A trial-based economic evaluation of 2 nurse-led disease management programs in heart failure

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Background Although previously conducted meta-analyses suggest that nurse-led disease management programs in heart failure (HF) can improve patient outcomes, uncertainty regarding the cost-effectiveness of such programs remains.

Methods To compare the relative merits of 2 variants of a nurse-led disease management program (basic or intensive support by a nurse specialized in the management of patients with HF) against care as usual (routine follow-up by a cardiologist), a trial-based economic evaluation was conducted alongside the COACH study.

Results In terms of costs per life-year, basic support was found to dominate care as usual, whereas the incremental cost-effectiveness ratio between intensive support and basic support was found to be equal to €532,762 per life-year; in terms of costs per quality-adjusted life-year (QALY), basic support was found to dominate both care as usual and intensive support. An assessment of the uncertainty surrounding these findings showed that, at a threshold value of €20,000 per life-year/€20,000 per QALY, basic support was found to have a probability of 69/62% of being optimal against 17/30% and 14/8% for care as usual and intensive support, respectively. The results of our subgroup analysis suggest that a stratified approach based on offering basic support to patients with mild to moderate HF and intensive support to patients with severe HF would be optimal if the willingness-to-pay threshold exceeds €45,345 per life-year/€59,289 per QALY.

Conclusions Although the differences in costs and effects among the 3 study groups were not statistically significant, from a decision-making perspective, basic support still had a relatively large probability of generating the highest health outcomes at the lowest costs. Our results also substantiated that a stratified approach based on offering basic support to patients with mild to moderate HF and intensive support to patients with severe HF could further improve health outcomes at slightly higher costs. (Am Heart J 2011;162:1096-104.)

With readmission rates varying between 13% and 50% over a period ranging from 15 days to 6 months, respectively, recurrent hospitalization in patients with heart failure (HF) poses an increasing demand on the scarce health care resources.[1] In addition, mortality after hospitalization for acute HF reaches up to 18.7% within the first 6 months after hospital discharge.[2] These alarming event rates provide ample justification for identifying opportunities to improve quality of care and treatment compliance and to lower the rates of hospital readmission.

Because of an increasing demand on health care services, provision of patient care by specialized nurses is on the rise in several Western nations.[3,4] The results of previously published meta-analyses suggest that nurse-led disease management programs can indeed improve clinical outcome and quality of life in patients with HF.[5,6] However, until now, only few articles have addressed the important question of whether such programs can produce these favorable effects in an affordable manner.[7-9]

The aim of the present study was to assess whether the nurse-led disease management programs from the COACH study were cost-effective.[10] To our knowledge, no cost-effectiveness analysis has yet been conducted alongside such a large-scale, multicenter trial in which different levels of intensity for nurse-led management of patients with HF were compared against routine follow-up visits to a cardiologist.

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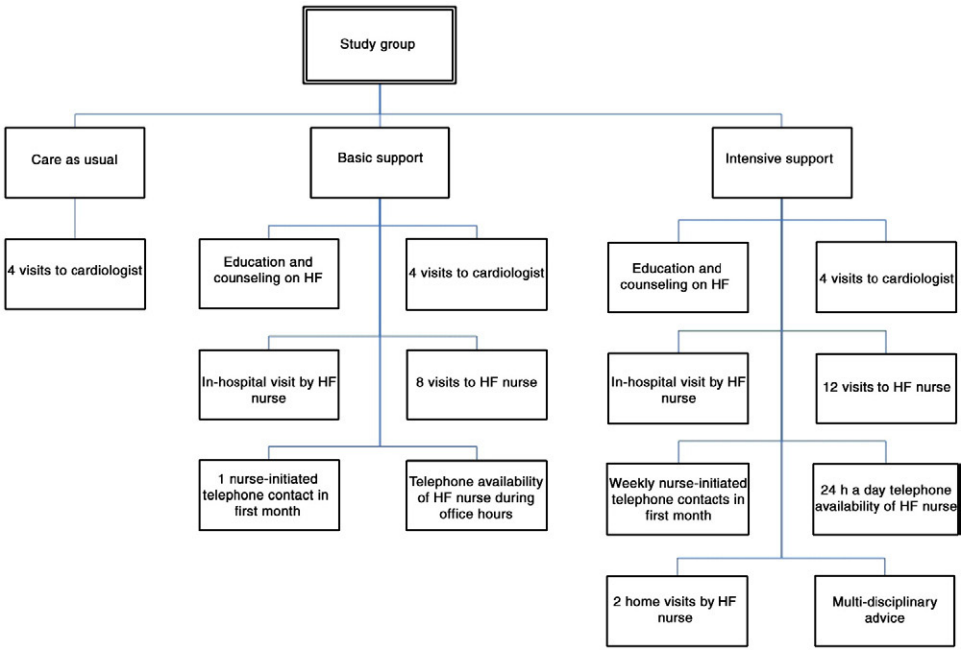
Figure 1



Follow-up visits within each of the 3 study groups.

Methods

Randomized controlled trial

The COACH study was a multicenter, randomized controlled trial in which 1,023 patients from 17 hospitals were enrolled during a hospitalization because of HF.[10] Patients were randomly assigned to either the care-as-usual group (routine follow-up by a cardiologist) or to 1 of the 2 intervention groups with additional basic or intensive support by a nurse trained in the management of patients with HF (see Figure 1 for a detailed overview). All patients were ≥18 years and had evidence of structural cardiac dysfunction (both patients with impaired and preserved left ventricle ejection fraction could participate). The major reasons for exclusion were concomitant enrollment in another trial, ongoing assessment for heart transplantation, recent history of an invasive procedure or cardiac surgery within the last 6 months, or plan of undergoing such a procedure within the next 3 months.

The first primary end point was a composite of HF readmission or death from any cause. *A hospitalization for HF* was defined as an unplanned overnight stay in a hospital due to progression of HF or directly related to HF. The second primary end point was the number of days lost because of death or HF readmission. The secondary end points were the 2 individual components of the combined end point: readmission for HF or death from any cause. Data on readmission and mortality were collected from the patient's medical record and by interviews with the patient during follow-up. The reason for readmission, the cause of death, and the date of the event were adjudicated by a central end point committee. The total follow-up time of the trial was 18 months.

Costs

The economic evaluation was conducted from a health services' perspective, meaning that only direct costs within the health care sector were included. Indirect costs, such as productivity losses, were considered to be less relevant because most patients had retired. In particular, the following 4 cost categories were identified:

1. the cost of the intervention;
2. the cost of cardiovascular- and non–cardiovascular-related short-stay hospital admissions (ie, hospital admissions that do not require an overnight stay in the hospital);
3. the cost of cardiovascular- and non–cardiovascular-related hospitalization; and
4. the costs of all recorded HF-related diagnostic procedures (ie, echocardiography, coronary angiography, and bike tests).

The major groups of HF-related medication used during the trial were angiotensin-converting enzyme inhibitors, β-blockers, angiotensin receptor blockers, and diuretics. The costs of these medicines were not included in the analysis because of their low-average costs, making them unlikely to have a significant impact on the differences in costs between the study groups. Moreover, the nurse-led intervention was primarily aimed at education and counseling and not at drug titration. The costs of the medical procedures conducted during hospitalization or short-stay hospital admission, such as percutaneous coronary intervention or implantation of a pacemaker, would be relevant to consider, but these procedures were not rigorously recorded during the COACH study. These costs could, therefore, not be taken into account in the analysis.

Table I. Overview of the various resources per cost category and their unit costs

Cost category	Measurement unit	Unit cost (€)
Intervention		
Inpatient hospital visits	Per visit	29
Home visits	Per visit	59
Outpatient visits	Per visit	110
Telephone contacts	Per call	5
Multidisciplinary advice	Per visit	31
Hospitalization		
Cardiovascular related	Per day	769
Non–cardiovascular related	Per day	522
Short-stay admission	Per admission	251
HF-related diagnostics	Per procedure	various

The cost of cardiovascular-related hospitalization is the main driver in the economic evaluation of disease management programs in HF.[11,12] In our study, we therefore used micro costing[13] to determine the real cost per overnight stay in a coronary care unit (CCU) and a general (cardiac) ward. Although the distribution of stay over different wards during hospitalization is important to consider from a cost perspective, it was not recorded during the COACH study. After seeking expert opinion from experienced cardiologists, we decided to roughly allocate 30% of a patient's length of stay to a CCU and 70% to a general ward for an admission related to a cardiovascular disease. For admissions unrelated to cardiovascular causes, the standard unit cost for an overnight stay in a Dutch general ward was applied.[14] The unit costs of an inpatient visit by the HF nurse, a home visit, and a telephone contact were estimated by multiplying the HF nurses' average time consumption by their salary costs and raised to a surcharge of 35% overhead and 10% housing wherever appropriate.[14] The unit costs of an outpatient visit to the HF nurse and/or cardiologist and a 30-minute session of multidisciplinary advice were obtained from The Dutch manual for costing.[14] This manual was also used to obtain the unit cost of a short-stay hospital admission and the unit costs of an echocardiogram, a coronary angiogram, and a bike test.

Table I provides an overview of the various resources per cost category and their unit costs. All costs were assessed in Euros and, wherever required, adjusted to 2009 prices by using a national consumer price index. Costs were calculated at the level of individual patients by multiplying the patients' volumes of resource use as recorded on the case report form by the obtained unit costs. Differences in resource use among the 3 study groups were assessed by using a Kruskal-Wallis rank test.

Health outcomes

The effectiveness of care as usual, basic support, and intensive support was assessed in terms of survival and quality-adjusted survival. Mean survival time for each of the 3 study groups was estimated by integration of the area under the Kaplan-Meier survival curves, and differences among the groups were tested for by means of a log-rank test. Mean quality-adjusted survival time was estimated by using inverse probability weighting.[15] The utilities underlying the quality-adjusted survival time calculations were derived from the patients' SF-36 scores—which were collected through self-reported questionnaires at baseline and 1, 6, 12, and 18 months postrandomization—by using the algorithm developed by Brazier et al.[16] Mixed-effect modeling was used to test whether the average evolution of utility over time was different among the 3 study groups. Visual inspection of the mean profiles per treatment group suggested that the average evolution of utility over time was best described by means of a quadratic function. The fixed-effects structure therefore included an intercept, the treatment indicator, time, time^2, and the interactions between the treatment indictor and the included time components. The most suitable random-effects structure was determined by means of a series of nested likelihood ratio tests. This resulted in a random-effects structure consisting of a random intercept and a random slope for the linear time effect.

Cost-effectiveness analysis

Base case analysis. To assess the balance between the costs and effects of the 2 nurse-led disease management programs and care as usual, we first explored whether any of the strategies was dominated by another strategy (or a linear combination of the other strategies) having both lower mean cost and greater mean (quality adjusted) survival time. Then, we calculated for each nondominated strategy the incremental cost-effectiveness ratio (ICER), that is, the ratio of the difference in mean cost and the difference in mean effect, of this strategy relative to the next less costly and less effective nondominated strategy and compared these ICERs against the willingness-to-pay threshold λ to identify the optimal treatment strategy.

To get insight into the sampling uncertainty associated with these mean values, simple random sampling with replacement was conducted to obtain 1,000 bootstrap resamples of equal size to the original sample. For each bootstrap resample, the strategies' mean costs and mean (quality adjusted) survival times were estimated, and the differences among them were calculated. The resulting sampling distributions of the incremental differences in mean cost and mean (quality adjusted) survival time were summarized graphically by plotting them on the cost-effectiveness plane. From a decision-maker's perspective, the probability that a certain strategy is optimal varies, depending on what the society is willing to pay per unit of heath gain. This information was summarized graphically by plotting for each strategy the probability that it was optimal against λ, resulting in the strategy's cost-effectiveness acceptability curve (CEAC).[17] For any given value of λ, this probability was determined by taking the fraction of bootstrap resamples for which the strategy was found to be optimal.

Subgroup analysis. It has previously been suggested that intensive support could have been more beneficial if it were explicitly targeted at patients who are likely to be most responsive to such a program, such as patients with severe HF[18] or patients without depressive symptoms.[19] To explore whether it would be worthwhile to provide different disease management strategies to different groups of HF patients, a subgroup analysis was conducted by performing separate analyses for patients with severe (New York Heart Association [NYHA] classes III and IV) and less severe (NYHA classes I and II) HF.

Sensitivity analysis. Because the distribution of stay over the different wards during cardiovascular-related hospitalization was not recorded during the COACH study, we allocated 30% of

Table II. Resource use per study group

Resources	Care as usual (n = 339)	Basic support (n = 340)	Intensive support (n = 344)	*P*
Intervention				
Inpatient hospital visits	0.16 (1.77)	0.41 (1.04)	0.89 (1.83)	<.001
Home visits	0	0.03 (0.26)	2.14 (1.58)	<.001
Outpatient visits	3.38 (2.07)	6.16 (3.35)	7.46 (4.37)	<.001
Telephone contacts	0.14 (0.49)	3.55 (3.96)	9.21 (5.99)	<.001
Multidisciplinary advice	0	0	1.28 (1.78)	<.001
Days in the hospital				
Cardiovascular related	8.44 (17.26)	7.58 (15.36)	8.10 (15.63)	.93
Non–cardiovascular related	3.76 (11.01)	4.39 (12.28)	4.96 (13.65)	.83
Short-stay admission	0.17 (0.50)	0.18 (0.61)	0.17 (0.48)	.75
HF-related diagnostics	1.20 (1.50)	1.10 (1.54)	1.42 (1.99)	.22

Values are presented as means (SD).

Table III. Mean cost (SD) per cost category

Mean cost	Care as usual	Basic support	Intensive support	*P*
Intervention	376 (239)	707 (369)	1,055 (516)	.002
Hospitalization	8458 (14 951)	8125 (13 940)	8818 (13 811)	.69
Short-stay admission	41 (129)	45 (148)	43 (111)	.75
HF-related diagnostics	1065 (1049)	1052 (1051)	1249 (1235)	.22
Total cost	9693 (15 227)	9616 (14 124)	10 794 (13 958)	.30

a patient's length of stay to a CCU and 70% to a general ward. To investigate the impact of this assumption on the study results, we varied the fraction of time that a patient spends in a CCU from 0% to 60%. We also assessed the consequences of doubling and halving the unit cost of an outpatient visit to the HF clinic, the main determinant of the intervention cost. Because the overall uncertainty in the ICER depends on the combined variability in these factors, we allowed the 2 parameter values to vary simultaneously.

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Results

Patients

A total of 1,023 patients were randomly assigned to the 3 study groups. The mean age of the participants was 71 years, and 62.4% were men. The baseline demographic and clinical characteristics of the 3 groups were comparable.[10]

Resource use and costs

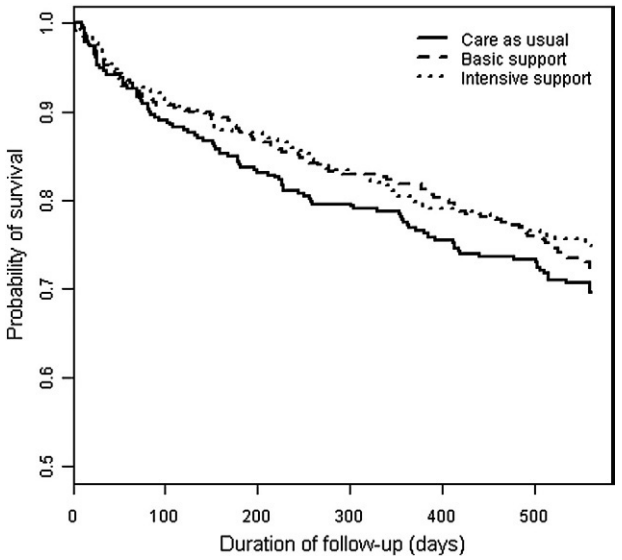
An overview of the resource use per study group is given in Table II. Although the average consumption of intervention-related resources was still significantly different among the 3 study groups ($P < .001$), the differences between basic and intensive support were smaller compared with what would be expected based on the study protocol.[10] The corresponding mean costs per cost category are given in Table III. Total cost were lowest in the basic support group and highest in the intensive support group, but the differences among the 3 groups were not statistically significant ($P = .30$).

Health outcomes

Survival. The mean survival time was 456.3 days in the care-as-usual group, 473.9 days in the basic-support group, and 474.7 days in the intensive-support group (Figure 2). The observed differences in survival among the 3 groups were not statistically significant, with a *P* value of .34 from the log-rank test.

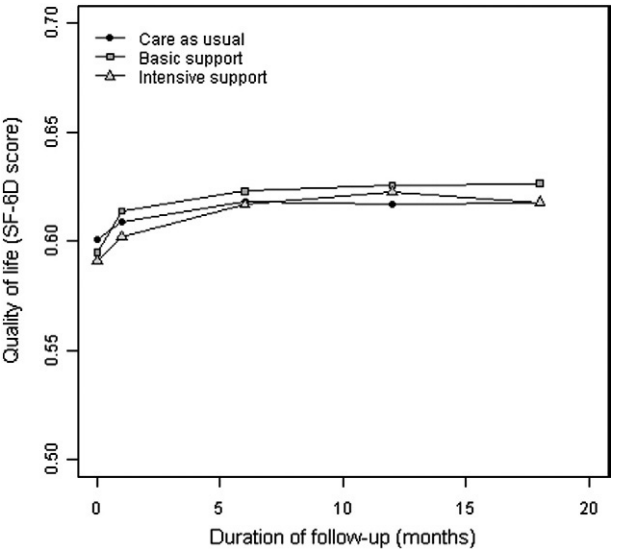
Quality-adjusted survival. The mean quality-adjusted survival time was 287.6 days in the care-as-usual group, 296.1 days in the basic-support group, and 294.6 days in the intensive-support group. The average change in SF-6D utility scores over time is depicted in Figure 3. The results of the mixed-effect modeling with treatment, time, time^2, and the interactions between treatment and time and treatment and time^2 (Table IV) showed that the average increase in quality of life over time was statistically significant, with *P* values for the time and time^2 components of .005 and .034, respectively. These results also showed that the differences in quality of life at baseline as well as the differences in the average evolution of quality of life over time were not statistically significant among the 3 study groups.

Figure 2



Kaplan-Meier survival curves for the 3 study groups.

Figure 3



Average evolution of quality of life (SF-6D scores) over time for the 3 study groups.

Cost-effectiveness

Base case analysis. Based on the mean values reported above, we can conclude that, in terms of cost per life-year, basic support dominated care as usual because it generated 0.048 additional life-years while saving €77. When comparing the 2 disease management programs, intensive support was found to generate 0.0022 additional life-years at an excess cost of €1,178, yielding an ICER of €532,762 per life-year. In terms of cost per quality-adjusted life-year (QALY), basic support was found to dominate both care as usual and intensive support because it generated 0.023 and 0.004 excess QALYs while saving €77 and €1,178, respectively.

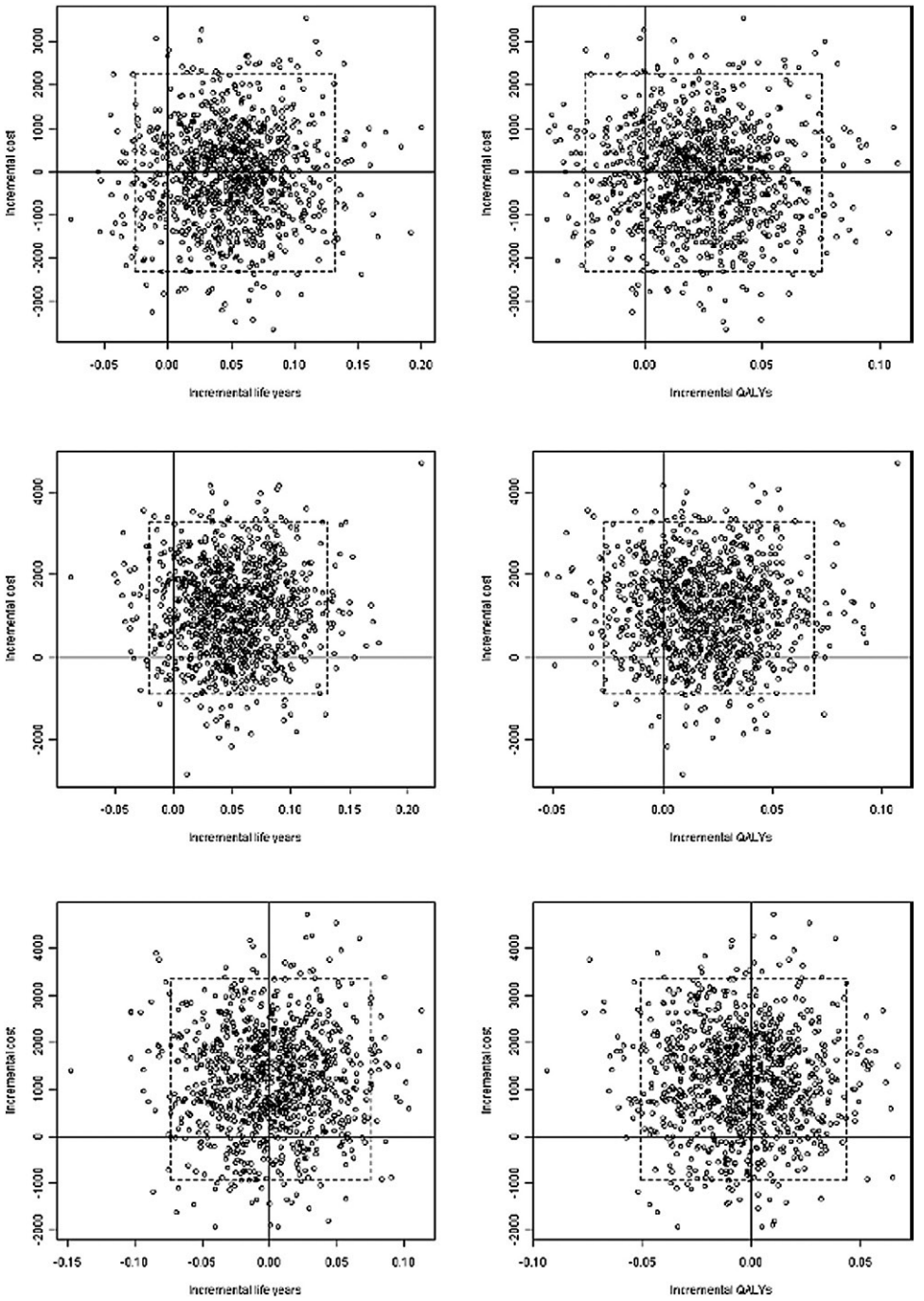
The results of the bootstrap analysis are presented in Figure 4. Each point on the cost-effectiveness plane represents a realization from the sampling distribution of the differences in mean cost and mean (quality adjusted) survival time. The lower and upper bounds of the 95% probability intervals for these differences are shown as vertical and horizontal dashed line segments, respectively. It can be seen from Figure 4 that there were bootstrap resamples for which basic support no longer dominated care as usual or intensive support (in terms of cost per QALY). The CEACs presented in Figure 5, nevertheless, suggest that basic support still has a large probability of being the preferred strategy; at a threshold value of €20,000 per life-year/€20,00 per QALY, basic support was found to have a probability of 69/62% of being optimal against 17/30% and 14/8% for care as usual and intensive support, respectively.

Subgroup analysis. The results of the subgroup analysis are summarized in Table V. For the patients with less severe HF, basic support was still found to dominate care and usual (both in terms of cost per life-year and cost per QALY) and intensive support (in terms of cost per QALY). In terms of cost per life-year, the ICER between intensive support and basic support was equal to €445,660 per life-year. For the patients with severe HF, basic support was no longer a dominating strategy. In fact, in terms of cost per QALY, basic support was now found to be extendedly dominated[20] by a linear combination of care as usual and intensive support, meaning that it is possible to produce the same health outcomes at a lower cost by giving a proportion of the patients care as usual and a proportion as intensive support. The ICER between intensive support and care as usual was equal to €59,289 per QALY. In terms of cost

Table IV. Maximum likelihood estimates for the fixed effects in the linear mixed model for the quality-of-life data (SF-6D scores)

Parameter	β Coefficient (SE)	*P*
Intercept	.6029 (0.004)	<.001
Basic support	−.00165 (0.006)	.774
Intensive support	−.00929 (0.006)	.106
Time	.00304 (0.001)	.0052
$Time^2$	−.00013 (0.00006)	.0335
Time*basic support	.00143 (0.002)	.342
Time*intensive support	.00218 (0.002)	.150
$Time^2$*basic support	−.00005 (0.00008)	.552
$Time^2$*intensive support	−.00009 (0.00008)	.290

Figure 4

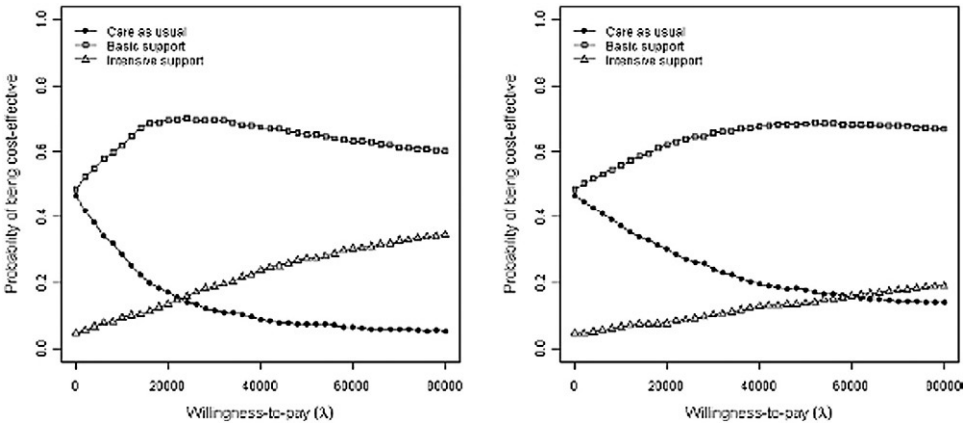


One thousand bootstrap estimates of the differences in mean cost and mean (quality adjusted) survival time between basic support and care as usual (top), intensive support and care as usual (middle), and intensive support and basic support (bottom).

per life-year, the ICERs between basic support and care as usual and intensive support and basic support were found to be equal to €25,923 per life-year and €45,345 per life-year, respectively.

Sensitivity analysis. Although there were combinations of parameter values for which basic support no longer dominated care as usual, the ICERs never exceeded €10,000 per life-year and €14,000 per QALY

Figure 5



The CEACs for the bootstrap analyses of cost per life-year (left) and cost per QALY (right).

Table V. Results of the subgroup analysis

	Cost	Survival time (d)	ICER (cost/life-year)	Quality-adjusted survival time (d)	ICER (cost/QALY)
Patients with less severe HF					
Care as usual	8955	483.3	Reference	307.4	Reference
Basic support	7170	504.2	Dominates care as usual	318.3	Dominates care as usual
Intensive support	9099	505.8	2338	313.3	8915
Patients with severe HF					
Care as usual	10 692	427.4	Reference	267.8	Reference
Basic support	11 793	442.9	25 923	273.0	77 335
Intensive support	12 462	448.3	30 933	278.7	59 289

(results not shown). For intensive support versus basic support, we obtained ICERs of €442,958 and €654,930 per life-year for the most optimistic and pessimistic scenarios, respectively. As far as cost per QALY is concerned, basic support dominated intensive support for all considered combinations of the 2 parameter values.

Discussion

This article reported the results of an economic evaluation conducted alongside the COACH study, one of the largest randomized, controlled trials of nurse-led disease management programs in HF. Although the differences in mean cost and mean (quality adjusted) survival time among the 3 study groups were not statistically significant, an assessment of the strategies' joint distributions on these 2 outcome measures, nevertheless, revealed that basic support had a relatively large probability of being the preferred strategy; at a threshold value of €20,000 per life-year/€20,000 per QALY, basic support was found to have a probability of 69/62% of being optimal against 17/30% and 14/8% for care as usual and intensive support, respectively. Based on these results, we can conclude that, from a decision-making perspective, basic support is clearly the favorable alternative. Although this conclusion may, at first glance, seem counterintuitive to some readers, it, in fact, reveals the limitations of applying the traditional rules of statistical inference to decision problems. Not only are trials rarely powered to detect statistically significant differences in costs or QALYs, but also traditional significance testing puts the emphasis on minimizing type I error (the probability of rejecting the null hypothesis when, in fact, that hypothesis is correct), whereas from a decision-making perspective, the probability of making a type II error (the probability of rejecting the alternative hypothesis when, in fact, that hypothesis is correct) is equally important.[13,21]

Although we anticipated that a comprehensive and intensive care would further decrease the number of readmissions and improve quality of life, our results proved otherwise. A possible explanation for this finding could be that intensive support leads to an increase in the number of cardiovascular-related hospitalizations

because of lower thresholds for admitting patients with mild to moderate HF. We can therefore not rule out the possibility that intensive support would have been more efficient if it were explicitly targeted at patients with severe HF. The results of our subgroup analysis indeed suggest that a stratified approach based on offering basic support to patients with mild to moderate HF and intensive support to patients with severe HF would be the preferred strategy if the willingness-to-pay threshold exceeds €45,345 per life-year/€59,289 per QALY.

A strong point of our study is that the analysis was based on individual patient data collected at 17 centers across the Netherlands. Our results therefore provide a realistic picture of the health benefits that could be achieved if the proposed disease management programs were implemented on a nationwide scale. Most of the previous studies on the (cost) effectiveness of nurse-led disease management programs in HF, in contrast, lack such a degree of generalizability because they were conducted in much more idealized and controlled settings. For example, in the Dutch context, the DEAL-HF study has shown a remarkable reduction in all-cause mortality and rehospitalization.[22] However, this study had a relatively small sample size and was only conducted at 2 regional centers. Likewise, a similar study was performed in the US setting, but this study was limited to inner city areas.[7] Finally, based on an expected 50% reduction in recurrent bed use, Stewart et al[9] projected that implementing a nurse-led disease management program on a nationwide scale is likely to reduce costs and improve the efficiency of the health care system. In light of our results, reductions in recurrent bed use of such large magnitudes seem not very realistic. Our findings, nevertheless, suggest that implementing a nurse-led disease management program with a medium intensity could still be cost saving.

A limitation of our trial-based economic evaluation is that the COACH study was not explicitly designed for performing a cost-effectiveness analysis. As a consequence of this, the recording of medical procedures was not very rigorous. A detailed listing of all relevant medical procedures would have increased the internal validity of our results. However, we did have complete data regarding the most important cost categories (ie, the consumption of the intervention-related resources and the number of hospital readmissions). Hence, the savings observed in the cost of rehospitalization, the driving cost category in the economics of HF,[9] would still be of utmost interest to a wider audience. In addition, although the distribution of stay over the different wards during cardiovascular-related hospitalization was not recorded during the COACH study, the results of the sensitivity analysis showed that our findings are robust to changes in the allocation of the amount of time that a patient spends in a CCU and a general ward.

To conclude, this article is the first to compare the costs and effects of 2 different variants of a nurse-led disease management program in HF. Our results provide a strong scientific case for a broader implementation of such programs, provided that the intensity of the program is tailored to the severity of the disease in individual patients with HF.

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