

EDITORIAL COMMENT

Championing Effectiveness Before Cost-Effectiveness*



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The proliferation of costly therapies has led to an increased focus on value. In the treatment of patients with advanced heart failure (HF), one such expensive intervention, CardioMEMS (CardioMEMS Heart Failure System, St. Jude Medical Inc., Atlanta, Georgia), is a permanently implanted device to monitor pulmonary artery pressure and enable adjustments in therapy that could avert the need for hospitalization. CardioMEMS was tested in the CHAMPION (CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Heart Failure Patients) trial, a randomized, single-blind multicenter study led by the founder of the company. It included 550 patients with New York Heart Association (NYHA) functional class III HF with ≥ 1 HF-related hospitalization in the past year (1). All patients underwent implantation with the CardioMEMS device. Treatment patients had specific pulmonary artery pressure targets and

treatment algorithms administered by local physicians with contact from study nurses; control patients received routine care. The device was associated with a statistically significant 12% absolute reduction (44% vs. 32%) in the primary efficacy endpoint of HF-related hospitalizations up to 6 months (2). Both primary safety endpoints were also met, including no pressure sensor failures and a 1% rate of device- or system-related complications.

Shortly after approval by the US Food and Drug Administration (FDA), St. Jude Medical completed its acquisition of the CardioMEMS company for \$435 million. The CardioMEMS device (sensor and delivery system) is priced at approximately \$17,750 plus an estimated \$68 monthly for device management. Given the large eligible population of hospitalized NYHA functional class III patients, the device could lead to enormous societal costs. St. Jude expects \$65 million in sales of CardioMEMS in 2016 and plans to apply for a Medicare National Coverage Determination (3). Meanwhile, the Centers for Medicare & Medicaid Services has authorized a supplemental new technology add-on payment for CardioMEMS. To qualify, a new intervention must fulfill multiple criteria, the most important of which is to be “an advance in medical technology that substantially improves, relative to technologies previously available, the diagnosis or treatment of Medicare beneficiaries” (4).

Two previous groups have estimated the cost-effectiveness of the device. In the initial publication of CardioMEMS’ 6-month results, the investigators, who included company employees, calculated a cost of \$13,979 per quality-adjusted life-year (QALY) gained (2). However, many assumptions for that analysis are unavailable. A more recent cost-effectiveness analysis, published in December 2015 by the Institute for Clinical and Economic Review, found a cost of \$57,933 per QALY gained (5).

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In this issue of *JACC: Heart Failure*, Sandhu et al. (6) report a cost-effectiveness analysis based on 17-month CardioMEMS follow-up data in the CHAMPION trial and find a cost of \$71,462 per QALY gained. This finding is the highest cost per QALY gained of the 3 analyses, and according to the American College of Cardiology/American Heart Association Statement on Cost/Value Methodology, this cost places CardioMEMS as an intermediate-value technology (7,8). Sandhu et al. (6) found that the incremental cost-effectiveness ratio depends most on CardioMEMS continuing to have a durable benefit and a device-driven reduction in hospitalizations being associated with increased survival. The analysis showed greater cost-effectiveness in HF patients with preserved ($\geq 40\%$) ejection fraction and lower cost-effectiveness in a lower risk cohort based on the CHARM (Candesartan in Heart Failure-Assessment of Reduction in Mortality and Morbidity) trials (9).

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Confidence in the value of CardioMEMS, however, depends on assumptions regarding the device's effectiveness, which has been questioned. Sensitivity analyses allow one to vary assumptions regarding effectiveness, but if there is no effectiveness, there is no need to calculate cost-effectiveness. Because of concerns about the evidence, the FDA initially denied approval in 2011; however, on the basis of additional analyses, the agency approved the device in May 2014 for patients with NYHA functional class III HF hospitalized for HF in the previous year (10).

What is the source of the uncertainty, given there is a positive pivotal trial? CHAMPION is the single trial of the device, and prior to FDA approval, it had not been marketed in any other country (11). Furthermore, the trial was only single-blinded, and knowledge of treatment allocation may have positively biased this study (12). A bigger problem was concern about contamination of the trial because company-employed nurses who reviewed pulmonary artery pressure readings and provided patient-specific treatment recommendations for treatment patients went beyond the scope of their work in addressing HF issues (13). The FDA reviewed a sample of e-mails between the sponsor and investigational sites (interaction that was completely unexpected) and concluded that the communications included management suggestions that extended beyond the approved study protocol. This conduct may have biased the study results toward reductions in hospitalizations in the treatment group. In essence, the intervention was a combination of the device and more generalized disease management.

In addition, even though the primary effectiveness endpoint was reported as positive, the FDA determined that statistical methods used by the device sponsor were not robust. Using an alternative bootstrap model, even 2 additional hospital stays in the treatment group would have caused the p value to exceed 0.1 (14). Regarding safety, the low rate of complications was reassuring, but because all patients received CardioMEMS implants, there was no true control group for the 2 safety endpoints that were compared versus pre-specified objective performance criteria (14). Furthermore, there appeared to be a difference in benefit according to sex: women in the treatment group had a nonstatistically significant increase in HF-related hospitalizations compared with control patients (14). The device sponsor argued that this outcome may have been related to excessive deaths in the female control patients, who then had a reduced possible study duration for HF-related hospitalizations. Regardless, the FDA advisory panel concluded that the data were insufficient to assess the device's impact on women (14). Ultimately, the panel voted in 2011 that the benefits did not outweigh the risks, and the FDA sent a "not approvable" letter to the CardioMEMS company recommending a new prospective clinical trial.

Instead of commencing a new study, the CardioMEMS company, with FDA input, ended sponsor site communication and followed patients longer. These additional follow-up data (collected after randomization had been revealed) led the company to conclude that the device's benefit persisted even without sponsor interaction with individual site physicians. However, the FDA commented that these follow-up analyses were ancillary because the follow-up study's success criteria were not defined a priori (15). Although p values were provided for those new analyses, there was no attempt to adjust for the multiple comparisons and, thus, any statistically significant device-related benefits were not as rigorous as they would have been in the first (randomized) phase of the trial. Furthermore, at the time of review, 37% of the initially implanted patients had not continued in the study after the initial randomized period, and results for these patients were not included in the follow-up analyses. To summarize, the FDA stated, "it is difficult, at best, to accurately estimate how many HF-related hospitalizations were avoided by the nurse communications." After considering these data, the FDA's advisory panel voted 7-4 that there was not reasonable assurance that CardioMEMS was effective in pre-specified patients, but it voted 6-4 (1 abstention) that the device's

benefits outweigh its risks (16). The FDA approved CardioMEMS in May 2014. The best one can say is that an expert advisory committee with access to all the data delivered a split decision and thus conveyed a strong lack of consensus about whether there was a benefit.

CardioMEMS was therefore approved with lingering uncertainty regarding the benefits underlying the effectiveness data used by Sandhu et al. (6). Additional concern may be related to quality of life, measured in the CHAMPION study by using the Minnesota Living With Heart Failure Questionnaire. Sandhu et al. used only 6-month differences in quality of life because one-half of patient scores were missing at 12 months. The limited 12-month data demonstrated no statistically significant difference in quality of life (15). Furthermore, the Minnesota Living with Heart Failure Questionnaire does not ask about treatment burden, which could be high for patients given that CardioMEMS involves a daily measurement.

Recently published data show that less than one-half ($n = 246$) of patients completed the most recent open-access period; 166 (30.2%) of the initial randomized patient population died, a high rate but not unexpected given that the patients had advanced HF. What is concerning is that 69 (12.5%) of the patients withdrew consent, whereas an additional 28 were noncompliant and 17 were lost to follow-up (16). Indeed, the FDA stated that increased noncompliance “raises questions of whether subjects will continue to comply with the device use requirements as time progresses following implantation” (15). Given that the model of Sandhu et al. depends foremost on a durable device benefit, the fact that patients with this permanently implanted

device are withdrawing consent or being deemed noncompliant would certainly diminish its cost-effectiveness.

The model of Sandhu et al. (6) also relied on a CardioMEMS-driven reduction in HF-related hospitalizations leading to a mortality benefit. If hospitalizations are prevented (a controversial assumption) but there is no survival advantage, then the cost would be more than \$150,000 per QALY gained, making CardioMEMS a low-value intervention. CHAMPION treatment patients had a trend toward improved survival, but this finding did not reach statistical significance, and the trial was not powered to mortality (17). Thus, a survival benefit to CardioMEMS remains a crucial question.

Important uncertainties remain about the ability of the CardioMEMS device to reduce HF-related hospitalizations, improve quality of life, and decrease mortality. The only new planned study of the device is an observational 1,200-patient post-marketing observational cohort with an estimated completion in June 2020 (NCT02279888), which will not answer these questions. We believe that a prospective, randomized trial free of sponsor contact with individual study investigators is required to identify, with more certainty, what the device can do. Until then, any cost-effectiveness calculations are only helpful in showing what the value would be if we knew that the device had benefit. Conviction in CardioMEMS’ cost-effectiveness requires conviction in its effectiveness.

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