JACC: HEART FAILURE VOL. ■, NO. ■, 2016

ISSN 2213-1779/$36.00
PUBLISHED BY ELSEVIER
http://dx.doi.org/10.1016/j.jchf.2016.10.014

Economic Value and Cost Effectiveness of Cardiac Resynchronization Therapy Among Patients With Mild Heart Failure

Projections From the REVERSE Long-Term Follow-Up

Michael R. Gold, MD, PhD,[a] Amie Padhiar, MSc,[b] Stuart Mealing, MSc,[b] Manpreet K. Sidhu, PhD,[c] Stelios I. Tsintzos, MD, MSc,[d] William T. Abraham, MD[e]

ABSTRACT

OBJECTIVES This study investigated the cost effectiveness of early cardiac resynchronization therapy (CRT) implantation among patients with mild heart failure (HF). The differential cost effectiveness between CRT using a defibrillator (CRT-Ds) and CRT using a pacemaker (CRT-P) was also assessed.

BACKGROUND Cardiac resynchronization has been shown to be cost effective in New York Heart Association (NYHA) functional classes III/IV but is less studied in class II HF. The incremental costs of early CRT implementation in mild HF compared with the costs potentially avoided because of delaying disease progression to advanced HF are also unknown. Finally, combined biventricular pacing and defibrillator (CRT-D) devices are more expensive than biventricular pacemakers (CRT-P), but the relative cost effectiveness is controversial.

METHODS Data from the 5-year follow-up phase of REVERSE (REsynchronization reVErses Remodeling in Systolic Left vEntricular Dysfunction) were used. The economics were evaluated from the U.S. Medicare perspective based on published clinical projections.

RESULTS Probabilistic estimates yielded $8,840/quality-adjusted life year (QALY) gained (95% confidence interval [CI]: $6,705 to $10,804/QALY gained) for CRT-ON versus CRT-OFF (i.e., programmed "ON" or "OFF" at pre-specified post-implantation timings) and $43,678/QALY gained for CRT-D versus CRT-P (95% CI: $35,164 to $53,589/QALY gained) over the patient's lifetime. Results were robust to choice of patient subgroup and alterations of ±10% to key model parameters. An "early" CRT-D class II strategy totaled $95,292 compared with $91,511 for a "late" implantation. An "early" implant offered on average 1.00 year of additional survival for $3,781, resulting in an ICER of $3,795/LY gained.

CONCLUSIONS This study demonstrates CRT cost effectiveness in mild HF. The incremental CRT-D costs are justified by the anticipated benefits, despite increased procurement costs and shorter generator longevities. "Early" CRT-D implants have essential cost parity with "late" implants while increasing the patient's survival. (REsynchronization reVErses Remodeling in Systolic Left vEntricular Dysfunction [REVERSE]; NCT00271154) (J Am Coll Cardiol HF 2016;■:■–■) © 2016 by the American College of Cardiology Foundation.

The risk of developing heart failure (HF) is approximately 20% among patients over 40 years of age, and more than 650,000 new cases are diagnosed annually in the United States. Heart failure patients generate more than a million hospital admissions per year and have a short-term readmission risk of 25%. This leads to an annual economic burden of more than $30 billion (1). Clinical (2–4) and cost (5) effectiveness of cardiac resynchronization therapy (CRT) have been demonstrated in

From the [a]Division of Cardiology, Medical University of South Carolina, Charleston, South Carolina; [b]ICON/Oxford Outcomes, Oxford, United Kingdom; [c]ICON/Oxford Outcomes, Morristown, New Jersey; [d]Medtronic Global Cardiac Rhythm and Heart Failure Headquarters, Global Health Economics, Reimbursement and Outcomes Research, Mounds View, Minnesota; and the [e]Division of Cardiovascular Medicine, Ohio State University, Columbus, Ohio. The REVERSE study was funded by Medtronic. ICON/Oxford Outcomes conducted the analysis after receiving funding from Medtronic. Dr. Gold has received funding from Boston Scientific Corp. and St. Jude Medical. Drs. Padhiar, Mealing, and Sidhu are employees of ICON/Oxford Outcomes. Dr. Tsintzos is employed by and owns shares in Medtronic. Dr. Abraham consults for St. Jude Medical.

Manuscript received March 14, 2016; revised manuscript received September 23, 2016, accepted October 27, 2016.

ABBREVIATIONS AND ACRONYMS

CRT = cardiac resynchronization therapy

CRT-D = cardiac resynchronization therapy defibrillator

CRT-P = cardiac resynchronization therapy pacemaker

HF = heart failure

ICD = implantable cardioverter-defibrillator

ICER = incremental cost effectiveness ratio

NYHA = New York Heart Association

QALY = quality-adjusted life year

OMT = optimal medical therapy

patients with New York Heart Association (NYHA) functional classes III/IV HF and QRS prolongation. However, there remain uncertainties regarding the incremental cost effectiveness of CRT devices with defibrillation therapy (CRT-D) compared with that with CRT devices that provide only pacing (CRT-P) (6).

Multiple trials demonstrated patients with mild HF (NYHA functional class II) benefit from CRT (7–9). Much less is known about the cost effectiveness in this population. An analysis from the MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial CRT) (10) determined that CRT-D implantation was cost effective by conventional thresholds in certain subgroups. Given the high initial device costs, longer term follow-up is needed to fully assess cost effectiveness. Moreover, a cost effectiveness evaluation of CRT-P was not possible because these devices were not included in that trial. To address this, a cost effectiveness analysis was performed from the REVERSE (REsynchronization reVErses Remodeling in Systolic Left vEntricular Dysfunction) trial. Importantly, long-term follow-up (11) enabled several analyses (12) that, along with enhanced statistical techniques (13–15), addressed many issues regarding the cost effectiveness of CRT in mild HF.

METHODS

TRIAL POPULATION. REVERSE enrolment criteria have been detailed elsewhere (11). In short, 610 North American and European subjects were randomized. Key inclusion criteria included NYHA functional classes I/II HF, QRS ≥120 ms, left ventricular ejection fraction ≤40%, and optimal medical therapy (OMT) for HF. Subjects received CRT devices that were randomly assigned (2:1) to be "CRT-ON" or "CRT-OFF." Randomization ended when all patients had CRT programmed "ON" at pre-specified post-implantation timing (12 months in North America and 24 months in Europe). The trial was approved by an institutional review committee, and all subjects gave informed consent (NCT00271154).

ECONOMIC MODEL DESIGN. A "proportion-in-state" model, with a 1-month cycle length was used to evaluate lifetime costs and benefits (16,17). Health states were defined by survival ("alive" and "dead") and NYHA functional class. Given the dataset's very small number of class IV patients at any time, this subgroup was combined with class III patients. All patients received biventricular pacing devices, with the controls having CRT initially off, whereas some received implants with a combined biventricular pacing and defibrillator device. All patients designated "alive" were assumed to receive OMT regardless of NYHA functional class. A 3-stage process was subsequently implemented, using statistical models generated and previously published in REVERSE outcome extrapolation (13).

Monthly, a parametric survival function was used to estimate the original cohort proportion still alive at a particular time. Conditional on being "alive," the second statistical model allocated patient proportions to each NYHA functional class subgroup. The final statistical model predicted the number of HF hospitalizations occurring at every time point, using NYHA functional class allocation information.

The covariates cause (ischemic vs. nonischemic), left bundle branch block (LBBB) morphology, median QRS duration (<138 ms to ≥138 ms). A subanalysis of CRT-ON-randomized patients informed the impact of a defibrillator and was used for CRT-D versus CRT-P.

The primary outcome measure was incremental cost effectiveness ratio (ICER), defined as the cost to offer an additional quality-adjusted life year (QALY). Discounting of 3% was applied (18). Probabilistic sensitivity analysis (PSA) was undertaken in main and subgroup analyses, using 1,000 Monte Carlo simulations. Cost effectiveness acceptability curves (CEACs) were also provided. Mean PSA results were presented with 95% credible intervals (CrIs). The model was coded in Excel 2010 software (Microsoft Corp., Redmond, Washington).

MORTALITY, HF DISEASE PROGRESSION AND HF HOSPITALIZATION. Analytical methods to estimate survival, disease progression, and HF hospitalization have been detailed elsewhere (13). In summary, statistical techniques (19) used for the first time in cardiology allowed an estimate of how CRT-OFF patients would have performed had they not turned biventricular pacing "ON" at the pre-specified time points.

ANALYTICAL PERSPECTIVE AND DEVICE IMPLANTATION COSTS. In all analyses, a Centers for Medicare and Medicaid Services (CMS) perspective was used. Device implantation costs (**Table 1**) were based on fiscal year 2014 (FY2014) national average payment rate. Calculations weighted average mixtures of inpatient Medicare Severity Diagnosis-Related Groups and outpatient ambulatory payment classification for device implantation payments and the anticipated physician-related payments for each type of device based on 2014 values. The mixture of inpatient and outpatient implantations was determined by the 2012 physician/supplier procedure