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RESEARCH LETTER

Clinical Outcomes in Patients With Acute Decompensated Heart Failure Randomly Assigned to Sacubitril/Valsartan or Enalapril in the PIONEER-HF Trial

David A. Morrow, MD, MPH
Eric J. Velazquez, MD
Adam D. DeVore, MD, MHS
Akshay S. Desai, MD, MPH
Carol I. Duffy, DO
Andrew P. Ambrosy, MD
Yared Gurmu, PhD
Kevin McCague, MA
Ricardo Rocha, MD
Eugene Braunwald, MD

In outpatients with chronic heart failure (HF) with reduced ejection fraction known to tolerate an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, substitution of the angiotensin-neprilysin inhibitor sacubitril/valsartan reduces the rate of cardiovascular death or HF hospitalization.[1] Accordingly, consensus guidelines recommend the use of sacubitril/valsartan to treat patients with symptomatic HF with reduced ejection fraction.[2] Until recently, however, the efficacy and safety of sacubitril/valsartan among patients hospitalized for acute decompensated heart failure (ADHF) was unknown. We have reported the primary results of the randomized double-blind PIONEER-HF trial (Comparison of Sacubitril-Valsartan versus Enalapril on Effect on NT-proBNP in Patients Stabilized from an Acute Heart Failure Episode) demonstrating that, in comparison with enalapril, in patients hemodynamically stabilized during hospitalization for ADHF, sacubitril/valsartan achieved a greater reduction in N-terminal pro-brain natriuretic peptide concentration, was safe and well-tolerated, and was associated with a significant reduction in the serious composite clinical end point of death, rehospitalization for HF, implantation of a left ventricular assist device, or listing for cardiac transplantation (hazard ratio, 0.54; 95% CI, 0.37–0.79).[3] By design,[4] our previously reported analyses of clinical end points relied on investigator-reported data.

We undertook an exploratory analysis of the end point of cardiovascular death or rehospitalization for HF to assess the consistency with the results of the pivotal trial in chronic HF.[1] A post hoc adjudication of rehospitalization for HF and cause of death according to standardized definitions[1,5] was performed by the same blinded clinical events committee (CEC) for rigorous confirmation of these end points. In this research letter, we report the results of these additional analyses from PIONEER-HF.

PIONEER-HF was an 8-week multicenter, randomized, double-blind, double-dummy, active-controlled trial of in-hospital initiation of sacubitril/valsartan in comparison with enalapril in patients stabilized during hospitalization for ADHF.[4] Eligible patients were to have a left ventricular ejection fraction ≤40% and signs and symptoms of HF along with an N-terminal pro-brain natriuretic peptide concentration ≥1600 pg/mL or brain natriuretic peptide concentration ≥400 pg/mL. Patients were enrolled ≥24 hours and up to 10 days after presentation while still hospitalized and were to be hemodynamically stable using protocol-defined criteria.[4] Institutional review boards approved the protocol at all sites. All participants provided written informed consent.

We evaluated the cumulative incidence of the adjudicated prespecified exploratory clinical composite end point of death from any cause, rehospitalization for HF, left ventricular assist device implantation, or listing for cardiac transplant, and the composite of cardiovascular death or rehospitalization for HF, as well. Adjudication of death and rehospitalization for HF was performed by a CEC blinded to

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Sources of Funding, see page xxx

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treatment arm. Cumulative event rates were calculated according to the Kaplan–Meier method and compared between randomized treatment groups using the log-rank test. Hazard ratios with associated CIs were calculated by using a Cox proportional hazards model. Tests for proportional hazards were met.

The analytic cohort included 881 patients, randomly assigned to receive sacubitril/valsartan (n=440) or enalapril (n=441). The median age was 62 years, 635 (72%) were men, and 316 (36%) self-identified as black. The median time from presentation to randomization was 68 (25th, 75th percentile: 48, 98) hours. Baseline characteristics of the population have been published and were similar between the randomized treatment groups.[1]

Over 8 weeks of follow-up, there were 25 deaths (2.8%) and 93 CEC-confirmed hospitalizations for HF (10.6%). Of the deaths, 16 were classified by the CEC as cardiovascular and the remaining deaths were classified as noncardiovascular. Two patients underwent

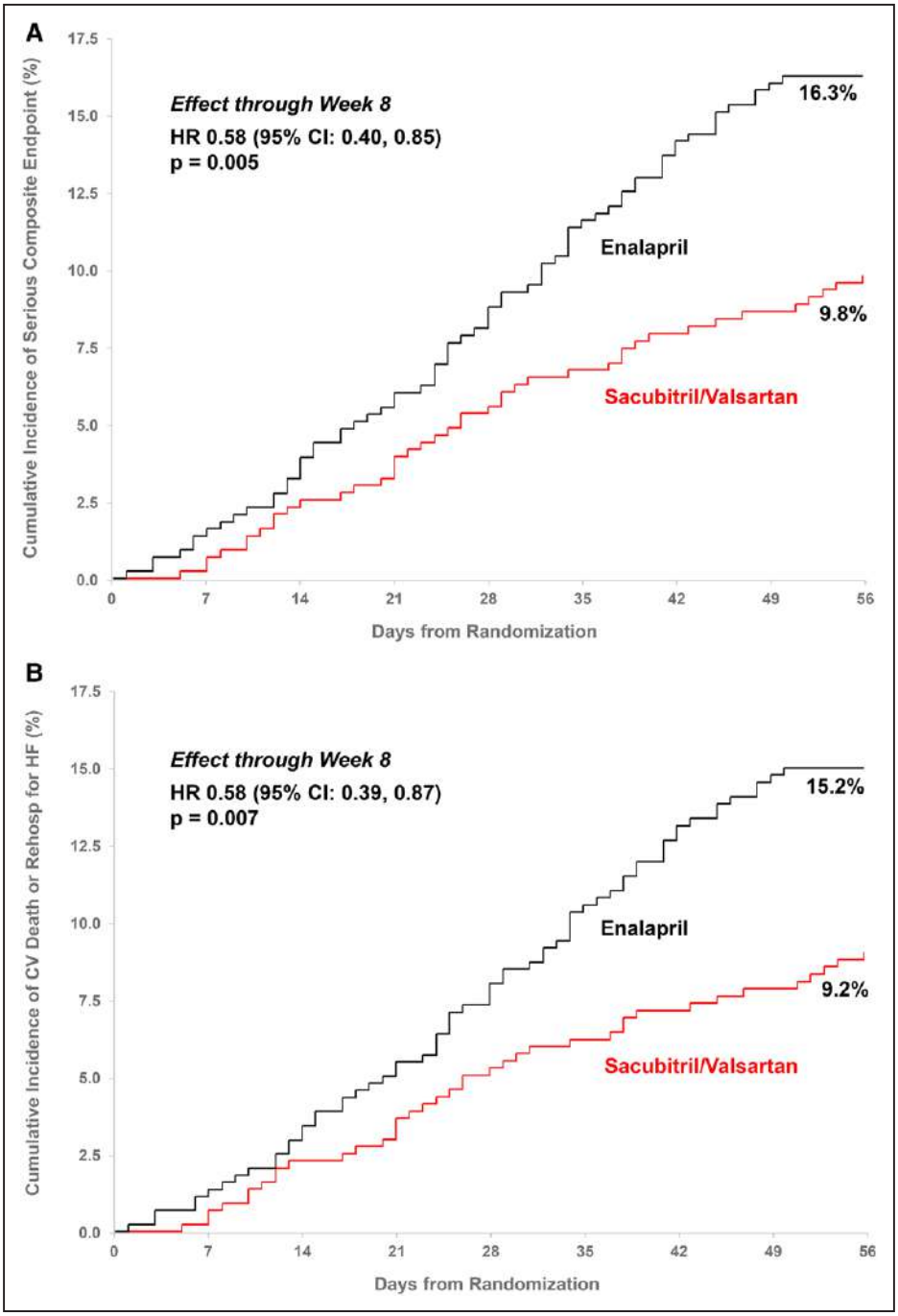

Figure. Effect of sacubitril/valsartan on clinical outcomes.
Kaplan–Meier estimated cumulative incidence of the clinical composite of death from any cause, rehospitalization for heart failure (HF), left ventricular assist device implantation, or listing for cardiac transplant (**A**); the composite of cardiovascular (CV) death or rehospitalization for HF (**B**); and rehospitalization for HF (*Continued*)

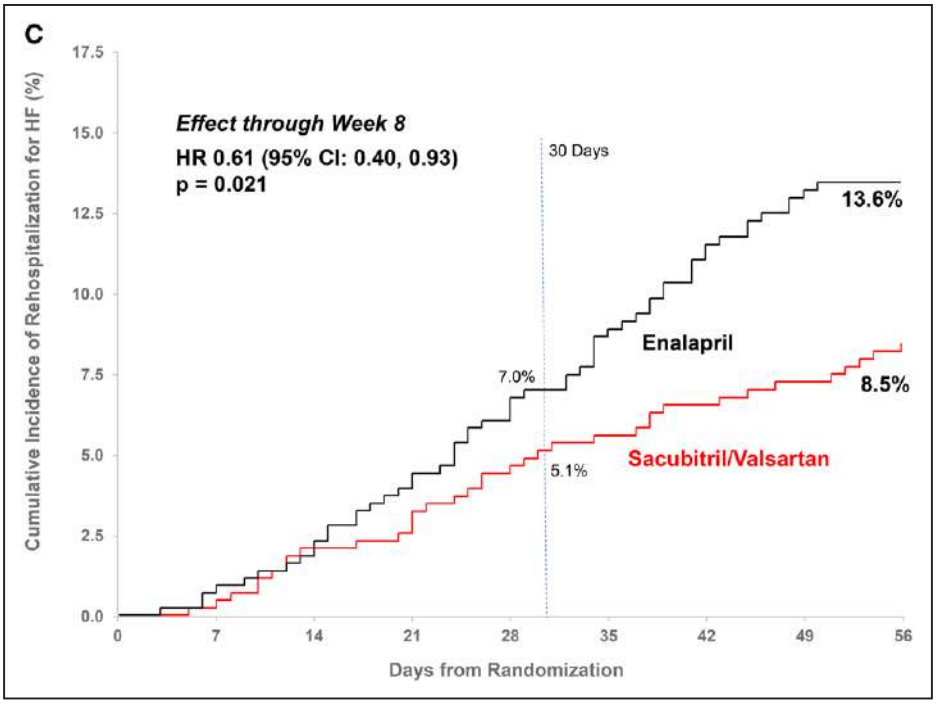

Figure Continued. (**C**). At 30 days, the rates of cardiovascular death or rehospitalization for HF were 5.8% vs 8.6% (HR, 0.67; 95% CI, 0.40–1.11) and for rehospitalization for HF the rates were 5.1% vs 7.0% (HR, 0.72; 95% CI, 0.42–1.25). HR indicates hazard ratio; and Rehosp, rehospitalization.

implantation of a left ventricular assist device, and no patients were listed for transplantation. Considering the prespecified serious clinical composite end point of all-cause death, rehospitalization for HF, left ventricular assist device implantation, or listing for cardiac transplant, CEC adjudication confirmed that patients randomly assigned to sacubitril/valsartan had a significantly lower risk than those randomly assigned to enalapril (hazard ratio, 0.58; 95% CI, 0.40–0.85; *P*=0.005; Figure). Similarly, considering the rates of CEC-adjudicated cardiovascular death or rehospitalization for HF, patients randomly assigned to sacubitril/valsartan were at lower risk (9.2% versus 15.2%; hazard ratio, 0.58; 95% CI, 0.39–0.87; *P*=0.007). Analysis of rehospitalization for HF alone revealed a significant reduction with sacubitril/valsartan for both the time to first event (Figure) and the total number of rehospitalizations for HF (41 versus 64 events; rate ratio, 0.64; 95% CI, 0.42–0.97; *P*=0.037).

Sacubitril/valsartan is more effective than enalapril among stabilized patients hospitalized with ADHF in reducing both N-terminal pro-brain natriuretic peptide and, in this exploratory analysis, the composite of rehospitalization for HF or cardiovascular death. Our analysis reveals early separation of the event curves for clinically relevant end points. Examining the end point of cardiovascular death or hospitalization for HF, we observed an effect of sacubitril/valsartan with the initiation of in-hospital treatment through 8 weeks that is consistent with its established efficacy in chronic HF.[1,2] These data reveal the benefits of administration of sacubitril/valsartan before the transition to home and throughout the subsequent 2 months when morbidity and mortality in patients with ADHF remain high. These data emphasize the value of in-hospital initiation of sacubitril/valsartan after clinical stabilization in patients with ADHF with reduced ejection fraction and extend the results from the PARADIGM-HF trial.[1]

ARTICLE INFORMATION

Data sharing: The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure. However, we encourage parties interested in collaboration and data sharing to contact the corresponding author directly for further discussions.

Correspondence

David A. Morrow, MD, MPH, Cardiovascular Division Brigham and Women's Hospital 75 Francis St, Boston, MA 02115. Email dmorrow@bwh.harvard.edu

Affiliations

TIMI Study Group (D.A.M., Y.G., E.B.) and Cardiovascular Division (D.A.M., A.S.D., E.B.), Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA. Department of Internal Medicine, Yale University School of Medicine, New Haven, CT (E.J.V.). Duke Clinical Research Institute, Duke University, Durham, NC (A.D.D.). Novartis Pharmaceuticals Corporation, East Hanover, NJ (C.I.D., K.M., R.R.). Department of Cardiology, Kaiser Permanente San Francisco Medical Center, San Francisco, CA (A.P.A.). Section on Cardiovascular and Metabolic Conditions, Division of Research, Kaiser Permanente Northern California, Oakland (A.P.A.).

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