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Estimated 5-Year Number Needed to Treat to Prevent Cardiovascular Death or Heart Failure Hospitalization With Angiotensin Receptor-Neprilysin Inhibition vs Standard Therapy for Patients With Heart Failure With Reduced Ejection Fraction

An Analysis of Data From the PARADIGM-HF Trial

Pratyaksh K. Srivastava, MD; Brian L. Claggett, PhD; Scott D. Solomon, MD; John J. V. McMurray, MD; Milton Packer, MD; Michael R. Zile, MD; Akshay S. Desai, MD, MPH; Jean L. Rouleau, MD; Karl Swedberg, MD; Gregg C. Fonarow, MD

IMPORTANCE The addition of neprilysin inhibition to standard therapy, including a renin-angiotensin system blocker, has been demonstrated to improve outcomes in patients with heart failure with reduced ejection fraction (HFrEF) compared with standard therapy alone. The long-term absolute risk reduction from angiotensin receptor neprilysin inhibitor (ARNI) therapy, and whether it merits widespread use among diverse subpopulations, has not been well described.

OBJECTIVE To calculate estimated 5-year number needed to treat (NNT) values overall and for different subpopulations for the Prospective Comparison of ARNI with Angiotensin-Converting Enzyme Inhibitor (ACEI) to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) cohort.

DESIGN, SETTING, AND PARTICIPANTS Overall and subpopulation 5-year NNT values were estimated for different end points using data from PARADIGM-HF, a double-blind, randomized trial of sacubitril-valsartan vs enalapril. This multicenter, international study included 8399 men and women with HFrEF (ejection fraction, ≤40%). The study began in December 2009 and ended in March 2014. Analyses began in March 2018.

INTERVENTIONS Random assignment to sacubitril-valsartan or enalapril.

MAIN OUTCOMES AND MEASURES Cardiovascular death or HF hospitalization, cardiovascular death, and all-cause mortality.

RESULTS The final cohort of 8399 individuals included 1832 women (21.8%) and 5544 white individuals (66.0%), with a mean (SD) age of 63.8 (11.4) years. The 5-year estimated NNT for the primary outcome of cardiovascular death or HF hospitalization with ARNI therapy incremental to ACEI therapy in the overall cohort was 14. The 5-year estimated NNT values were calculated for different clinically relevant subpopulations and ranged from 12 to 19. The 5-year estimated NNT for all-cause mortality in the overall cohort with ARNI incremental to ACEI was 21, with values ranging from 16 to 31 among different subgroups. Compared with imputed placebo, the 5-year estimated NNT for all-cause mortality with ARNI was 11. The 5-year estimated NNT values were also calculated for other HFrEF therapies compared with controls from landmark trials for all-cause mortality and were found to be 18 for ACEI, 24 for angiotensin receptor blockers, 8 for β-blockers, 15 for mineralocorticoid antagonists, 14 for implantable cardioverter defibrillator, and 14 for cardiac resynchronization therapy.

CONCLUSIONS AND RELEVANCE The 5-year estimated NNT with ARNI therapy incremental to ACEI therapy overall and for clinically relevant subpopulations of patients with HFrEF are comparable with those for well-established HF therapeutics. These data further support guideline recommendations for use of ARNI therapy among eligible patients with HFrEF.

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Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Gregg C. Fonarow, MD, Ahmanson-University of California, Los Angeles Cardiomyopathy Center, University of California Los Angeles Medical Center, 10833 LeConte Ave, Room 47-123 CHS, Los Angeles, CA 90095-1679 (gfonarow@mednet.ucla.edu).

In the Prospective Comparison of Angiotensin Receptor-Neprilysin Inhibitor (ARNI) with Angiotensin-Converting Enzyme Inhibitor (ACEI) to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial, randomization to sacubitril-valsartan vs enalapril led to a 20% relative risk reduction in the primary outcome of death from cardiovascular causes or first hospitalization for worsening heart failure (HF) among patients with heart failure with reduced ejection fraction (HFrEF) over a median follow-up of 27 months.[1] While short-term risk reductions for the overall PARADIGM-HF cohort have been reported, absolute risk reduction and number needed to treat (NNT) values for long-term (5-year) follow-up have not. Here, we report estimated multiyear, long-term NNT values for neprilysin inhibition added to standard therapy including renin-angiotensin system (RAS) blockade (ARNI incremental to ACEI) compared with standard therapy with RAS blockade alone and for a neprilysin inhibitor combined with a RAS blocker (ARNI) compared with imputed placebo for the overall patient population as well as for clinically relevant subpopulations in PARADIGM-HF and compare them with those for other well-established HFrEF therapies.

Key Points

Question What is the long-term absolute risk reduction from adding a neprilysin inhibitor to standard therapy, including a renin-angiotensin system blocker, in patients with heart failure with reduced ejection fraction (HFrEF) for cardiovascular death or HF hospitalization and all-cause mortality as quantified by number needed to treat (NNT)?

Findings In this study, the 5-year estimated NNT for the primary outcome of cardiovascular death or HF hospitalization with angiotensin receptor-neprilysin inhibitor therapy incremental to angiotensin-converting enzyme inhibitor was 14 in the overall cohort and ranged from 12 to 19 among different subpopulations. The 5-year estimated NNT was 21 for all-cause mortality incremental to angiotensin-converting enzyme inhibitor and 11 for all-cause mortality when compared with imputed placebo.

Meaning The 5-year estimated NNT with adding a neprilysin inhibitor to standard therapy, including a renin-angiotensin system blocker for HFrEF, overall and for clinically relevant subpopulations are comparable with those estimated for other well-established HF therapies, supporting current guideline recommendations for use of angiotensin receptor-neprilysin inhibitor therapy among eligible patients.

Methods

PARADIGM-HF was a double-blind, randomized clinical trial of sacubitril-valsartan vs enalapril in 8399 men and women with HFrEF (ejection fraction, ≤40%). The primary end point was death from cardiovascular causes or first hospitalization for worsening HF. Full details of the study have been previously described.[1] The trial was approved by the ethics committee at each study center. All enrolled patients provided written informed consent. The study took place from December 2009 to March 2014, and analyses began in March 2018.

In PARADIGM-HF, NNT values for ARNI therapy incremental to ACEI therapy were estimated for trial years 1 to 5 for the primary end point as well as for the end points of death from cardiovascular causes and for all-cause mortality. The NNT values were estimated as the inverse of the difference in estimated absolute risk between the enalapril and ARNI groups at each time point. For years 1 to 3, absolute risk for the enalapril group was calculated directly from Kaplan-Meier estimates. For years 4 and 5, absolute risk in the enalapril group was projected by first calculating annualized incidence rates (incident events per patient-year) during the first year of follow-up postrandomization (r1) and separately for follow-up beyond the first year (r2). The cumulative risk at year 4 was then estimated as 1 year of exposure to the first-year incidence rate followed by 3 years of exposure to the subsequent incidence rate (ie, 4-year cumulative risk = 1 − exp [−{r1 + 3 × r2}]). Absolute risk for the ARNI group was estimated by applying the end point-specific hazard ratio (HR) (ie, $\text{Risk}_{\text{ARNI}} = 1 - \exp[\log\{1 - \text{Risk}_{\text{ENALAPRIL}}\} \times \text{HR}]$) at each time point. Number needed to treat values for ARNI therapy compared with imputed placebo were similarly calculated using data from a previously published ARNI vs imputed placebo analysis from PARADIGM-HF.[2]

Five-year NNT values for other HFrEF therapies were estimated by taking the inverse of the difference in 5-year absolute risk between original trial intervention and control groups for the outcome of all-cause mortality. Five-year risks were estimated using previously published data on event rates with the assumption that all-cause mortality rates and treatment effects were constant after trial conclusion.[2-8] All statistical analysis was performed using STATA (version 14).

Results

The mean (SD) age of the randomized cohort was 63.8 (11.4) years. Of 8399 individuals, 1832 (21.8%) were women and 5544 (66.0%) were white.

Initial trial event and incident rates, as well as NNT values for the overall cohort by year, are displayed in **Table 1**. The 5-year estimated NNT with ARNI therapy incremental to ACEI for the study's primary end point was 14. The 5-year estimated NNT values for the end points of cardiovascular death and all-cause mortality were 19 and 21, respectively. The 5-year estimated NNT values for different subgroups are shown in **Table 2**. Values ranged from 12 to 19 among the different groups for the study's primary end point, from 14 to 31 for the end point of any cardiovascular death, and from 16 to 31 for the end point of all-cause mortality.

The 5-year estimated NNT with ARNI therapy compared with imputed placebo for the study's primary end point and the end points of cardiovascular death and all-cause mortality were 5, 9, and 11, respectively (Table 1). Five-year estimated NNT values for ARNI compared with placebo for different subgroups in PARADIGM-HF are shown in the eTable in the Supplement.

The 5-year estimated NNT values for other well-established HFrEF therapies, compared with control, from selected landmark clinical trials are shown in **Table 3**. For the end

Table 1. Event Rates, Incidence Rates, and NNT for Different End Points for Comparison of Sacubitril-Valsartan With Enalapril and Imputed Placebo

Variable	End Point		
	Primary End Point	Any Cardiovascular Death	All-Cause Mortality
Sacubitril-Valsartan vs Enalapril			
Events			
Enalapril	1117	693	835
Sacubitril-valsartan	914	558	711
Incidence rate[a]			
Enalapril	13.2	7.5	9.0
Sacubitril-valsartan	10.5	6.0	7.6
Difference	2.7	1.5	1.4
Relative risk reduction, %	20	20	15
NNT (incremental to ACEI), y[b]			
1	38	70	77
2	23	38	41
3	19	27	29
4	16	22	24
5	14	19	21
Sacubitril-Valsartan vs Imputed Placebo			
Incidence rate[a]			
Placebo	18.4	9.1	10.6
Sacubitril-valsartan	10.5	6.0	7.6
Difference	7.9	3.1	3.0
Relative risk reduction, %	43	34	28
NNT (vs imputed placebo), y[b]			
1	13	34	38
2	8	19	21
3	7	13	15
4	6	11	12
5	5	9	11

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; NNT, number needed to treat.

[a] Incidence rates are reported per 100 patient-years.

[b] Four- and five-year NNT values projected using original 1- to 3-year trial data.

point of all-cause mortality, the 5-year estimated NNT values were 18 for ACEI, 24 for angiotensin receptor blockers, 8 for β-blockers, 15 for mineralocorticoid antagonists, 14 for implantable cardioverter defibrillator, and 14 for cardiac resynchronization therapy.

Discussion

In this analysis of PARADIGM-HF, we present overall and for clinically relevant subpopulations, the 1- to 5-year estimated NNT values for the addition of neprilysin inhibitor therapy to standard background therapy for the end points of cardiovascular death or hospitalization for HF, any cardiovascular death, and all-cause mortality. The 5-year estimated NNT for ARNI therapy incremental to ACEI therapy was 14 for the primary end point of cardiovascular death or hospitalization for HF and 21 for the end point of all-cause mortality. The 5-year estimated NNTs across clinically relevant subgroups were all in a relatively narrow range, reflecting the lack of significant heterogeneity in clinical benefits of ARNI therapy across different subpopulations.

In our analysis, we demonstrate 5-year estimated NNT values of 12 to 31 for ARNI therapy incremental to ACEI therapy overall and among diverse clinically relevant subgroups of patients with HFrEF across a range of end points including all-cause mortality, cardiovascular mortality, and hospitalization for HF. These 5-year values are similar to or better than currently well-accepted therapies for cardiovascular disease. For example, aspirin for primary prevention has a 5-year estimated NNT of 346 in men and 426 in women for the end point of myocardial infarction, stroke, or cardiovascular death.[9,10] Statins for primary prevention have a 5-year NNT ranging from 20 to 63 across a variety of end points including myocardial infarction, stroke, and all-cause mortality.[9,11] These 5-year estimated NNT values for ARNI therapy are comparable with other well-established HFrEF therapies compared with placebo with background therapy standard at the time for the end point of all-cause mortality.

Neprilysin inhibitor therapy has the potential to significantly impact cardiovascular morbidity and mortality among patients with HFrEF. Cost-effectiveness analyses of ARNI therapy have found it to have an incremental cost per quality-adjusted life-year of $45 000 to $50 000.[12,13] We previously re-

Table 2. Estimated 5-Year NNT for Comparison of Sacubitril-Valsartan With Enalapril

Variable	No.	Incidence Rate: Primary End Point (Enalapril Group)[a]	Estimated 5-y NNT (Incremental to ACEI)[b]		
			Primary End Point	Cardiovascular Death	All-Cause Mortality
Overall cohort	8399	13.2	14	19	21
Age, y					
<65	4279	12.8	15	20	23
≥65	4120	13.5	14	17	19
<75	6836	12.8	14	20	22
≥75	1563	14.8	14	16	18
Sex					
Male	6567	13.8	14	18	20
Female	1832	11.1	16	23	25
Race/ethnicity					
White	5544	12.5	15	20	22
Black	428	19	13	19	20
Asian	1509	14	14	17	21
Other	918	13.2	14	15	18
Region					
North America	602	16.4	13	19	20
Latin America	1433	13.2	14	16	18
Western Europe	2051	10.9	15	23	24
Central Europe	2826	13.9	14	19	21
Asia Pacific	1487	13.5	14	17	21
New York Heart Association Class					
I or II	6308	12.1	15	20	22
III or IV	2078	16.7	13	16	18
Estimated glomerular filtration rate, mL/min/1.73m^2					
<60	3061	16	13	16	18
≥60	5338	11.6	15	21	23
Diabetes mellitus					
No	5492	11.6	15	19	21
Yes	2907	16.2	13	18	20
Systolic blood pressure					
≤Median	4597	14	14	18	20
>Median	3802	12.2	15	20	22
Ejection fraction					
≤Median	4514	15.1	13	17	20
>Median	3884	11.1	15	21	23
≤35%	7437	13.9	14	18	20
>35%	961	9	18	24	23
NT-proBNP					
≤Median	4195	8.8	17	26	27
>Median	4190	18.2	13	15	18
Prior hospitalization for heart failure					
No	3125	10.7	15	20	22
Yes	5274	14.7	14	18	20
Time since diagnosis of heart failure, y					
≤1	2523	9.3	18	22	24
>1 to 5	3232	13.6	14	19	21
>5	2644	16.4	13	17	19

(continued)

Table 2. Estimated 5-Year NNT for Comparison of Sacubitril-Valsartan With Enalapril (continued)

Variable	No.	Incidence Rate: Primary End Point (Enalapril Group)[a]	Estimated 5-y NNT (Incremental to ACEI)[b]		
			Primary End Point	Cardiovascular Death	All-Cause Mortality
MAGGIC score					
Quintile 1 (4-15)	1762	7.6	19	31	31
Quintile 2 (16-18)	1637	12.0	15	22	25
Quintile 3 (19-21)	1675	13.6	14	19	21
Quintile 4 (22-25)	1842	14.2	14	17	19
Quintile 5 (26-40)	1459	20.6	12	14	16

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; MAGGIC, Meta-analysis Global Group in Chronic Heart Failure; NNT, number needed to treat; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

[a] Incidence rates are reported per 100 patient-years.

[b] Five-year NNT values projected using original 1- to 3-year trial data.

Table 3. Estimated 5-Year Risk and NNT for Evidence-Based Heart Failure With Reduced Ejection Fraction Therapies for the Outcome of All-Cause Mortality

Evidence-Based Therapy	Clinical Trial	Relative Treatment Effect (Hazard Ratio)	Estimated 5-y Risk, %			Estimated 5-y NNT for All-Cause Mortality
			Control Group	Intervention Group	Difference	
ACEI	SOLVD[3]	0.84	43.8	38.3	5.5	18
ARB	CHARM-Alternative[8]	0.87	40.5	36.3	4.2	24
β-Blocker	MERIT-HF[4]	0.66	42.3	30.4	11.9	8
MRA	EMPHASIS-HF[5]	0.78	35.8	29.3	6.5	15
ICD	SCD-HeFT[6]	0.77	36.1	28.9	7.2	14
CRT	RAFT[7]	0.75	32.4	25.4	7.0	14
ARNI	PARADIGM-HF (vs enalapril)[1]	0.84	36.7	31.9	4.8	21
ARNI	PARADIGM-HF (vs imputed placebo)[2]	0.72	41.3	31.9	9.4	11

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; CHARM-Alternative, Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity; CRT, cardiac resynchronization therapy; EMPHASIS-HF, Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure; ICD, implantable cardioverter defibrillator; MERIT-HF, Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure; MRA, mineralocorticoid receptor antagonist; NNT, number needed to treat; PARADIGM-HF, Prospective Comparison of ARNI With an ACE-Inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure; RAFT, Resynchronization-Defibrillation for Ambulatory Heart Failure Trial; SCD-HeFT, Sudden Cardiac Death in Heart Failure Trial; SOLVD, Studies of Left Ventricular Dysfunction.

ported an anticipated yearly reduction of 28 484 deaths with optimal implementation of ARNI therapy in the United States, and other data have demonstrated an estimated extension of 1 to 2 years in mean survival with ARNI use compared with ACEI therapy as well as improvement in quality of life.[14-16] Our analysis adds to this work by providing 5-year estimated NNTs that further quantify long-term benefit of ARNI therapy incremental to ACEI overall and among diverse patient subpopulations. Taken together, these results further support current guidelines recommendations for optimal implementation of ARNI therapy among eligible patients with HFrEF.

Limitations

This analysis is limited by the methodology used to calculate 5-year estimated NNT values. For patients in PARADIGM-HF, absolute risk at 4 and 5 years had to be projected using risk from years 1 to 3 given the smaller sample size available at years 4 and 5. To the extent that actual risk differences may vary from this assumption, the NNT values overall and for subpopulations would also differ. Given this limitation, we recommend caution when interpreting subgroup results, although it should be noted that the subpopulations were prespecified and that the NNT values were projected directly from observed event rates in these particular groups during the course of the trial. Direct study data at 5 years were not available for the other reported HFrEF therapies, and so absolute risk at 5 years was estimated by extrapolating published trial data with the assumption that all-cause mortality rates and treatment effects were constant after study completion. Our comparison of ARNI therapy incremental to ACEI to other HF therapies is limited by the difference in trial patient populations and by the difference in baseline goal-directed medical therapy available at the time of each study.

Conclusions

The 5-year estimated NNT values for adding a neprilysin inhibitor to standard therapy, including a RAS blocker, among patients with HFrEF overall and for clinically relevant subpopulations are comparable with those of other well-established HF interventions and are better than those of commonly prescribed drugs for primary prevention. These data support the current guidelines recommendations for ARNI therapy for eligible patients with HFrEF.

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Author Affiliations: Division of General Internal Medicine, University of California Los Angeles

Medical Center, Los Angeles (Srivastava); Division of Cardiovascular Medicine, Brigham and Women's Hospital, Boston, Massachusetts (Claggett, Solomon, Desai); British Heart Foundation Cardiovascular Research Centre, University of Glasgow, Glasgow, United Kingdom (McMurray); Department of Clinical Sciences, University of Texas Southwestern Medical Center, Dallas (Packer); Medical University of South Carolina and Ralph H. Johnson Veterans Affairs Medical Center, Charleston (Zile); Montreal Heart Institute, University de Montréal, Montreal, Quebec, Canada (Rouleau); Department of Molecular and Clinical Medicine, University of Gothenburg, Gothenburg, Sweden (Swedberg); Ahmanson-UCLA Cardiomyopathy Center, University of California Los Angeles Medical Center, Los Angeles (Fonarow); Associate Editor, *JAMA Cardiology* (Fonarow).

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Concept and design: Solomon, Packer, Zile, Swedberg, Fonarow.
Acquisition, analysis, or interpretation of data: Srivastava, Claggett, Solomon, McMurray, Packer, Zile, Desai, Rouleau, Fonarow.
Drafting of the manuscript: Srivastava, Claggett, Fonarow.
Critical revision of the manuscript for important intellectual content: Srivastava, Claggett, Solomon, McMurray, Packer, Zile, Desai, Rouleau, Swedberg, Fonarow.
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