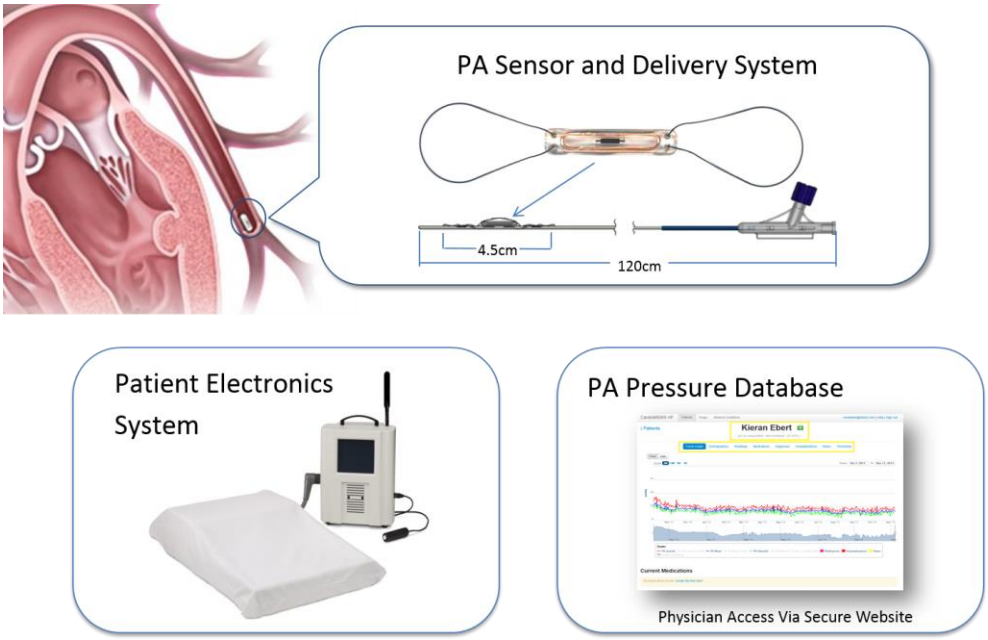
Fluid overload is one of the primary causes of CHF-related hospitalizations. Although regular monitoring of signs and symptoms of fluid overload, such as shortness of breath, swelling, fatigue, and weight gain, is a common component of CHF management, these signs and symptoms are not sensitive enough to reflect early pathophysiologic changes that increase the risk of decompensation.[5-9] Several studies have demonstrated that elevations in pulmonary artery pressure closely correlate with worsening heart failure and may increase several days or weeks before signs and symptoms manifest.[53-58] These findings prompted the development of new implantable devices to assess cardiopulmonary filling pressures. One such device was Medtronic's Chronicle®, a diagnostic implantable hemodynamic monitor (Medtronic, Minneapolis, MN), that consisted of a pressure sensor placed in the right ventricle to monitor intracardiac pressures. In the COMPASS-HF trial, the primary RCT upon which Medtronic's FDA application was based, 274 patients with Class III and IV heart failure showed a non-statistically significant trend in reduction of heart failure events, and a post hoc analysis showed a reduction in first CHF hospitalization.[56,59] Although FDA did not approve the device, it was acknowledged to be safe and supported the possibility that hemodynamic monitoring could be useful in managing patients with Class III heart failure.[6]

CardioMEMS

The CardioMEMS HF System was developed to build upon the findings from trials of previous devices.[53,55-57,59] The CardioMEMS device includes a small wireless sensor that is permanently implanted via right heart catheterization[d] into the pulmonary artery to measure pulmonary artery pressure (see Figure 2). The sensor is paired with a portable electronic transmitter that allows patients to wirelessly transmit pressure readings to a secure website where clinicians can monitor the data. The Medicare price of CardioMEMS is $17,750, which does not include costs associated with device implantation or monitoring.[10,11] St. Jude Medical has developed a comprehensive modular training program for physicians, hospitals, and patients, which details implantation, deployment, procedural, and management processes.[60]

[d]Right heart catheterization is the passing of a thin tube to the right side of the heart into the pulmonary artery in order to monitor pressures and blood flow. Right heart catheterization is used to implant and calibrate the CardioMEMS sensor.

Figure 2. CardioMEMS HF System



Source: GIE Media, Inc. 2015. http://www.onlinetmd.com/measuring-pulmonary-artery-pressures-cardiomems-6214.aspx#.Ve9JtxHBzGc

Entresto

ACE inhibitors have been the cornerstone of pharmacologic treatment for heart failure in patients with CHF due to reduced ejection fraction for more than two decades.[12] Over the same time period, researchers have explored strategies to bolster the effects of naturally occurring natriuretic peptides, a family of hormones the body releases to help maintain fluid balance.[13,14] One strategy has been to inhibit neprilysin, the enzyme that breaks down natriuretic peptides. Neprilysin inhibitors promote natriuresis (i.e., sodium excretion and fluid loss in the urine) but also increase concentrations of angiotensin II. Development of two orally delivered neprilysin inhibitors, candoxatril and ecadotril, was halted after the drugs failed to demonstrate efficacy.[61-63] Subsequently, omapatrilat, a drug that acted through dual neprilysin and renin-angiotensin-aldosterone system (RAAS) inhibition by combining an ACE inhibitor with a neprilysin inhibitor, showed promising results in lowering blood pressure and improving hemodynamics. Further development of this drug was halted, however, due to high incidence of angioedema that was attributed to the increase in angiotensin II.[64-66] Entresto was subsequently designed to combine the neprilysin inhibitor sacubitril with an ARB (i.e., angiotensin II receptor *blocker*) instead of an ACE inhibitor in order to suppress RAAS without potentiating angioedema to the same degree.[15] Entresto is available in three dose combinations of sacubitril/valsartan (24/26 mg, 49/51, and 97/103); the recommended starting dose is 49/51 twice-daily, which should be doubled to the

target maintenance dose of 97/103 after 2-4 weeks, as tolerated. The annual wholesale acquisition cost (WAC) of Entresto is $4,560 for twice-daily administration regardless of dose.[16]

3. Summary of Coverage Policies

3.1 Coverage Policies for the CardioMEMS HF Device

At the time of this report, we identified only one proposed local coverage decision (LCD) pertaining to the CardioMEMS HF device from the Centers for Medicare & Medicaid Services (CMS). Local Medicare Administrative Contractor (MAC) Novitas, which has jurisdiction over 11 states, not including California, issued a proposed LCD that would limit coverage for the CardioMEMS HF device to clinical trial participants (i.e., "coverage with evidence development").[67] CMS currently reimburses the device through both the New Technology Add-on Payment (NTAP) and Transitional APC Pass-Through Status programs.[37,68,69]

We were unable to locate any policies from CIGNA or UnitedHealthcare. Anthem, Aetna, Blue Shield of California, Health Net, and Humana all consider the device to be investigational and not medically necessary, and they do not cover it.[70-74]

3.2 Coverage Policies for Entresto

At the time of this report, Medi-Cal, the California Medicaid agency, has not yet issued a coverage determination. Similarly, we could find no publicly available policies or formularies from CVS-Caremark.

Formulary Tier Placement

Commercial payers generally include Entresto at the non-preferred or brand tier of their formularies. Aetna generally covers Entresto at the third (i.e., non-preferred) tier of its three-, four-, and five-tier commercial plans, and at the second (i.e., brand-name) tier of its two-tier commercial plans, subject to prior authorization in most cases. Entresto is listed as a non-formulary drug for members with a two-tier closed formulary Aetna Value plan.[75] CIGNA places Entresto in the third (i.e., non-preferred) tier of its three-tier national drug list and requires prior authorization.[76] Humana covers Entresto with prior authorization on tier two of its Rx2 Traditional plans, and at tier three of its Rx3 Traditional, Rx4 Traditional, and high deductible health plan (HDHP) formularies. The drug is listed under Group B (i.e., drugs for controlling long-term conditions) for Humana's RxImpact plan, which pays a fixed amount toward drugs in one of four categories based on their ability to prevent serious medical episodes.[77] Blue Shield of California places Entresto on the third tier of its standard drug formulary, which denotes a non-formulary brand drug, and requires prior authorization with unspecified requirements.[78] Regional private payer Health Net covers Entresto on the third tier (i.e., non-preferred, covered drugs not on the Health Net drug list, or drugs

approved as medically necessary by Health Net) of their Essential Rx Drug List and their 3-tier formularies.[79] Anthem is the only payer to list Entresto as a preferred drug, placing it on the second tier of its three- and four-tier plans, but the drug is excluded from the 2015 and 2016 California Select Drug formulary.[80]

Prior Authorization

Of the payers that include Entresto in their publicly available formularies, several offer more detailed descriptions of their prior authorization policies. Humana covers Entresto in adult patients (age ≥18) with a diagnosis of NYHA Class II, III, or IV systolic heart failure and LVEF ≤35%; patients must be stable on therapy with a beta-blocker or ARB for at least four weeks, and the drug must be prescribed by or in consultation with a cardiologist.[81] Anthem, whose pharmacy benefit is managed by Express Scripts, requires prior authorization; when approved, the drug has a one-year approval duration for patients meeting similar criteria: age 18 or older with NYHA Class II-IV heart failure and LVEF ≤35%.[82] We were unable to determine the placement of Entresto on any UnitedHealthcare formulary, but located a prior authorization policy that requires the diagnosis of NYHA Class II-IV heart failure with ejection fraction ≤ 40%; initial authorization is issued for 12 months, with subsequent 12-month authorizations contingent upon documented positive clinical response to therapy.[83] Health Net, which requires prior authorization, covers Entresto for patients with diagnosed chronic heart failure of NYHA Class II through IV.[84]

4. Comparative Clinical Effectiveness

4.1 Overview

Evidence on comparative clinical effectiveness is described separately for the CardioMEMS HF System and Entresto in the sections that follow. Evidence was culled from Phase II or III RCTs of adult individuals (age 18+) with moderate or severe heart failure (NYHA Class II, III, or IV); case series were also included in our review but are discussed separately. The comparator treatment for each intervention of interest included usual CHF monitoring for the CardioMEMS device and ACE inhibitor or ARB treatment with co-administration of beta blockers for Entresto. Our review focused on clinical benefits (e.g., improvements in mortality, heart failure, and quality of life) as well as potential harms (device-based complications and drug-related adverse events). We also evaluated evidence on health care utilization outcomes such as hospitalizations, emergency department visits, and intensification of treatment.

4.2 Methods

Data Sources and Searches

Procedures for the systematic literature review assessing the evidence on CHF followed established best methods used in systematic review research.[85] We conducted the review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[86] The PRISMA guidelines include a checklist of 27 items, further detail of which is available in Appendix Table A1.

We conducted separate searches for each of the interventions of interest. The timeframe for both searches spanned the period from January 1990 to the most recently published data available and focused on MEDLINE and EMBASE-indexed articles. We limited each search to English-language studies of human subjects and excluded articles indexed as guidelines, letters, editorials, narrative reviews, case reports, conference abstracts, or news items. The search strategies included a combination of indexing terms (MeSH terms in MEDLINE and EMTREE terms in EMBASE), as well as free-text terms. To supplement the above searches and ensure optimal and complete literature retrieval, we performed a manual check of the references of recent relevant reviews and meta-analyses. Further details on the search algorithm are available in Appendix Table A2.

Study Selection

We performed screening at both the abstract and full-text level. A single investigator screened all abstracts identified through electronic searches according to the inclusion and exclusion criteria described in section 1.1. A second investigator reviewed a proportion of the extracted data for additional quality assurance (see Appendix E). We did not exclude any study at abstract-level screening due to insufficient information. For example, an abstract that did not report an outcome of interest would be accepted for further review in full text.

We retrieved the citations that were accepted during abstract-level screening for full text appraisal. One investigator reviewed full papers and provided justification for exclusion of each excluded study.

We also included FDA documents related to both CardioMEMS and Entresto. For CardioMEMS, these included the manufacturer's submission to the agency, internal FDA review documents, and the transcript of Advisory Committee deliberations and discussions.[19,87-91] Because Entresto was approved using a fast track designation, there was no Advisory Committee meeting; an "approval package" document was posted publicly after approval, however.[43] All literature that did not undergo a formal peer review process is described separately.

Data Extraction and Quality Assessment

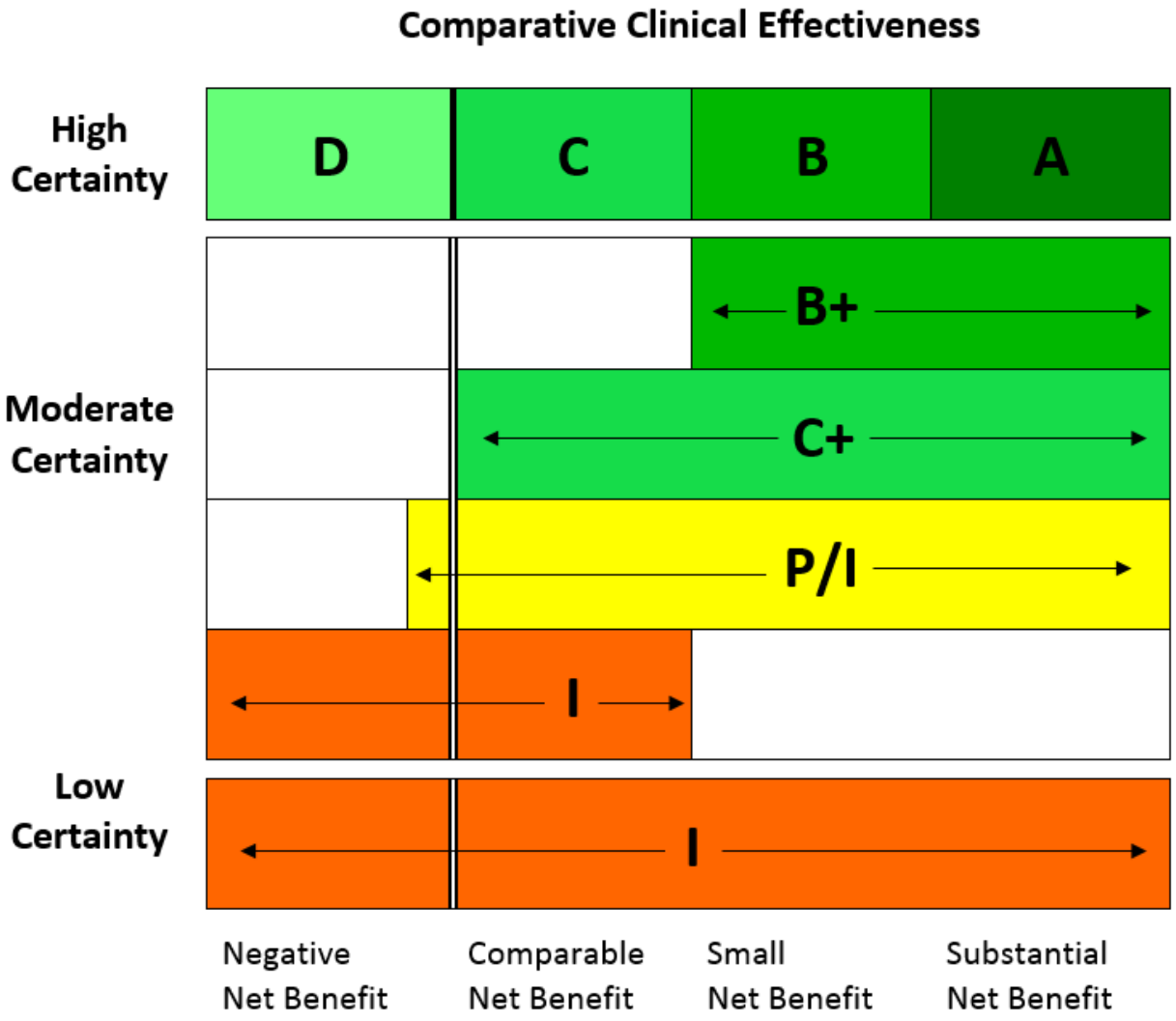
Our data extraction and review process is detailed in Appendix E. Summary tables are available in Appendix Tables E1 and E2 for evidence related to the CardioMEMS HF System and Entresto, respectively. We used criteria published by the US Preventive Services Task Force (USPSTF) to assess the quality of RCTs and comparative cohort studies, using the categories "good," "fair," or "poor."[92]

Assessment of Level of Certainty in Evidence

We used the ICER Evidence Rating Matrix (see Figure 3) to evaluate the evidence for a variety of outcomes. The evidence rating reflects a joint judgment of two critical components:

a) The **magnitude** of the difference between a therapeutic agent and its comparator in "net health benefit" – the balance between clinical benefits and risks and/or adverse effects AND
b) The level of **certainty** in the best point estimate of net health benefit.[93]

Figure 3. ICER Evidence Rating Matrix



A = "Superior" **-** High certainty of a substantial (moderate-large) net health benefit
B = "Incremental" **-** High certainty of a small net health benefit
C = "Comparable"**-** High certainty of a comparable net health benefit
D="Negative"**-** High certainty of an inferior net health benefit
B+="Incremental or Better" **–** Moderate certainty of a small net health benefit, with high certainty of at least incremental net health benefit
C+="Comparable or Better" **-** Moderate certainty of a comparable net health benefit, with high certainty of at least comparable net health benefit
P/I = "Promising but Inconclusive" - Moderate certainty of a small or substantial net health benefit, small (but nonzero) likelihood of a negative net health benefit
I = "Insufficient" **–** Either moderate certainty that the best point estimate of comparative net health benefit is comparable or inferior; or any situation in which the level of certainty in the evidence is low

Assessment of Bias

As part of our quality assessment, we evaluated the evidence base for the presence of potential publication bias represented by general or specific study designs used in the assessment of each intervention. Given the emerging nature of the evidence base for these newer treatments, we performed an assessment of publication bias using the clinicaltrials.gov database of trials. We scanned the site to identify studies completed more than two years ago that would have met our inclusion criteria and for which no findings have been published. Any such studies identified provided qualitative evidence for use in ascertaining whether there was a biased representation of study results in the published literature.

Data Synthesis and Statistical Analyses

Given the small numbers of relevant studies for CardioMEMS and Entresto, we judged that it would not be helpful or appropriate to perform formal meta-analysis to generate pooled estimates of treatment effect.

4.3 Results: CardioMEMS HF System

Study Selection

The literature search for CardioMEMS identified 23 potentially relevant references (see Appendix Figure A1), of which five publications concerning a single RCT (the CHAMPION trial) and one case series met our inclusion criteria. Details of the included studies are summarized in Appendix Table E1.

Scanning of the ClinicalTrials.gov site to identify additional studies completed more than two years ago that would have met our inclusion criteria but have not been published revealed no such studies (see Appendix D for ongoing studies).

Key Studies

The CHAMPION trial was a single-blind RCT of 550 patients (mean age 61.5; 72% male; 21.5% with preserved ejection fraction) with NYHA class III heart failure and a CHF-related hospitalization within the 12 months prior to screening.[17] All patients underwent implantation of a wireless sensor and took daily readings of pulmonary artery pressure using a home electronic console. Clinicians received pressure readings from the treatment group but did not have access to pressure data from the control group. The control group continued to receive standard of care management, which consisted of medication changes in response to patients' clinical signs and symptoms and routine clinic appointments. All patients remained blinded to their assigned groups until the last patient

completed six months of follow-up, resulting in a mean duration of follow-up of 15 months for the entire patient population. The authors reported outcomes at 6 months and over the entire duration of follow-up. In subsequent submission to FDA, the mean blinded follow-up period was cited as 17.6 months.[18]

Quality of Individual Studies

As noted earlier, we used criteria from USPSTF to rate the quality of the CHAMPION trial and all other studies included in our sample. Based on these criteria, we considered both the CHAMPION trial and subsequent subgroup publications to be of good quality, as study arms were comparable at baseline, the authors used valid instruments to evaluate outcomes, and no differential attrition occurred in the six months of patient-blinded pressure monitoring. As discussed in the section on controversies and uncertainties, however, the FDA expressed concerns about the validity of results and potential for bias in the CHAMPION trial's design. Because these uncertainties are not pertinent to USPSTF's study quality criteria, we discuss them separately.

Clinical Benefits

The CHAMPION trial was statistically powered to detect differences in the incidence of CHF hospitalization. Mortality was assessed based on a secondary endpoint of time to first CHF hospitalization or death. Over the full follow-up period, a total of 107 patients in the treatment group either died or had a hospitalization for CHF versus 138 in the control group (hazard ratio [HR] 0.73; 95% confidence interval [CI] 0.57-0.94, p=.0146). In addition, there was a statistically-significant, albeit modest, increase in the mean number of days alive outside of the hospital in the treatment group (174.4 vs. 172.1; p=0.02). Additional secondary endpoints from the CHAMPION trial are reported in Appendix Table E3.

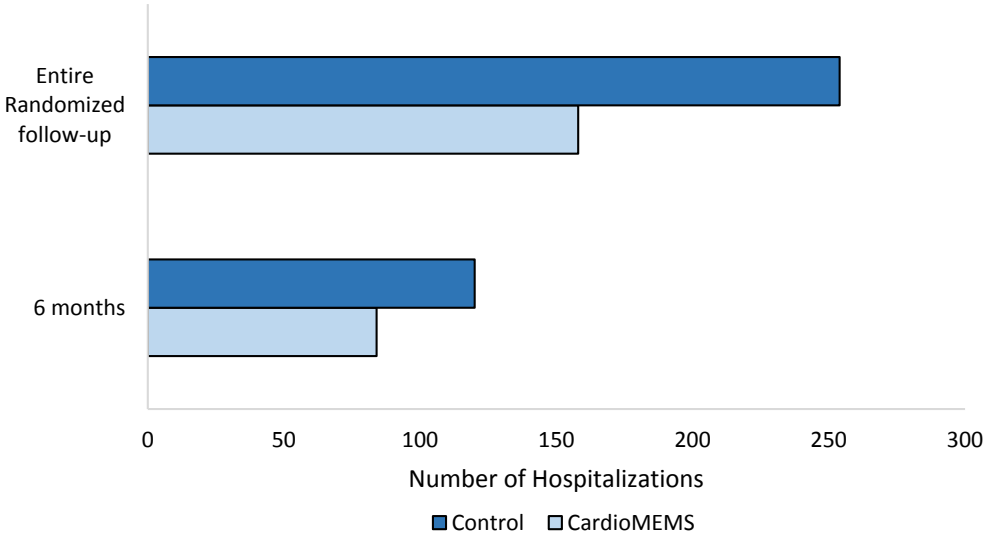
The CHAMPION trial also measured quality of life using the Minnesota Living with Heart Failure (MLHF) questionnaire. This 21-item questionnaire uses a zero to five scale to measure the extent to which CHF can affect the physical, emotional, social, and mental dimensions of a patient's life. The total MLHF score can range from 0 to 105, with a lower score indicating less effect of CHF on the patient's quality of life. At six months, the treatment group had a statistically-significantly better MLHF score than the control group (45 vs. 51; p=0.02).[17] Although the study publication did not report baseline MLHF scores or change in scores at follow-up, supplemental analysis provided in the FDA panel pack describes a greater change in patients' MLHF score between baseline and month six in the treatment group (-10.6) compared to the control group (-7.4; p=0.04).[19]

Health Care Utilization Outcomes

As mentioned above, the primary efficacy endpoint of the CHAMPION trial was the rate of CHF-related hospitalizations. This endpoint is presented in Figure 4. In the first six months after device

implantation, the treatment group had fewer CHF-related hospitalizations (84; 0.32 hospitalizations per patient) relative to the control group (120; 0.44 hospitalizations per patient; HR 0.72; 95% CI: 0.60-0.85; p=0.0002). The treatment group also had a shorter length of stay for CHF-related hospitalizations (2.2 days vs. 3.8 days; p=0.02). Over the entire 15-month follow-up period, the treatment group had a 37% reduction in CHF-related hospitalizations, with 158 and 254 hospitalizations in the treatment and control groups, respectively (HR 0.63; 95% CI: 0.52-0.77; p<0.0001). The authors calculated that during the first six months of follow-up, eight patients would need to be managed with the CardioMEMS HF System to prevent one additional hospitalization for CHF; this number decreased to four over the entire 15-month follow-up period.

Figure 4. CHF Hospitalizations



Harms

Both primary safety endpoints negotiated with the FDA as part of the clinical development program were met in the CHAMPION trial: 98.6% of patients were free from device- or system-related complications, and no pressure-sensor failures occurred. Fifteen serious adverse events (SAEs) occurred, of which eight (1% of total sample) were related to the device or system and seven (1% of total sample) were related to the implant procedure. SAEs included four bleeding events, three hospitalizations related to anticoagulation treatment, two exacerbations of pre-existing atrial dysrhythmias during right heart catheterization, two febrile illnesses, one pulmonary in-situ thrombus during right-heart catheterization, one cardiogenic shock, one atypical chest pain, and one delivery-system failure. There were no episodes of pulmonary infarction or embolism associated with the sensor, and no events required sensor removal.

Subgroup Analyses

The CHAMPION trial was not powered to detect differences in outcomes across subgroups. It also did not report subanalyses by race, ethnicity, or other indicators of health care disparities. However, our review identified four publications of clinical subgroup analyses involving trial participants. These analyses are described in further detail below.

Two studies evaluated patients with and without World Health Organization (WHO) Group II pulmonary hypertension (PH).[e, 94,95] Of the 529 patients with complete baseline hemodynamic data, 59.4% were diagnosed with PH (151 in the treatment group and 163 in the control group). Irrespective of treatment assignment, patients with PH had significantly higher rates of CHF-related hospitalization than patients without PH (0.77/year vs. 0.37/year; HR 0.49; 95% CI: 0.39-0.61; p<0.001). Among patients with PH, the effects of the CardioMEMS device were similar to findings for the overall patient population (annualized rate of CHF hospitalization: 0.60 vs. 0.94 in the control group; HR 0.64; 95% CI: 0.51-0.81; p=0.0002); the annual rate of CHF hospitalizations was lower in patients *without* PH who received CardioMEMS (0.28 vs. 0.47 in the control group), although patients in this subgroup experienced a similar relative risk reduction with the CardioMEMS device compared to those *with* PH (HR 0.60; 95% CI: 0.41-0.89; p=0.0109).[94] There was no difference in survival among patients with PH despite physician access to pulmonary artery pressure data, but use of the CardioMEMS device helped identify more patients with pulmonary hypertension than did right heart catheterization alone.[94,95]

In another subgroup analysis, Adamson and colleagues (2014) examined patients with preserved (LVEF ≥40%) versus reduced (LVEF <40%) ejection fraction.[96] Whereas control patients in the preserved and reduced ejection fraction subgroups had similar annualized rates of CHF-related hospitalizations over 17.6 months of follow-up (0.86-0.90), the authors noted that patients with a preserved ejection fraction who were monitored with the CardioMEMS HF System had a lower annualized rate of CHF-related hospitalization (0.43) compared to treatment group patients with a reduced ejection fraction (0.67; p-value not reported). Among the patients with preserved ejection fraction, the incidence rate ratio of CHF-related hospitalization was 0.50 for the treatment versus control group (95% CI: 0.35-0.70; p<0.0001); within the reduced ejection fraction subgroup, the corresponding ratio was 0.74 (95% CI: 0.63-0.89; p<0.001).

A final subgroup analysis of the CHAMPION trial evaluated patients with and without chronic obstructive pulmonary disease (COPD), with similar findings for both groups.[97] Within the COPD

[e] Pulmonary hypertension (PH) is an elevation in the pressure in the arteries of the lungs. The World Health Organization (WHO) has categorized PH into 5 groups: 1) pulmonary arterial hypertension, 2) pulmonary hypertension due to left heart disease, 3) pulmonary hypertension due to lung disease, 4) pulmonary hypertension due to blood clots, and 5) pulmonary hypertension due to miscellaneous diseases. There is a high prevalence of coexistent PH among CHF patients (almost 60% of CHAMPION trial participants were diagnosed with PH), who have a higher risk of morbidity and mortality.

subgroup, the treatment group had a 41% reduction in CHF hospitalization rates (HR: 0.59; 95% CI: 0.44-0.81; p=0.0009); in the non-COPD subgroup, the treatment group had a 34% reduction in CHF hospitalization rates (HR 0.66; 95% CI: 0.51-0.85); p=0.0017).

Case Series

We identified a single case series that met our inclusion criteria.[98] Seventeen patients (mean age 61; 82% male) with NYHA Class III CHF underwent implantation with the CardioMEMS HF System's wireless sensor. Similar to the findings of the CHAMPION trial, there were no reported cases of pulmonary infarction or thromboembolism, vascular complications, or other adverse events related to the device during implantation or follow-up. Daily patient adherence to home monitoring was 90.0% during the 60 days after implantation; 100% of patients adhered to a minimum of one pressure transmission per week during each of 138 weeks.

Controversies and Uncertainties

Upon initial FDA review in 2011, the manufacturer of CardioMEMS[f] was asked to collect additional data to inform FDA's ultimate approval decision. These additional data and analyses were discussed during the 2013 FDA Advisory Committee's consideration of the CardioMEMS pre-marketing application.[18,19,88,91] In the face of these new data and analyses, this Committee continued to raise several methodological concerns about the efficacy of the CardioMEMS device. Many on the FDA Advisory Committee were still not convinced that CardioMEMS alone could contribute meaningfully to CHF disease management. One of the primary objections was that patients in the treatment arm of the CHAMPION trial received some form of study nurse involvement in addition to having their PA pressures sent to the treating clinician. These study nurses communicated information about the patient to the treating physicians in a way that was not completely mimicked in the control arm. The other key issues pertained to differences in outcomes between men and women and questions about why an independent survival benefit could not be detected given reductions in hospitalization rates.[18,20]

To address these concerns, the CardioMEMS manufacturer conducted unblinded additional longitudinal analyses of the patients enrolled in the CHAMPION trial with PA pressures sent to treating clinicians for an additional 13 months (see Appendix Tables E5, E6, and E7). These results have recently been published in *The Lancet*.[99] Neither arm received any type of treatment intervention from study investigators, referred to as "nurse communications" in the discussions with the FDA Advisory Committee and as "sponsor communications" in *The Lancet* paper. However, since these subsequent analyses were not planned *a priori*, they are interpreted with caution. For example, the former treatment and former control arms may no longer have had equivalent "new" baseline characteristics because the two populations may have differed non-randomly six or more

[f] St. Jude Medical Inc. acquired CardioMEMS, Inc. in 2014 following FDA approval of the CardioMEMS HF System.

months after initial enrollment into the trial. The risk of future CHF hospitalizations may not have been similar at the onset of the extended period of data collection; in fact, both subsequent arms may have included healthier patients since inclusion criteria for initial study enrollment included hospitalization in the previous 12 months. This concern arises in part because the mortality rate in the former control group is lower than in the former treatment group (12.4% versus 17.5%). Mortality rate improved for the control group once PA pressure monitoring became available (from 22.9% during the initial study to 12.4% after transmission of information was allowed), but this does not explain why it should be so much lower than the former treatment arm. Hospitalization rates were similar between former control and former treatment groups (0.36 vs. 0.45, respectively); however, the hospitalization rate was significantly lower among former controls whose treatment team had access to PA pressure monitoring versus the original control group. A third party auditor was hired to examine the frequency and content of the nurse communications. This audit suggested that the majority of the content was rather mundane and did not significantly alter the management decisions of the treating physicians, though some communications were quite detailed with specific management recommendations. FDA concluded that these communications represented a confounding variable with the potential to introduce bias regardless of the fact that the analyses consistently indicated a positive treatment effect in reducing hospitalization rates.[18]

The manufacturer conducted a propensity score analysis to further address the concern of nurse communications by examining the treatment given to patients who had no nurse communications in the treatment arm compared to matched controls. As with the overall population, the rate of CHF-related hospitalization was lower among treated patients relative to matched controls. However, this relationship was considered difficult to interpret because this subset of treatment arm patients may have been healthier than those who received nurse communications.

The additional gender analysis used a composite of time to death or first hospitalization to determine that there was not a significant treatment-by-gender interaction. However, the small number of females enrolled in the study and the small number of events (death or hospitalization) made an examination of treatment effect among women difficult to substantiate. FDA required a post-approval study be conducted to evaluate treatment effects in women.

Ultimately, the second FDA Advisory Committee in 2013 voted on three questions:[88-90]

- "*Is there reasonable assurance that the CardioMEMS HF Pressure Measurement System is safe for use in patients who meet the criteria specified in the proposed indication?*" All eleven panel members affirmed that this was evident. This was similar to the initial nine to one vote in 2011, wherein one panel member voted against because of the conflicting findings with female recipients.
- "*Is there reasonable assurance that the CardioMEMS HF Pressure Measurement System is effective for use in patients who meet the criteria specified in the proposed indication?*"

Seven panel members believed this was not the case, and four members believed it was. This is similar to the seven to three vote in 2011, when panel members objected to the confounding of nurse communications.

"*Do the benefits of the CardioMEMS HF Pressure Measurement System for use in patients who meet the criteria specified in the proposed indication outweigh the risk for use in patients who meet the criteria specified in the proposed indication?*" Six panel members believed this was the case, four voted "no," and one abstained. In 2011, the panel voted in the opposite direction – six opposed and four in favor.

Although FDA disagreed with the Advisory Committee's vote that there is not reasonable assurance that the device is effective, they concluded that the bias introduced by the existence of nurse correspondence in the treatment arm was impossible to fully neutralize despite extended data collection and subsequent analyses. FDA considered the safety of the device and the consistency of the results to support the conclusion of positive treatment effect, but noted uncertainty regarding the magnitude of this effect.[18] CardioMEMS ultimately received FDA approval on May 28, 2014 with the requirement that the manufacturer perform two post-approval prospective, multi-center, open-label US-based trials in order to 1) examine the device's safety and effectiveness among new recipients with enough sample size to detect gender differences, and 2) compare post-market effectiveness to a subset of pre-market recipients with specific attention to certain subgroups (women vs. men, reduced vs. preserved ejection fraction, ischemic vs. non-ischemic etiology, and implantable cardioverter-defibrillator [ICD] or cardiac resynchronization with defibrillator [CRT-D] vs. non-ICD/CRT-D).[21] Details of the ongoing trials are provided in Appendix D.

Alternative Management Strategies

We did not systematically review alternative methods of CHF management, as these were not direct comparators of CardioMEMS. However, to provide appropriate context for CardioMEMS, below we present a summary of information regarding the effectiveness of such management strategies.

Several RCTs, systematic reviews, and technology assessments have evaluated the effectiveness of programs of varying intensity for reducing readmissions of patients with heart failure after a first hospitalization.[2,22-26] Certain interventions have become common components of usual care, including education on symptoms, instruction on self-management, dietary advice, medication review, exercise recommendations, and weight monitoring; however, there is considerable heterogeneity in the content, intensity, duration, setting, personnel, and combination of components employed in CHF management across programs, and systematic reviews of CHF management strategies employ varied definitions of usual care.[26]

In a series of meta-analyses, Raman and colleagues compared various non-pharmacological interventions for post-discharge care to usual care (defined variably, but generally described as

"unstructured" and consisting of patient instruction on medications and providing information for follow-up appointments).[26] The authors found that home-visit interventions (relative risk [RR] 0.82; 95% CI: 0.69-0.97), increased clinic visits (RR 0.78; 95% CI: 0.64-0.95), and multidisciplinary care (RR 0.63; 95% CI: 0.44-0.90), in tandem with a combination of program components, such as education reinforcement and telephone follow-up, significantly decreased the risk of all-cause readmissions compared to usual care. Moreover, the authors discovered that programs that were initiated in an inpatient setting (RR 0.80; 95% CI: 0.71-0.90) and followed patients for durations longer than 12 months (RR 0.80; 95% CI: 0.67-0.94) significantly reduced all-cause readmissions; few individual studies that initiated an intervention in the inpatient setting reported statistical differences in mortality or length of hospital stay during readmission between the intervention and usual care groups.

Another systematic review by Feltner and colleagues revealed that structured telephone support (i.e., monitoring, education, and/or self-care management via telephone in a structured format) reduced heart failure-specific readmissions (132/833 patients were hospitalized vs. 207/957 with usual care; RR 0.74; 95% CI: 0.61-0.90), as well as all-cause mortality over 3-6 months (79/808 vs. 108/811 with usual care; RR 0.74; 95% CI: 0.56-0.97) relative to usual care, routine care, or standard care (as defined by primary studies used in the systematic review). Telephone support did not have an effect on the rate of emergency department (ED) visits or quality of life but did significantly reduce the total number of days spent in the hospital (weighted mean difference -2.49; 95% CI: -3.93 – -1.04). In addition, Feltner and colleagues found that face-to-face contact with care delivery personnel, streamlined mechanisms for contacting care delivery personnel outside of scheduled visits, mechanisms for post-discharge medication adjustment, and patient education were crucial components of any CHF management program.[2]

Appendix Table E4 reports the relative risk and crude absolute rates of all-cause hospitalizations, all-cause mortality, and heart failure-specific hospitalizations from a series of systematic reviews comparing alternative management strategies for CHF to usual care. This information is provided only for general context given requests from multiple stakeholders to understand how the results on CardioMEMS compare to the results found for other CHF management strategies. Even though the populations studied in CHAMPION and trials of other CHF management strategies may seem comparable, there may be significant unknown confounders that introduce bias into any attempt to indirectly compare the results of treatment arms across these different studies.

Across the systematic reviews, patients receiving usual care had an average 27% (range 11-40%) rate of heart failure-specific hospitalizations, which is similar to the rate in the control arm of the CHAMPION trial in which 29% experienced a heart-failure specific hospitalization. The rate of CHF hospitalizations among patients monitored with the CardioMEMS device in the CHAMPION trial (20%) is similar to that for patients in trials who received other non-pharmacological interventions such as structured telephone support, multidisciplinary care, or patient education and self-

management (mean 20%; range 15-27%). Of note, evaluations of telemonitoring strategies compared to usual care failed to demonstrate statistically-significant reductions in CHF hospitalizations in the systematic reviews we evaluated as well as in several recently-published RCTs.[100-102]

Summary

For patients with Class III CHF with either reduced or preserved ejection fraction who have been hospitalized in the prior 12 months, we judge there to be moderate certainty of a small net benefit for the CardioMEMS HF System compared with usual monitoring of patients' signs and symptoms. There is moderate certainty because while the CHAMPION trial indicated that patients had fewer hospitalizations when care was informed by the CardioMEMS HF System, the results of the CHAMPION study are limited by concerns regarding the potential confounding influence of the study nurse on the superior outcomes in the treatment arm. In addition, while post-hoc analyses have been presented illustrating reductions in cardiovascular mortality with CardioMEMS, there have been no published data from trials powered to detect mortality differences. It seems reasonable to surmise that ongoing post-marketing trials evaluating the device may demonstrate a wide variety of outcomes, from substantial net health benefit to a small likelihood of overall "negative" benefit given the potential harms associated with device placement. Therefore, we judge the current body of evidence on CardioMEMS to be "promising but inconclusive" using the ICER Evidence Rating framework.

4.4 Results: Entresto

Study Selection

The combined search results for Entresto identified 134 potentially relevant studies for this assessment (see Appendix Figure A2). After elimination of duplicate and non-relevant references, we identified seven reports containing information from two RCTs. Details of the included studies are summarized in Appendix Table E2.

Scanning of the ClinicalTrials.gov site to identify additional studies completed more than two years ago that would have met our inclusion criteria but have not been published revealed no such studies.

Key Studies

The first good quality RCT that met our inclusion criteria was the PARADIGM-HF trial. In this double-blind Phase III trial, 8,442 patients (mean age 63.8; 78.2% male) with NYHA Class II-IV CHF and

reduced ejection fraction (LVEF ≤35%) were randomly assigned to Entresto (200 mg BID) or enalapril (10 mg BID) in addition to other recommended therapy. After a median duration of 27 months follow-up, the study's executive committee voted to stop the trial because the pre-specified boundary for an overwhelming benefit had been crossed.[38]

The second good quality RCT we reviewed was PARAMOUNT, a Phase II double-blind trial of 149 patients (mean age 71.1; 43% male) with NYHA Class II-III heart failure and preserved ejection fraction (LVEF ≥45%).[40] Patients were randomized to receive either Entresto (200 mg BID) or valsartan (160 mg BID) alone for 36 weeks and received additional undefined background therapy (exclusive of ACE inhibitors or ARBs) at the discretion of treating physicians. A larger ongoing trial will compare Entresto to valsartan in 4,300 patients with preserved ejection fraction (see Appendix D for further details about this study).

Overall Evidence Quality

Using criteria from USPSTF, we rated six publications of two RCTs to be of good quality. We judged these studies to be good quality because study arms were comparable at baseline, the authors used valid instruments to evaluate outcomes, and no differential attrition occurred in either trial. We rated an additional publication comparing PARADIGM-HF participants to those of two other major heart failure trials to be fair quality, given that there were some differences in baseline characteristics across each study's participants.

Certain elements of the PARADIGM-HF trial's protocol have generated controversy, and the validity of the study's results have been called into question. Because these controversies are not pertinent to USPSTF's study quality criteria, we discuss them separately in the controversies and uncertainties subsection.

Clinical Benefits

Over 27 months of follow-up in the PARADIGM-HF trial, the primary composite endpoint of death from cardiovascular causes or first hospitalization for worsening heart failure occurred in 21.8% of the Entresto group and 26.5% of the enalapril group (HR 0.80; 95% CI: 0.73-0.87; p<0.001); the number needed to treat (NNT) in order to avoid one event of either cardiovascular death or first CHF hospitalization was 21. Investigators also made indirect comparisons of this composite endpoint between PARADIGM-HF participants in the Entresto group and participants with similar baseline characteristics who belonged to the placebo arms of two other large heart failure RCTs (SOLVD[103] and CHARM-Alternative[104,105]). The results of their exploratory analysis revealed a relative risk reduction of 39-43% with Entresto versus a putative placebo.

In addition to the composite endpoint of death from cardiovascular causes or first heart failure-specific hospitalization, investigators of the PARADIGM-HF trial also reported mortality and

hospitalization outcomes separately (see the section below on health care utilization for hospitalization outcomes). A total of 558 patients (13.3%) in the Entresto group and 693 patients (16.5%) in the enalapril group died from cardiovascular causes (HR 0.80; 95% CI: 0.72-0.89; p<0.001), with an NNT of 31 patients needing to be treated with Entresto to avoid one cardiovascular death. Death from any cause occurred in 711 (17.0%) patients in the Entresto group and 835 patients (19.8%) in the enalapril group (HR 0.84; 95% CI: 0.76-0.93; p<0.001); the NNT for death from any cause was 36 patients.[38,39] NNTs for the primary outcomes of interest are reported in Table 1.

Table 1. Numbers Needed to Treat in PARADIGM-HF Trial

Event	NNT
Death from cardiovascular causes or first hospitalization for worsening CHF	21
Death from cardiovascular causes	31
First hospitalization for worsening CHF	36
Death from any cause	36
Emergency department visit	83

NNT: Number Needed to Treat

Worsening of CHF, as determined by NYHA classification, was evaluated in both the PARADIGM-HF and PARAMOUNT trials. Of the patients surviving at 12 months in the PARADIGM-HF trial, NYHA class worsened in fewer patients receiving Entresto (225 [6.1%]) vs. enalapril (271 [7.4%]; p=0.023).[42] Although there was not an appreciable difference between groups in the proportion of patients whose NYHA class *worsened* at week 36 of the PARAMOUNT trial, 24% of the Entresto group experienced an *improvement* in NYHA class compared to 17% of the valsartan group (p=0.05).[g,40]

Another patient-centered outcome of interest for this review was quality of life, which was assessed using the Kansas City Cardiomyopathy Questionnaire (KCCQ) in both the PARADIGM-HF and PARAMOUNT trials. This 23-item questionnaire quantifies physical function, symptoms (frequency, severity, and change over time), social function, self-efficacy, and quality of life. The summary score ranges from 0-100, where higher scores indicate better status.[106] While the PARAMOUNT trial did not find statistical differences in the KCCQ summary score between treatment groups, the PARADIGM-HF trial reported a mean reduction in quality of life of 2.99 points in the Entresto group and 4.63 points in the enalapril group between baseline and month 8 (between-group difference 1.64 points; 95% CI: 0.63-2.65; p=0.001).[38,40]

[g] Note that because the results for NYHA worsening were not reported in the text of the PARAMOUNT trial publication, we were obligated to interpolate the proportions from a chart; thus, the estimates may not be exact.

Health Care Utilization Outcomes

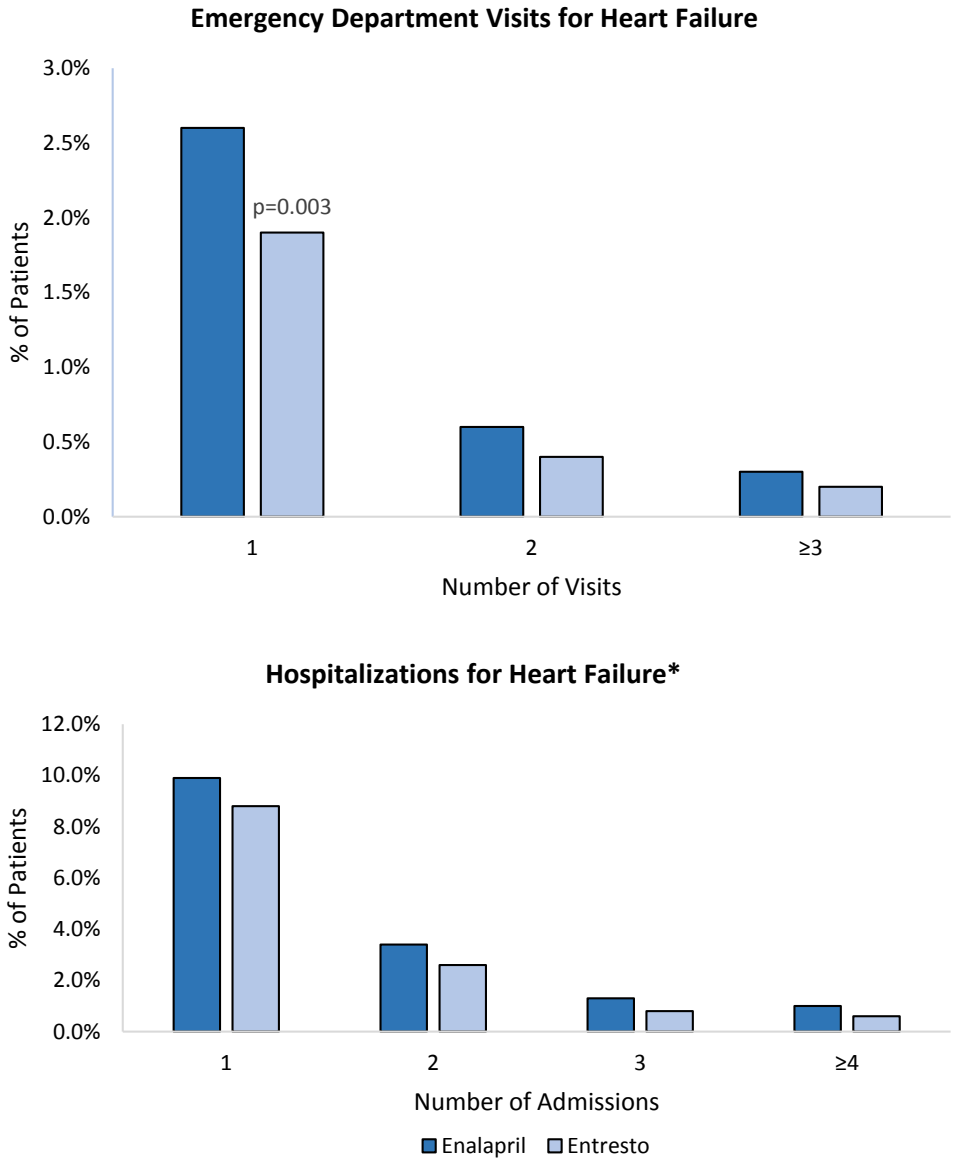
Two publications of the PARADIGM-HF trial reported outcomes related to health care utilization.[38,42] Relative to patients in the enalapril arm, intensification of outpatient therapy related to worsening heart failure occurred in fewer patients in the Entresto group (520 [12.4%] vs. 604 [14.3%] for enalapril; HR 0.84; 95% CI: 0.74-0.94; p=0.003). Moreover, the authors reported a lower likelihood of first CHF-related hospitalization in the Entresto group (537 [12.8%]) compared to the enalapril group (658 [15.6%]; HR 0.79; 95% CI: 0.71-0.89; p<0.001), fewer ED visits (208 vs. 151; HR 0.70; 95% CI: 0.52-0.94; p=0.017), and fewer patients treated in the ED relative to the enalapril group (102 [2.4%] vs. 150 [3.6%]; HR 0.66; 95% CI: 0.52-0.85; p=0.001). Hospitalizations and ED visits are stratified by frequency in Figure 5: in comparison with enalapril, patients treated with Entresto were significantly less likely to have repeat hospitalizations and were significantly less likely to have one ED visit for worsening heart failure.

Harms

In the PARADIGM-HF trial, 46.1% of the Entresto group and 50.7% of the enalapril group experienced at least one serious adverse event. The most commonly reported adverse events (AEs) were hypotension, cardiac failure, hyperkalemia, renal impairment, and cough. Discontinuation of study medication due to an adverse event occurred in 10.7% of the Entresto group and 12.3% of the enalapril group (p=0.03). Nineteen patients (0.5%) in the Entresto group and 10 patients (0.2%) in the enalapril group experienced angioedema (p=0.13).[38]

In the PARAMOUNT trial, 15% of the Entresto group and 20% of the valsartan group experienced one or more SAEs. There was one death in the Entresto group and two deaths in the valsartan group. The overall adverse event rate did not statistically differ between groups, nor did the percentage of patients discontinuing their randomized treatment due to an adverse event (10% with Entresto vs. 11% with valsartan). One patient in the Entresto group experienced angioedema but was not hospitalized.[40]

Figure 5. Hospitalizations and ED Visits by Frequency



*p<0.001 for all between group comparisons of hospitalizations for heart failure

Subgroup Analyses

Both RCTs included subgroup analyses for the primary outcomes of interest. The authors of the PARADIGM-HF trial reported a consistent effect of Entresto across all pre-specified subgroups, including sex, age, race, medical and heart failure history, and ejection fraction for the composite endpoint of death from cardiovascular causes or first CHF-related hospitalization.[38] Entresto functioned better than enalapril in patients with NYHA Class I or II heart failure (HR 0.74) relative to

patients with Class III or IV heart failure (HR 0.94; p=0.03);[h] however, FDA review materials for the drug suggest that these variations may not represent clinically meaningful differences in efficacy given the relatively small numbers of patients with Class I, III, or IV CHF in the study sample. Furthermore, other markers of disease severity, such as ejection fraction and levels of NT-proBNP[i] were not markedly different across subgroups.[43,107]

Materials from the FDA's medical review of Entresto further indicate that there may be an interaction between race and angioedema. Adjudicated events of angioedema were more common in subjects who were black (2.3% vs. 0.5% in the Entresto and enalapril arms, respectively) relative to non-black subjects (0.35% vs. 0.22% with enalapril). The incidence of angioedema among black patients taking Entresto was particularly high in the US (5.6% vs. 0% with enalapril). As black patients were underrepresented in the PARADIGM-HF trial (5% of total sample), the FDA is requiring the manufacturer to conduct an epidemiologic study to further investigate the incidence of angioedema in black patients as a post-marketing requirement.[43] However, the primary endpoint of cardiovascular death or first heart failure hospitalization for black patients (HR 0.81; 95% CI: 0.57-1.15) was similar to that for the overall patient population (HR 0.80; 95% CI: 0.73-0.87).[43]

Controversies and Uncertainties

Criticisms of Entresto center on the PARADIGM-HF trial having compared the combination neprilysin inhibitor and ARB valsartan to the ACE inhibitor enalapril rather than to valsartan alone. Some commentators have argued that the most direct comparison of efficacy would have been to compare Entresto to valsartan at a bioequivalent dose. The drug maker's contention is that ACE inhibitors are most often first-line therapy for CHF and that this was even more likely to be true in 2010 when the study protocol was amended.[43] Lisinopril as an ACE inhibitor comparator may have simulated typical clinical practice more closely than the older enalapril, but much of the evidence base supporting ACE inhibitor use in CHF examined enalapril as a comparator.[108-111]

Without an additional study comparing Entresto to valsartan at bioequivalent doses (200mg twice daily Entresto delivers the equivalent of 160mg twice daily valsartan), FDA deliberations indicated that it is problematic to clearly determine how much the neprilysin inhibition assists with CHF management compared to ARB-suppression of the renin-angiotensin-aldosterone system. There have been earlier trials (ATLAS,[112] Val-HeFT,[112] CHARM-Added[113]) that compared ACE inhibition and ARB use that did not suggest mortality benefit of one over the other. There have also been trials

[h] HRs interpolated from a forest plot in the study publication.
[i] NT-proBNP (N-terminal pro b-type natriuretic peptide) is a type of natriuretic peptide (a hormone that the body releases to help maintain fluid balance). Levels of NT-proBNP are correlated with the clinical severity of the disease according to the NYHA heart failure classification.

that demonstrated mortality benefits of ACE inhibitors when compared to placebo,[103,108,111] but similar benefits have not been demonstrated in comparisons of ARBs to placebo.[112,114]

Another critique of the evidence on Entresto relates to the fact that the pivotal trial was conducted only among patients who tolerated a "run-in" phase of treatment with enalapril followed by treatment with Entresto. More than 2,000 enrolled patients dropped out before the end of the "run-in" phase because they could not tolerate one of the agents, usually because of hypotension. One concern is that patients naïve to ACE inhibitors and ARBs may experience intolerable hypotension on the trial's treatment dose, which would attenuate health improvements in the general population. Hypotension was more common among patients treated with Entresto than with enalapril, but in almost all cases the patient was able to continue taking Entresto. Concerns about hyperkalemia and angioedema exist with enalapril and valsartan therapy as they do with all drugs in their classes. There is also concern that neprilysin inhibition itself can potentiate angioedema. In fact, more patients in the treatment arm developed angioedema than did in the enalapril arm of the PARADIGM-HF trial (0.5% versus 0.2%). As noted above, the FDA is requiring post-marketing epidemiologic research of angioedema complications among black patients treated with Entresto compared to a control drug.

The patients enrolled in PARADIGM-HF had fewer ICD devices than would be expected among patients on guideline-adherent therapy for similar classes of heart failure today in the United States, raising additional questions about the study's generalizability. However, subanalyses of US-enrolled patients and those with and without ICDs showed no significant differences in relative risk compared with the overall trial findings. Although ICD devices would be expected to prevent sudden cardiac death, they would not necessarily affect hospitalization rates.

Investigators in the PARADIGM-HF trial gave patients in the control arm 10mg twice daily dosing of enalapril rather than 20mg twice daily dosing, which is the maximum (and goal) dose. The stated reason was that few patients in practice consistently tolerate 20mg twice daily. For example, in the 1987 CONSENSUS and 1991 SOLVD trials, which demonstrated improved outcomes for patients on ACE inhibitors, the majority of patients were maintained on less than 20mg twice daily dosing (mean 18.4mg daily and 16.7mg daily, respectively, compared with 18.9mg daily in the PARADIGM-HF trial).[41,108,111]

Neprilysin inhibition is an emerging practice, which means there is limited experience using drugs like sacubitril long-term and the risks that might be associated with it are unknown. There is a theoretical risk that neprilysin inhibitors contribute to harmful beta-amyloid deposition in the brain, potentially increasing the risk of Alzheimer's dementia. FDA has required Entresto's manufacturer to conduct a multi-center, randomized, double-blind, active-controlled trial to examine its effects compared to valsartan on cognitive function in patients with CHF and preserved ejection fraction. The argument for proceeding with drug approval before cognitive function studies are complete is

that average life expectancy in patients with CHF is much shorter than the amount of time it usually takes to develop dementia.

One final criticism raised in regards to Entresto is that it forces patients to take a combination therapy rather than the two agents separately. At present, there is no approved neprilysin inhibitor marketed individually. Some have suggested that FDA should approve sacubitril as a single agent rather than as a combination drug because it is difficult to prove that each component of the drug contributed to the improved health outcomes. Novartis suggested that treatment with sacubitril alone could detrimentally increase angiotensin II without concurrent treatment with an ACE inhibitor or ARB, but little evidence has been presented to support this claim.[43]

Summary

We judge there to be moderate certainty of an incremental to substantial net benefit for Entresto compared to standard of care with ACE inhibitor treatment in patients with Class II-IV CHF and reduced ejection fraction. There is moderate certainty because the PARADIGM-HF trial was a large, good quality study in which Entresto produced significant reductions in cardiovascular and all-cause mortality as well as in heart failure specific hospitalization and ED visits in comparison to an agent that itself has demonstrated clinical benefits in these domains. Some uncertainties remain, however, including the relative contribution of sacubitril versus valsartan to these results, the expected tolerability of Entresto, its clinical performance in real-world practice, and its potential for harm in certain patient subgroups.

Given the entire body of evidence, our rating of comparative clinical effectiveness in the ICER Integrated Evidence Rating framework is B+ (“Incremental or better”).

5. Other Benefits or Disadvantages

Our reviews seek to provide information on other benefits or disadvantages offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. Examples include but are not limited to:

1. Methods of administration that improve or diminish patient acceptability and adherence
2. A public health benefit, e.g., reducing new infections
3. Treatment outcomes that reduce disparities across various patient groups
4. More rapid return to work or other positive effects on productivity (if not considered a benefit as part of comparative clinical effectiveness)
5. New mechanisms of action for treatments of clinical conditions for which the response to currently available treatments varies significantly among patients for unknown reasons (substantial heterogeneity of treatment effect)

With CardioMEMS being an implanted device, there exist potential disadvantages to patients who must undergo a medical procedure, both with respect to minor anxiety over the procedure itself as well as over the understanding that it is a permanent device. The latter point may well serve as a benefit to some patients and their caregivers who may feel reassured by the continual monitoring offered by the device. We have not noted potential other benefits or disadvantages associated with CardioMEMS implantation and monitoring.

We have noted no potential other benefits or disadvantages associated with Entresto therapy not already covered in this report.

6. Comparative Value

Overview

To assess the incremental costs per outcomes achieved, we conducted a cost-effectiveness analysis using a simulation model of CHF outcomes and costs in representative populations for CardioMEMS and Entresto (see section 6.2). We estimated the incremental cost-effectiveness of CardioMEMS and Entresto using device and drug cost estimates derived from current prices and estimates of reductions in clinical and economic outcomes (hospitalizations, procedures, and chronic disease care costs) derived from relevant clinical trial data.

Outputs from this model were also used to inform a population-based analysis of the one- and five-year budgetary impact of CardioMEMS and Entresto, by key subpopulation and on an overall basis (see section 6.3). Budgetary impact was assessed using assumed levels of uptake over these timeframes and included assessment of drug or device costs as well as cost savings from averted hospitalizations and deaths. We also define a "value-based price benchmark" for CardioMEMS and Entresto based on a calculated threshold for policy intervention to manage the costs of a new pharmaceutical or a new device.

6.1 Prior Published Evidence on Costs and Cost-Effectiveness of CardioMEMS HF System

Abraham and colleagues, in reporting on the results of a single-blinded RCT of the CardioMEMS HF System, modeled the cost-effectiveness of that system compared to standard-of-care management (the control group).[17] They used a Markov cohort simulation to model the costs and effects of five years of treatment for a hypothetical cohort of patients, with patients' utilities measured using the European Quality of Life-5 Dimensions (EQ-5D) and Kaplan-Meier survival curves for the treatment and control arms. They found that the average patient in the treatment arm gained 2.506 quality-adjusted life years (QALYs) at a cost of $68,919, while the average patient in the control arm gained 2.200 QALYs at a cost of $64,637, for an incremental cost-effectiveness ratio of $13,979 per QALY gained. The lack of detail on the simulation model described in the aforementioned study makes it difficult to evaluate the generalizability of this result.

6.2 Incremental Costs per Outcomes Achieved

Overview and Methods

We developed a Markov model to evaluate the cost-effectiveness of 1) the CardioMEMS HF System, and 2) Entresto compared with standard-of-care therapy in patients with congestive heart failure. We constructed a model of the natural history of chronic heart failure using event rates from the published literature.[17,18,27-36] For the CardioMEMS HF System, we specifically modeled the device in the CHAMPION trial cohort of NYHA Class III heart failure patients who had a heart failure hospitalization in the previous year, both in patients with reduced ejection fraction and preserved ejection fraction.[17] For Entresto, we modeled a cohort of NYHA Class II-IV heart failure patients with reduced ejection fraction based on the PARADIGM-HF trial and other published literature.[38,42,44,45] We compared the CardioMEMS device to routine care (i.e., treatment adjustments based on signs and symptoms), using event rates from the CHAMPION trial to determine the probabilities of hospitalization and mortality in the routine care arm.[17,18,29] We compared Entresto with standard treatment with lisinopril, using event rates from the PARADIGM-HF trial to determine the probabilities of hospitalization and mortality in the routine care comparison. We used this instead of enalapril 10mg twice daily (the comparator in PARADIGM-HF) because it is less expensive and much more widely used.[16,46] We utilized the efficacy of the CardioMEMS device and Entresto demonstrated in the CHAMPION trial and PARADIGM-HF trial, respectively, to estimate numbers of heart failure hospitalizations, costs, deaths, life-years, and QALYs. These estimates were used to calculate the cost per QALY gained via the intervention, also known as the incremental cost-effectiveness ratio.

For the CardioMEMS HF System, we performed an analysis of the entire trial cohort along with subgroup analyses of those with reduced or preserved ejection fraction. We additionally performed the analysis in an alternative, possibly more broadly representative cohort of patients from the Effect of Candesartan in Patients with Chronic Heart Failure (CHARM) trials, with NYHA Class II-IV heart failure and a previous heart failure hospitalization.[35]

For the Entresto model, we assumed the use of Entresto 200mg twice daily (400mg/day), consistent with the dosing in PARADIGM-HF. For the ACE inhibitor arm or those who developed intolerance to Entresto, we modeled the use of lisinopril 20mg daily (target dose for lisinopril). We assumed treatment equivalence between these moderate-dose ACE inhibitors. To account for those patients who had intolerance to an ACE inhibitor, we modeled the use of losartan 100mg daily, which is a comparable but less expensive ARB than valsartan. We did not compare Entresto to a third therapeutic arm with initiation of ARB therapy due to the lack of direct comparison between the two treatments and the absence of evidence regarding any difference in effectiveness between ACE inhibitors and ARBs in the treatment of chronic heart failure.[115]

We performed all analyses using TreeAge Pro 2015, Microsoft Excel 2011, and Stata 2013.

Perspective

We utilized the perspective of a third-party health care payer. We limited our analysis to direct medical costs (including costs of non-cardiac medical care) and did not include non-health care costs or changes in productivity. All costs and effects were discounted at 3% annually except as noted.[116]

We utilized a series of willingness-to-pay thresholds based on the American Heart Association and World Health Organization's cost-effectiveness guidelines, ranging from $50,000 per QALY gained (approximately gross domestic product [GDP] per capita x1) to $150,000 per QALY gained (approximately GDP per capita x3).[117]

Patient Population

CardioMEMS HF System: We modeled a cohort of 62-year-old patients with NYHA Class III chronic heart failure who had a hospitalization for heart failure within the previous year. Our modeled cohort had a similar composition as that of the CHAMPION trial, with 78% having reduced ejection fraction and 22% with preserved ejection fraction.[17] In a sensitivity analysis, we also modeled a cohort of patients with prior heart failure hospitalization that mirrored subjects included in the CHARM trial. Overall, this group had a less severe burden of heart failure, with 45% of patients having Class II, 52% Class III, and 3% Class IV heart failure. This group had lower hospitalization and mortality rates than in the CHAMPION trial. We adjusted event rates to represent a similar proportion of patients with reduced and preserved ejection fraction as in the CHAMPION trial, using literature estimates of the relative risk of events between each subgroup.[17,30,31,33,36]

Entresto: We modeled a cohort of 64-year-old patients with NYHA Class II-IV chronic heart failure and reduced ejection fraction (<40%). Our modeled cohort had a similar composition as that of the PARADIGM-HF trial, with 72.9% having Class II, 26.2% Class III, and 0.9% Class IV heart failure.[38] We excluded patients with Class I heart failure (4.7% of the trial), as the treatment was not FDA approved for that group.[45] We adjusted the trial event rates and the treatment efficacy to account for the lack of NYHA Class I patients in our modeled cohort, using the distribution of events by NYHA class, the relative risk of non-cardiovascular death between each subgroup, and estimates of subgroup-specific patient follow-up.

Model Structure

For each of the two interventions, identical patient cohorts were entered in the model's treatment arm and routine care arm. A monthly time cycle was used, and the model had a lifetime horizon.

CardioMEMS HF System: In the CardioMEMS treatment arm, patients initially underwent placement of the device, which could lead to a successful placement without complication, a successful placement with a peri-procedural complication, or a failed placement. Each month, patients in both arms were at risk for a heart failure hospitalization, a non-heart failure hospitalization, and death from any cause. In the CardioMEMS arm, patients were also at risk for a device-related complication and sensor failure. Patients who have a heart failure exacerbation requiring hospitalization additionally had a risk of inpatient mortality and an increased risk of post-discharge mortality for a two-month period. Patients with sensor failure no longer had the benefits or costs of the CardioMEMS treatment.

Entresto: For the Entresto evaluation, patients entered the model on a stable dosage of Entresto or ACE inhibitor. Each month, patients were at risk for a heart failure hospitalization, angioedema requiring hospitalization, any other non-heart failure hospitalization, an ED visit for heart failure not requiring hospitalization, intolerance to their treatment agent, and a cardiovascular or non-cardiovascular death. Those who suffered an intolerance or angioedema were switched to an alternative agent – an ACE inhibitor for those taking Entresto and an ARB for those unable to tolerate an ACE inhibitor.

Transition Probabilities

CardioMEMS HF System: The baseline transition probabilities (i.e., likelihood of moving from one health state to another) were derived from the CHAMPION trial, the CHARM trials, and the published literature (see Table 2). The probabilities were adjusted to account for a decreasing risk of rehospitalization with increasing time from the baseline hospitalization in the CardioMEMS analysis and to adapt the mortality seen in the trial to a lifetime horizon in both analyses.

In the CHAMPION trial, the monthly rate of heart failure hospitalizations was higher in the initial six months than over 17 months, a trend that is supported in the literature.[18,28-30] Therefore, we modeled a decrease in the probability of heart failure hospitalizations over the mean trial duration (17 months). After the trial duration, we maintained the hospitalization probability at the 17-month level. We calibrated the model's hospitalization rates in both arms to the hospitalization rates seen in the CHAMPION trial.

In the CHAMPION trial, the device arm had a non-significant hazard ratio of 0.84 for mortality. Because this was not significant, we did not assume the trial's exact point estimate of mortality reduction and, instead, limited the benefits to an estimate of reduced mortality arising from reduced rates of heart failure hospitalization. Mortality in patients with heart failure is markedly increased after a heart-failure hospitalization but decreases with increased time from the index hospitalization.[30,36] Additionally, all-cause mortality increases with age. Due to the lack of trial-based data on mortality change over the trial, we used a constant mortality probability over the trial period, with an increased relative risk of mortality in the month of a hospitalization and in the

subsequent month, prior to returning to baseline mortality.[34] After the trial period, we used an exponential annual increase in the baseline all-cause mortality to reflect mortality risk with aging.[118,119] We also incorporated an inpatient mortality risk for each heart failure hospitalization.[27,28] We calibrated our model's mortality rate in the routine care arm to the mortality rate seen in the control arm of the CHAMPION trial.

We determined the event probabilities of preserved ejection fraction patients compared to reduced ejection fraction patients using estimates of the relative risks of each event from the literature.[30,31,33,36] We used literature estimates instead of the group-specific rates in the trial because the total number of preserved ejection fraction patients in the trial was low (119 patients) and thereby may not accurately reflect the relationship between the two groups in the natural history of disease. We did, however, use subgroup-specific device efficacy estimates from the trial.[17]

We calculated probabilities for the CHARM cohort similarly. However, we only adjusted the baseline heart failure hospitalization and mortality probabilities of the routine care arm to the results of the CHARM trials, accounting for patients with a previous heart failure hospitalization.[30,32,35] The remaining modeled probabilities were kept the same as in the CHAMPION cohort.

Non-heart failure hospitalizations, sensor failures, and device complications were estimated from the CHAMPION trial data.[17,18,29]

Table 2. Transition Probabilities and Costs (Monthly)*

CHAMPION cohort – Reduced Ejection Fraction	Base Case	Range	Source
Baseline All-Cause Mortality (%)†	0.99	0.66-1.31	17,18,29
Baseline Heart Failure Hospitalization (HFH) (%)‡	9.13	4.56-13.69	17,18,29
Relative Risk of Death after HFH	3.32	1.00-4.98	34
Relative Risk (RR) of Preserved Ejection Fraction (pEF) Subgroup, compared to Reduced Ejection Fraction (rEF) Subgroup			
RR of All-Cause Mortality, pEF vs. rEF	0.52	0.43-1.00	30,31,33,36
RR of HFH, pEF vs. rEF	0.64	0.54-1.00	30,31,33,36
CHARM Cohort§ - Reduced Ejection Fraction			
Heart Failure Mortality (%)	0.66	0.43-0.89	30,32,35
Baseline HFH (%)	3.17	2.37-3.97	30,32,35
CardioMEMS Arm Specific Parameters			
RR of HFH, compared to usual care (both arms)	0.63	0.57-0.80	17,18,29
Peri-procedural Complication (%)	1.91	0.77-3.06	18,29
CardioMEMS Costs ($)			
Cost of Heart Failure Hospitalization#	12,832	8,341-16,750	120,10
Cost of CardioMEMS Placement	1,129	564-2,258	11,37
Cost of CardioMEMS Device	17,750	8,875-35,500	23
Monthly Cost of CardioMEMS	27	13-54	11
Utility Values			
Utility Increment of CardioMEMS Device, first 12 months	0.010	0-0.015	17,18,29,121,122
Utility Increment of CardioMEMS Device, after 12 months	0.004	0-0.010	17,18,29,121,122
HF (& Non-HF) Hospitalization	- 0.059	0-0.012	121

* Listed probabilities represent the event probabilities for patients with reduced ejection fraction.
† The baseline mortality probability was held constant for the trial duration. After that, there is an annual exponential increase in the mortality risk.
‡ The baseline probability of CHF hospitalization decreased from month 1 to month 17. After month 17, the probability is held constant.
§ Only differed from CardioMEMS with regards to baseline hospitalization probability and baseline mortality probability.
# Includes hospital costs and physician costs.

Entresto: For those treated with an ACE inhibitor or ARB, the probability of CHF hospitalizations, cardiovascular deaths, and ED visits were based on the total number of events in the enalapril arm over the trial duration (see Table 3).[38,42,43] To account for the effect of age, the probability of cardiovascular death was increased by 3.7% annually based on an estimate in the literature;[118,119] the baseline probability was calibrated so the modeled mortality matched the mortality seen in the trial.[118,119] The above probabilities were assumed to be the same in patients receiving ACE inhibitor therapy and ARB therapy. Angioedema requiring hospitalization and intolerance probabilities were derived from the event rates during the randomized period for the enalapril arm. Patients on ARB therapy were assumed to have no risk of angioedema or intolerance.

For the Entresto arm, the probabilities of CHF hospitalization, cardiovascular death, and ED visit not requiring hospitalization were based on the baseline probability of the ACE inhibitor arm and the relative risk with Entresto based on the PARADIGM-HF trial results.[38,42,43] Relative risks were calculated using the event rates in both arms excluding the events of patients with NYHA Class I heart failure. The probabilities of angioedema requiring hospitalization and intolerance were based on the rate of events in the Entresto arm in the PARADIGM-HF trial during the randomized period.

The probability of non-CHF hospitalizations and non-cardiovascular death in patients on Entresto therapy was the same as that used in the ACE inhibitor arm. In both cases, the event probability was calculated using the total events and follow-up time in both arms. The change in probability of non-cardiovascular death was based on life tables from the Centers for Disease Control and Prevention (CDC) excluding cardiovascular disease, which we calibrated to the non-cardiovascular mortality seen in the trial in both arms.[123]

Subgroup event rates for patients with NYHA Class II or Class III/IV were based on the number of events and follow-up time in each subgroup. The event distribution by NYHA class was available for cardiovascular deaths and first CHF hospitalizations. We assumed the distribution of total CHF hospitalizations and ED visits for heart failure not requiring hospitalization approximated that of first CHF hospitalizations. Subgroup-specific total follow-up time was estimated using the subgroup-specific numbers of patients, subgroup-specific numbers of cardiovascular deaths, total non-cardiovascular deaths, and literature-based estimates of the relative risk of non-cardiovascular death by NYHA class.[38,42-44] Subgroup-specific relative risks were estimated using calculated subgroup-specific event numbers and follow-up time.

Table 3. Select Entresto Model Inputs

Input Parameter	Point Estimate	Range	Source
Enalapril Arm			
Probability of Heart Failure Hospitalization	0.99%	0.87% - 1.11%	[38,42,43]
Baseline Probability of Cardiovascular Mortality*	0.64%	0.54%-0.74%	[38,43]
Probability of Angioedema with Enalapril	0.0009%	0-0.0065%	[38,43]
Entresto Arm			
Relative Risk of Heart Failure Hospitalization†	0.78	0.72-0.86	[38,42,43]
Relative Risk of Cardiovascular Death†	0.78	0.70-0.87	[38,43]
Probability of Angioedema with Entresto	0.0027%	0-0.0104%	[38,43]
Treatment Costs, Monthly			
Cost of Entresto	380	190-570	[124]
Cost of ACE Inhibitor	3	1-5	[124]
Cost of Angiotensin Receptor Blocker	7	3-10	[124]
Cost of Heart Failure Hospitalization	12,832	8,341-16,750	[120]
Utility Values			
Utility, Baseline	0.822	0.705-0.938	[125]
Utility Increment in Entresto Arm	0.009	0.002-0.016	[125]
HF (& Non-HF) Hospitalization	-0.071	0- -0.134	[121]

* The monthly baseline probability of cardiovascular mortality was increased by 3.7% per year to adjust for the lifetime horizon and the effect of aging. The baseline probability was adjusted so the model matched the mortality rate seen in the trial period.

† Probability in the Entresto arm was based on the probability in the enalapril arm and the relative risk of the event with Entresto therapy, as observed in the PARADIGM-HF trial.

Costs

The cost of CHF hospitalization was extracted from estimates in the literature using the Agency for Healthcare Research and Quality (AHRQ) National Inpatient Sample.[120] The costs of non-CHF hospitalization were based on an estimate of the baseline Medicare reimbursement of a pneumonia hospitalization, the most common non-CHF hospitalization in patients with heart failure.[37,69,126] The additional costs of mortality were taken from literature estimates of inpatient care during the last year of care prior to death, from which model-based estimates of hospitalization costs were subtracted to avoid double counting.[10,126,127] Finally, additional health care costs were taken from the literature and adjusted for age and NYHA class.[128] All costs were inflated to 2014 US dollars using the medical consumer price index (CPI).[129]

CardioMEMS HF System: The costs of the CardioMEMS device were estimated from the Medicare price ($17,750).[37] The procedural cost of implantation was estimated using reimbursement guides from St. Jude Medical along with Medicare reimbursement data.[10,11] The cost of routine monitoring of the device was based on the Medicare reimbursement of remote monitoring.[10,11] The cost of

device-related complications was estimated to be equal to the cost of a bleeding episode requiring hospitalization, the most common peri-procedural adverse event seen in the trial.[29,30]

Entresto: Costs of all three treatments were estimated using wholesale acquisition prices from *The Red Book*, with Entresto assigned a monthly cost of $380.[16] The range of prices tested in deterministic sensitivity analyses were derived from the minimum to maximum wholesale acquisition prices of a package of at least 90 pills for both ACE inhibitor and ARB therapy. For Entresto, it was set to +/-50% of the base case due to the current lack of variation in wholesale acquisition prices and the uncertainty of the cost for different health care payers. The cost of medication intolerance was set to the Medicare reimbursement for one primary care appointment.[10] The cost of angioedema requiring hospitalization was set to the Medicare reimbursement for an anaphylaxis hospitalization.[37,69]

Quality of Life/Utility

CardioMEMS HF System: We estimated baseline utility using the trials' estimates of quality of life.[18,29,96,130] We mapped the Minnesota Living with Heart Failure (MLHF) score into EQ-5D scores using a regression estimate developed from the CARE-HF trial.[122] We used the utility score at six months because the baseline score likely incorporates the short-term disutility of a recent hospitalization and the implantation procedure. We estimated the utility benefit of the CardioMEMS device as the difference-in-difference of patients with the device compared to those without it in the CHAMPION trial. We applied the difference in six-month MLHF scores for the first year. After one year, we applied the difference in 12-month MLHF scores. The 12-month utility measurements, not significantly different in the two arms, were limited by nearly half of the patients not having recorded responses.[18,29]

Entresto: The baseline quality of life was based on the average EQ-5D measurement during the course of the trial.[125] The incremental utility for receiving Entresto was based on the least squares mean of difference between the changes from baseline in the two arms.[125] Heart failure exacerbations requiring an ED visit but not hospitalization were assumed to incur two days of disutility. A disutility of one day was estimated for therapy intolerance, and a disutility of two days was estimated for angioedema requiring hospitalization.

For both CardioMEMS and Entresto, disutilities were applied for CHF hospitalization and non-CHF hospitalization of approximately three days in a monthly cycle, based on an estimate in the literature.[121]

Sensitivity Analyses

We performed one-way sensitivity analyses on all variables to determine which parameters most affected the cost-effectiveness of each intervention (CardioMEMS and Entresto). We also

performed two-way sensitivity analyses on correlated variables, including the baseline probability of hospitalization and cardiovascular mortality risks.

CardioMEMS HF System: We focused on areas of substantial uncertainty, including the assumptions regarding mortality reduction and the effect of the device on quality of life. We also performed two-way sensitivity analyses on the CardioMEMS device durability and efficacy. Sensitivity analyses that affected the cost per QALY substantially were repeated in the CHARM cohort.

Entresto: We performed two-way sensitivity analyses on the treatment-related risk reduction of mortality and CHF hospitalization. We also performed two-way sensitivity analyses on each of the baseline event probabilities (CHF hospitalization, cardiovascular mortality, ED visit) and the relative risk of that event with Entresto. Finally, we performed two-way sensitivity analyses on the cost of Entresto and each of the parameters that were highly sensitive in one-way sensitivity analyses.

Entresto Risk-Sharing Analysis

For Entresto treatment, we also conducted an analysis of risk-sharing models given the interest in alternative payment plans expressed by the manufacturer.[47] We assumed that such an agreement would involve the effect of the treatment on CHF hospitalization rates and cardiovascular deaths, and it would place part of the financial risk regarding drug efficacy on the manufacturer. We modeled a risk-sharing approach in which payers do not pay for the drug for six months after any CHF hospitalization that occurred following treatment initiation. Additionally, if the patient dies of cardiovascular disease, any payments made in the previous six months are refunded. In the risk-sharing model, drug manufacturers were assumed to receive the full WAC as reimbursement. In the "conventional" comparison model, we assumed manufacturers would give payers a 10% rebate on the WAC. We displayed the results as the distribution of costs per QALY gained under a conventional model versus a risk-sharing model in a probabilistic sensitivity analysis. In this analysis, we vary all input parameters across their respective distributions over 10,000 simulations.

CardioMEMS Cost-Effectiveness Model Results

Base Case Results

In the base case, the CardioMEMS arm experienced 2.19 CHF hospitalizations per patient compared to 3.18 in the routine care arm (see Table 4). The CardioMEMS arm had 5.72 life-years and 2.74 QALYs per patients compared to 5.28 life-years and 2.44 QALYs in the routine care arm. The total costs in the CardioMEMS arm were $174,037 per patient compared to $156,764 in the routine care arm. The CardioMEMS arm achieved its increased life expectancy of 0.44 years and 0.30 QALYs at an increased cost of $17,274. The resulting cost per QALY gained of the CardioMEMS intervention was $57,933.

Subgroup Results

Patients with reduced ejection fraction had shorter survival, fewer QALYs, and lower costs than patients with preserved ejection fraction (see Table 4). For patients with reduced ejection fraction, the CardioMEMS arm had an average of 0.84 fewer CHF hospitalizations, 0.39 additional life-years, 0.26 additional QALYs, and $17,791 in additional costs compared with the routine care arm. This equated to a cost per QALY gained of $68,150. For patients with preserved ejection fraction, the CardioMEMS arm had an average of 1.51 fewer CHF hospitalizations, 0.65 additional life-years, 0.43 additional QALYs, and $15,410 in additional costs compared with the routine care arm. This equated to a cost per QALY gained of $35,663.

Table 4. CardioMEMS Base Case Results and Subgroup Results

Strategy	HFH (# per patient)*	Survival (Years)	QALY	Cost (2014 USD)	$/Life Year	ICER ($/QALY)
CHAMPION Cohort						
Usual Care	3.18	5.28	2.44	156,764		---
CardioMEMS	2.19	5.72	2.74	174,037	38,877	57,933
Reduced Ejection Fraction Subgroup						
Usual Care	3.16	4.71	2.16	148,903		---
CardioMEMS	2.32	5.10	2.42	166,694	45,899	68,150
Preserved Ejection Fraction Subgroup						
Usual Care	3.23	7.32	3.46	185,125		---
CardioMEMS	1.72	7.97	3.89	200,535	23,745	35,663

* Undiscounted
ICER: Incremental Cost-effectiveness Ratio; HFH: Heart Failure Hospitalizations; QALY: Quality-adjusted Life Year

CHARM Cohort

As described earlier, the alternative patient population modeled for the CardioMEMS analyses was based on the cohort of patients in the CHARM study. Patients in the CardioMEMS treatment arm had an average of 0.59 fewer CHF hospitalizations, 0.25 additional life-years, 0.23 additional QALYs, and $19,353 in additional costs compared with those in the routine care arm, resulting in a cost per QALY gained of $88,884/QALY.

Sensitivity Analyses

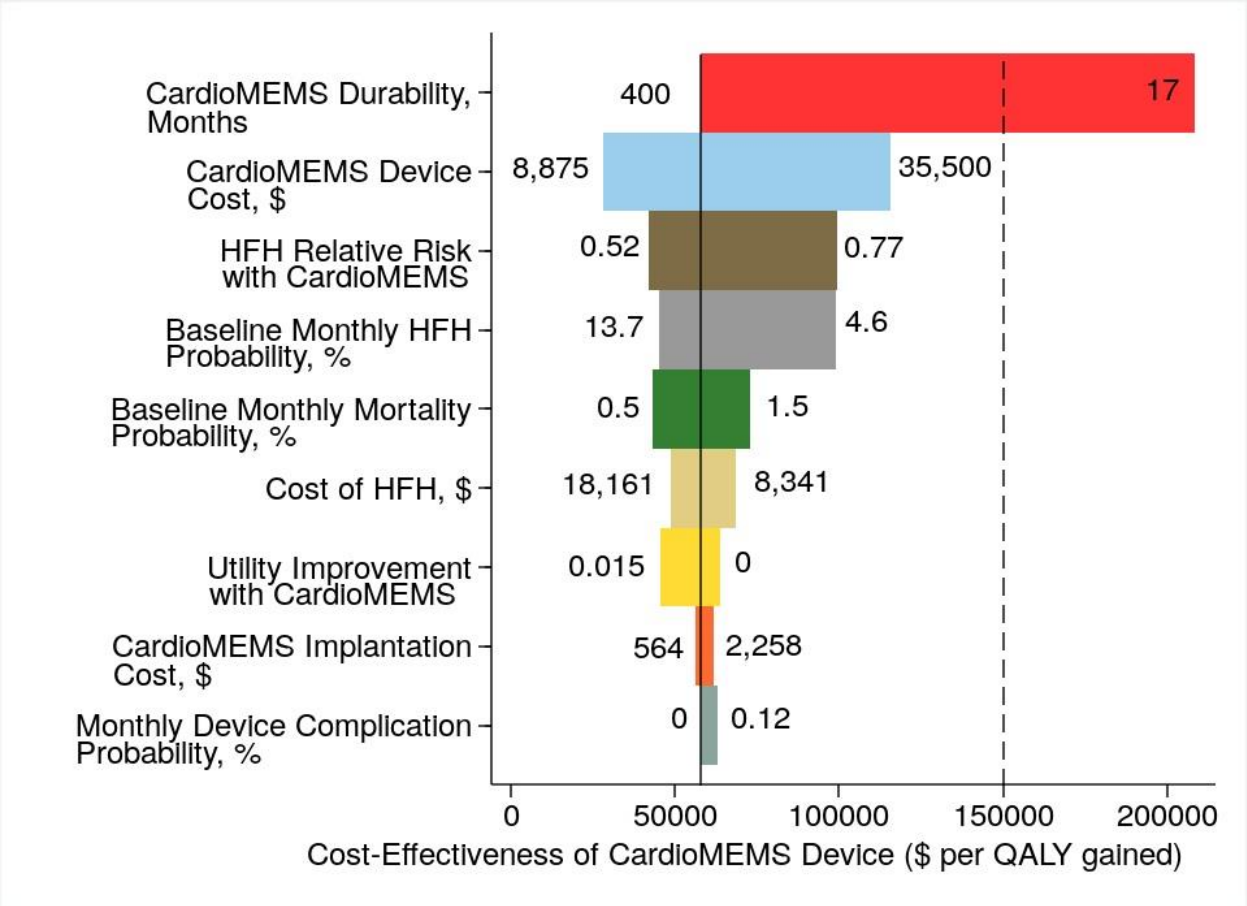
We performed sensitivity analyses on all input parameters (see Figure 6). The model was most sensitive to the durability of the CardioMEMS device. We assumed a lifelong benefit of the device in the base case although the CHAMPION trial had a mean patient follow-up of 17 months, and the

open access, non-randomized data submitted to the FDA had a follow-up duration of 25.5 months. If the device were no longer effective after 17 months, the cost per QALY gained would be $208,545. The cost per QALY decreased with a longer duration of effectiveness; the incremental cost-effectiveness ratio was $100,000/QALY when the duration of effect was reduced to 56 months, and was $150,000/QALY when the duration of effect was reduced further to 29 months duration.

The second most sensitive model parameter was the device cost. The CardioMEMS device costs $17,750 in the base case. It would cost less than $50,000 per QALY gained if the price were lower than $13,012 in those with reduced ejection fraction and lower than $23,945 in those with preserved ejection fraction (see Appendix Figure F1). It would cost more than $150,000 per QALY gained if the price were greater than $39,117 in the reduced ejection fraction subgroup or $67,157 in the preserved ejection fraction subgroup.

The device's cost per QALY gained was also affected by the effectiveness of the device in reducing CHF hospitalizations. In the CHAMPION trial, patients with the device were shown to have a 0.63 hazard rate (95% CI 0.52-0.77) of CHF hospitalizations over the entire duration of the trial. Decreasing the relative risk of CHF hospitalizations with the CardioMEMS device to 0.52 decreased the cost per QALY gained to $41,894. On the other hand, increasing it to 0.77 (decreasing the device efficacy) would increase the cost per QALY gained to $99,408.

Figure 6. CardioMEMS Tornado Diagram: Series of One-way Sensitivity Analyses



Note: This figure demonstrates the model parameters that most affect the cost per QALY of the CardioMEMS device. The solid black line represents the cost-effectiveness in the base case. Only the analysis of device durability crosses the $150,000 threshold (dashed black line).

The effect of the use of the CardioMEMS device on mortality is highly uncertain; the trial showed a trend towards overall mortality benefit that was not statistically significant (HR 0.80 [95% CI 0.55-1.15]). We assumed heart failure exacerbations requiring hospitalization had an associated inpatient mortality risk and a post-hospitalization increase in mortality; we modeled that avoidance of these exacerbations would also obviate this increased mortality risk. In the base case, our model demonstrated a 10.8% relative reduction in mortality risk with the CardioMEMS device compared with the routine care arm over the trial duration. If we assumed a 20% relative reduction in monthly mortality, based on the point estimate of the trial, the CardioMEMS device would cost $47,748 per QALY gained. However, if we assumed that prevented exacerbations were milder, with half of the inpatient mortality risk of a typical heart failure exacerbation and no increase in post-hospitalization mortality, the device would cost $86,087 per QALY gained. Finally, in the CHAMPION cohort, if the CardioMEMS device had no effect on mortality, the device cost increased to $114,825 per QALY

gained. In the CHARM cohort, composed of patients with lower baseline hospitalization and mortality risk, the cost per QALY gained increased to $226,122 with this assumption.

The baseline morbidity of the patient population has a smaller effect on the cost-effectiveness. The cost decreases to $45,129 per QALY gained with an increase in the baseline monthly CHF hospitalization probability (probability in the first month) to 13.69%; it increases to $99,253 with a decrease in the baseline monthly CHF hospitalization probability to 4.56%. If the baseline mortality probability is decreased to 0.66%, the cost per QALY gained decreases to $43,293, while if the baseline monthly mortality probability is increased to 1.31%, the cost per QALY gained increases to $72,740. The composite effect of the device in a healthier cohort with lower hospitalization and mortality probabilities and higher quality of life can be seen with the CHARM cohort analysis.

The device's cost-effectiveness was not substantially affected by variation in the cost of device implantation, the monthly cost of device management, or the cost of CHF hospitalization. It was also not sensitive to the range of probabilities tested for sensor failure or device-related complication. The disutility of CHF hospitalizations or the incremental benefit of the device on quality of life also did not change the cost per QALY substantially.

Threshold Analyses

As shown in Table 5, we also evaluated the drug costs at which CardioMEMS would be considered cost-effective under conventional willingness-to-pay thresholds of $50,000/QALY, $100,000/QALY, and $150,000/QALY. The Medicare price of CardioMEMS of $17,750 is relatively close to the price of $15,400 at which the cost/QALY = $50,000 and far lower than the $30,293 price that the device could have if a willingness-to-pay threshold of $100,000/QALY is assumed.

Table 5. Threshold Analyses: Device Cost at which CardioMEMS Would Be Cost-Effective under Varying Willingness-to-Pay Thresholds

	Willingness-to-Pay Threshold		
	$50,000/QALY	$100,000/QALY	$150,000/QALY
ALL SUBPOPULATIONS	$15,400	$30,293	$45,202

Entresto Cost-Effectiveness Model: Results

Base Case Results

Our model predicted 6.78 years of survival in the ACE inhibitor arm with 0.97 undiscounted CHF hospitalizations per patient (see Table 6). Corresponding figures in the Entresto arm were 7.41 years of survival and 0.90 CHF hospitalizations. The ACE inhibitor arm had averages of 5.56 QALYs and total costs of $123,578. The Entresto arm had an additional 0.57 QALYs and an additional $29,138 in costs. The resulting cost per QALY gained with Entresto therapy was $50,915.

In patients with NYHA Class II heart failure, Entresto therapy was associated with an increase of 0.64 additional QALYs and $31,576 in incremental costs, with a cost per QALY gained of $48,802. For patients with NYHA Class III/IV heart failure, Entresto therapy was associated with 0.44 more QALYs and $28,858 in costs, with a cost per QALY gained of $64,957.

Table 6. Entresto Base Case Results and Subgroup Results

Strategy	HFH (# per patient)*	Survival (Years)	QALY	Cost (2014 USD)	$/Life Year	ICER ($/QALY)
All Patients						
ACE inhibitor	0.97	6.78	5.56	123,578		
Entresto	0.90	7.41	6.13	152,716	46,251	50,915
NYHA Class II						
ACE inhibitor	1.16	8.02	6.78	132,360		
Entresto	1.01	8.72	7.42	163,936	45,109	48,802
NYHA Class III/IV						
ACE inhibitor	0.96	6.28	4.72	126,319		
Entresto	1.07	6.80	5.16	155,177	55,496	64,957

* Undiscounted
ICER: Incremental Cost-effectiveness Ratio; HFH: Heart Failure Hospitalizations; QALY: Quality-adjusted Life Year

Sensitivity Analyses

We performed one-way sensitivity results on all input parameters (see Figure 7). The model was most sensitive to the duration of effectiveness of the treatment. If the treatment were only effective for the mean duration of the trial (26 months), the cost per QALY gained would increase to $135,815. The cost per QALY gained was less than $100,000 if the treatment was effective for at least 40 months.

The cost of Entresto also affected its cost-effectiveness. If the monthly cost of Entresto were increased by 50% to $570, the cost would increase to $73,735 per QALY gained. If the cost were decreased by 50% to $190, the cost per QALY gained would decrease to $28,095. The monthly cost

of Entresto would have to be greater than $790 per month for the cost-effectiveness ratio to exceed $100,000.

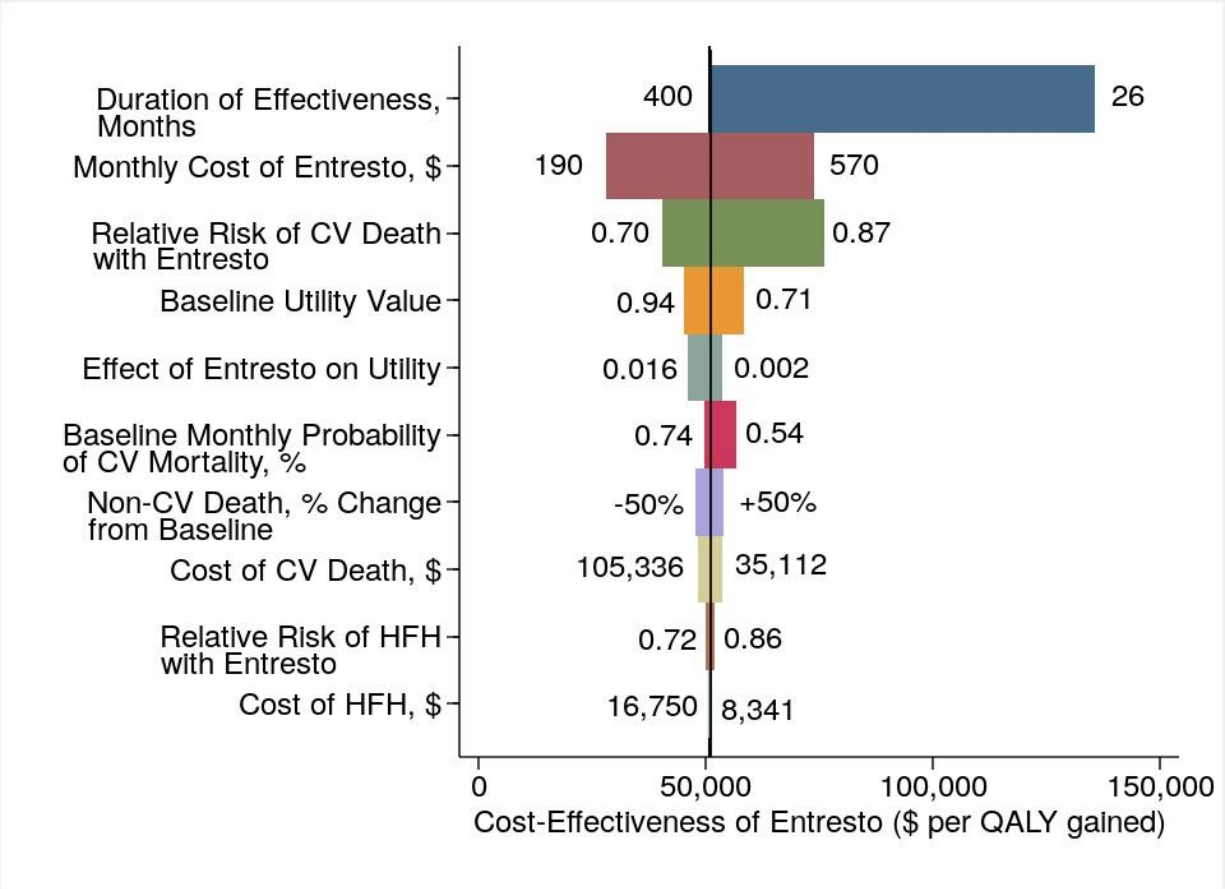
We estimated a relative risk of cardiovascular mortality of 0.78 in the base case with a 95% confidence interval of 0.70-0.87. If the effectiveness in reducing cardiovascular death was increased to a relative risk of 0.87 (less effective than the base case), the incremental cost-effectiveness ratio of Entresto would increase to $76,129 per QALY gained. If the relative risk were decreased to 0.70 (more effective than the base case), the incremental cost-effectiveness ratio would decrease to $40,493 per QALY gained. Changes to other measures of treatment effectiveness, including the relative risk of CHF hospitalization, the relative risk of ED visits, and the incremental utility with Entresto do not change the cost per QALY substantially.

The baseline quality of life estimate also affected the cost per QALY gained. In our base case, we used EQ-5D estimates of utility from the trial, with an average utility score of 0.822 and a 95% confidence interval of 0.705-0.939. If we assumed a utility of 0.705, the cost per QALY increased to $58,467. With an average utility of 0.939, the cost per QALY decreased to $45,108.

The baseline probabilities of mortality and hospitalization were derived from the enalapril arm of the PARADIGM-HF trial. Decreases in the probability of cardiovascular mortality or increases in non-cardiovascular mortality led to small increases in the cost per QALY gained with Entresto. If the monthly probability of cardiovascular mortality decreased from 0.64% to 0.54%, the cost would increase to $55,523 per QALY gained.

The cost per QALY of the treatment was not substantially affected by changes to the probability of intolerance or angioedema. It was also not sensitive to changes in the estimates of costs or disutilities of adverse events. Finally, the range of costs tested for ACE inhibitor and ARB therapy did not affect the cost-effectiveness.

Figure 7. Entresto Tornado Diagram: Series of One-way Sensitivity Analyses



Note: This figure represents a series of one-way sensitivity analyses for the parameters that have the largest influence on the cost per QALY gained with Entresto therapy. The vertical black line represents the cost-effectiveness in the base case analysis. None of the analyses lead to a cost per QALY gained greater than $150,000.

Threshold Analyses

As shown in Table 7, we also evaluated the annual drug costs at which Entresto would be considered cost-effective under conventional willingness-to-pay thresholds of $50,000/QALY, $100,000/QALY, and $150,000/QALY. The price to achieve a $50,000/QALY threshold is very similar to the current list price ($4,464 vs. $4,560 respectively). This price could more than double and still remain under a cost-effectiveness threshold of $100,000/QALY.

Table 7. Threshold Analyses: Annual Drug Cost at which Entresto Would Be Cost-Effective under varying Willingness-to-Pay Thresholds

	Willingness-to-Pay Threshold		
	$50,000/QALY	$100,000/QALY	$150,000/QALY
ALL SUBPOPULATIONS	$4,464/year	$9,480/year	$14,472/year

Risk-Sharing Analysis

In our risk-sharing model, in which the payer did not pay for medication for the six months following CHF hospitalization and was refunded any medication payments from the previous six months in the event of a cardiovascular death, this approach translated into an effective 8.6% discount on the drug price (i.e., $4,168 annually vs. $4,560), and a cost per QALY gained of $47,000. See Appendix Figure F3 for a full presentation of the probabilistic sensitivity analysis that informed these calculations.

6.3 Potential Budget Impact

We also used the cost-effectiveness model to estimate the potential total budgetary impact of CardioMEMS and of Entresto with different uptake assumptions. We then combined consideration of the price range between cost-effectiveness thresholds of $100,000 to $150,000 per QALY with potential budget impact to calculate value-based price benchmarks.

Budget Impact Model: Methods

We used the same models employed for the cost-effectiveness analyses to estimate total budgetary impact. Budgetary impact was defined as the total incremental cost of the therapy for the treated population, calculated as incremental health care costs (including drug or device costs) minus any offsets in these costs from averted CHF-related hospitalizations or cardiovascular deaths. All costs were undiscounted and estimated over one- and five-year time horizons. The five-year timeframe was of primary interest, given the potential for cost offsets to accrue from averted hospitalizations and deaths.

Of note, while the cost-effectiveness analyses do present data by patient subgroup (i.e., NYHA Class II vs. III-IV for Entresto and reduced vs. preserved ejection fraction for CardioMEMS), we chose to focus budget impact analysis on the entire candidate population for treatment based on product labeling (i.e., Class II-IV with reduced ejection fraction for Entresto, Class III with CHF-related hospitalization in prior 12 months for CardioMEMS). In addition, findings from our cost-effectiveness analyses suggested that cost-effectiveness ratios did not vary widely (i.e., approximately $40,000-$70,000 per QALY gained) across the subgroups analyzed.

To estimate the size of the potential candidate population for Entresto, we used the projected prevalence for 2015 in the US population (6.2 million)[131] and adjusted it to reflect Class II-IV only. The prevalence of Class I disease was assumed to be 25.1%, based on data from a large observational study of CHF in an integrated health care system.[132] Then, we used an estimate of the proportion of patients with symptomatic CHF and reduced versus preserved ejection fraction

from a recently-published population-based study (48% vs. 52% respectively) to further restrict the patient pool to reduced ejection fraction only.[133] This resulted in a candidate population size of approximately 2.2 million individuals.

For CardioMEMS, the starting point for a population size estimate was the number of hospitalizations annually for CHF, which has been relatively steady at approximately 1 million over the last decade.[3] Data supplied by the manufacturer indicates that approximately 45% of these hospitalizations remain NYHA Class III following discharge. However, CHF patients are often hospitalized more than once in a given year. Data from a large (N=~60,000) CHF cohort followed longitudinally in the Kaiser Permanente system indicates a rate of 1.57 hospitalizations per patient among those hospitalized.[134] The candidate population was therefore estimated to total 286,990 patients each year (i.e., 450,000 ÷ 1.57), or 1.4 million over five years.

ICER's methods for estimating budget impact and calculating value-based benchmark prices are described in detail elsewhere. Briefly, our calculations assume that utilization of new drugs/devices occurs without payer, provider group, or pharmacy benefit management controls in place in order to provide an estimate of "unmanaged" drug/device uptake by five years after launch.

We examine six characteristics of the drug/device and marketplace to estimate unmanaged drug/device uptake. These characteristics are listed below:

- Magnitude of improvement in clinical safety and/or effectiveness
- Patient-level burden of illness
- Patient preference (ease of administration)
- Proportion of eligible patients currently being treated
- Primary care versus specialty clinician prescribing/use
- Presence or emergence of competing treatments of equal or superior effectiveness

Based on our assessment of these criteria, we assign a new drug or device to one of four categories of unmanaged drug uptake patterns: 1) very high (75% uptake by year 5); 2) high (50% uptake by year 5); 3) intermediate (25% uptake by year 5); and 4) low (10% uptake by year 5). In this analysis, we assumed a "very high" uptake pattern for Entresto given that it is the first agent in well over a decade to demonstrate both mortality and hospitalization benefit relative to an active comparator that represents the current standard of care. In contrast, we assumed an "intermediate" uptake pattern for CardioMEMS given evidence of significant clinician interest in the device and a more flexible and user-friendly monitoring approach compared to earlier-generation devices, both of which are moderated by potential patient reluctance to undergo the implantation procedure.

Resulting population sizes after five years, adjusted for estimated uptake, were approximately 1.7 million and 360,000 for Entresto and CardioMEMS, respectively. For consistency, uptake was assumed to occur in equal proportions across the five-year timeframe, and we adjusted both

drug/device costs and cost offsets accordingly. For example, in populations estimated to have a 25% five-year uptake, 5% of patients would be assumed to initiate therapy each year. Patients initiating therapy in year one would accrue all drug costs and cost offsets over the full five years, but those initiating in other years would only accrue a proportional amount of five-year costs.

Using this approach to estimate potential budget impact, we then compared our estimates to a budget impact threshold that represents a potential trigger for policy mechanisms to improve affordability through changes to pricing, payment, or patient eligibility. As described in ICER's methods presentation (http://www.icer-review.org/wp-content/uploads/2014/01/Slides-on-value-framework-for-national-webinar1.pdf), this threshold is based on an underlying assumption that health care costs should not grow much faster than growth in the overall national economy. From this foundational assumption, our potential budget impact threshold is derived using an estimate of growth in US gross domestic product (GDP) +1%, the average number of new drug/device approvals by the FDA each year, and the contribution of spending on a) retail and facility-based drugs, and b) devices to total health care spending. Calculations are performed as shown in Table 8.

For 2015-16, therefore, the five-year annualized potential budget impact threshold that should trigger policy actions to manage affordability is calculated to total approximately $904 million per year for new drugs. The corresponding amount for new devices is $603 million.

Table 8. Calculation of Potential Budget Impact Threshold

Item	Parameter	Estimate (Drugs)	Estimate (Devices)	Source
1	Growth in US GDP, 2015-2016 (est.) +1%	3.75%	3.75%	World Bank, 2015
2	Total health care spending ($)	$3.08 trillion	$3.08 trillion	CMS NHE, 2014
3	Contribution of drug/device spending to total health care spending (%)	13.3%	6.0%	CMS NHE, Altarum Institute, 2014
4	Contribution of drug/device spending to total health care spending ($) (Row 2 x Row 3)	$410 billion	$185 billion	Calculation
5	Annual threshold for net health care cost growth for ALL new drugs/devices (Row 1 x Row 4)	$15.4 billion	$6.9 billion	Calculation
6	Average annual number of new molecular entity or device approvals, 2013-2014	34	23	FDA, 2014
7	Annual threshold for average cost growth per individual new molecular entity or device (Row 5 ÷ Row 6)	$452 million	$301 million	Calculation
8	Annual threshold for estimated potential budget impact for each individual new molecular entity or device (doubling of Row 7)	$904 million	$603 million	Calculation

Potential Budget Impact and the Value-based Price Benchmark

We combine consideration of the potential budget impact with the threshold prices presented in Section 6.2 above (i.e., prices based on incremental costs per outcomes achieved) to calculate a value-based price benchmark for each new drug or device. This price benchmark begins with the price range to achieve cost-effectiveness ratios of $100,000-$150,000 per QALY for the population being considered, but it has an upper limit determined by the price at which the new drug or device would exceed the potential budget impact threshold (i.e., $904 million and $603 million for drugs and devices, respectively). If the potential budget impact does not exceed these thresholds, then the value-based price benchmark remains the full price range determined from the analysis of incremental costs per outcomes achieved.

Budget Impact Model: Results

Tables 9a and 9b present the budgetary impact of one year and five years of CardioMEMS and Entresto in the candidate populations, assuming the uptake patterns previously described.

Detailed calculations for adjustment of drug costs and cost offsets are provided in Appendix Table F1. Results are presented for both one-year and five-year time horizons.

CardioMEMS

Results for CardioMEMS indicate a higher budgetary impact per patient (given the device acquisition and implantation costs); weighted across the five-year timeframe, budgetary impact totals nearly $14,000 (see Table 9a). Total budgetary impact at one year is similar to the annual average over five years; this is because nearly all CardioMEMS costs are incurred at the time of implantation, and ongoing monitoring and other costs are minimal ($27 per month). Because equal proportions of patients are assumed to receive the device each year, budget impact varies only according to these ongoing costs as well as the potential for cost offset (i.e., patients who receive the device earlier in the timeframe have more potential for offset). On an annualized basis, cost-offset (equally weighted by timing of device implant over the five-year time horizon) is estimated to be $2,265. Total budgetary impact of CardioMEMS is estimated to be approximately $5 billion, or $1 billion annually under our assumed pattern of uptake (~360,000 patients receiving the device by year 5). This is above the device budgetary impact threshold of $603 million per year. In order to not exceed this threshold, approximately 16% of the 287,000 Class III patients hospitalized each year could receive CardioMEMS at the current Medicare device price of $17,750.

Entresto

Results from the budget impact model showed that, with the uptake pattern assumptions mentioned above, 334,000 individuals would receive Entresto in the first year (see Table 9b). After one year of treatment, cost offsets due to reductions in the CHF hospitalization were $1,043 per

patient, or approximately 25% of the drug cost. Including this cost offset, one-year budget impact is estimated to be approximately $1.2 billion.

Over the entire five-year time horizon, we estimate that "unmanaged" uptake would lead to approximately 1.7 million persons taking Entresto for one or more years. Drug cost and cost-offset adjustments for the full five-year time horizon are described in detail in Appendix Table F1; across this timeframe, the weighted budgetary impact (i.e., adjusted for differing periods of drug utilization and associated cost-offsets) is slightly less than $9,000 per patient. Total budgetary impact over five years is approximately $15 billion, or approximately $3 billion in net cost growth per year, despite cost offsets that would average $1,462 per year of treatment. This annualized potential budget impact is well above the budget impact threshold of $904 million for a new drug. In order to not exceed this budget impact threshold, approximately 9% of eligible patients could be treated each year at the list price of $4,560 annually.

Table 9a. Total Budget Impact (BI) of CardioMEMS Based on Assumed Patterns of Uptake

		Analytic Horizon = 1 Year			Analytic Horizon = 5 Years		
	Eligible Population (thousands)	Number Treated (thousands)	Weighted BI per Patient ($)*	Total BI (billions)	Number Treated (thousands)	Weighted BI per Patient ($)*	Total BI per year (billions)
CardioMEMS	1,435	72	$15,760	$1.1B	359	$13,988	$1.0B

*Weighted budget impact calculated by subtracting cost offsets from device costs for one-year horizon. For five-year horizon, device costs and cost offsets apportioned assuming 20% of patients in uptake target undergo device implantation each year. Those initiating in year 1 receive full device costs and cost offsets, those initiating in year 2 receive full device costs and 80% of cost offsets, etc.

Table 9b. Total Budget Impact (BI) of Entresto Based on Assumed Patterns of Uptake

		Analytic Horizon = 1 Year			Analytic Horizon = 5 Years		
	Eligible Population (thousands)	Number Treated (thousands)	Weighted BI per Patient ($)*	Total BI (billions)	Number Treated (thousands)	Weighted BI per Patient ($)*	Total BI per year (billions)
Entresto	2,226	334	$3,481	$1.2B	1,669	$8,856	$3.0B

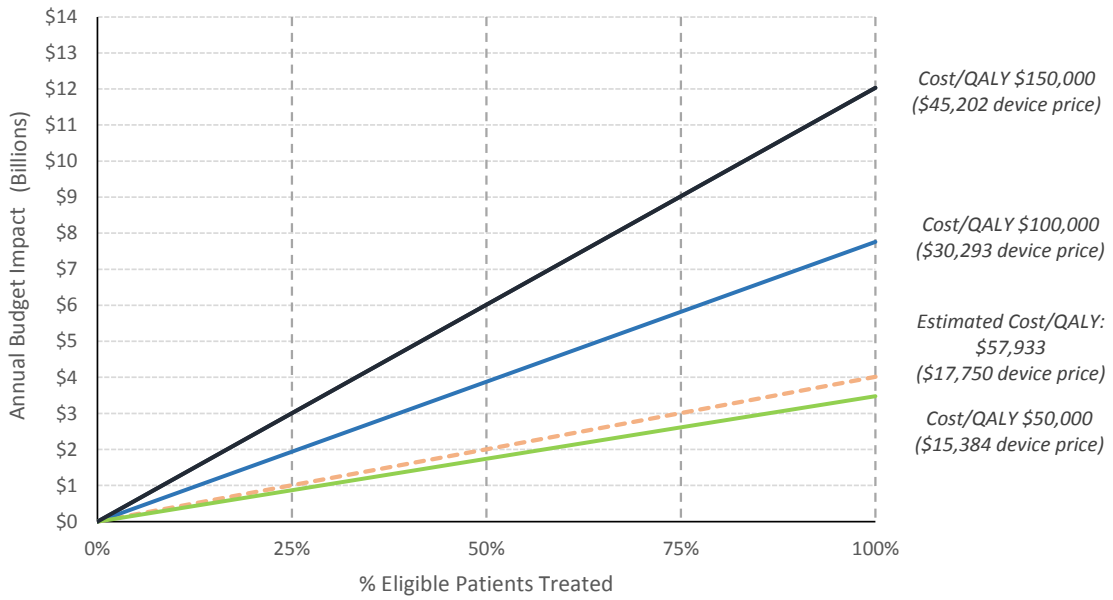
*Weighted budget impact calculated by subtracting cost offsets from drug costs for one-year horizon. For five-year horizon, drug costs and cost offsets apportioned assuming 20% of patients in uptake target initiate therapy each year. Those initiating in year 1 receive full drug costs and cost offsets, those initiating in year 2 receive 80% of drug costs and cost offsets, etc.

Figures 8 and 9 provide findings of multiple analyses that give perspective on the relationship between varying possible drug and device prices, cost-effectiveness ratios, uptake patterns, and potential budget impact. The vertical axis shows the annualized budget impact, and the horizontal axis represents the percentage of eligible patients treated over a five-year period. The colored lines demonstrate how quickly the annual budget impact increases with increasing percentages of

patients treated at four different prices: those at which the cost/QALY = $50,000, $100,000, and $150,000; and the Medicare and list prices used in this analysis (i.e., $17,750 for the CardioMEMS device and $4,560 annually for Entresto, respectively).

The CardioMEMS price to achieve a cost/QALY of $50,000 is relatively close to that for the list-price analysis ($15,400 vs. $17,750 respectively), and so the trend lines in Figure 8 track fairly closely. However, annualized budgetary impact still exceeds the $603 million threshold for devices at levels of uptake exceeding 15%. Raising the price to achieve higher cost/QALY thresholds would dramatically affect budgetary impact. If device pricing is essentially tripled (to approximately $45,000), annual budget impact would exceed $12 billion if all candidate patients received the device.

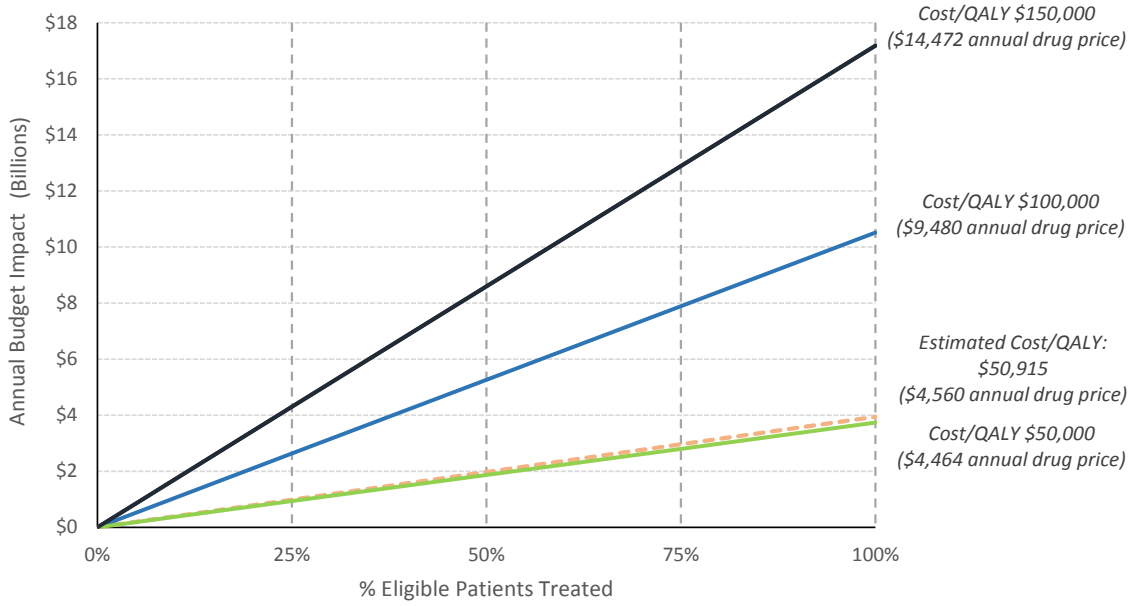
Figure 8. ICER Combined Cost-Effectiveness and Potential Budget Impact Graph for CardioMEMS. Colored lines represent the annualized budget impact of different uptake patterns (eligible patients treated) at the actual Medicare price of the device (dashed line), and at device prices needed to achieve common incremental cost-effectiveness ratios.



As can be seen in Figure 9, the price of Entresto that would achieve a cost/QALY of $50,000 is also very similar to the list price, and so the trend lines also track very closely in this analysis. For both of these scenarios, however, if only 50% of all eligible patients are ultimately treated over a five-year time period (rather than the 75% we assumed), the annualized budget impact is nearly $2 billion per year. Even if only 25% of eligible patients were treated, the annualized budget impact still slightly exceeds the $904 million threshold ($932-$985 million on an annualized basis). Not surprisingly, higher prices that would achieve cost/QALY figures of $100,000 and $150,000 would

result in exponential increases in budgetary impact, topping out at a $17 billion annual budget impact for a drug price ($14,472 per year) that would achieve a cost/QALY of $150,000 if all patients received Entresto.

Figure 9. ICER Combined Cost-effectiveness and Potential Budget Impact Graph for Entresto. Note: Colored lines represent the annualized budget impact of different uptake patterns (eligible patients treated) at the actual list price of the drug (dashed line), and at drug prices needed to achieve common incremental cost-effectiveness ratios.



Draft Value-based Benchmark Prices

Our draft value-based benchmark prices for CardioMEMS and Entresto are provided in Table 10. As noted in the ICER methods document, the draft value-based benchmark price for a drug or device is defined as the price range that would achieve cost-effectiveness ratios between $100,000 and $150,000 per QALY gained, without exceeding the $904 or $603 million budgetary impact thresholds. Detailed calculations for the value-based price benchmarks presented below are available in Appendix Table F2.

As shown in Table 10, the price range based on cost-effectiveness thresholds is much higher than the Medicare and list prices for CardioMEMS and Entresto, respectively, as our analyses indicated a cost/QALY very close to $50,000 for each of these interventions. However, as noted previously, the budgetary impact of both interventions exceeds our stated thresholds when annualized over a five-

year time horizon. The device price for CardioMEMS that would not exceed the $603 million annual device benchmark is $10,665, and the price of Entresto that could be charged and not exceed the $904 million annual benchmark is $4,168 per year. Note that the Entresto value-based price benchmark is coincidentally the same as the price arrived at in the risk-sharing analysis; it should be noted, however, that different assumptions and calculations were used in the risk-sharing and value-based price benchmark analyses.

Therefore, the draft ICER value-based price benchmark for CardioMEMS, with all the assumptions mentioned previously regarding five-year uptake patterns and cost offsets, is $10,665, which represents a 40% discount from the full Medicare price ($17,750). The corresponding value-based price benchmark for Entresto is $4,168. This figure represents a 9% discount from the full wholesale acquisition cost assumed in our analysis ($4,560 annually).

Table 10. Draft Value-based Price Benchmarks for CardioMEMS Device and Entresto Therapy

Population	Price to Achieve $100K/QALY	Price to Achieve $150K/QALY	Max Price at Potential Budget Impact Threshold	Draft Value-Based Price Benchmark
CardioMEMS (n=358,738)	$30,293	$45,202	$10,665	$10,665
Entresto (n=1,669,235)	$9,480/year	$14,472/year	$4,168/year	$4,168/year

6.4 Summary and Comment

The findings of our analysis indicate that both CardioMEMS and Entresto have the potential to provide clinical benefit over standard approaches to CHF management (i.e., use of ACE inhibitors for the former and usual monitoring approaches for the latter). The primary estimate for the cost-effectiveness of CardioMEMS was ~$58,000 per QALY gained, based on reductions in the rate of CHF hospitalization relative to usual care, at the current device price of $17,750. Results for these analyses were at or below typical cost-effectiveness thresholds in a variety of secondary and sensitivity analyses, including stratified by preserved vs. reduced ejection fraction, use of baseline hospitalization and mortality rates from a more broadly-representative CHF trial population, and the duration of benefit seen with the device.

Similarly, for Entresto, a cost-effectiveness ratio of ~$51,000 per QALY gained versus ACE inhibitor treatment was generated based on reductions in both cardiovascular mortality and CHF hospitalization, at its current wholesale price of $4,560 annually. Ratios remained at or below generally-accepted thresholds for cost-effectiveness even when stratified by CHF severity or in sensitivity analyses testing a variety of ranges in parameter estimates.

However, when intervention costs and potential cost savings are evaluated on a population basis, and likely patterns of intervention uptake are considered, the annual costs of both CardioMEMS and Entresto exceed ICER's documented budget impact thresholds for devices ($603 million) and drugs ($904 million). In order to not exceed these thresholds, current Medicare and list prices would need to be discounted by approximately 40% and 9% for the device and the drug, respectively, to approximately $10,700 for the CardioMEMS device and $4,200 annually for Entresto.

We note a number of limitations to our analysis. First, while both CardioMEMS and Entresto were evaluated in large Phase III multi-center clinical trials, data are currently available from a single trial for each. Follow-on studies are ongoing for both that should shed additional light on their likely performance (e.g., comparisons of post-market to pre-market effectiveness for CardioMEMS, use of Entresto in patients with preserved ejection fraction). Second, there may be treatment benefits that are not captured in our model, such as use of the CardioMEMS device for identification of patients who need to initiate advanced therapy. Third, analysis of the efficacy of both device and drug in alternative cohorts of patients is dependent on the assumption that efficacy would not differ from that observed in the CHAMPION and PARADIGM-HF trials; while these assumptions were tested in sensitivity analyses, further clinical investigation will be required to evaluate performance in broadly defined populations.

Fourth, aspects of both the CHAMPION and PARADIGM-HF trials have been called into question, such as CardioMEMS' differential performance by gender and Entresto's clinical benefit versus valsartan alone. However, because no conclusive data are published or presented in regulatory discussions regarding the likely effect of these controversies on overall estimates of treatment effect, we needed to make assumptions about how these effects might vary in sensitivity analyses. We await further clinical data to understand the likely impact of these controversies. Finally, our assumed levels of uptake of Entresto and CardioMEMS in the marketplace by five years were based on reasoned assumptions, but actual uptake may vary from these estimates. We also present potential budget impact across a range of uptake possibilities in sensitivity analyses.

7. Summary of the Votes and Considerations for Policy

7.1 About the CTAF Process

During CTAF public meetings, the CTAF Panel deliberates and votes on key questions related to the systematic review of the clinical evidence, an economic analysis of the applications of the medical technologies or treatments under examination, and the supplementary information presented. Panel members typically serve for two or more years and are intentionally selected to represent a range of expertise and diverse perspectives. To maintain the objectivity of the CTAF Panel and ground the conversation in the interpretation of the published evidence, they are not pre-selected based on the topic being addressed. Acknowledging that any judgment of evidence is strengthened by real-life clinical and patient perspectives, subject matter experts are recruited for each meeting topic and provide input to CTAF Panel members before the meeting to help clarify their understanding of the different interventions being analyzed in the evidence review. The same clinical experts serve as a resource to the CTAF Panel during their deliberation, and they help form recommendations with the CTAF Panel on ways the evidence can be applied to policy and practice.

At each meeting, after the CTAF Panel votes, a policy roundtable discussion is held with the CTAF Panel, clinical experts, and representatives from provider groups, payers, and patient groups. This is intended to bring stakeholders into the discussion on how best to apply the evidence to guide patient education, clinical practice, and coverage and public policies. Participants on policy roundtables are selected for their expertise on the specific meeting topic, are different for each meeting, and do not vote on any questions.

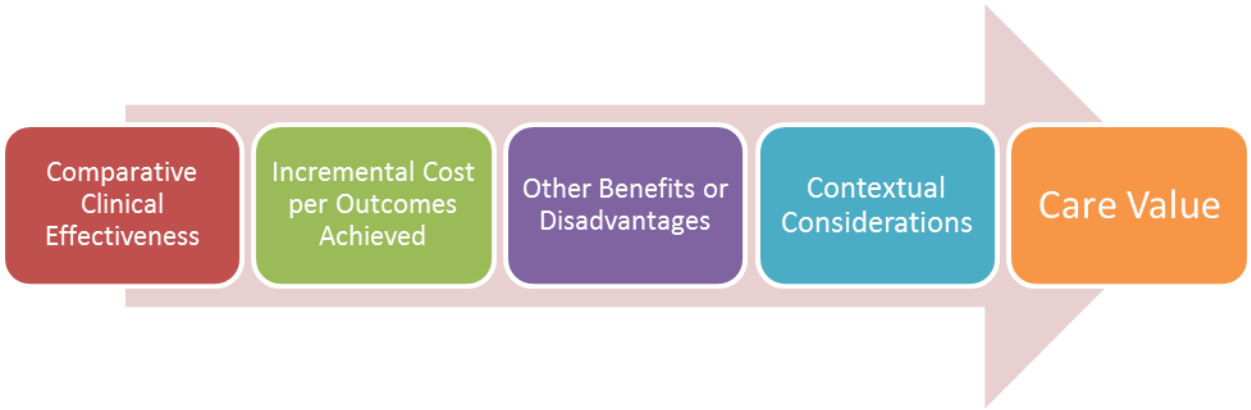
At the October 29, 2015 meeting, the CTAF Panel discussed issues regarding the application of the available evidence to help patients, providers, and payers address the important questions related to the management of congestive heart failure. Following the evidence presentation and public comments, the CTAF Panel voted on key questions concerning the comparative clinical effectiveness and comparative value of Entresto and, separately, of CardioMEMS. These questions are developed by the ICER research team for each assessment, with input from the CTAF Advisory Board to ensure that the questions are framed to address the issues that are most important in applying the evidence to support clinical practice and medical policy decisions. The voting results are presented below, along with comments reflecting considerations mentioned by CTAF Panel members during the voting process.

In its deliberations and voting related to value, the CTAF Panel made use of a value assessment framework with four different components of *care value*, a concept which represents the long-term

perspective, at the individual patient level, on patient benefits and the incremental costs to achieve those benefits. The four components of care value are comparative clinical effectiveness, incremental cost per outcomes achieved, additional benefits or disadvantages, and contextual considerations regarding the illness or therapy.

Once they made an overall assessment of care value as low, intermediate, or high considering these four components, the CTAF Panel then explicitly considered the affordability of Entresto and of CardioMEMS in assessing *provisional* health system value as low, intermediate, or high (see Figures 10 and 11, as well as the detailed explanation that follows).

Figure 10. Care Value Framework



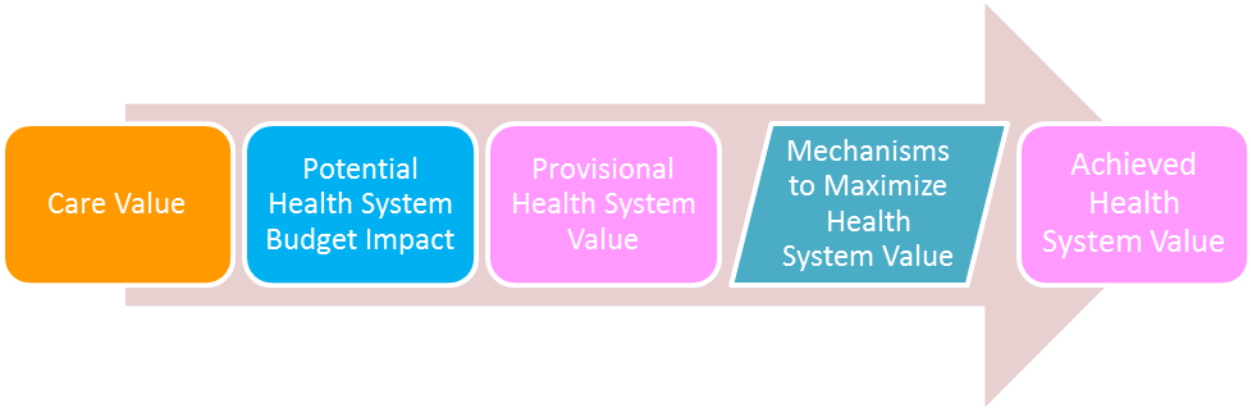
There are four elements to consider when deliberating on care value:

1. ***Comparative clinical effectiveness*** is a judgment of the overall difference in clinical outcomes between two interventions (or between an intervention and placebo), tempered by the level of certainty possible given the strengths and weaknesses of the body of evidence. CTAF uses the ICER Evidence Rating Matrix as its conceptual framework for considering comparative clinical effectiveness.
2. ***Incremental cost per outcomes achieved*** is the average per-patient incremental cost of one intervention compared to another to achieve a desired "health gain," such as an additional stroke prevented, case of cancer diagnosed, or gain of a year of life. Alternative interventions are compared in terms of cost per unit of effectiveness, and the resulting comparison is presented as a ratio: a "cost per outcome achieved." Relative certainty in the cost and outcome estimates continues to be a consideration. As a measure of incremental costs per outcomes achieved, ICER follows common academic and World Health Organization (WHO) standards by using cost per quality-adjusted life years (QALYs) and adopting thresholds at $100,000 per QALY and $150,000 per QALY as guides to reasonable ratios of incremental costs per outcomes achieved.

3. ***Other benefits or disadvantages*** refers to any significant benefits or disadvantages offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. Examples of additional benefits include mechanisms of treatment delivery that require many fewer visits to the clinician's office, treatments that reduce disparities across various patient groups, and new potential mechanisms of action for treating clinical conditions that have demonstrated low rates of response to currently available therapies. Additional disadvantages could include increased burden of treatment on patients or their caregivers. For each intervention evaluated, it will be open to discussion whether additional benefits or disadvantages such as these are important enough to factor into the overall judgment of care value. There is no quantitative measure for additional benefits or disadvantages.
4. ***Contextual considerations*** include ethical, legal, or other issues (but not cost) that influence the relative priority of illnesses and interventions. Examples of contextual considerations include whether there are currently any existing treatments for the condition, whether the condition severely affects quality of life or not, and whether the condition affects priority populations. There is no quantitative measure for the role of contextual considerations in an overall judgment of care value.

In assessing provisional health system value, the CTAF Panel was asked to vote whether interventions represent a "high," "intermediate," or "low" value.

Figure 11. Health System Value Framework



1. ***Potential Health System Budget Impact*** is the estimated *net* change in *total* health care costs over a 5-year time-frame.
2. ***Provisional "Health System Value"*** represents a judgment integrating consideration of the long-term care value of a new intervention with an analysis of its potential short-term budget impact if utilization is unmanaged. The CTAF Panel votes reflect a judgement on the provisional health system value of an intervention.

3. ***Mechanisms to Maximize Health System Value*** is an action step, ideally supported by enhanced early dialogue among manufacturers, payers, and other stakeholders.
4. ***Achieved Health System Value*** is the real-world result of health care stakeholder efforts to maximize the value of a given intervention.

Usually, the care value and the provisional health care system value of an intervention or approach to care will align, whether it is "high," "intermediate," or "low." For example, a treatment that is judged to represent high care value from the perspective of per-patient costs and benefits will almost always represent a high health system value as well. But health system value also takes into consideration the short-term effects of the potential budget impact of a change in care across the entire population of patients. Rarely, when the additional per-patient costs for a new care option are multiplied by the number of potential patients treated, the short-term budget impact of a new intervention of intermediate or even high care value could be so substantial that the intervention would be "unaffordable" unless the health system severely restricts its use, delays or cancels other valuable care programs, or undermines access to affordable health insurance for all patients by sharply increasing health care premiums. Under these circumstances, unmanaged change to a new care option could cause significant harm across the entire health system, in the short-term possibly even outweighing the good provided by use of the new care option itself.

Provisional health system value builds upon the judgment of care value by integrating consideration of the potential short-term budget impact of a new intervention, a figure highly dependent upon an estimation of the potential uptake of the new drug across the entire population. In the ICER framework, the theoretical basis for the budget impact threshold is based on societal willingness to pay. This foundation rests upon the assumption that society would prefer health care costs to grow at a rate that does not exceed growth in the overall national economy. ICER has used estimates based on data from the World Bank, the Centers for Medicare & Medicaid Services (CMS), and other public sources to calculate a budget impact threshold for individual new drugs or devices that would identify those whose potential budget impact would contribute significantly to excessive health care cost growth.

It should be noted that if, after considering potential budget impact, a health intervention judged to have high care value receives a judgment of "low" provisional health system value from the CTAF Panel, this does not imply that the health system should not adopt the intervention; rather, the vote indicates that policy makers should consider implementing mechanisms related to patient selection, step therapy, pricing, and/or financing to ensure that the short-term budget impact of a high care value intervention does not lead to more harm than good. CTAF votes on provisional health system value will therefore serve an important function by highlighting situations when policymakers need to take action and work together to align care value with health system value.

7.2 Summary of the Votes

Entresto

1. For patients with Class II-IV levels of CHF and reduced ejection fraction, is the evidence adequate to demonstrate that the net health benefit of Entresto is greater than that of usual care with ACE inhibitors?

   CTAF Panel Vote: 9 Yes (90%) 1 No (10%)

   Comment: CTAF Panel members voiced concerns that there was only one industry-sponsored trial on Entresto and expressed a desire for additional studies comparing Entresto to an ARB to isolate the magnitude of effect provided by sacubitril. These concerns were outweighed, however, by the improvements in clinical outcomes and quality of life provided by the drug.

2. Given the available evidence for patients with Class II-IV CHF and reduced ejection fraction, what is the care value of Entresto vs. usual care with ACE inhibitors?[j]

   CTAF Panel Vote: a. 2 Low (22%) b. 5 Intermediate (56%) c. 2 High (22%)

   Comment: In written comments describing the rationale behind their care value votes, the majority of CTAF panelists considered the *comparative clinical effectiveness* of Entresto to be incremental to superior when compared to care with an ACE inhibitor. With regard to *incremental costs per outcome achieved*, panelists noted that Entresto produced a cost per quality-adjusted life year (QALY) gained below the $100,000 threshold set out in the ICER Value Framework. No significant *additional benefits or disadvantages* were noted. Under the category of *contextual considerations*, several Panel members expressed concern that the drug was associated with safety concerns among black patients in the clinical trial. Overall, panelists who found Entresto to provide superior clinical benefit judged the drug to provide high care value; the majority of panelists who eventually arrived at a judgment of intermediate care value found the drug provided incremental benefits.

3. Given the available evidence for patients with Class II-IV CHF and reduced ejection fraction, what is the provisional health system value of Entresto vs. usual care with ACE inhibitors?[j]

   CTAF Panel Vote: a. 7 Low (78%) b. 1 Intermediate (11%) c. 1 High (11%)

[j] Nine members of CTAF voted on questions relating to care value and provisional health system value, with one abstention. The panel member who abstained from voting on value questions provided input on the economic modeling section of the ICER report.

Comment: Some CTAF panelists who voted that Entresto provides a low provisional health system value noted that the short-term budget impact estimated for the treatment exceeded the $904 million per year threshold established in the ICER Value Assessment Framework.

CardioMEMS

4. For patients with Class III CHF and a hospitalization in the prior 12 months, is the evidence adequate to demonstrate that the net health benefit of CardioMEMS is greater than that of usual care?

   CTAF Panel Vote: 6 Yes (60%) 4 No (40%)

   Comment: CTAF panelists noted that although there is limited evidence to date on CardioMEMS, the evidence that does exist demonstrates a positive effect on rehospitalizations. One of the predominant concerns among the Panel was the difficulty in quantifying the effect study nurse communication had in the active arm of the trial, and residual concerns about bias, even with the extensive additional analysis required of the manufacturer by the FDA.

5. Given the available evidence for patients with Class III CHF and a hospitalization in the prior 12 months, what is the care value of CardioMEMS vs. usual care?[k]

   CTAF Panel Vote: a. 5 Low (56%) b. 2 Intermediate (22%) c. 2 High (22%)

   Comment: In written comments, the majority of the CTAF Panel found the *comparative clinical effectiveness* of CardioMEMS compared to usual care to be either an incremental improvement, or promising but inconclusive; two panelists felt the device produced comparable benefits. The Panel noted that CardioMEMS produces *incremental costs per QALY gained* below $100,000 per year in comparison to routine monitoring. For *additional benefits or disadvantages*, three panelists believed that the device would substantially increase patient engagement and two panelists felt that the device would improve the independence of patients with CHF. One panelist who found CardioMEMS to provide low *care value* judged there to be substantial uncertainties around the magnitude of benefit provided by the device. A different panelist voted that the device holds low *care value* due to the existence of only one clinical trial, a lack of data demonstrating a reduction in mortality, and a lack of published information on real-world effectiveness.

[k] Nine members of CTAF voted on questions relating to care value and provisional health system value, with one abstention. The panel member who abstained from voting on value questions provided input on the economic modeling section of the ICER report.

6. Given the available evidence for patients with Class III CHF and a hospitalization in the prior 12 months, what is the provisional health system value of CardioMEMS vs. usual care?[k]

   CTAF Panel Vote: a. 7 Low (78%) b. 1 Intermediate (11%) c. 1 High (11%)

   Comment: Panelists who voted that CardioMEMS provides low *provisional health system value* noted that unmanaged uptake of the device would exceed the $603 million per year threshold established in the ICER Value Assessment Framework, although two panelists noted that proper patient selection could improve the achieved health system value of the device.

7.3 Roundtable Discussions and Key Policy Implications

Following its deliberation on the evidence and subsequent voting, the CTAF Panel engaged in a moderated discussion with a Policy Roundtable that included clinical experts, medical directors of two private payers, a representative from a pharmacy benefits manager (PBM), and a representative from a manufacturer. The policy roundtable discussion with the CTAF Panel reflected multiple perspectives and opinions, and therefore, none of the recommendations below should be taken as a consensus view held by all participants. The names of the Policy Roundtable participants are shown in Table 11.

Table 11. Policy Roundtable Participants

Phil Adamson, MD	Medical Director and Vice President for Medical Affairs, Global Research and Development, St. Jude Medical
Luanda Grazette, MD, MPH, FACC	Associate Professor of Medicine, Division of Cardiovascular Medicine, Keck Medical Center of USC
Dipti Itchhaporia, MD, FACC	Robert and Georgia Roth Chair of Cardiac Excellence and Medical Director of Disease Management, Hoag Heart and Vascular Institute
George Louie, MD	Vice President and Medical Director, SCAN Health Plan
Glen Stettin, MD	Senior Vice President – Clinical Research & New Solutions, Express Scripts
Tony Van Goor, MD, MMM, CPE, FACP	Senior Director, Medical Affairs, Medical Director for Policy and Technology Assessment, Blue Shield of California

The roundtable discussion was facilitated by Jed Weissberg, MD, Senior Fellow at ICER. The main themes and recommendations from the discussion are summarized below.

Entresto:

1. ***Provider groups and payers may wish to limit prescribing of Entresto to cardiologists or, at a minimum, require other clinicians to prescribe in consultation with a cardiologist, due to***

the potential for side effects at initiation, importance of selecting appropriate patients, and relatively large expense when compared to generic ACE inhibitors or ARBs. In the pivotal clinical trial, Entresto was tested only among patients who tolerated a "run-in" phase of treatment with enalapril followed by treatment with Entresto, which is not reflective of typical clinical practice. Given uncertainties about possible side effects (e.g., possibility of increased risk of angioedema in certain subgroups) and the fact that neprilysin inhibition is an emerging practice and the long-term risks associated with it are unknown, appropriate patient identification and cardiologist oversight are needed. Per its label, Entresto is approved for patients with Class II-IV heart failure and reduced ejection fraction. Clinicians on the policy roundtable stated that patients should be carefully assessed to ensure that they are appropriate candidates for Entresto (e.g., do not have low blood pressure, have worsening disease despite optimized therapy) and that they should be closely monitored. Finally, it was noted that despite its positive effects on outcomes, Entresto is not cost saving even with all calculated cost offsets, and the price vastly exceeds that of generic ACE inhibitors and ARBs.

2. ***Based on the combination of its clinical benefits, pricing aligned with patient benefit, and short-term affordability, payers and purchasers should consider placing Entresto in the "preferred brand" category, especially if discounts can be obtained that bring the price in line with thresholds for health-system affordability.*** As noted in the full report, Entresto positively affects patient outcomes (i.e., significant reductions in cardiovascular and all-cause mortality, and in heart failure-specific hospitalization and ED visits), the cost per QALY gained (estimated to be $51,000 versus ACE inhibitor treatment) does not exceed commonly accepted thresholds, and the ICER budget impact threshold for Entresto was just 9% lower than the full wholesale acquisition cost. Given these factors, some payers and purchasers have placed Entresto in the "preferred brand" tier of their formulary. If price discounts of 9% or greater are obtained, more widespread adoption of this tier placement may encourage Entresto's use, but as stated in recommendation #1 above, placement of Entresto in the "preferred brand" tier should be coupled with requirements for cardiologist oversight and appropriate patient identification.

3. ***Further research and real-world experience with Entresto are needed to help identify the most appropriate patients among those who have Class II-IV heart failure and reduced ejection fraction.*** The FDA has required Entresto's manufacturer to conduct two post-marketing studies to examine a) its effects compared to valsartan on patient cognitive function, and b) angioedema complications among black patients. Additional information on the tolerability of Entresto and its ability to improve patient outcomes in real-world practice is also needed.

CardioMEMS:

4. ***Within the labeled indications, clinicians should carefully select patients for whom CardioMEMS would offer the best chance of clinical benefit and reduced costs.*** Participants on the policy roundtable noted that CardioMEMS is not an appropriate treatment for all Class III CHF patients, and in reality, access to the device may be limited based on both the availability of providers/centers implanting the device and on health plan coverage policies. CardioMEMS should be most useful for patients 1) whose disease course has been relatively unstable while on optimal medication regimens and who have had more than one hospitalization in a relatively short period of time, and 2) who are likely to engage with providers and participate in the interactions required to gather and act upon the information provided by CardioMEMS. For patients whose CHF might become more severe (i.e., from Class III to Class IV), centers implanting the device should discuss the associated risks along with odds of disease progression and what care would be provided if the underlying CHF progressed (i.e., palliative care options).

   To help clinicians decide if CardioMEMS is an appropriate treatment, brain natriuretic peptide (BNP) or other chemical and physiological markers may be useful. Along with the additional information being gathered in the two post-approval trials required by the FDA when CardioMEMS was approved, large administrative and/or electronic health record databases may allow for identification of combinations of comorbidities or other patient characteristics associated with the greatest likelihood of benefit from CardioMEMS.

5. ***Provider groups that are starting to use CardioMEMS should explore providing care within a Center of Excellence paradigm, as should payers that are considering covering it.*** In all practice settings and for all patients with Class II-IV heart failure, it would be ideal to have a wrap-around program that includes a systematic approach to selecting patients, dedicated staff to regularly monitor and contact the patients, and resources to manage data collection and provide feedback. Payers should consider only covering CardioMEMS in the context of a Center of Excellence that ensures wrap-around care and continues to gather data on outcomes and costs.

6. ***Further research into the benefits of CardioMEMS is needed to address some of the uncertainties that impact its adoption by clinicians and coverage by payers.*** Residual uncertainties about the clinical effectiveness of CardioMEMS are due to the single clinical trial and the potential confounding influence of study nurse communications. More information is also needed with regard to start-up and monitoring costs. Additional research is needed to explore whether providing patients with information about their pulmonary artery (PA) pressures empowers and engages them, thereby helping them manage their lifestyle decisions.

Both Entresto and CardioMEMS:

7. ***Manufacturers and payers should consider performance-based agreements (i.e., reduced costs or refunds) for both Entresto and CardioMEMS.*** Past experience has proven that, in order to be acceptable to all parties, these types of agreements must be very simple to administer. Participants on the policy roundtable stated that while potentially interested in such arrangements, any codes needed to monitor outcomes must be simple and universally available, and that these types of agreements would not work if they required additional personnel to manage. It was noted that data collection systems and electronic health records allowing an intervention to be tied to quality and cost outcomes are still in need of further development. Sending personal health information to patients via email or text messages in compliance with federal regulations was also identified as a limiting factor but was not perceived as insurmountable.

8. ***Clinicians and patients should work together to prevent and intensively manage health conditions that are a precursor to CHF, as this may improve patient outcomes including quality of life and reduce costs.*** Most patient interactions with the health care system are episodic, based either on acute need or scheduled periodic visits to monitor a chronic health condition. While the health care system is designed to meet medical needs as they arise, there is increasing awareness that prevention efforts designed to keep people as healthy as possible for as long as possible are also needed. Prevention can involve education and counseling, screening/testing, or treatment of a condition to prevent development of another more serious condition. In the case of heart failure, education about the role of maintaining a healthy weight, avoiding smoking, engaging in exercise, and eating a healthy diet may help patients reduce their risk of developing conditions such as diabetes and hypertension. For patients who do develop diseases like these that can be precursors to heart failure, a close partnership between clinicians and patients in which there is more continuous, rather than episodic, monitoring and management may reduce the development of more serious disease and the need for advanced therapies.

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This is the first CTAF review of CardioMEMS and Entresto.

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APPENDICES

Appendix A. Search Strategies and Results

Table A1. PRISMA 2009 Checklist

Section/topic	#	Checklist item
		TITLE
Title	1	Identify the report as a systematic review, meta-analysis, or both.
		ABSTRACT
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.
		INTRODUCTION
Rationale	3	Describe the rationale for the review in the context of what is already known.
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).
		METHODS
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.

Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.
RESULTS		
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).
DISCUSSION		
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.
FUNDING		
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

Table A2. Search Strategies for CardioMEMS and Entresto

Ovid MEDLINE search strategy for CardioMEMS HF

1. exp Heart failure, congestive/
2. (chf or hf).ti,ab.
3. (heart adj25 failure).ti,ab.
4. (cardiac adj25 (failure or insufficiency)).ti,ab.
5. or/1-4
6. (wireless adj25 monitor$ adj25 (pulmonary or arter$)).ti,ab.
7. cardiomems.ti,ab.
8. 6 or 7
9. 5 and 8
10. limit 9 to (english language and humans and yr="1990 -Current")
11. (Guideline or practice guideline or letter or editorial or review or news or case reports or in vitro).pt.
12. 10 not 11

EMBASE search strategy for CardioMEMS HF

1. 'heart failure'/exp
2. chf:ab,ti OR hf:ab,ti
3. (heart NEAR/25 failure):ab,ti
4. (cardiac NEAR/25 (failure OR insufficien*)):ab,ti
5. #1 OR #2 OR #3 OR #4
6. (wireless NEAR/25 monitor* NEAR/25 (pulmonary OR arter*)):ti,ab
7. Cardiomems:ti,ab
8. #6 OR #7
9. #5 AND #8
10. #9 AND [humans]/lim AND [english]/lim AND [1990-2015]/py
11. [conference abstract]/lim OR [conference review]/lim OR [editorial]/lim OR [erratum]/lim OR [letter]/lim OR [note]/lim OR [review]/lim OR [short survey]/lim
12. #10 NOT #11

Ovid MEDLINE search strategy for Entresto

1. exp Heart failure, congestive/
2. (chf or hf).ti,ab.
3. (heart adj25 failure).ti,ab.
4. (cardiac adj25 (failure or insufficiency)).ti,ab.
5. or/1-4
6. exp Receptors, angiotensin/
7. arb?.ti,ab.
8. (angiotensin$ adj25 receptor$ adj25 (block: or antagon$ or inhibit$)).ti,ab.
9. valsartan.ti,ab.
10. or/6-9
11. ((neprilysin adj25 inhibit$) or (NEP adj25 inhibit$) or sacubitril or AHU?377).ti,ab.
12. (lcz?696 or entresto).ti,ab.
13. 10 and 11
14. 12 or 13
15. 5 and 14
16. limit 15 to (english language and humans and yr="1990 -Current")
17. (Guideline or practice guideline or letter or editorial or review or news or case reports or in vitro).pt.
18. 16 not 17

EMBASE search strategy for Entresto

1. 'heart failure'/exp
2. chf:ab,ti OR hf:ab,ti
3. (heart NEAR/25 failure):ab,ti
4. (cardiac NEAR/25 (failure OR insufficien*)):ab,ti
5. #1 OR #2 OR #3 OR #4
6. 'angiotensin receptor antagonist'/exp
7. ARB?:ab,ti OR valsartan:ab,ti
8. #6 OR #7
9. 'neprilysin inhibitor'/exp
10. 'neprilysin inhibitor':ab,ti OR nep NEAR/25 inhibit* OR sacubitril:ab,ti OR ahu*377:ab,ti
11. #9 OR #10
12. 'sacubitril plus valsartan'/exp
13. Entresto:ab,ti OR LCZ*696:ab,ti
14. #12 OR #13
15. #8 AND #11
16. #14 OR #15

17. #5 AND #16
18. #17 AND [humans]/lim AND [english]/lim AND [1990-2015]/py
19. [conference abstract]/lim OR [conference review]/lim OR [editorial]/lim OR [erratum]/lim OR [letter]/lim OR [note]/lim OR [review]/lim OR [short survey]/lim
20. #18 NOT #19

Figure A1. PRISMA flow Chart Showing Results of Literature Search for CardioMEMS HF System

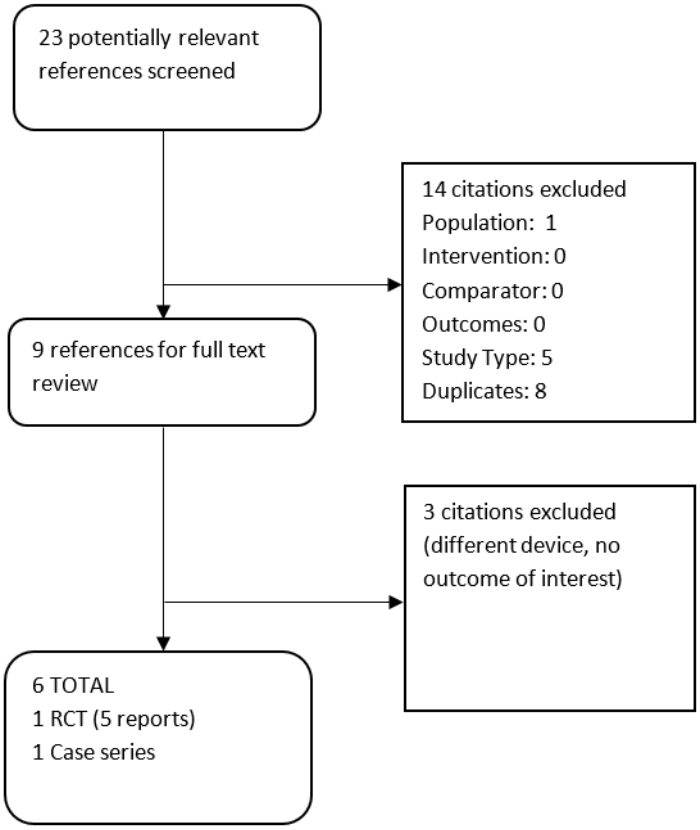
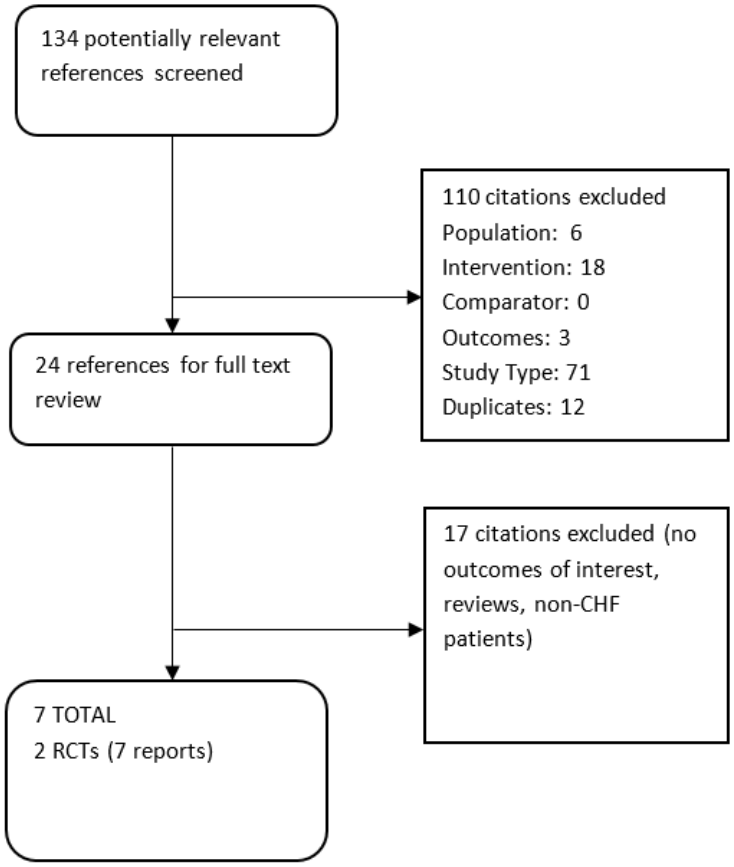


Figure A2. PRISMA Flow Chart Showing Results of Literature Search for Entresto



Appendix B. Clinical Guidelines

National Institute for Health and Care Excellence (NICE) (2013)

http://www.nice.org.uk/guidance/ipg463

A guidance statement from NICE recommends that the use of implantable pulmonary artery pressure monitors be limited to "special arrangements for clinical governance, consent and audit or research" due to limited evidence on safety and efficacy. They recommend that all patients be adequately informed of the uncertainties surrounding the safety and efficacy of these devices.

Appendix C. Previous Systematic Reviews and Technology Assessments

We found no previous systematic reviews or technology assessments of either the CardioMEMS HF System or Entresto, however the National Institute for Health and Care Excellence (NICE) has released a draft scope for an appraisal of the clinical and cost-effectiveness of Entresto planned for November 2015.[135] NICE's review will evaluate Entresto, in comparison to ACE inhibitors and ARBs, for patients with NYHA Class II-IV heart failure and reduced ejection fraction; the primary endpoints of interest for the appraisal are heart failure symptoms, CHF-related hospitalizations, mortality, cardiovascular mortality, adverse effects, quality of life, and cost-effectiveness.

Appendix D. Ongoing Studies

Title/ Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Estimated Completion Date
CardioMEMS HF System					
CardioMEMS HF System Post Approval Study **NCT02279888**	Observational	CardioMEMS HF System	N = 1,200 Age ≥ 18 Men and women NYHA Class III HF At least 1 CHF hospitalization in past 12 months Body Mass Index (BMI) < 35 kg/m^2 or BMI > 35 kg/m^2 with chest circumference < 65 inches No active infection No recurrent pulmonary embolism or deep vein thrombosis No inability to tolerate right heart catheterization No major cardiovascular event within past 2 months No cardiac resynchronization device implant within past 3 months No patients likely to undergo heart transplant or ventricular assist device within next 6 months No coagulation disorders No hypersensitivity or allergy to aspirin, clopidogrel	Freedom from device or system-related complication up to 2 years Freedom from pressure sensor failure up to 2 years Heart failure hospitalization rate up to one year	June 2020

Title/ Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Estimated Completion Date
Entresto					
Study of Efficacy and Safety of Entresto in Japanese Patients with Chronic Heart Failure and Reduced Ejection Fraction **NCT02468232**	RCT	Entresto 50 mg, 100mg, 200mg Placebo to match Enalapril 2.5 mg, 5 mg, 10 mg Enalapril 2.5 mg, 5 mg, 10mg Placebo to match Entresto 50 mg, 100 mg, 200 mg	N = 220 Age ≥ 20 Men and women CHF NYHA Class II-IV, reduced ejection fraction NT-proBNP ≥ 600 pg/ml at first visit or NT-proBNP ≥ 400 pg/ml and CHF hospitalization within past 12 months No hypersensitivity to study drugs No ACE inhibitor or ARB intolerance No known angioedema No acute decompensated CHF No acute coronary syndrome, stroke, transient ischemic attack, cardiac, carotid or major cardiovascular (CV) surgery, percutaneous coronary intervention (PCI), or carotid angioplasty in 3 months prior to first visit	Time to first occurrence of CV death or CHF hospitalization, up to 40 months.	November 2018

Title/ Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Estimated Completion Date
Efficacy and Safety of Entresto Compared to Valsartan, on Morbidity on Mortality in Heart Failure Patients with Preserved Ejection Fraction (PARAGON-HF) **NCT01920711**	RCT	Entresto 50 mg, 100 mg, 200 mg Valsartan 40 mg, 80 mg, 160 mg	N = 4,300 Age ≥ 55 Men and women LVEF ≥ 45% prior to study entry Symptoms of CHF, treatment with diuretic for CHF ≥ 30 days Structural heart disease CHF hospitalization in 9 months prior to study entry and/or elevated NT-proBNP No prior LVEF < 45% No acute coronary syndrome, cardiac surgery, major CV surgery within 3 months of trial entry, or urgent percutaneous coronary intervention (PCI) within 30 days of trial entry No myocardial infarction (MI), coronary artery bypass graft, or other event within 6 months prior to trial entry unless post-event LVEF ≥ 45% No acute decompensated HF requiring therapy No current treatment with two or more of: ACE inhibitor, ARB, or renin inhibitor No significant pulmonary disease or COPD, hemoglobin < 10g/dl, body mass index (BMI) > 40 kg/m^2 No systolic blood pressure (SBP) ≥ 180 mmHg at entry, or SBP 150-180 mmHg at entry unless undergoing treatment with 3+ antihypertensive drugs	Cumulative number of primary composite events of CV death and total CHF hospitalizations up to 57 months	May 2019

Title/ Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Estimated Completion Date
Safety and Tolerability During Open-Label Treatment With Entresto in Patients With CHF and Reduced Ejection Fraction **NCT02226120**	Non-RCT	Entresto 200mg	N = 4,900 Age ≥ 18 Men and women Patients who completed PARADIGM-HF and are able to safely enroll based on investigator opinion No current or recent (<5 half-lives) use of investigational drugs No hypersensitivity or allergy to Entresto, similar drugs, ACE inhibitors, ARBs, or neprilysin inhibitors No history of angioedema No simultaneous treatment with both ACE inhibitors and ARBs No acute decompensated CHF No symptomatic hypotension and/or SBP < 100 mmHg No hepatic disease No pregnant or lactating women, or women of child-bearing potential	Number of patients with adverse events including angioedema, AEs suspected to be related to Entresto, AEs leading to drug discontinuation, and SAEs including death	April 2017

Appendix E. Comparative Clinical Effectiveness Supplemental Information

We extracted data in the following steps:

1. One investigator independently extracted information from the full articles.
2. A second investigator reviewed a proportion of the extracted data for additional quality assurance.

Our review team extracted information from the accepted studies and developed data summary tables (Appendix Tables E1 and E2). We relied on a number of control measures to ensure the quality and consistency of data extraction in this project. These included pilot testing of the extraction form on several included studies, resolution of potential ambiguities and differences in the interpretation of findings, and written instructions on outcome measures to be extracted from the full papers.

We used criteria published by the US Preventive Services Task Force (USPSTF) to assess the quality of RCTs and comparative cohort studies, using the categories "good," "fair," or "poor."[92] Guidance for quality ratings using these criteria is presented below, as is a description of any modifications we made to these ratings specific to the purposes of this review.

Good: *Meets all criteria: Comparable groups are assembled initially and maintained throughout the study; reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention is paid to confounders in analysis. In addition, intention to treat analysis is used for RCTs.*

Fair: *Studies were graded "fair" if any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred with follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are addressed. Intention to treat analysis is done for RCTs. Specifically for this review, differences in baseline characteristics and/or duration of follow-up were allowed only if appropriate statistical methods were used to control for these differences (e.g., multiple regression, survival analysis).*

Poor: *Studies were graded "poor" if any of the following fatal flaws exists: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. For RCTs, intention to treat analysis is lacking.*

Note that case series are not considered under this rating system – because of the lack of comparator, these are generally considered to be of poor quality. Nevertheless, we restricted our use of case series to those that met specific criteria, including a minimum of six months follow-up, clearly defined entry criteria, and use of consecutive samples of patients.

Table E1. Summary Evidence Table for CardioMEMS HF System

Author & Year	Study Quality	Study Design	Interventions	# of Patients	Study Duration	Entry Criteria	Patient Characteristics	Outcomes
Abraham 2011_A	Good	RCT The CHAMPION Trial	1) CardioMEMS HF System 2) Standard of care management (drug changes in response to patients' clinical signs and symptoms)	n=550 1) 270 2) 280	15 months	Age>=18 NYHA Class III for at least 3 months CHF-related hospitalization within past 12 months Given drug and device treatments at optimum or best-tolerated stable doses according to national guidelines	Age: 61.5 % male: 72.5 % LVEF (>=40%): 21.5 % white: 73% BMI: 31 % with CRT or CRT-D device: 34.5	CHF-related hospitalizations during entire randomized follow-up (n) 1) 158 2) 254 HR: 0.63 95% CI: 0.52-0.77 p<0.0001 Days alive outside hospital at 6 months (n) 1) 174.4 2) 172.1 p=0.02 6-month Minnesota Living with Heart Failure Questionnaire score 1) 45 2) 51 p=0.02 Device- or system-related complications (n; %) 1) 3 (1%) 2) 3 (1%)

Author & Year	Study Quality	Study Design	Interventions	# of Patients	Study Duration	Entry Criteria	Patient Characteristics	Outcomes
Abraham 2011_B	Poor	Case series	CardioMEMS HF System	n=17	12 months	Age>18 Stable NYHA Class III for >=30 days before enrollment Estimated life expectancy of >=1 year	Mean age: 61 14 Males/3 Females 15 whites/2 African Americans Preexisting ICD or CRT: 11	Average difference for systolic pulmonary artery pressure (PAP) (compared to Swan-Ganz (SG) catheter): -4.4 Average difference for diastolic PAP (compared to SG catheter): 2.5 Average difference for mean PAP (compared to SG catheter): −0.8 Adherence to daily home monitoring (min. 1 transmission per day): 90.0% in 60 days after implantation Weekly adherence: 100% Avg. readings/week: 8.6

Author & Year	Study Quality	Study Design	Interventions	# of Patients	Study Duration	Entry Criteria	Patient Characteristics	Outcomes
Adamson 2014	Good	Subgroup analysis of CHAMPION patients by LVEF	1) CardioMEMS HF System 2) Standard of care management (drug changes in response to patients' clinical signs and symptoms)	See Abraham, 2011_A	See Abraham, 2011_A	See Abraham, 2011_A	LVEF >=40% (n) 1) 62 2) 57 LVEF <40% (n) 1) 208 2) 222 Patients with LVEF >=40% were older, more often white females with higher BMIs than patients with LVEF <40%. Baseline medical therapies and comorbidity burden was similar between groups	**6-month CHF hospitalization (n)** LVEF >=40% 1) 11 2) 19 Incidence Rate Ratio: 0.54 (95% CI: 0.38-0.70) p<0.0001 LVEF <40% 1) 73 2) 101 Incidence Rate Ratio: 0.76 (95% CI: 0.61-0.91) p=0.0085) **Total medication changes (Mean, sum)** LVEF >=40% 1)8.0, 495 2) 4.1, 232 p<0.0001 LVEF <40% 1) 9.5, 1973 2) 3.7, 825 p<0.0001

Author & Year	Study Quality	Study Design	Interventions	# of Patients	Study Duration	Entry Criteria	Patient Characteristics	Outcomes
Benza 2015	Good	Subgroup analysis of CHAMPION trial patients with and without WHO Group II Pulmonary Hypertension [PH]	1) CardioMEMS HF System 2) Standard of care management (drug changes in response to patients' clinical signs and symptoms)	n=529 1) 258 2) 271	1) 449 days 2) 437 days	See Abraham, 2011_A	WHO Group II PH 1) 151 2) 163 PH patients more likely to have LVEF <40% (83% vs. 71%, p=0.0037), and more frequently had prior cardiac resynchronization therapy (38% vs. 28%, p=0.019), compared with non-PH patients	**CHF Hospitalization Rates (annualized rate) in Patients with and without PH** <u>Mean PAP<=25 mmHg</u> 1) 40 (0.28) 2) 66 (0.47) Relative risk reduction: 40% HR: 0.60 95% CI: 0.41-0.89 p=0.0109 <u>Mean PAP>25 mmHg</u> 1) 113 (0.60) 2) 186 (0.94) Relative risk reduction: 36% HR: 0.64 95% CI: 0.51-0.81 p=0.0002 Total medication changes in response to elevated PAP: 1,192

Author & Year	Study Quality	Study Design	Interventions	# of Patients	Study Duration	Entry Criteria	Patient Characteristics	Outcomes
Krahnke 2014	Good	Subgroup analysis of subjects with COPD from the CHAMPION trial	1) CardioMEMS HF System 2) Standard of care management (drug changes in response to patients' clinical signs and symptoms)	n=550 1) 270 2) 280 Subjects with COPD n=187 1) 91 2) 96	15 months	COPD; (see Abraham 2011_A for CHAMPION trial criteria)	Characteristics of subjects with COPD Mean age: 63 % female 1) 33% 2) 27% % nonwhite 1) 15% 2) 24% Mean BMI: 31.5 CRT/CRT-D: 33.5% LVEF>=40%: 23%	**CHF hospitalization n(annualized rate)** <u>COPD group</u> 1) 66 (0.55) 2) 110 (0.92) RRR: 41% HR: 0.59 95% CI: 0.44-0.81 p=0.0009 <u>Non-COPD group</u> 1) 92 (0.41) 2) 144 (0.62) RRR: 34% HR: 0.66 95% CI: 0.51-0.85 p=0.0017 **6-month mean CHF medication changes** <u>COPD group</u> 1) 7.1 2) 3.7 p<0.0001 <u>Non-COPD group</u> 1) 7.9 2) 3.1 p<0.0001

Author & Year	Study Quality	Study Design	Interventions	# of Patients	Study Duration	Entry Criteria	Patient Characteristics	Outcomes
Raina 2015	Good	Secondary analysis of CHAMPION trial to assess diagnosis of pulmonary hypertension (PH) with implantable hemodynamic monitor (IHM) and right heart catheterization (RHC)	1) CardioMEMS HF System 2) Standard of care management (drug changes in response to patients' clinical signs and symptoms)	n=537 PH with IHM but not RHC: n=106 1) 54 2) 52 No PH with RHC or IHM: 111 1) 57 2) 54	See Abraham, 2011_A	See Abraham, 2011_A	Mean age: 62 Mean SBP: 122 mmHg Preserved ejection fraction: 22%	**CHF Hospitalizations** <u>No PH (from RHC or IHM):</u> 1): 15 2): 22 Incidence rate ratio: 0.58 95% CI: 0.28-1.17 p=0.098 <u>PH with IHM but not RHC:</u> 1): 25 2): 43 Incidence rate ratio: 0.58 95% CI: 0.34-0.98 p=0.0304 **CHF hospitalization rate** <u>No PH (from RHC or IHM):</u> 0.25 <u>PH with IHM but not RHC:</u> 0.49 Incidence rate ratio: 0.51 95% CI: 0.33-0.77 p=0.0007 **Patient mortality HR:** 0.85 95% CI: 0.36-2.00 p=0.71

Table E2. Summary Evidence Table for Entresto

Author & Year	Study Quality	Study Design	Interventions	# of Patients	Mean/Median Duration of follow-up	Inclusion Criteria	Patient Characteristics	Outcomes
Desai 2015	Good	Secondary analysis of PARADIGM-HF trial according to mode of death	1) Entresto 2) Enalapril	n=8,399 1) 4,187 2) 4,212	27 months	See McMurray 2014	See McMurray 2014	*n, % of patients* Total deaths 1) 711, 17.0 2) 558, 13.3 HR: 0.84 95% CI: 0.76-0.93 p=0.001 Sudden death 1) 250, 6.0 2) 311, 7.4 HR: 0.80 95% CI: 0.68-0.94 p=0.008 Death from worsening CHF 1) 147, 3.5 (20.7) 2) 184, 4.4 (22.0) HR: 0.79 95% CI: 0.64-0.98 p=0.034

Author & Year	Study Quality	Study Design	Interventions	# of Patients	Mean/Median Duration of follow-up	Inclusion Criteria	Patient Characteristics	Outcomes
Jhund 2014	Good	Secondary analysis of PARAMOUNT trial subjects to evaluate whether effects of Entresto were independent of lowering of systolic blood pressure	1) Entresto 2) Valsartan	n=301 1) 149 2) 152	36 weeks	See Solomon 2012	See Solomon 2012	***Systolic Blood Pressure Tertiles*** *1: 1- 61 mmHg* *2: -11 to 0 mmHg 3: -48 to -12 mmHg* **Change in NYHA class at 36 weeks by tertile 1/2/3 (%)** Worsened 1) ~5/0/7 2) ~6/0/7 Unchanged 1) ~67/79/77 2) ~82/88/77 Improved 1) 28/21/16 2) 12/12/16

Author & Year	Study Quality	Study Design	Interventions	# of Patients	Mean/Median Duration of follow-up	Inclusion Criteria	Patient Characteristics	Outcomes
McMurray 2014	Good	RCT PARADIGM-HF Trial	1) Entresto 2) Enalapril	n=8,399 1) 4,187 2) 4,212	27 months	Age>=18 years NYHA Class II-IV LVEF <=40% BNP>=150 pg/mL (or NT-proBNP>=600 pg/mL) If hospitalized for CHF in previous 12 months, a BNP>=100 pg/mL (or NT-proBNP>=400 pg/mL) Taking stable dose of beta-blocker and ACE inhibitors or ARB equivalent to >=10 mg enalapril/day for at least 4 weeks prior to screening	Mean age: 63.8 % female: 21.8 % white: 66.0 % NYHA Class I: 4.7 II: 70.5 III: 24.0 IV: 0.7 BMI: 28.2	Death from cardiovascular causes or 1st CHF hospitalization (%) 1) 21.8 2) 26.5 p<0.001 Change in KCCQ summary score 1) -2.99 2) -4.63 p=0.001 Worsening CHF by NYHA Class I or II HR: ~0.71 NYHA Class III or IV HR: ~0.89 p=0.03 *No other subgroup had statistical differences in outcomes* Discontinuation from an AE (%) 1) 10.7 2) 12.3 p=0.03

Author & Year	Study Quality	Study Design	Interventions	# of Patients	Mean/Median Duration of follow-up	Inclusion Criteria	Patient Characteristics	Outcomes
McMurray 2015	Fair	Putative placebo analysis using PARADIGM-HF trial data compared to data from SOLVD-T and CHARM-Alt trials	1) SOLVD-T 2) CHARM-Alt 3) PARADIGM-HF	1) 2,569 2) 2,028 3) 8,399	1) 41.4 months 2) 33.7 months 3) 27 months	1) NYHA Class II–IV with LVEF≤35%; age ≤80 years; not treated with ACE inhibitors 2) NYHA Class II-IV with LVEF ≤40%; not receiving ACE inhibitor due to previous intolerance 3) See McMurray 2014	Age 1) 61 2) 67 3) 64 % female 1) 20 2) 32 3) 22 NYHA Class (%) I/II/III/IV 1) 11/57/30/2 2) 0/48/49/4 3) 5/70/24/1 LVEF (%) 1) 25 2) 30 3) 29	Composite of death from cardiovascular causes or CHF hospitalization, HR (95% CI) 1) 0.72 (0.64-0.80) 2) 0.77 (0.67-0.89) 3) (from SOLVD-T) 0.57 (0.50-0.66) (from CHARM-Alt) 0.61 (0.52-0.73) All-cause mortality 1) 0.85 (0.75-0.97) 2) 0.87 (0.74-1.03) 3) (from SOLVD-T) 0.72 (0.61-0.84) (from CHARM-Alt) 0.74 (0.61-0.89)

Author & Year	Study Quality	Study Design	Interventions	# of Patients	Mean/Median Duration of follow-up	Inclusion Criteria	Patient Characteristics	Outcomes
Packer 2015	Good	Secondary analysis of measures of nonfatal worsening of CHF in PARADIGM-HF trial subjects	1) Entresto 2) Enalapril	n=8,399 1) 4,187 2) 4,212	27 months	See McMurray 2014	See McMurray 2014	Patients with worsening CHF leading to intensification of outpatient therapy 1) 520 (12.4%) 2) 604 (14.3%) RR: 0.84 (95% CI: 0.74-0.94) p=0.003 Patients with worsening NYHA class in those surviving at 12 months 1) 225 (6.1%) 2) 271 (7.4%) p=0.023 Patients with worsening KCCQ score (>=5 pts) at 12 months 1) 964 (29.0%) 2) 1,029 (31.5%) p=0.03 Days in hospital per admission per patient 1) 10.8 2) 9.7 p<0.001

Author & Year	Study Quality	Study Design	Interventions	# of Patients	Mean/Median Duration of follow-up	Inclusion Criteria	Patient Characteristics	Outcomes
Solomon 2012	Good	RCT (Phase II) PARAMOUNT trial	1) Entresto 2) Valsartan	n=301 1) 149 2) 152 Included in analysis of Primary endpoint: 1) 134 2) 132	36 weeks	Age>=40 LVEF >=45% Documented history of CHF NT-proBNP>400 pg/mL at screening Diuretic therapy Systolic BP<140 mm Hg or <=160 mm Hg if on 3+ BP drugs at randomization eGFR >=30 mL/min per 1.73 m2 at screening Potassium concentration <=5.2 mmol/L	Age: 71.1 % female: 57 % NYHA Class I: 1 II: 79.5 III: 20 BMI: 30.0 NT-proBNP (pg/mL) 1) 828 2) 939	NYHA class worsened 1) ~4% 2) ~3% NYHA class unchanged 1) ~72% 2) ~80% NYHA improved 1) ~24% 2) ~17% Any SAE 1) 22 (15%) 2) 30 (20%) p=0.32 Death 1) 1 (1%) 2) 2 (1%) p=0.99 Any AE 1) 96 (64%) 2) 111 (73%) p=0.14 Discontinuation due to AE 1) 15 (10%) 2) 17 (11%) p=0.90

Author & Year	Study Quality	Study Design	Interventions	# of Patients	Mean/Median Duration of follow-up	Inclusion Criteria	Patient Characteristics	Outcomes
Voors 2015	Good	Secondary analysis of renal function in PARAMOUNT trial subjects	1) Entresto 2) Valsartan	n=301 1) 149 2) 152	36 weeks	See Solomon 2012	See Solomon 2012	Worsening renal function (increase in creatinine>0.3 g/dL & increase in serum creatinine>25% compared with baseline) 12 weeks 1) 6 (5%) 2) 9 (7%) p=0.60 36 weeks 1) 7 (6%) 2) 16 (13%) p=0.08 Anytime 1) 16 (12%) 2) 26 (18%) p=0.18

Table E3. Additional Secondary Endpoints from the CHAMPION Trial

Endpoint	Treatment	Control	
Patients admitted to hospital for CHF at 6 months (n, %)	55 (20%)	80 (29%)	P=0.03
Days alive outside hospital (mean, standard deviation)	174.4 (31.1)	172.1 (37.8)	p=0.02
Change from baseline in pulmonary artery mean pressure at 6 months (mm Hg x days)	-156	33	P=0.008
Medication changes (number of changes, mean per patient)	2,468 (9.1)	1,061 (3.8)	p<0.0001

Table E4. Systematic Reviews of Alternative Management Strategies for Heart Failure*

Intervention	All-cause Hospitalizations			All-cause mortality			CHF Hospitalizations		
	Intervention	Usual Care	RR (95% CI)	Intervention	Usual Care	RR (95% CI)	Intervention	Usual Care	RR (95% CI)
Structured Telephone Support									
Clark 2007	41%	43%	0.94 (0.87-1.02)	13%	14%	0.85 (0.72-1.01)	19%	23%	0.78 (0.68-0.89)
Feltner 2014	38%	40%	0.92 0.77-1.10)	10%	13%	0.74 (0.56-0.97)	16%	22%	0.74 (0.61-0.90)
McAlister 2004	42%	42%	0.98 (0.80-1.20)	10%	11%	0.91 (0.67-1.29)	20%	27%	0.75 (0.57-0.99)
Telemonitoring									
Clark 2007	57%	54%	0.98 (0.84-1.15)	13%	19%	0.62 (0.45-0.85)	36%	42%	0.86 (0.57-1.28)
Feltner 2014	40%	36%	1.11 (0.87-1.42)	11%	13%	0.93 (0.25-3.48)	19%	11%	1.70 (0.82- 3.51)
Patient Education/Self-Management									
Feltner 2014	48%	43%	1.14 (0.84-1.54)	10%	8%	1.20 (0.52-2.76)	15%	28%	0.53 (0.31-0.90)
McAlister 2004	31%	42%	0.73 (0.57-0.93)	17%	14%	1.14 (0.67-1.94)	27%	40%	0.66 (0.52-0.83)
Multidisciplinary CHF Clinic									
Feltner 2014	36%	52%	0.70 (0.55-0.89)	8%	15%	0.56 (0.34-0.92)	13%	19%	0.70 (0.29-1.70)
McAlister 2004	39%	48%	0.76 (0.58-1.01)	15%	21%	0.66 (0.42-1.05)	27%	35%	0.76 (0.58-0.99)
CHF Disease Management Program									
Roccaforte 2005	14%	17%	(OR) 0.80 (0.68-0.94)	15%	18%	(OR) 0.80 (0.69-0.93)	NR	NR	NR

*All intervention and usual care estimates are the crude percent of patients who experienced the outcome; RRs were derived from meta-analyses conducted in each of the individual systematic reviews

RR: Relative Risk

Table E5. Comparisons of Hospitalization Rates in Supplemental Analyses Presented to FDA Prior to CardioMEMS Approval[18]

Comparison*	Hazard Ratio	95% C.I.	
1. Unblinded Controls in supplemental analyses compared with Controls in CHAMPION trial	0.52	(0.40-0.69)	P<0.0001
2. Unblinded Treatment in supplemental analyses compared with Treatment in CHAMPION trial	0.93	(0.70-1.22)	P=0.5838
3. Unblinded Controls in supplemental analyses compared with Unblinded Treatment in supplemental analyses	0.80	(0.56-1.14)	P=0.2178
4. Unblinded Controls to Unblinded Treatment in supplemental analyses compared with Controls to Treatment in CHAMPION trial	0.56	(0.38-0.83)	P=0.0040
5. Unblinded Controls in supplemental analyses to Controls in CHAMPION trial compared with Unblinded Treatment in supplemental analyses to Treatment in CHAMPION trial	0.56	(0.38-0.83)	P=0.0040

*Results from Andersen-Gill Model with Frailty comparing heart failure hospitalization rates

Table E6. Number of Patients and Hospitalization Rates by Treatment Arm in Supplemental Analyses Presented to FDA Prior to CardioMEMS Approval[102]

Treatment Arm	Number of Patients	Number of CHF Hospitalizations	Hospitalization Rate (Hospitalizations/Patient-Year)
Treatment arm in CHAMPION trial	270	182	0.48
Unblinded Treatment arm in supplemental analyses	177	78	0.45
Control arm in CHAMPION trial	280	279	0.68
Unblinded Control arm in supplemental analyses	170	64	0.36

*Results from Andersen-Gill Model with Frailty comparing heart failure hospitalization rates

Table E7. Mortality Outcomes of Patients by Treatment Arm in Supplemental CardioMEMS Analyses Presented in *The Lancet*[99]

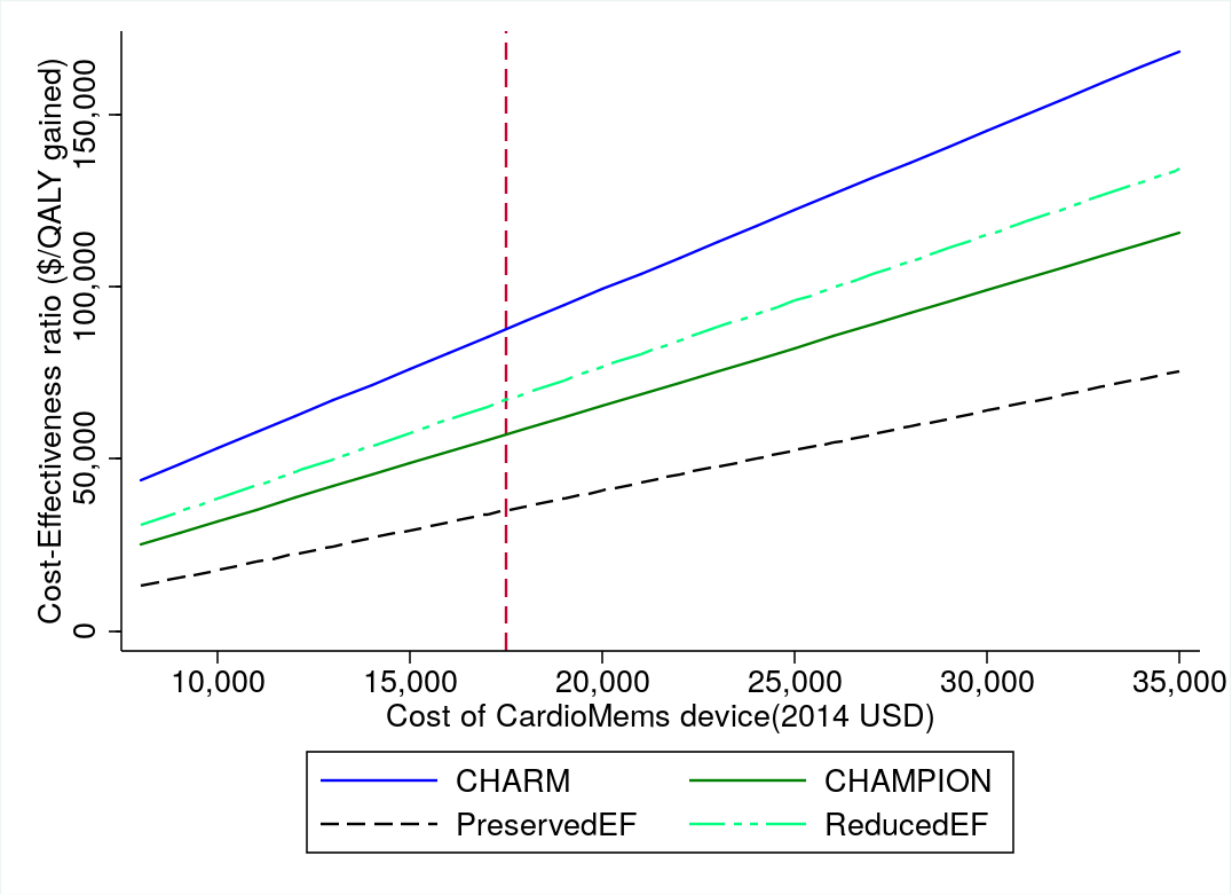
Treatment Arm (n)	Death		Death and admission to hospital for heart failure	
	n (%)	Statistical comparisons	n (%)	Statistical comparisons
Treatment arm in CHAMPION trial (n=270)	50 (19)	HR 1.40 (95% CI: 0.89-2.23); p=0.15*	232 (0.61)	HR 1.09 (95% CI: 0.86-1.39); p=0.46†
Unblinded Treatment arm in supplemental analyses (n=177)	31 (18)		109 (0.67)	
Control arm in CHAMPION trial (n=280)	64 (23)	HR 0.71 (95% CI: 0.43-1.17); p=0.17*	343 (0.84)	HR 0.61 (95% CI: 0.48-0.78); p<0.0001†
Unblinded Control arm in supplemental analyses (n=170)	21 (12)		85 (0.51)	

*Results from Cox proportional hazards and log-rank test

†Results from Andersen-Gill Model

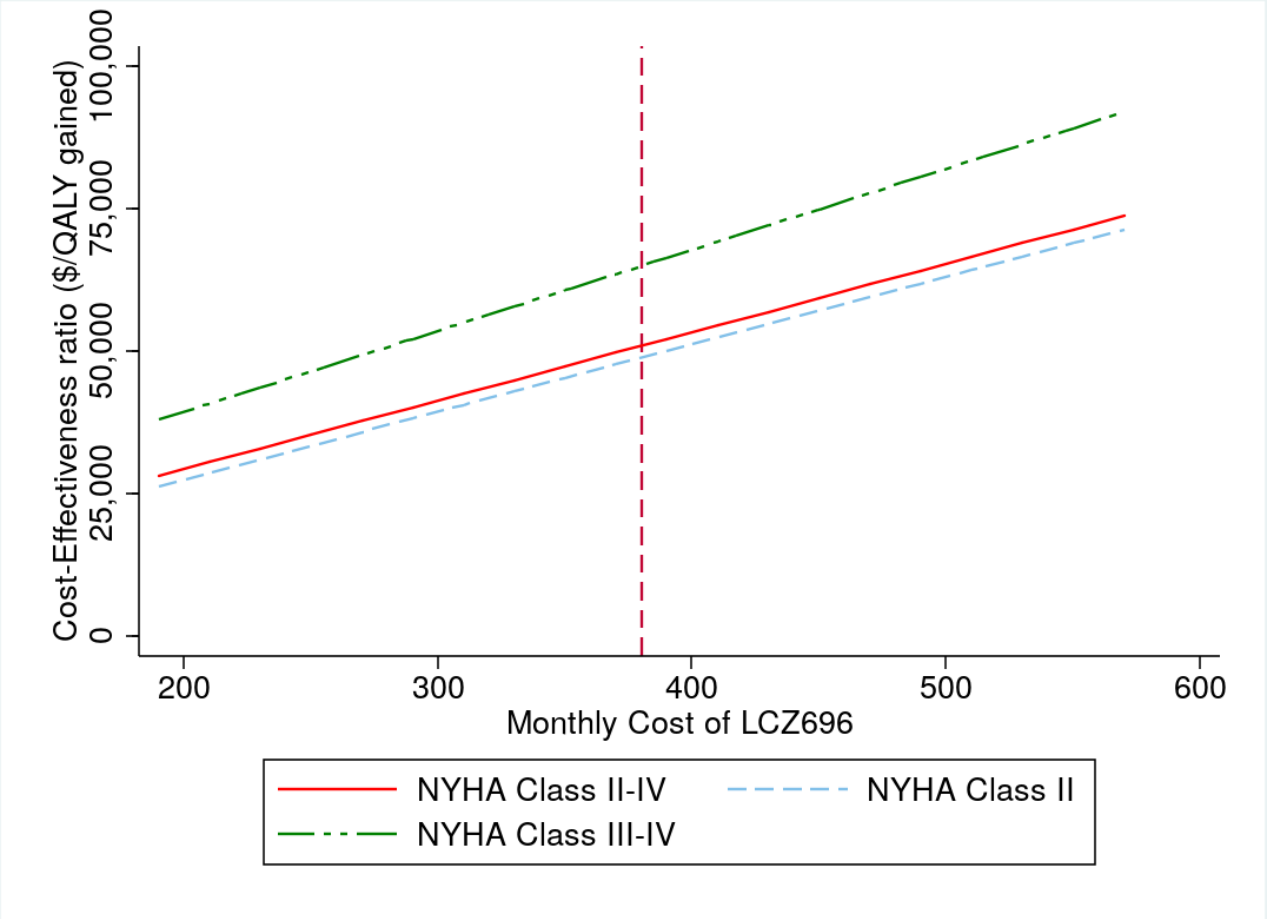
Appendix F. Comparative Value Supplemental Information

Figure F1. Cost-Effectiveness as a Function of the Cost of the CardioMEMS Device



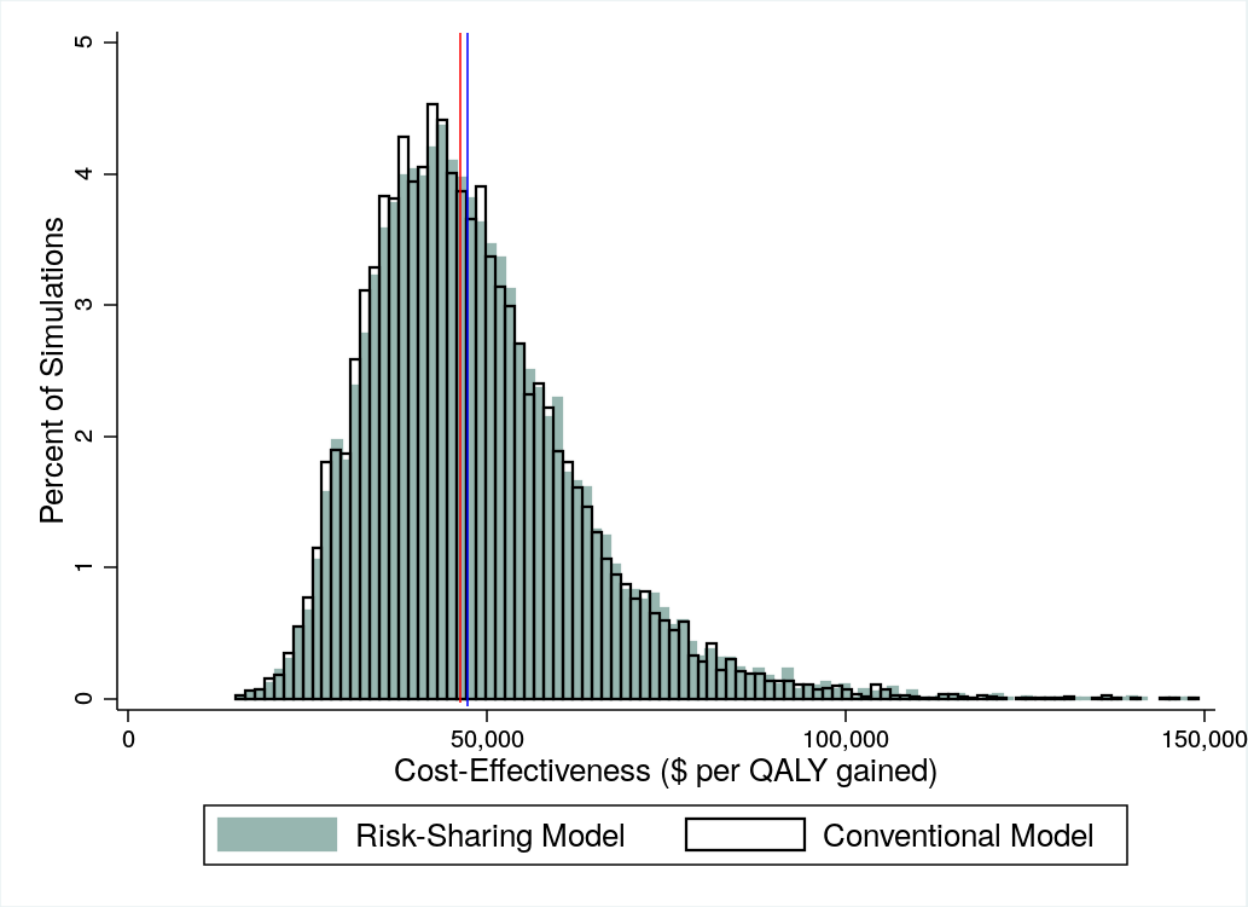
Note: This figure demonstrates the increase in cost per QALY gained with increases in the cost of the CardioMEMS device. The cost per QALY was highest in the CHARM cohort and lowest in the preserved ejection fraction cohort. The cost per QALY gained increases more with increases in device price in the reduced ejection fraction cohort than in the preserved ejection fraction cohort.

Figure F2. Association between Price of Entresto and Cost-Effectiveness



Note: This figure demonstrates the change in cost-effectiveness with different prices of Entresto therapy. There are separate lines for the overall cohort and for both subgroups. The dotted red line represents the cost-effectiveness in the base case.

Figure F3. Histograms: Comparison of the Cost-Effectiveness Ratios in the Conventional Model with 90% WAC Price and the Risk-Sharing Model with 100% WAC Price



Note: This figure overlays the cost-effectiveness estimates in the conventional model and risk-sharing model. The histogram for the conventional model is shifted slightly to the left compared to the risk-sharing model, showing that more simulations demonstrated a lower cost per QALY gained in that model. However, the shape of the two curves is highly similar, demonstrating minimal difference in the uncertainty of the cost-effectiveness in the two models.

Table F1. Calculation of Drug Costs and Cost Offsets over Five-Year Time Horizon

		Cost Offset by Duration of Drug or Device Exposure ($)	Annual Budget Impact by Duration of Drug or Device Exposure ($)	Total Budget Impact by Duration of Drug or Device Exposure ($)
		Calculations (per Patient)		
CardioMEMS	One Year	3,443	15,760	15,760
	Two Years	2,551	7,213	14,426
	Three Years	2,074	4,543	13,629
	Four Years	1,753	3,291	13,165
	Five Years	1,508	2,592	12,961
Weighted Avg.		*2,265*	*6,680*	*13,988*
Entresto	One Year	1,043	3,481	3,481
	Two Years	1,366	3,158	6,316
	Three Years	1,524	3,000	9,001
	Four Years	1,639	2,885	11,541
	Five Years	1,736	2,788	13,941
Weighted Avg.		*1,462*	*3,062*	*8,856*

Table F2. Calculation of Potential Budgetary Impact Threshold Price

Population/ Intervention	(A) Five-Year N	(B) Five-Year Price Benchmark*	(C) Weighted Cost-Offset per Patient (Table F1)	(D) Total Cost-Offset (A) x (C)	(E) PBI Threshold Price ((B) + (D)) ÷ (A)
CardioMEMS	358,738	$3,013,141,305	$2,265	$812,699,164	$10,665
Entresto	1,669,235	$4,518,234,926	$1,462	$2,439,653,725	$4,168

*Price benchmarks are approximately $904 million and $603 million annually for drugs and devices respectively. See http://www.icer-review.org/wp-content/uploads/2014/01/Value-Assessment-Framework-9-71.pdf for further details on benchmark calculations.