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Cost-Effectiveness of N-Terminal Pro-B-Type Natriuretic-Guided Therapy in Elderly Heart Failure Patients

Results From TIME-CHF (Trial of Intensified versus Standard Medical Therapy in Elderly Patients with Congestive Heart Failure)

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Objectives This study aimed to assess cost-effectiveness of N-terminal pro-B-type natriuretic peptide (NT-proBNP)-guided versus symptom-guided therapy in heart failure (HF) patients ≥60 years old.

Background Cost-effectiveness of NT-proBNP guidance in HF patients is unclear. It may create additional costs with uncertain benefits.

Methods In the TIME-CHF (Trial of Intensified versus Standard Medical Therapy in Elderly Patients with Congestive Heart Failure), patients with left ventricular ejection fraction (LVEF) of ≤45% were randomized to receive intensified NT-proBNP-guided therapy or standard, symptom-guided therapy. For cost-effectiveness analysis, 467 (94%) patients (age 76 ± 7 years, 66% male) were eligible. Incremental cost-effectiveness was calculated as incremental costs per gained life-year and quality-adjusted life-year (QALY) within the 18-month trial period, as defined per protocol.

Results NT-proBNP-guided therapy was dominant (i.e., more effective and less costly) over symptom-guided therapy, saving $2,979 USD (2.5 to 97.5% confidence interval [CI]: $8,758 to $3,265) per patient, with incremental effectiveness of +0.07 life-years and +0.05 QALYs. The probability of NT-proBNP-guided therapy being dominant was 80%, and the probability of saving 1 life-year or QALY at a cost of $50,000 was 97% and 93%, respectively. Exclusion of residence costs resulted in an incremental cost-effectiveness ratio (ICER) of $5,870 per life-year gained. Cost-effectiveness of NT-proBNP-guided therapy was most pronounced in patients <75 years old and in those with <2 significant comorbidities, being dominant in all sensitivity analyses. In the worst-case scenario (excluding residence costs in those with ≥2 comorbidities), the ICER was $11,935 per life-year gained.

Conclusions NT-proBNP-guided therapy has a high probability of being cost effective in HF patients with reduced LVEF, particularly in patients age 60 to 75 years or with less than 2 comorbidities. (Trial of Intensified versus standard Medical therapy in Elderly patients with Congestive Heart Failure [TIME-CHF]; ISRCTN43596477) (J Am Coll Cardiol HF 2013;1:64–71) © 2013 by the American College of Cardiology Foundation

Heart failure (HF) is a large-scale health care problem in developed countries and presently one of the costliest chronic diseases, accounting for ~2% of the total health care budget in Western countries (1,2). Expected increases in the number of patients experiencing HF (2) and the large-scale implementation of expensive device therapy (i.e. implantable

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cardioverter-defibrillators [ICDs] and cardiac resynchronization therapy [CRT]) (3,4) may increase the need for resources devoted to HF treatment even further. With growing demands on limited health care budgets, optimal resource allocation in HF patients is essential. Thus, the adoption of new medical treatments depends increasingly on evidence of cost-effectiveness (5). HF therapy guided by natriuretic peptides, mainly N-terminal pro-B-type natriuretic peptides (NT-proBNP), has been shown to reduce all-cause mortality in patients with chronic HF compared with conventional, symptom-guided clinical care (6,7), especially in patients < 75 years old (8,9), but results were not uniform. It was previously suggested that NT-proBNP-guided therapy might be cost effective, but true cost-effectiveness including sensitivity analyses was not calculated in those studies (10,11). Because NT-proBNP therapy guidance in HF is believed to create additional costs with uncertain benefits, it is not yet recommended. Therefore, we studied cost-effectiveness of the largest randomized trial to date that compared intensified NT-proBNP-guided therapy with standard, symptom-guided therapy. This analysis was predefined by protocol of the TIME-CHF (Trial of Intensified versus Standard Medical Therapy in Elderly patients with Chronic Heart Failure) (8,12).

Methods

Study design and patients. Study design of the TIME-CHF randomized, multicenter trial was published in detail previously (8,12). Briefly, 499 patients age ≥60 years (no upper age limit), with New York Heart Association (NYHA) functional class ≥II HF, left ventricular ejection fraction (LVEF) of ≤45%, and elevated NT-proBNP levels were randomized to receive intensified NT-proBNP-guided therapy or standard, symptom-guided therapy. Guideline-recommended HF therapy (13) was intensified based on predefined escalation rules (12) guided by symptoms alone (symptom-guided group) or additionally by NT-proBNP levels (NT-proBNP-guided group). Patients were followed for 18 months.

Patients who withdrew consent before 90 days of follow-up (n = 30) or who were lost to follow-up (n = 2) were excluded from cost-effectiveness evaluation. Patients without any valid short form-12 (SF-12) questionnaire (n = 19) were removed from the quality-adjusted life-year (QALY) analysis (Online Fig. 1). Patients with missing data in questionnaires (n = 172) or cost data (n = 29) were included on an intention-to-treat basis, and missing data were imputed, using the last telephone contact as censoring date.

The study obtained primary ethics approval from the Ethics Committees of the University Hospital Basel and complies with World Medical Association's 2008 Declaration of Helsinki. All participants gave informed consent before taking part in the study.

Outcome measures: effectiveness estimates. Effectiveness was expressed as life-years and QALYs gained. Life-years are based on overall survival during the 18-month study period. QALYs were calculated using SF-6D preference weights from the SF-12 questionnaire at baseline, 12, and 18 months (14).

Outcome measures: resource volumes and unit costs. Resource use was collected on a patient level at every study visit, as defined per protocol (8,12). A bottom-up cost accounting approach was used, wherein the sum of resources times their unit price yielded the total costs. Unit prices are summarized in Online Tables I to III (15,16). Costs for absence of paid work were not taken into account (most were >65 years old). Costs were determined from the perspective of third party payers. Costs were collected in Swiss currency, 2006 price level, and converted to US dollars, using the January 1, 2006 conversion rate (where $1 US = 1.28 Swiss francs). Costs were not discounted due to the limited follow-up of 18 months.

Abbreviations and Acronyms

CEAC = cost-effectiveness acceptability curve
CRT = cardiac resynchronization therapy
HF = heart failure
ICD = implantable cardioverter-defibrillator
ICER = incremental cost-effectiveness ratio
LVEF = left ventricular ejection fraction
NT-proBNP = N-terminal pro-B-type natriuretic peptide
QALY = quality-adjusted life year
SF-12 = short form-12

Cost-effectiveness outcomes. The primary outcome measure was incremental costs per life-year gained; the secondary outcome measure, was incremental costs per QALY gained. These were expressed as incremental cost-effectiveness ratios (ICERs): where Δ costs (between groups)/Δ effectiveness (between groups). The uncertainty surrounding the ICER is presented in cost-effectiveness planes and cost-effectiveness acceptability curves (CEACs) (17).

Statistical analysis. Baseline results are presented as mean ± SD, median interquartile ranges (IQR), or as frequencies with percentages. Between-group comparisons were performed using the *t*-test, the Mann-Whitney *U* test, or the Pearson chi-square test, as appropriate. Resource use data are presented as means with standard error of the mean despite non-normal distribution because they better represent per patient data than median values and were compared using nonparametric testing. Costs, life-years, and QALYs are presented as means with 2.5 to 97.5% bootstrapped intervals. Between-group comparisons of costs were performed using the bootstrap *t*-test (5). Between-group comparisons of effects were performed using nonparametric testing. Multiple imputation was performed using predictive mean matching, incorporating random variation, and including relevant variables for estimation, with 5 repetitions. A joint comparison of costs and effects was performed by nonparametric bootstrapping with 1,000 resamples (18). Subgroup analyses were performed according to age (pre-specified) and to number of comorbidities and presence of kidney disease (not pre-specified) (12). Sensitivity analyses were conducted to account for uncertainties that could influence cost-effectiveness outcomes and consisted of 1) varying the price of NT-proBNP measurement by ±50%; 2) varying price levels of

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inpatient costs in steps of 10%, up to ±30%; 3) excluding residence costs; 4) excluding subjects with imputed cost data; 5) including all patients on an intention-to-treat basis and treating those who were lost or withdrew as dead; and 6) applying a method for CEACs that does not accept losing effectiveness (19).

Sample size was based on the primary outcome measure of the trial (i.e., hospital-free survival). To show cost-effectiveness at a threshold of $50,000, a power of 80%, and a significance level of 5%, the required sample size would be n = 445 per treatment arm (17). A w-sided p value of 0.05 was considered statistically significant. Analyses were done using SPSS version 18.0 software (SPSS Inc., Chicago, Illinois).

Results

Patient characteristics. Patients were 76 ± 7 years of age, two-thirds were male, mean LVEF was 30 ± 8%, and ischemia was the primary cause of HF in most patients. At baseline, characteristics were matched between treatment groups (Table 1). Patients in the older age group were characterized by more severe symptoms, higher NT-proBNP levels, more comorbidities, lower usage of HF medication, and higher LVEF than the younger age group (Table 1). Patients who were excluded from this analysis (n = 32) differed significantly from the included patients regarding age, clinical presentation, medical history, and medication use (Online Appendix).

Effectiveness estimates. At the 18-month follow-up visit, effect in terms of life-years was in favor of NT-proBNP-guided therapy, at borderline statistical significance (Table 2). NT-proBNP-guided therapy was significantly more effective than symptom-guided therapy in the younger patients (Table 2) and in patients with <2 comorbidities (life-years 1.45, 2.5 to 97.5% confidence interval [CI]: 1.39 to 1.49, in the NT-proBNP-guided group versus 1.34 life-years, 2.5 to 97.5% CI: 1.25 to 1.42, in the symptom-guided group; p = 0.04). The effect in terms of QALYs showed similar but nonsignificant results with smaller effect sizes (Table 2).

Resource use and costs. NT-proBNP-guided treatment introduced more use of HF medication and fewer days in an home for the elderly than for the symptom-guided group (Table 3). Use of other categories of resources was similar between the 2 treatment groups.

A net mean cost reduction of $2,979 (2.5% to 97.5% CI: $8,758 to $3,265; p = 0.24) was achieved with NT-proBNP-guided therapy compared with symptom-guided therapy (Table 2), which was caused mainly by a net saving of $3,626 in residence costs (2.5% to 97.5% CI: −$7,587 to $208; p = 0.09). Cost composition into several categories is shown in Figure 1A, showing that inpatient costs accounted for most of the total costs (i.e., >50%). Costs of NT-proBNP measurements added very little to the total costs (i.e., $184, 0.9%). Medical HF therapy costs were significantly higher in the NT-proBNP-guided group than in the symptom-guided group ($747 vs. $668, respectively; p = 0.04), but accounted for <5% of total costs in both treatment groups. Total costs were significantly higher in the older age group than in the younger age group ($16,872 vs. $26,692, respectively; increment, $9,819; 2.5 to 97.5% CI: $4,568 to $15,773; p = 0.001), which was also caused largely by residence costs. Costs over time are presented in Figure 1B, showing a slight

Table 1 Baseline Characteristics of Patients Separated by Treatment and Age Groups

Parameter	Symptom-Guided (n = 228)	NT-proBNP-Guided (n = 239)	p Value	Age <75 yrs (n = 204)	Age ≥75 yrs (n = 263)	p Value
Age (yrs)	76 ± 8	75 ± 7	0.30	69 ± 4	81 ± 4	<0.001
Male (%)	146 (64)	164 (69)	0.33	152 (75)	158 (60)	0.001
NYHA functional class ≥III (%)	166 (73)	174 (73)	1.00	132 (65)	208 (79)	0.001
CAD cause of HF (%)	138 (61)	128 (54)	0.35	99 (49)	167 (64)	<0.001
Renal failure (%)	123 (54)	132 (55)	0.85	90 (44)	165 (63)	<0.001
Comorbidities ≥2 (%)	167 (73)	172 (72)	0.84	130 (64)	209 (80)	<0.001
Systolic BP (mm Hg)	118 ± 18	118 ± 18	0.67	116 ± 18	119 ± 18	0.05
LVEF (%)	30 ± 11	30 ± 10	0.65	28 ± 10	31 ± 10	0.005
NT-proBNP (pg/ml)	4,472 (2,428–7,371)	3,849 (1,944–6,895)	0.09	2,968 (1,655–5,611)	4,948 (2,819–8,286)	<0.001
RAS blockade (%)	216 (95)	226 (95)	1.00	194 (95)	248 (94)	0.84
Daily dose (% of target dose)	50 (25–100)	50 (25–100)	0.45	50 (44–100)	50 (25–100)	0.13
Beta-blocker (%)	188 (83)	184 (77)	0.17	171 (84)	201 (76)	0.05
Daily dose (% of target dose)	25 (12.5–50)	25 (6.25–50)	0.13	25 (12.5–50)	25 (6.25–50)	0.04
Spironolactone (%)	94 (41)	97 (41)	0.93	96 (47)	95 (36)	0.02
Daily dose (mg)	0 (0–25)	0 (0–25)	0.78	0 (0–25)	0 (0–25)	0.03
Loop diuretics (%)	214 (94)	221 (93)	0.59	185 (91)	250 (95)	0.07
Daily dose (mg furosemide equivalent)	80 (40–100)	60 (40–80)	0.09	40 (40–80)	80 (40–120)	0.03
Residing in nursing facility or home for the elderly (%)	9 (4)	3 (1)	0.08	1 (1)	11 (4)	0.02

Values are mean ± SD, n (%), or median (interquartile range). Dose of RAS-blockade and beta-blockers is given in % of target dose as stated in the European HF guidelines (13).

BP = blood pressure; CAD = coronary artery disease; HF = heart failure; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; RAS = renin angiotensin system.

Table 2 Effects and Costs Between Treatment Groups and Age Groups

Parameter*	NT-proBNP-Guided Treatment (range)	Symptom-Guided Treatment (range)	Increment (Δ) Between Groups (range)	p Value
Life-years				
Overall	1.33 (1.28 to 1.38)	1.26 (1.20 to 1.32)	+0.07 (0.00 to 0.14)	0.05
Age <75 yrs	1.41 (1.34 to 1.45)	1.28 (1.20 to 1.37)	+0.13 (0.02 to 0.21)	0.03
Age ≥75 yrs	1.27 (1.20 to 1.34)	1.24 (1.16 to 1.31)	+0.03 (−0.08 to 0.14)	0.53
QALYs				
Overall	0.91 (0.87 to 0.96)	0.87 (0.82 to 0.92)	+0.05 (−0.02 to 0.11)	0.35
Age <75 yrs	1.00 (0.95 to 1.05)	0.91 (0.83 to 0.98)	+0.10 (0.00 to 0.19)	0.12
Age ≥75 yrs	0.84 (0.78 to 0.90)	0.84 (0.77 to 0.90)	0.005 (−0.08 to 0.10)	0.86
Total costs (U.S. $)				
Overall	20,949 (17,181 to 25,406)	23,928 (19,272 to 8,633)	−2,979 (−8,758 to 3,265)	0.24
Age <75 yrs	16,509 (11,689 to 21,949)	17,275 (12,802 to 2,525)	−765 (−8,072 to 6,952)	0.58
Age ≥75 yrs	24,547 (18,724 to 30,569)	28,854 (21,760 to 36,443)	−4,307 (−13,142 to 4,446)	0.33
Costs minus residence (U.S. $)				
Overall	16,792 (13,980 to 19,551)	16,364 (13,407 to 9,367)	384 (−3,462 to 4,803)	1.0
Age <75 yrs	15,169 (11,177 to 19,782)	14,519 (10,932 to 8,178)	648 (−5,113 to 6,221)	0.53
Age ≥75 yrs	18,107 (14,869 to 21,758)	17,730 (13,721 to 2,057)	378 (−5,165 to 5,917)	0.55

*n for overall = 467; 204 for age <75 years; and 263 for age ≥75 years. Costs, life years, and quality-adjusted life-years (QALYs) represent means with bootstrapped confidence intervals of 2.5 to 97.5%. The p values for life-years and QALYS were derived with the nonparametric Mann-Whitney *U* test. The p values for costs represent bootstrapped *t*-test results.

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

peak in costs in the first month of follow-up, with relatively stable costs over the following 17 months.

Cost-effectiveness. NT-proBNP-guided therapy has an 80% chance of being dominant (i.e., more effective and less costly relative to symptom-guided therapy) (Fig. 2), whereas the chance of NT-proBNP-guided therapy being inferior is only 0.1%. The probability of NT-proBNP-guided therapy being either dominant or having an ICER below $50,000/life-year gained is 97% (Online Table 4, Online Fig. 2A).

Age and number of comorbidities considerably reduced the probability of NT-proBNP-guided therapy being cost effective, whereas the presence of renal disease did not influence cost-effectiveness (Fig. 2, Online Table 4, Online Fig. 2A). Nonetheless, the ICER was dominant for all subgroups, and NT-proBNP-guided therapy had a high probability (>75%) of being cost effective at threshold of $50,000 in all subgroups.

After exclusion of residence costs, the ICER for NT-proBNP-guided therapy was $5,870/life-year saved, and the probability of cost-effectiveness at $50,000 was 86%. Excluding residence cost (Online Fig. 2) or defining ICERs in the less-effective and less costly (i.e., southwestern) quadrant as not acceptable (Online Fig. 2C) lowered the

Table 3 Resource Use for Cumulative 18-Month Estimates

Parameter	Symptom-Guided (n = 228)	NT-proBNP-Guided (n = 239)	p Value	Age <75 yrs (n = 204)	Age ≥75 yrs (n = 263)	p Value
Hospitalization days	15.9 (1.7)	15.6 (1.7)	0.79	13.9 (1.8)	17.2 (1.6)	0.02
ICU days	0.80 (0.16)	0.64 (0.12)	0.64	0.81 (0.16)	0.65 (0.13)	0.82
No. of procedures	0.16 (0.024)	0.19 (0.025)	0.39	0.19 (0.03)	0.16 (0.02)	0.52
No. of CV procedures	0.21 (0.04)	0.27 (0.04)	0.40	0.27 (0.05)	0.22 (0.03)	0.50
No. of standard visits	5.6 (0.13)	5.6 (0.12)	0.63	5.8 (0.12)	5.5 (0.12)	0.12
No. of extended visits	0.78 (0.065)	0.67 (0.058)	0.31	0.74 (0.07)	0.71 (0.06)	1.0
Mean HF medication daily dose						
Beta-blocker	27 [14–50]	35 [19–57]	0.30	42 [20–63]	27 [13–50]	0.001
RAS blockade	69 [48–100]	85 [54–100]	0.007	89 [54–100]	69 [46–100]	0.001
Spironolactone	5 [0–21]	11 [0–24]	0.04	12 [0–24]	4.4 [0–23]	0.06
Loop diuretics	61 [39–103]	55 [32–102]	0.18	54 [28–96]	61 [37–111]	0.11
No. of echocardiography studies	0.097 (0.026)	0.059 (0.016)	0.46	0.12 (0.03)	0.05 (0.01)	0.01
No. of chest radiographs	0.11 (0.023)	0.080 (0.019)	0.33	0.12 (0.03)	0.07 (0.02)	0.09
No. of NT-proBNP measurements	—	3.9 (0.080)	<0.001	2.1 (0.15)	1.9 (0.13)	0.53
Rehabilitation days	7.7 (1.6)	9.2 (1.6)	0.09	4.5 (0.82)	11.6 (1.9)	0.003
Nursing home days	14.6 (4.9)	7.0 (2.9)	0.70	3.7 (2.7)	16.0 (4.5)	0.003
Elderly home days	26.6 (7.2)	7.8 (3.7)	0.003	3.9 (2.9)	27.1 (6.7)	0.009

Values are mean (standard error of mean) or median [interquartile range]. *Mean dosage over the total 18 month study period.

CV = cardiovascular; HF = heart failure; ICU = intensive care unit; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

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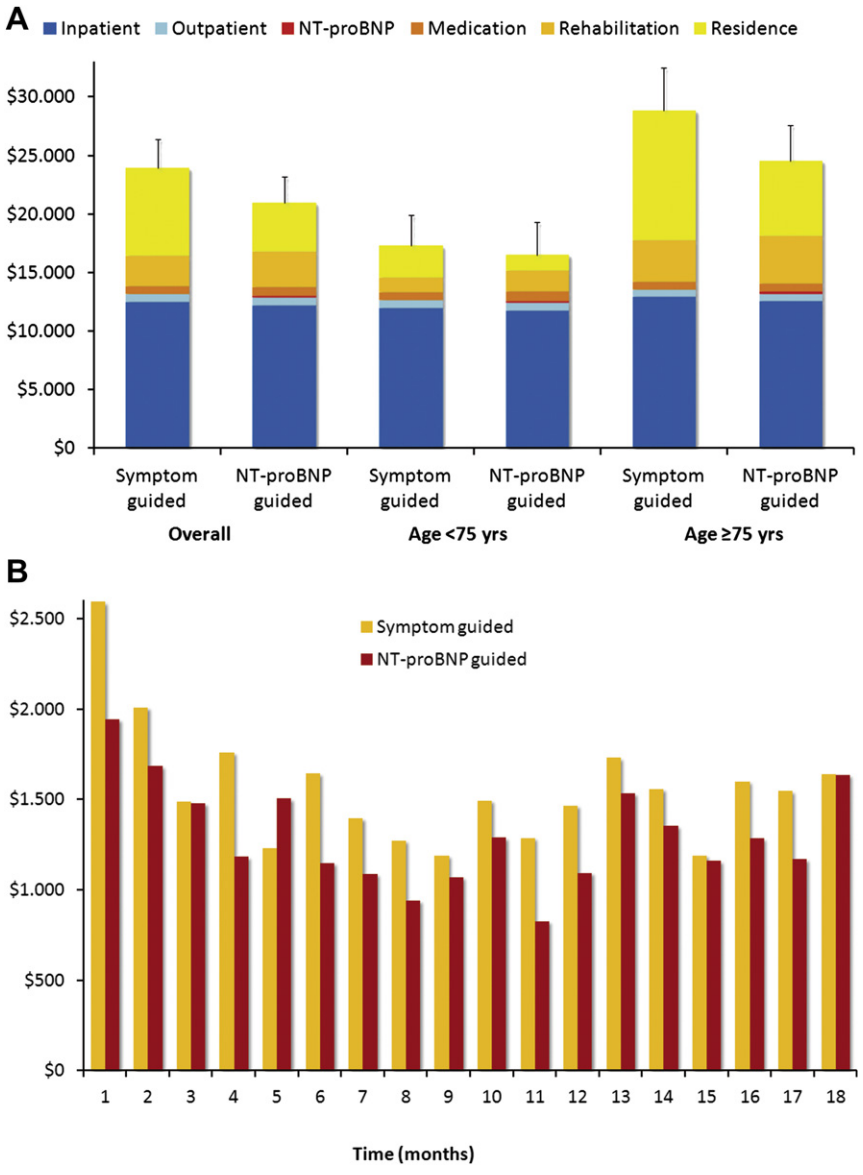

Figure 1 Cost Categories and Costs Over Time

Cost categories during 18-month follow-up by treatment group for the overall population, divided by age groups **(A)**, and costs per month by treatment group **(B)**. NT-proBNP = N-terminal pro-brain natriuretic peptide.

probability of cost-effectiveness by approximately 30% in patients ≥75 years of age and in patients with >2 comorbidities. Importantly, results were robust when residence costs were excluded in patients with <2 comorbidities and patients younger than 75 years of age. Other sensitivity analyses, such as changing price levels of NT-proBNP and inpatient costs, excluding patients with imputed cost data, including all 499 patients, and considering those lost or withdrawn as dead, did not alter the results (Online Table 4). Cost-effectiveness outcome regarding QALYs was similar overall to cost-effectiveness outcomes regarding life-years (Online Table 5).

Discussion

Although the TIME-CHF was negative with regard to the primary endpoint (i.e., hospital-free survival), the secondary endpoint of HF hospital-free survival was favorably affected by NT-proBNP-guided therapy and there was a trend toward improved overall survival (8). Notably, NT-proBNP-guided therapy significantly improved overall survival and HF-free survival in the pre-stratified group of patients <75 years of age but not in those ≥75 years of age. Other studies using NT-proBNP guidance in HF patients confirmed this finding (8,9), but results were not consistent. Thus, it is of particular

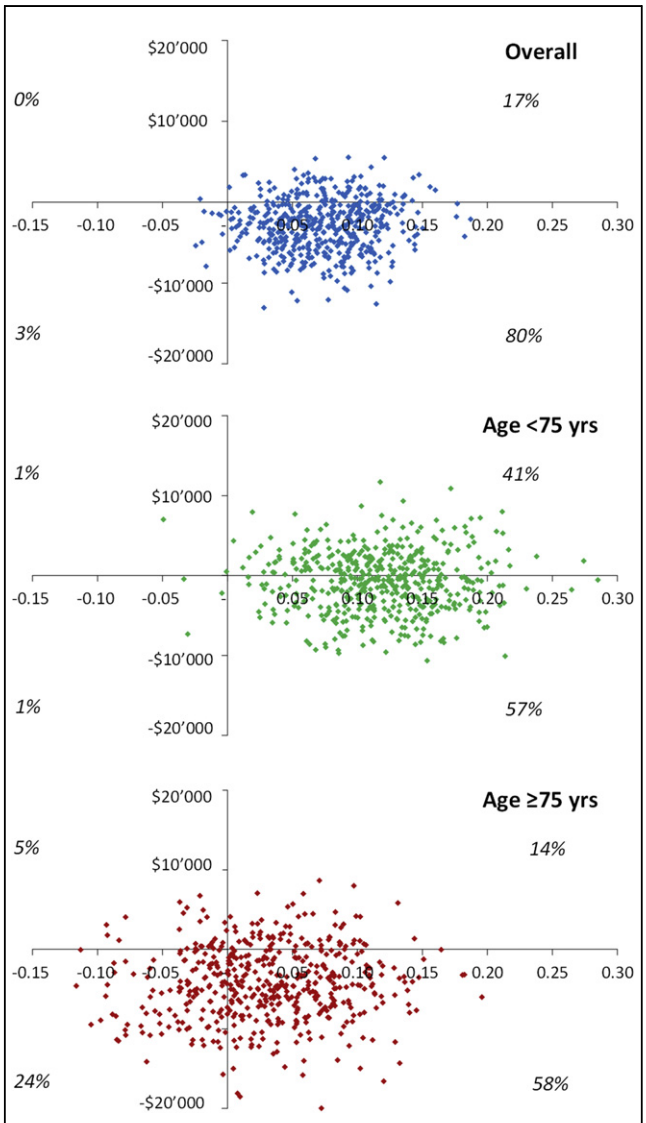

Figure 2 Cost-Effectiveness Planes for Life-Years Gained

Joint difference in effectiveness (Δ life-years, x-axis) and costs (Δ total costs, y-axis) from among 1,000 bootstrap samples, representing the uncertainty surrounding the ICER. The percentage of joint density occupying each quadrant indicates the likelihood that cost-effectiveness lies in that quadrant. Southeast = more effective and less costly (i.e., dominant); Northeast = more effective and more costly; Northwest = less effective and less costly (i.e., inferior); Southwest = less effective and less costly. For SW and NE quadrants, cost-effectiveness depends on the threshold applied.

interest to learn about the cost-effectiveness of NT-proBNP-guided care, as the fact that no significant differences between effects were found does not rule out the possibility that an investigated therapy is good value for the cost (i.e., cost effective) (5). Whereas the use of NT-proBNP levels was proposed to be cost effective in other settings, such as the diagnosis and initial management of patients with dyspnea in the emergency department (20,21) and screening of asymptomatic left ventricular dysfunction (22), data for cost-effectiveness of NT-proBNP-guided outpatient management of HF patients are limited. One simulation model and 1 relatively small prospective trial concluded that introduction of NT-proBNP measurement in chronic HF may be cost effective (10,11). These studies were limited by the fact that no or only little actual cost data were collected. This comprehensive cost-effectiveness analysis alongside a prospective randomized trial shows that NT-proBNP-guided therapy has a high chance of being cost effective in HF patients with reduced LVEF, who are ≥60 years of age. The probability of cost-effectiveness was most pronounced in patients 60 to 74 years of age and in patients with <2 comorbidities.

Costs directly associated with the intervention (i.e., NT-proBNP measurements) accounted for <1% of the total cost, and changing price levels of NT-proBNP measurement did not alter our results. Results were also robust relative to changes in price level of inpatient care. The net cost reduction in our study was caused mainly by a reduction in residence costs (i.e., staying in a nursing home or home for the elderly). Whether this is a direct and causative result of NT-proBNP-guided therapy, however, is difficult to determine. Factors that might be associated with residency, like the SF-12 mental and physical component and 6-min walking distance, did not differ between the treatment groups, nor did the improvement in these factors over time (8). Despite randomization, there was some, although not statistically significant, imbalance between baseline residency. Because we examined a real-life elderly HF population for whom residence costs have large socioeconomic consequences (23), it seemed reasonable to include residence costs in our cost-effectiveness analysis. However, to avoid overinterpreting the potential benefit of NT-proBNP-guided therapy in HF, we performed a sensitivity analysis in which residence costs were excluded. Even in that scenario, the ICER was still very acceptable ($5,870/life-year gained), and the chance of NT-proBNP-guided therapy being cost effective remained 86% at a threshold of $50,000/life-year gained. In patients ≥75 years of age and in those with significant comorbidities, however, the probability of cost-effectiveness was considerably lowered when residence costs were excluded, making cost-effectiveness questionable in these subgroups. In the younger patients and those with <2 comorbidities, results remained highly in favor of NT-proBNP-guided therapy.

In comparison with well-established therapies in HF, NT-proBNP-guided therapy has at least comparable if not more economic benefits (24). The ICER of NT-proBNP-guided therapy was well below the range of most established HF therapies and outpatient strategies, even after exclusion of residence costs (Online Table 6) (25–30). As there is no consensus on reasonable threshold value for cost-effectiveness, thresholds vary widely, up to $100,000 (4,31); we applied an arbitrary threshold of $50,000/life-year gained (Online Fig. 2 illustrates how readers may apply their own threshold).

Study strengths and limitations. A particular strength of our study is that we included a real-life HF population as

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seen in clinical practice, which is reflected by age and high number of comorbidities in our population. Also, comprehensive costing was performed on a patient level in a prospective manner.

Several limitations need to be noted. First, cost data and SF-6D data were not complete for all patients. Therefore, we imputed missing cost data and SF-6D data by multiple imputation on an intention-to-treat basis. The influence of imputed data in sensitivity analysis was negligible. Still, 32 patients were excluded from the life-year analysis, and an additional 19 were excluded from QALY analysis because data were too limited for these patients and imputing data would be based on assumptions only. Excluded patients differed in many aspects from those included with regard to baseline characteristics, but a sensitivity analysis including all 499 patients and treating those lost or withdrawn as dead at last time of contact did not alter our results. Second, our analyses were not restricted to costs related to HF only. However, real-life health care costs and responses to interventions are influenced by comorbidities and expenses cannot easily be attributed to 1 single disease. To explore this issue, we performed several subgroup and sensitivity analyses and showed important influences of comorbidities and residence costs on our results. Third, our study was underpowered to perform a test of hypothesis on cost-effectiveness. This is a very common limitation of health economics evaluations. To deal with this concern, we report the estimated probability and display the uncertainty of cost-effectiveness, as appropriate (17). As it is likely that cost-effectiveness studies will become more important regarding the currently overloaded economic situation, future studies should be more aware of sample size calculations to be able to draw definite conclusions. Finally, the generalizability of our findings could be debated as we did not consider differences across countries or health systems. However, we performed sensitivity analyses with varying price levels to account for possible uncertainty in this regard and found that changing price levels did not alter our results.

Conclusions

NT-proBNP-guided therapy has a high probability of being cost effective. Importantly, incremental costs of NT-proBNP measurements themselves were negligible, and the chance of NT-proBNP-guided therapy increasing costs without any health benefit is extremely low. Although future research is required to replicate the study results in a large trial, our results encourage use of NT-proBNP guidance in HF care with reduced LVEF, especially in patients <75 years of age and those with <2 comorbidities.

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Key Words: cost effectiveness ■ heart failure ■ NT-proBNP.

APPENDIX

For expanded Methods and Results sections and supplemental figures and table, please see the online version of this article.