Improvements in Cardiac Biomarkers Are Associated With Better Health-Related Quality of Life in Patients With Light Chain Amyloidosis

Kristen L. McCausland,[1] Spencer D. Guthrie,[2] Tiffany Quock,[3] Miyo Yokota,[1] Martha S. Bayliss,[1] Michelle K. White,[1] Vaishali Sanchorawala[4]

[1]Optum, Johnston, RI, USA; [2]San Francisco, CA, USA; [3]Prothena Biosciences Inc, South San Francisco, CA, USA; [4]Amyloidosis Center, Boston University School of Medicine, Boston, MA, USA

INTRODUCTION

- Amyloid light chain (AL) amyloidosis is a rare, progressive, and typically fatal disease caused by extracellular deposition of misfolded immunoglobulin light chain protein[1-3]
- AL amyloidosis can lead to progressive failure of critical organs and systems. Cardiac involvement, in particular, is associated with significant morbidity and mortality
- Serum levels of brain natriuretic peptide (BNP) or the N-terminal fragment of the probrain natriuretic peptide (NT-proBNP) are widely used to monitor disease progression and response to treatment among patients with AL amyloidosis and cardiac involvement
- Relationships between these cardiac biomarkers and health-related quality of life (HRQoL) are poorly understood in patients with this disease

METHODS

Patient Samples

- Data were drawn from the following AL amyloidosis studies
  - Community-based sample: patients with cardiac involvement who participated in a longitudinal, noninterventional, online study and answered survey items pertaining to previous NT-proBNP response on the initial survey (ClinicalTrials.gov, NCT02574676; N = 108)
  - Center of Excellence (COE) sample: patients seen at the Amyloidosis Center at the Boston University School of Medicine between 1994 and 2014 with complete SF-36® Health Survey (SF-36) and BNP data (N = 95)

Measures of HRQoL

SF-36® Health Survey

- The SF-36 is a 36-item, self-report measure of generic HRQoL; both data sources used the standard (4-week recall) version.[4,5] The online study administered the most recent version of the SF-36 measure, the SF-36v2. The COE data were based on an earlier, but similar, version (SF-36v1). We refer to the measure as SF-36 regardless of the version used
- The survey allows for the calculation of 8 domains of functional health and well-being and 2 summary scores, shown here
  - Physical functioning (PF)
  - Role physical (RP)
  - Bodily pain (BP)
  - General health (GH)
  - Physical Component Summary (PCS)
  - Vitality (VT)
  - Social functioning (SF)
  - Role emotional (RE)
  - Mental health (MH)
  - Mental Component Summary (MCS)
- Each scale/summary measure is calculated and standardized to 50 ± 10 (mean ± SD), as instructed by the published manual for each version of the instrument. A score of 50 is the average in the general population; higher scores represent better functioning
- The SF-36 was administered to patients in the community-based sample as part of the initial online survey
- Patients in the COE sample were encouraged to complete the SF-36 at each clinic visit to help clinicians monitor their health status. SF-36 data were extracted from patient records retrospectively for these analyses

Kansas City Cardiomyopathy Questionnaire

- The Kansas City Cardiomyopathy Questionnaire–Short Form (KCCQ-12),[6] a validated HRQoL measure specific to heart failure, was administered to patients in the community-based sample as part of the initial survey
- KCCQ-12 survey scales range between 0 and 100. Higher scores indicate better functioning. KCCQ-12 items were used to derive a total summary score and the following subscale scores
  - Social limitations (SL)
  - Quality of life (QoL)
  - Physical limitations (PL)
  - Symptom frequency (S)

Statistical Analysis

Cross-Sectional Analyses (community-based sample, N = 108)

- History of NT-proBNP response was based on patients' self-reports that they had responded to treatment with a ≥30% decrease in NT-proBNP
- Generalized linear models were used to compare adjusted least-squares mean SF-36 and KCCQ-12 scores by history of an NT-proBNP response at the time of initial data collection. Means were adjusted by self-reported complete hematologic response
- HRQoL scores were reported in comparison with existing benchmarks, including
  - Mean SF-36 scores from both a general population sample (GP; n = 4040) and patients with congestive heart failure (CHF; n = 137)[5]
    - Analysis of variance was used to compare SF-36 scores with age- and sex-adjusted benchmarks
  - Mean KCCQ scores according to New York Heart Association (NYHA) functional classes based on previously reported data[7]

Longitudinal Analyses (COE sample, N = 95)

- Because of the lack of NT-proBNP data in the COE data set, BNP was used as an alternative measure of cardiac response. BNP response was defined as a ≥30% decrease in BNP between baseline and follow-up evaluations
- Data from the COE sample were extracted retrospectively from patient records. There was no standard schedule for the collection of SF-36 and BNP data at specific study time points
- The sample was limited to patients with complete SF-36 and BNP data from both the initial evaluation and a follow-up visit. Follow-up data were restricted to observations occurring ≥180 days after the initial evaluation
  - Mean follow-up time was 623 days (median, 490; range, 182-1715)
- Generalized linear models were used to examine the longitudinal relationship between SF-36 change scores and BNP responses. The models controlled for baseline SF-36 scores

RESULTS

Patient Characteristics

- Demographic and clinical characteristics of patients from the community-based sample (N = 108) and the COE sample (N = 95) are provided in **Table 1** and **Table 2**, respectively

Table 1. Characteristics of Patients in Community-Based Sample (N = 108)

		NT-proBNP Response		
	All N = 108	No Response n = 33	Response n = 75	Between-Groups Comparison *P* Value
Demographic characteristics, %				
Age, mean years (SD)	59.6 (10.4)	60.1 (12.3)	59.3 (9.6)	0.74
Male	44.4	48.5	42.7	0.58
White	89.8	90.9	89.3	0.55
Employed	34.4	17.2	41.8	0.02
Married	84.9	87.5	83.8	0.43
College degree or higher	57.4	57.6	57.3	0.58
Clinical characteristics, %				
≥3 organs involved	60.2	69.7	56.0	0.13
Organ involvement (other than cardiac)				
Gastrointestinal	54.6	57.6	53.3	0.42
Kidney	59.3	66.7	56.0	0.21
Liver	16.7	18.2	16.0	0.49
Nerve	44.4	54.6	40.0	0.12
≥1 year from symptom onset to diagnosis	51.9	60.6	48.0	0.16
Time since diagnosis, mean years (SD)	4.4 (3.4)	4.8 (4.4)	4.2 (2.9)	0.40

NT-proBNP, N-terminal fragment of the probrain natriuretic peptide; SD, standard deviation.

Table 2. Characteristics of Patients in COE Sample (N = 95)

		BNP Response		
	All N = 95	No Response n = 58	Response n = 37	Between-Groups Comparison *P* Value
Demographic characteristics, %				
Age, mean years (SD)	61.2 (9.9)	63.1 (9.6)	58.2 (9.7)	0.02
Male	63.2	63.8	62.2	0.87
White	93.7	96.6	89.2	0.20
Employed	66.3	64.8	68.8	0.71
Married	82.6	79.2	87.9	0.30
College degree or higher	67.4	66.7	68.8	0.84
Clinical characteristics, %				
≥3 organs involved	62.1	62.1	62.2	0.99
Organ involvement (other than cardiac)				
Gastrointestinal	17.9	20.7	13.5	0.37
Kidney	77.9	86.2	64.9	0.01
Liver	12.6	13.8	10.8	0.76
Nerve	23.2	24.1	21.6	0.78
Time since diagnosis, mean years (SD)	0.52 (1.39)	0.72 (1.8)	0.21 (0.22)	0.03

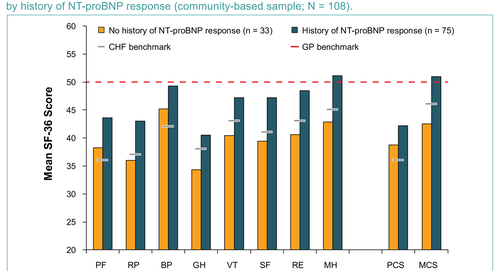
BNP, brain natriuretic peptide; COE, Center of Excellence; SD, standard deviation.

Cross-Sectional Results (community-based sample)

SF-36 Results (Figure 1)

- Differences in SF-36 scores for patients with and without NT-proBNP response were statistically significant ($P < 0.05$ for all domains and both summary components) and clinically meaningful
- Patients who reported a history of NT-proBNP response reported SF-36 scores that were
  - Comparable to the GP benchmark for BP, SF, RE, MH, and MCS
  - Significantly worse than the GP benchmark for PF, RP, GH, VT, and PCS
  - Significantly better than the CHF benchmark across all SF-36 domains and both summary components
- With the exception of GH, patients who did not report a history of NT-proBNP response reported scores that were comparable to the CHF benchmark across all SF-36 domains and both summary components

Figure 1. Burden of disease as measured by SF-36 compared with normative and CHF benchmarks by history of NT-proBNP response (community-based sample; N = 108).

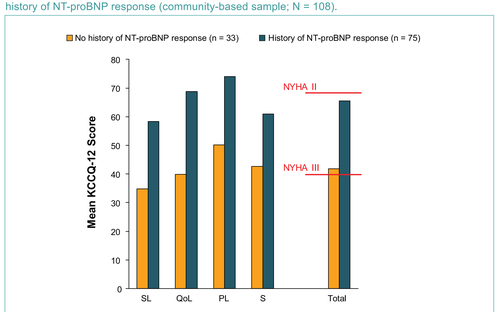


BP, bodily pain; CHF, congestive heart failure; GH, general health; GP, general population; MCS, Mental Component Summary; MH, mental health; NT-proBNP, N-terminal fragment of the probrain natriuretic peptide; PCS, Physical Component Summary; PF, physical functioning; RE, role emotional; RP, role physical; SF, social functioning; VT, vitality.
All SF-36 scores were significantly different by NT-proBNP response ($P < 0.05$ for all).
Community-based sample means were adjusted by self-reported complete hematologic response.

KCCQ-12 Results (Figure 2)

- Differences in KCCQ-12 scores for patients with and without previous NT-proBNP response were statistically significant ($P < 0.05$ for all subscales)
- The average total KCCQ-12 score for patients who reported a history of NT-proBNP response was 66, which corresponds to scores previously observed in patients with NYHA functional class II symptoms
- The average total KCCQ-12 score for patients who did not report a history of NT-proBNP response was 42, which corresponds to scores previously observed in patients with NYHA functional class III symptoms

Figure 2. Burden of disease as measured by KCCQ-12 compared with NYHA functional class by history of NT-proBNP response (community-based sample; N = 108).

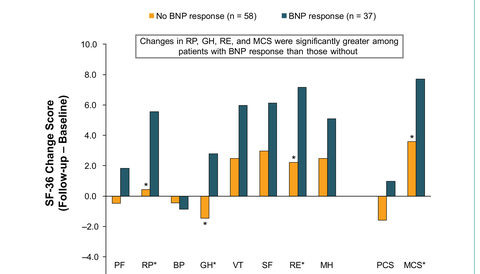


KCCQ-12, Kansas City Cardiomyopathy Questionnaire–Short Form; NT-proBNP, N-terminal fragment of the probrain natriuretic peptide; NYHA, New York Heart Association; PL, physical limitations; S, symptom frequency; SL, social limitations; QoL, quality of life; Total, total score.
All KCCQ-12 scales were significantly different by NT-proBNP response ($P < 0.05$ for all).
Community-based sample means were adjusted by self-reported complete hematologic response.
NYHA II: slight limitation of physical activity, comfortable at rest; fatigue, palpitation, and/or dyspnea caused by ordinary physical activity.
NYHA III: marked limitation of physical activity, comfortable at rest; fatigue, palpitation, and/or dyspnea caused by less than ordinary physical activity.

Longitudinal Results (COE sample)

- BNP response was significantly associated with mean change scores in RP, GH, RE, and MCS (**Figure 3**)

Figure 3. Change in SF-36 scores between baseline and follow-up by BNP response (COE sample; N = 95).



Difference in Change Scores (BNP – No BNP)	PF	RP*	BP	GH*	VT	SF	RE*	MH	PCS	MCS*
	1.8	5.5	-0.3	4.4	2.8	2.7	5.0	2.0	2.7	3.7

BNP, brain natriuretic peptide; BP, bodily pain; COE, Center of Excellence; GH, general health; MCS, Mental Component Summary; MH, mental health; PCS, Physical Component Summary; PF, physical functioning; RE, role emotional; RP, role physical; SF, social functioning; VT, vitality.
*$P < 0.05$; mean change scores are adjusted by baseline scores.

CONCLUSIONS

- This study provided consistent preliminary evidence of a relationship between cardiac biomarkers and HRQoL using multiple data sources and different analytic approaches
- Although these cardiac biomarkers have been commonly used as surrogate treatment measures for survival in AL amyloidosis,[8] the data further support that NT-proBNP may be a useful surrogate for clinical measures such as HRQoL and NYHA class
- Limitations of this study included small sample sizes and cardiac responses based on patient self-report
- Additional research should be performed in larger longitudinal samples with linkages to NT-proBNP laboratory results

REFERENCES

1. Merlini G et al. *N Engl J Med.* 2003;349:583-596.
2. Sanchorawala V et al. *Clin J Am Soc Nephrol.* 2006;1:1331-1341.
3. Mahmood S et al. *Haematologica.* 2014;99:209-221.
4. Ware JE Jr, Sherbourne CD. *Med Care.* 1992;30:473-483.
5. Maruish ME. *User's manual for the SF-36v2 health survey (3rd ed).* Lincoln, RI: QualityMetric, Inc; 2011. https://campaign.optum.com/optum-outcomes.html. Accessed August 16, 2017.
6. Cardiovascular Outcomes Inc. The Kansas City Cardiomyopathy Questionnaire. http://cvoutcomes.org/pages/3214. Accessed August 16, 2017.
7. Green CP et al. *J Am Coll Cardiol.* 2000;35:1245-1255.
8. Merlini G et al. *Leukemia.* 2016;30:1979-1986.

ACKNOWLEDGMENTS

Medical writing assistance was provided by ApotheCom (San Diego, CA, USA) and was funded by Prothena Biosciences Inc.

Disclosures of Interest

Kristen L. McCausland, Miyo Yokota, Martha S. Bayliss, and Michelle K. White are full-time employees of Optum and received funding from Prothena Biosciences Inc to complete the study. Tiffany Quock is an employee of Prothena Biosciences Inc and owns stock in Prothena Corporation plc. Vaishali Sanchorawala has received grant or research support from Takeda, Celgene, Prothena, and Janssen.

SF Health Surveys

Poster

http://bit.ly/2xjuaLJ

Presented at Heart Failure Society of America 2017 (21st Annual Scientific Meeting); September 16–19, 2017; Grapevine, TX, USA