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HVAD: The ENDURANCE Supplemental Trial

Carmelo A. Milano, MD,[a] Joseph G. Rogers, MD,[a] Antone J. Tatooles, MD,[b] Geetha Bhat, PhD, MD,[b] Mark S. Slaughter, MD,[c] Emma J. Birks, MB, BS, PhD,[c] Nahush A. Mokadam, MD,[d] Claudius Mahr, MD,[d] Jeffrey S. Miller, MD,[e] David W. Markham, MD, MSc,[e] Valluvan Jeevanandam, MD,[f] Nir Uriel, MD, MSc,[f] Keith D. Aaronson, MD, MS,[g] Thomas A. Vassiliades, MD,[h] Francis D. Pagani, MD, PhD,[g] for the ENDURANCE Investigators

ABSTRACT

OBJECTIVES The aim of this study was to prospectively evaluate the impact of blood pressure management on stroke rates in patients receiving the HeartWare HVAD System.

BACKGROUND The ENDURANCE trial demonstrated noninferiority of the HeartWare HVAD System versus control (HeartMate II) in patients with advanced heart failure ineligible for heart transplantation. However, stroke was more common in HVAD subjects. Post hoc analyses demonstrated increased mean arterial blood pressure as a significant independent risk factor for stroke.

METHODS The ENDURANCE Supplemental Trial was a prospective, multicenter evaluation of 465 patients with advanced heart failure ineligible for transplantation, randomized 2:1 to HVAD (n = 308) or control (n = 157). The primary endpoint was the 12-month incidence of transient ischemic attack or stroke with residual deficit 24 weeks post-event. Secondary endpoints included the composite of freedom from death, disabling stroke, and need for device replacement or urgent transplantation, as well as comparisons of stroke or transient ischemic attack rates in HVAD cohorts in ENDURANCE Supplemental and ENDURANCE.

RESULTS The enhanced blood pressure protocol significantly reduced mean arterial blood pressure. The primary endpoint was not achieved (14.7% with HVAD vs. 12.1% with control, noninferiority [margin 6%] p = 0.14). However, the secondary composite endpoint demonstrated superiority of HVAD (76.1%) versus control (66.9%) (p = 0.04). The incidence of stroke in HVAD subjects was reduced 24.2% in ENDURANCE Supplemental compared with ENDURANCE (p = 0.10), and hemorrhagic cerebrovascular accident was reduced by 50.5% (p = 0.02).

CONCLUSIONS The ENDURANCE Supplemental Trial failed to demonstrate noninferiority of HVAD versus control regarding the pre-specified primary endpoint. However, the trial confirmed that BP management is associated with reduced stroke rates in HVAD subjects. HVAD subjects, relative to control subjects, more commonly achieved the composite endpoint (freedom from death, disabling stroke, and device replacement or urgent transplantation). (A Clinical Trial to Evaluate the HeartWare™ Ventricular Assist System [ENDURANCE SUPPLEMENTAL TRIAL] [DT2]; NCT01966458) (J Am Coll Cardiol HF 2018;■:■-■) © 2018 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

From the [a]Departments of Surgery and Medicine, Duke University School of Medicine, Durham, North Carolina; [b]Center for Heart Transplant and Assist Devices, Advocate Christ Medical Center, Oak Lawn, Illinois; [c]Cardiovascular and Thoracic Surgery and Department of Cardiovascular Medicine, University of Louisville, Louisville, Kentucky; [d]Divisions of Cardiothoracic Surgery and Cardiology, University of Washington, Seattle, Washington; [e]Departments of Cardiac Surgery and Medicine, St. Joseph's Hospital of Atlanta, Atlanta, Georgia; [f]Heart and Vascular Center, University of Chicago Medicine, Chicago, Illinois; [g]Divisions of Cardiovascular Medicine and Cardiothoracic Surgery, University of Michigan, Ann Arbor, Michigan; and [h]Department of Clinical and Medical Affairs, Medtronic (formerly HeartWare), Framingham, Massachusetts. This study was supported by Medtronic (formerly HeartWare). HeartWare (now Medtronic) sponsored this clinical trial and partnered with us in this analysis, but the authors had access to all the data and provided critical review, writing, and content control. The authors have reported that they have no relationships relevant to the contents of this paper to disclose. John R. Teerlink, MD, served as Guest Editor for this paper.

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ABBREVIATIONS AND ACRONYMS

HCVA = hemorrhagic cerebrovascular accident

HR = hazard ratio

IBPM = improved blood pressure management

LVAD = left ventricular assist device

MAP = mean arterial pressure

mRS = modified Rankin scale

NYHA = New York Heart Association

TIA = transient ischemic attack

Heart failure is one of the leading causes of death in the developed world and is characterized by limitations in survival despite treatment with guideline-directed medical therapies (1). Projections indicate that the prevalence of heart failure will increase by 46% from 2012 to 2030 (2). Patients with heart failure progress to advanced stages and require cardiac transplantation or implantation of durable left ventricular assist devices (LVADs) to extend survival and improve quality of life and functional status (1). As the number of suitable heart donors and patient comorbidities place restrictions on the feasibility of cardiac transplantation, implantation of durable LVADs has emerged as the most frequently applied surgical treatment for end-stage heart failure as either a bridge to transplantation or permanent therapy (i.e., destination therapy) (3,4). Considerable data have documented improvements in survival, functional status and quality of life offered by destination therapy (5-7).

We previously reported the outcomes of the ENDURANCE trial, a prospective, multicenter, randomized controlled trial evaluating the use of the HVAD LVAD (HeartWare, Miami Lakes, Florida) compared with control (HeartMate II, a U.S. Food and Drug Administration-approved LVAD for destination therapy, Abbott, Abbott Park, Illinois) for destination therapy in 445 patients with advanced heart failure not eligible for cardiac transplantation (8). ENDURANCE demonstrated noninferiority of the HVAD compared with control in survival at 2 years free from disabling stroke and alive on the originally implanted device. Although the rate of device exchange was lower with the HVAD, the rate of stroke for the HVAD cohort was significantly greater than the rate for the control device, with the greatest difference seen in the rate of hemorrhagic events. Retrospective multivariable analyses of the data from the HVAD pivotal trial for bridge-to-transplantation indication (9,10) determined that elevated blood pressure was a highly significant, independent risk factor for stroke in patients on HVAD support (11). This observation was corroborated in a post hoc multivariable analysis of data from ENDURANCE (completed by the sponsor but not yet published). It was also observed in ENDURANCE that most strokes occurred early, in the first 6 months post-implantation. The ENDURANCE Supplemental Trial was designed to prospectively determine effectiveness of a blood pressure management strategy to reduce neurological injury in patients receiving the HVAD System. The data from the ENDURANCE trial and the Supplemental Trial data presented here led to Food and Drug Administration approval in September 2017 for the HVAD System as destination therapy in patients with advanced heart failure.

METHODS

The ENDURANCE Supplemental Trial was a prospective, randomized controlled, unblinded, multicenter trial in patients with chronic American Heart Association stage D/New York Heart Association (NYHA) functional class IIIB or IV heart failure in whom optimal medical management was unsuccessful and who were deemed ineligible for transplantation. A total of 465 subjects enrolled at 47 centers were randomly assigned in a 2:1 ratio to receive either the study device (HeartWare HVAD System) (12) or control (HeartMate II). After implantation, device performance, laboratory data, and medications were recorded until hospital discharge and at follow-up visits scheduled at 3, 6, and 12 months. Functional capacity and quality-of-life measurements were performed at 3, 6, and 12 months. All HVAD subjects received oral anticoagulation with a target international normalized ratio of 2.0 to 3.0 and antiplatelet therapy (recommended starting dose of aspirin 325 mg/day). Management of patients who received the control device was at the discretion of their providers and by the device-specific instructions for use.

The primary endpoint was the incidence of neurological injury (defined as any stroke with a modified Rankin scale [mRS] score >0 at 24 weeks post-stroke or any transient ischemic attack [TIA] or spinal cord infarct) at 12 months, including only time on the originally implanted LVAD. Strokes with mRS scores of 0 at 24 weeks ($n = 13$ for HVAD, $n = 5$ for control) were not included in the primary endpoint of neurological injury. The composite secondary efficacy endpoint was freedom from death, disabling stroke (mRS score ≥4), and device malfunctions or failures requiring exchange, explantation, or urgent transplantation over 1 year from implantation, including only time on the originally implanted LVAD. Additional endpoints also included rates for adverse events, which were classified according to the Interagency Registry for Mechanically Assisted Circulatory Support definitions and were adjudicated by an independent clinical events committee (13). Additionally, a pre-specified secondary endpoint analysis called for a comparison of the stroke or TIA rate for the HVAD subjects in the ENDURANCE Supplemental Trial against a performance goal of 17.7%, which was based on the lower bound of the confidence interval in the sintered cohort of the ENDURANCE trial.