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Natriuretic Peptides as Biomarkers of Treatment Response in Clinical Trials of Heart Failure

Muthiah Vaduganathan, MD, MPH,[a] Brian Claggett, PhD,[a] Milton Packer, MD,[b] John J.V. McMurray, MD,[c] Jean L. Rouleau, MD,[d] Michael R. Zile, MD,[e] Karl Swedberg, MD,[f] Scott D. Solomon, MD[a]

ABSTRACT

OBJECTIVES This study sought to determine whether treatment-related changes in natriuretic peptides (NPs) predict longer-term therapeutic effects in clinical trials of heart failure (HF).

BACKGROUND The lack of reliable predictors of efficacy of drugs and devices in HF has presented a major hurdle to the development and evaluation of novel therapies.

METHODS The study conducted a trial-level analysis of 16 phase III chronic HF trials completed between 1987 and 2013 studying 18 therapeutic comparisons in 48,844 patients. Weighted Pearson correlation coefficients were calculated between average control- or placebo-corrected changes in NPs and longer-term treatment effects on clinical endpoints (expressed as log-transformed hazard ratios).

RESULTS Median follow-up for clinical endpoints was 28 (25th to 75th percentile range: 18 to 36) months. NPs were available in a median of 748 (25th to 75th percentile range: 270 to 1,868) patients and measured at a median of 4 (25th to 75th percentile range: 3 to 6) months after randomization. Treatment-related changes in NPs were not correlated with longer-term treatment effects on all-cause mortality ($r = 0.12$; $p = 0.63$), but were correlated with HF hospitalization ($r = 0.63$; $p = 0.008$). Correlation with HF hospitalization improved when analyses were restricted to trials completed in the last decade (>2010; $r = 0.92$; $p = 0.0095$), using N-terminal pro-B-type NP assays ($r = 0.65$; $p = 0.06$), and evaluating inhibitors of the renin-angiotensin-aldosterone system ($r = 0.97$; $p = 0.0002$).

CONCLUSIONS When examining a broad range of interventions, therapy-related changes in NPs appeared modestly correlated with longer-term therapeutic effects on hospitalization for HF, but not with effects on all-cause mortality. These observations raise important caveats regarding the use of NPs in phase II trials for decision making regarding phase III trials. (J Am Coll Cardiol HF 2018;6:564–9) © 2018 by the American College of Cardiology Foundation.

The identification of potential signals of treatment response to an investigational therapy is an important goal of early-phase clinical trials. Sponsors and clinical trialists are often faced with decisions regarding whether to continue therapeutic development and invest time and resources in subsequent testing. These critical decisions are often based on limited evidence, informed by small phase II trials of short duration.

Various laboratory- and imaging-based markers have been used as phase II trial endpoints in the hope that changes in physiological measures might predict

From the [a]Cardiovascular Division, Brigham and Women's Hospital, Boston, Massachusetts; [b]Baylor Heart and Vascular Institute, Baylor University Medical Center, Dallas, Texas; [c]British Heart Foundation Cardiovascular Research Centre, University of Glasgow, Glasgow, United Kingdom; [d]Montreal Heart Institute, University of Montreal, Montreal, Quebec, Canada; [e]Division of Cardiology, Department of Medicine, Medical University of South Carolina and Ralph H. Johnson Veterans Administration Medical Center, Charleston, South Carolina; and the [f]Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden. Dr. Vaduganathan is supported by a National Heart, Lung, and Blood Institute T32 postdoctoral training grant (T32HL007604). Dr. Packer has served as a consultant for Novartis, Pfizer, Sanofi, Cytokinetics, Cardiokinetix, Amgen, and Cardiorentis. Dr. McMurray's employer, University of Glasgow, was paid by Novartis for Dr. McMurray's time spent as co-chairman of the PARADIGM-HF trial. Dr. Rouleau has served as a consultant for Novartis, AstraZeneca, and Bayer. Dr. Zile has served as a consultant for and received grants from Novartis. Dr. Swedberg has received research support or honoraria from Amgen, AstraZeneca, Novartis, and Servier. Dr. Solomon has served as a consultant for and received grants from Novartis, Amgen, AstraZeneca, Alnylam, Bristol-Myers Squibb, Bayer, Ionis, Theracos, and GlaxoSmithKline. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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the findings of a subsequent definitive phase III study. Natriuretic peptides (NPs) (atrial NP [ANP], B-type NP [BNP], and prohormones of each) have been and continue to be widely used markers of treatment response in early-phase clinical trials in heart failure (HF). In February 2018, according to ClinicalTrials.gov, NPs were being measured in more than 20 phase II HF studies that were actively enrolling or poised for enrollment. Despite this frequent reliance on NPs, data supporting their utility as predictors of efficacy in subsequent trials are limited.

We determined whether treatment-related changes in NPs were correlated with long-term therapeutic effects in HF by examining a broad range of phase III HF trials conducted over the last 3 decades.

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METHODS

We identified completed phase III chronic HF trials that: 1) included at least 100 patients with available NP data; 2) included follow-up measurements of NPs at least 1 month after drug initiation or device application; and 3) evaluated study treatments that were administered for at least 1 month. We excluded all acute HF trials, phase II trials, pilot studies, and trials of patients with post-myocardial infarction left ventricular dysfunction. As individual patient-level data were not consistently available across trials, we instead relied on trial-level estimates of treatment effects on NPs and clinical outcomes. We determined the effect of treatment on NPs by extracting data on the change in NPs in the 2 treatment groups over at least 1 month of follow-up. In trials that reported multiple post-randomization NP values, we selected the time point with the largest available sample. We extracted information on the magnitude of the treatment effects, using reported hazard ratios and 95% confidence intervals for clinical endpoints. Given the wide variability in the primary endpoints selected across trials, we extracted data for all-cause mortality and for hospitalization for HF (when available) from each trial. If published data were insufficient to calculate hazard ratios, then rate ratios were used instead.

Using a previously used approach (1), we plotted the between-group differences in the change in log-transformed NPs against the magnitude of the treatment effect on clinical endpoints. The between-group difference in log-transformed N-terminal pro-BNP (NT-proBNP) was calculated as the ratio of the change (baseline to follow-up) in the treatment arm to that in the control arm (values <1 reflect treatment-related reduction in NT-proBNP). If published data were insufficient to calculate confidence limits around the NP change ratio, we estimated these parameters using the reported sample size and extrapolated SEs from individual patient-level data from the PARADIGM-HF (Prospective Comparison of ARNI With an ACE-Inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure) and ATMOSPHERE (Aliskiren Trial to Minimize Outcomes in Patients with Heart Failure) trials.

We calculated weighted Pearson product-moment correlation coefficients (r) between average control- or placebo-corrected changes in NPs and the longer-term treatment effects on clinical endpoints (expressed as log-transformed hazard ratios). Pearson r values were weighted based on available sample of follow-up NP measurements per trial. The primary analysis was stratified by timing of NP sampling for trials in which NPs were reported 1 to 3 months, 4 to 6 months, and >6 months after randomization. In addition, we determined correlations in subsets of trials based on target population, trial completion date, and type of intervention. No statistical adjustment was made for multiple comparisons. All statistical analyses were conducted using STATA version 14.1 (StataCorp, College Station, Texas).

ABBREVIATIONS AND ACRONYMS

ANP = atrial natriuretic peptide

BNP = B-type natriuretic peptide

HF = heart failure

NP = natriuretic peptide

NT-proBNP = N-terminal pro-B-type natriuretic peptide

RAAS = renin-angiotensin-aldosterone-system

RESULTS

THERAPY-INDUCED CHANGES IN NPs ACROSS HF CLINICAL TRIALS. We identified 16 phase III active or placebo-controlled trials of investigational drug and device therapies completed between 1987 and 2013; these studied 18 unique therapeutic comparisons in 48,844 patients (Table 1). Median trial enrollment was 2,284 (25th to 75th percentile range: 1,553 to 3,834) patients, and patients were followed for a median of 28 (25th to 75th percentile range: 18 to 36) months.

NP SAMPLING. Eleven trials reported follow-up post-randomization NP levels at a single time point. Five trials reported more than 1 post-randomization NP value at a median of 3 sampling time points (range: 1 to 36 months post-randomization). For these 5 trials, the time point with greatest available sample size was selected. Overall, NPs were available in a median subset of 748 (25th to 75th percentile range: 270 to 1,868) patients and measured at a median of 4 (25th to 75th percentile range: 3 to 6) months after enrollment. Time frames of NP sampling were consistently assessed on shorter timescales than follow-up periods for clinical endpoints. NPs were variably sampled across trials: 1 to 3 months (n = 6), 4 to 6 months (n = 7), or >6 months (n = 5) after randomization. The 4 trials completed between 1986 and 1996 used assays of ANP (or its prohormone). Eight of the

TABLE 1 Phase III Clinical Trials Examining Chronically Administered Therapies in Heart Failure

Trial	Ref. #	NP	Comparison (Therapy A vs. B)	Publication Year	End of Enrollment	Total	Follow-Up for Clinical Endpoints (Months)	Available NP Data	Time Point of NP Change Assessment (Months)
CONSENSUS	(8)	ANP	Enalapril vs. placebo	1987	1986	253	6.3	226	1.5
V-HeFT III	(9)	ANP	Felodipine extended release	1997	1994	450	18	385	3
PROFILE	(5)	NT-ANP	Flosequinan vs. placebo	2017	1994	2,345	10.3	234	1
MACH-1	(10)	ANP	Mibefradil vs. placebo	2000	1996	2,950	19.3	352	6
BEST	(11)	BNP	Bucindolol vs. placebo	2001	1998	2,708	24	175	3
COMET	(12)	NT-proBNP	Carvedilol vs. metoprolol	2003	1999	1,511	58	309	12–36
COPERNICUS	(7)	NT-proBNP	Carvedilol vs. placebo	2001	2000	2,289	10.4	815	>6
Val-HeFT	(13)	BNP	Valsartan vs. placebo	2001	2000	5,010	23	3,740	4
CARE-HF	(14)	NT-proBNP	CRT vs. control	2005	2003	813	29.4	813	3
A-HeFT	(15)	BNP	FDC isosorbide dinitrate and hydralazine vs. placebo	2004	2004	1,050	10	683	6
I-PRESERVE	(16)	NT-proBNP	Irbesartan vs. placebo	2008	2005	4,128	49.5	4,128	6
MADIT-CRT	(17)	BNP	CRT-D vs. ICD	2009	2008	1,820	28.8	957	12
RED-HF	(18)	NT-proBNP	Darbepoetin vs. placebo	2013	2012	2,278	28	1,647	6
PARADIGM-HF	(4)	NT-proBNP	Sacubitril/valsartan vs. enalapril	2014	2012	8,442	27	1,942	1
TOPCAT Americas	(19)	NT-proBNP	Spironolactone vs. placebo	2014	2012	1,767	34.8	257	12
TOPCAT Russia/Georgia	(19)	NT-proBNP	Spironolactone vs. placebo	2014	2012	1,678	44.4	143	12
ATMOSPHERE	(20)	NT-proBNP	Aliskiren vs. enalapril	2016	2013	4,676	36.6	3,551	4
ATMOSPHERE	(20)	NT-proBNP	Combination aliskiren/enalapril vs. enalapril	2016	2013	4,676	36.6	3,522	4

A-HeFT = African-American Heart Failure Trial; ANP = atrial natriuretic peptide; ASTRONAUT = Aliskiren Trial on Acute Heart Failure Outcomes; ATMOSPHERE = Aliskiren Trial to Minimize Outcomes in Patients with Heart Failure; BEST = Beta-Blocker Evaluation in Survival Trial; BNP = B-type natriuretic peptide; CARE-HF = Cardiac Resynchronization in Heart Failure; COMET = Carvedilol Or Metoprolol European Trial; CONSENSUS = COoperative North Scandinavian ENalapril SUrvival Study; COPERNICUS = Carvedilol Prospective Randomized Cumulative Survival; CRT = cardiac resynchronization therapy; CRT-D = cardiac resynchronization therapy with defibrillator; EVEREST = Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan; FDC = fixed-dose combination; ICD = implantable cardioverter-defibrillator; I-PRESERVE = Irbesartan in Patients with Heart Failure and Preserved Ejection Fraction; MACH = Mortality Assessment in Congestive Heart Failure; MADIT-CRT = Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy; NT-ANP = N-terminal atrial natriuretic peptide; NT-proBNP = N-terminal pro-B-type natriuretic peptide; PARADIGM-HF = Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure; PROFILE = Prospective Randomized Flosequinan Longevity Evaluation; RED-HF = Reduction of Events with Darbepoetin alfa in Heart Failure; TOPCAT = Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist; V-HeFT = Vasodilator-Heart Failure Trial; Val-HeFT = Valsartan Heart Failure Trial.

12 trials completed thereafter used assays of NT-proBNP (whereas 4 used assays of BNP).

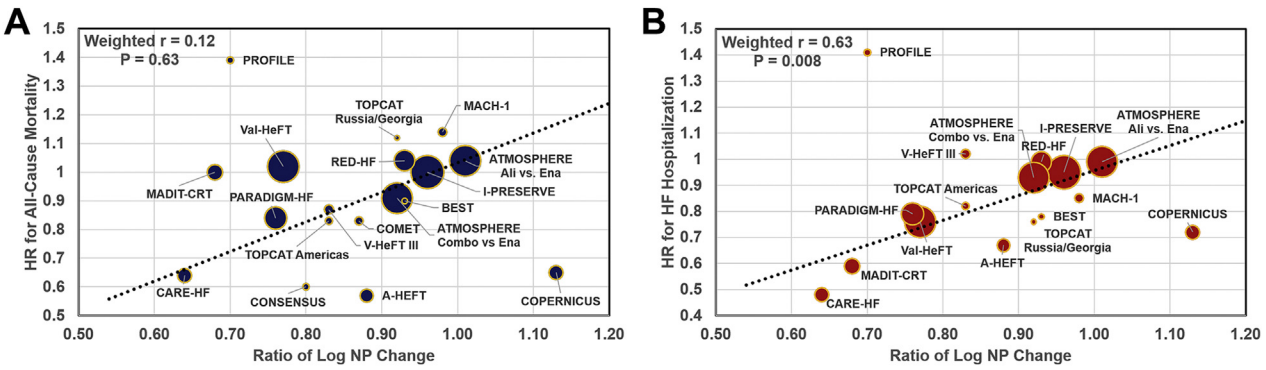
ALL-CAUSE MORTALITY. Treatment-related changes in NPs were not well correlated with therapeutic effects on all-cause mortality across trials (weighted r = 0.12; p = 0.63) (Figure 1A). No major trial-level factors, including timing of NP sampling, identified an improved correlation between therapy-related changes in NPs and longer-term effects on mortality (Table 2).

HOSPITALIZATION FOR HF. In the 16 therapeutic comparisons that had data on the risk of first hospitalization for HF, therapy-induced changes in NPs were significantly correlated with treatment effects on hospitalization for HF (weighted r = 0.63; p = 0.008) (Figure 1B). Correlations between changes in NPs and treatment effects were consistently observed by timing of NP assessment. Significant correlations with hospitalization for HF were observed across several key trial-level subgroups: trials completed in the last decade (>2010 n = 6; weighted r = 0.92; p = 0.0095), using NT-proBNP assays (n = 9; weighted r = 0.65; p = 0.06), and evaluating inhibitors of the renin-angiotensin-aldosterone system (RAAS) (n = 7; weighted r = 0.97; p = 0.0002) (Table 2).

DISCUSSION

In contemporary trials of chronic HF which collectively enrolled nearly 50,000 patients, therapy-related changes in NPs were inconsistently associated with treatment effects on different clinical endpoints. These data are consistent with prior reports that changes in NPs may better reflect therapeutic effects on HF hospitalization (2) than effects on mortality (3). This relationship was influenced by several factors including the NP assay used and therapy tested. Indeed, NPs reflect ventricular wall stress and cardiac filling pressures, which are pathophysiologically linked to symptoms that ultimately lead to worsening

FIGURE 1 Plot of Treatment-Related Changes in Natriuretic Peptides Against Clinical Effects on Cardiovascular Endpoints Across 18 Therapeutic Comparisons



Treatment effects on **(A)** all-cause mortality and **(B)** hospitalization for heart failure (HF) were extracted from each trial. The between-group difference in log-transformed natriuretic peptides (NPs) was calculated as the ratio of change (baseline to follow-up) in the treatment arm to that in the control arm (values <1 reflect treatment-related reduction in NPs) and related to hazard ratio (HR) for each clinical endpoint. The **size of each circle** reflects the number of patients with available follow-up NP levels in each trial. Pearson product-moment correlation coefficients (r) were weighted based on available sample of follow-up natriuretic peptide measurements per trial. Rate ratios were used instead of HRs, if data were not available for the hospitalization for HF endpoint. A-HeFT = African-American Heart Failure Trial; ANP = atrial natriuretic peptide; ASTRONAUT = Aliskiren Trial on Acute Heart Failure Outcomes; ATMOSPHERE = Aliskiren Trial to Minimize Outcomes in Patients with Heart Failure; BEST = Beta-Blocker Evaluation in Survival Trial; CARE-HF = Cardiac Resynchronization in Heart Failure; COMET = Carvedilol Or Metoprolol European Trial; CONSENSUS = COoperative North Scandinavian ENalapril SUrvival Study; COPERNICUS = Carvedilol Prospective Randomized Cumulative Survival; Ena = enalapril; EVEREST = Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan; I-PRESERVE = Irbesartan in Patients with Heart Failure and Preserved Ejection Fraction; MACH = Mortality Assessment in Congestive Heart Failure; MADIT-CRT = Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy; PARADIGM-HF = Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure; PROFILE = Prospective Randomized Flosequinan Longevity Evaluation; RED-HF = Reduction of Events with Darbepoetin alfa in Heart Failure; TOPCAT = Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist; V-HeFT = Vasodilator-Heart Failure Trial; Val-HeFT = Valsartan Heart Failure Trial.

TABLE 2 Weighted Pearson Product-Moment Correlation Coefficients Between Treatment-Related Changes in NPs and Therapeutic Effects

		All-Cause Mortality			Heart Failure Hospitalization		
		Therapeutic Comparisons	Weighted r	p Value	Therapeutic Comparisons	Weighted r	p Value
Overall		18	0.12	0.63	16	0.63	0.008
Time to NP assessment	1-3 months	6	0.34	0.51	5	0.60	0.29
	4-6 months	7	0.11	0.82	7	0.85	0.02
	>6 months	5	−0.91	0.03	4	0.69	0.31
NP assay	ANP	4	0.03	0.97	3	−1.00	0.14
	BNP	4	−0.69	0.31	4	0.43	0.57
	NT-proBNP	10	0.43	0.21	9	0.65	0.06
Target population	Chronic HFpEF	3	0.79	0.42	3	0.80	0.41
	Chronic HFrEF	15	0.06	0.82	13	0.60	0.03
Date of trial completion	<2000	6	−0.01	0.98	4	−0.95	0.05
	2000-2010	6	−0.11	0.83	6	0.68	0.14
	>2010	6	0.86	0.03	6	0.92	0.0095
Intervention	RAAS inhibitor	8	0.38	0.35	7	0.97	0.0002
	Vasodilator	4	−0.24	0.76	4	−0.68	0.32
	β-blocker	3	−0.95	0.21	2	–	–
	Device	2	–	–	2	–	–
	Other	1	–	–	1	–	–

Pearson product-moment correlation coefficients (r) were weighted based on available sample of follow-up natriuretic peptide measurements per trial. Rate ratios were used instead of hazard ratios, if data were not available for the hospitalization for heart failure endpoint.

ANP = atrial natriuretic peptide; BNP = B-type natriuretic peptide; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; RAAS = renin-angiotensin-aldosterone system; other abbreviations as in Table 1.

HF requiring hospitalization. Our finding of a relationship, however, might have been biased by the fact that (in many trials) hospitalizations for HF were adjudicated by a process that often included knowledge of NP levels in individual patients. Although changes in NPs appear to closely reflect treatment effects on hospitalization for HF at the population level, our data do not inform the use of serial NP measurements in predicting therapeutic response in individual patients in clinical practice.

The relationship between changes in NPs and treatment effects on hospitalization for HF were consistently observed across several trial subgroups, namely more recent trials, trials using NT-proBNP assays, and trials evaluating RAAS inhibitors. Although BNP and NT-proBNP have been most extensively studied in contemporary HF clinical trials, other NP assays used in older trials with potentially less rigorous and standardized measurement may be less reliably correlated with treatment effects. Furthermore, the specific mechanism of the investigational therapy in question may be important. As NP levels are stimulated by a well-understood, biologically driven pathway (e.g., increased wall stress), their application may be limited to select trials. For instance, in PARADIGM-HF, NPs appeared to be an optimal marker of therapeutic efficacy. Patients treated with sacubitril/valsartan were more likely to experience significant reductions in NT-proBNP than were those treated with enalapril, which in turn were closely associated with lower risk of subsequent clinical events (4). Indeed, across contemporary chronic HF trials evaluating the RAAS inhibitors, changes in NP were robustly associated with treatment effects on hospitalization for HF.

In contrast, our trial-level analysis indicated that changes in NPs are not associated with changes in mortality. Such a finding is not surprising. The factors that determine mortality in HF are complex, and drugs for HF may have effects on these determinants that are independent of the physiological mechanisms that can be discerned by changes in NPs. For example, the oral vasodilator flosequinan produced sustained reductions in N-terminal pro-ANP levels up to 12 months in the PROFILE (Prospective Randomized Flosequinan Longevity Evaluation) trial (5); yet, long-term therapy increased both the risk of death and of hospitalization for HF. This finding may have been related to a deleterious effect on the myocardium that was related to the drug's positive inotropic effects or its predilection to cause neurohormonal activation (6); neither effect would be expected to be predicted by changes in NPs. Conversely, the β-blocker carvedilol produced short-term increases in NPs (7), but reduced all-cause mortality during long-term treatment, presumably because the drug acts to shield the myocardium from the detrimental effects of prolonged increases in the activity of sympathetic nervous system; short-term changes in NPs would not reflect these cardioprotective actions. In addition, changes in NPs would not be expected to predict the mortality benefits of long-term use of an implantable cardioverter-defibrillator or noncardiac drug actions that may adversely influence prognosis.

STUDY LIMITATIONS. Trials were selected for this analysis by convenience sampling in an effort to capture large, representative phase III chronic HF experiences with sufficient NP samples. It is possible we missed certain trials that would have met eligibility criteria for this analysis if we used a more structured query. Although we aggregated trial-level data from a substantial number of phase III trials, we could not include those that did not measure NPs or did not publish NP measurements that might have been carried out, which might have led to publication bias. We did not have access to patient-level data for all included trials, and thus relied on published reports for treatment effect estimates. As such, we expect that the resulting estimated correlation is likely to be conservative and attenuated in the presence of uncertainty surrounding the exact magnitudes of both sets of treatment effects. Older NP assays that relied on the measurement of ANP or its prohormone might have been less stable or less standardized; this lack of reliability (if present) might have contributed to the particularly poor association between NPs and treatment responses in early trial experiences.

CONCLUSIONS

Our analyses highlight important issues related to our reliance on short-term changes in NPs in a phase II trial to predict the long-term response in a subsequent phase III study. Changes in NPs may be useful in making decisions about the development of select therapies that mechanistically may result in reductions in ventricular wall stress. However, the use of NPs cannot reliably be used to estimate the probable effect of a drug or device on the risk of death. Investigators should continue to be cautious about designating NPs as the primary approach to decision making at the completion of phase II or as a means of determining the most appropriate dose of a drug to be evaluated in a phase III program.

ADDRESS FOR CORRESPONDENCE: Dr. Scott D. Solomon, Cardiovascular Division, Brigham and Women's Hospital, 75 Francis Street, Boston, Massachusetts 02115. E-mail: ssolomon@rics.bwh.harvard.edu.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Short-term treatment-related changes in NP levels are often used as endpoints of interest in early-phase trials of HF therapeutics. Across 18 trial-level comparisons of therapeutic interventions in chronic HF, treatment-related changes in NPs were modestly correlated with longer-term therapeutic effects on hospitalization for HF, but not with effects on mortality. This relationship was influenced by several factors including the NP assay employed and therapy tested.

TRANSLATIONAL OUTLOOK: These aggregate data across a broad range of chronic HF therapeutics tested over the last 3 decades raise important caveats about the use of NPs changes in phase II trials for decision making regarding phase III trials. Accordingly, investigators should remain cautious about designating NPs as the primary approach to decision making at the completion of phase II or as a means of determining the most appropriate dose of a drug to be evaluated in a phase III program. Integrating data from multiple markers of response rather than single measures may be a more "mature" and less risky approach to determining whether a phase II program is successful; the utility of this multimarker approach requires further investigation.

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KEY WORDS biomarker, clinical trial methodology, heart failure, natriuretic peptides, surrogate endpoints