Chapter 2

Economic Evaluation of Valsartan in Patients with Chronic Heart Failure: Results from Val-HeFT Adapted to The Netherlands

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SUMMARY

The Valsartan Heart Failure Trial (Val-HeFT) was a multinational randomised trial of valsartan versus placebo in a total of 5,010 patients with heart failure. During the study period, valsartan resulted in significant reductions in hospitalisations due to heart failure.

The objective of this study was to evaluate the economic impact of valsartan in Dutch heart failure patients.

Resource use during Val-HeFT was multiplied by Dutch cost estimates. Mean patient follow-up was 23 months and costs for hospitalisations were €617 lower among valsartan patients. Mean total costs for valsartan and placebo patients were €8,810 and €8,441, respectively, resulting in incremental costs of €368. In patients receiving an angiotensin-converting enzyme (ACE) inhibitor but no beta-blocker, these incremental costs were even lower (€171). There were overall net savings of €1,311 in patients not receiving an ACE inhibitor at baseline.

Valsartan provides clinical benefits at modest costs in The Netherlands. In patients not receiving an ACE inhibitor at baseline, valsartan was dominant.

INTRODUCTION

Cardiovascular diseases are still a great burden to healthcare budgets in Europe. In The Netherlands, the cost of cardiovascular diseases amounted to approximately 10% of total Dutch healthcare expenditures. Of these expenditures, 8% were due to heart failure. Congestive heart failure
(CHF) is a prevalent condition, affecting approximately 200,000 patients in The Netherlands. As in other European countries, the prevalence and incidence of heart failure is growing. It is a leading cause of hospitalisation in the elderly and is expected to continue to be a heavy economic burden to society owing to the ageing of many European populations. It is estimated that up to 70% of the healthcare budget spent on heart failure is due to (re)admissions to hospital. In The Netherlands, approximately 25,000 admissions were recorded in 1999, representing an increase of approximately 75% compared with the early 1980s. There are, however, indications that age-adjusted hospitalisation rates are decreasing, probably owing to improvements of in the management of heart failure. Despite recent advances (i.e. pharmacotherapy and implementation of treatment guidelines), there is still much room for further improvement.

In the light of the above, the Valsartan Heart Failure Trial (Val-HeFT) was designed to assess additional benefits of the angiotensin receptor blocker valsartan over already proven favourable long-term effects on mortality and morbidity of angiotensin-converting enzyme (ACE) inhibitors and beta-blockers in patients with heart failure. The Val-HeFT study can be characterised as a randomised, double-blind, multinational trial of valsartan. Benefits were defined in terms of reduced morbidity, mortality, disease-specific quality of life, heart failure-related symptoms and medical costs. Details and results of the Val-HeFT study are reported elsewhere. In short, the study enrolled 5,010 heart failure patients from 16 countries, of which 11% were from the Netherlands. Mean patient follow-up was 23 months. Patients with New York Heart Association (NYHA) class II, III, IV on a stable regimen of heart failure medication were eligible for inclusion. Patients were allocated to the valsartan group or placebo (added to background therapy).

During the study follow-up, no statistically significant differences in mortality rates were found between the valsartan and placebo groups. However, valsartan showed a significant effect on the combined endpoint of mortality and morbidity (relative risk reduction = 13.2%; p = 0.009). Most of the benefit resulted from a 22.4% reduction in the risk of hospitalisation due to the worsening of heart failure. Patients who were not on a background therapy of ACE inhibitors did have mortality benefits: a 33% relative risk reduction of death during the Val-HeFT study. Maggioni et al. concluded from the Val-HeFT study that valsartan may offer an effective therapy in ACE-intolerant CHF patient.

These risk reductions, together with an estimated favourable cost-effectiveness in the USA and the recent registration of valsartan for treatment of chronic heart failure in The Netherlands, enhances the relevance of studying the economic impact of valsartan treatment for
heart failure in The Netherlands. The aim of this study was, therefore, to conduct an evaluation of the economic impact in The Netherlands of valsartan, based on the Val-HeFT study, including subgroup analyses.

**Patients and methods**

*General*

To estimate the cost-consequence of valsartan in heart failure in The Netherlands, a country-specific adaptation of the Val-HeFT study results was applied. Country adaptation was undertaken by applying Dutch cost estimates and prices to the within-trial medical resource use for all patients participating in the Val-HeFT study. Approximately 80% of the participating patients were men and the mean age was approximately 63 years (table 1). Persons using an angiotensin receptor blocker at baseline were excluded. Health outcomes included in this analysis comprise progression of heart failure, signs and symptoms of heart failure, total hospitalisations and hospitalisations due to heart failure. Widely accepted pharmacoeconomic methods were used.\(^{10}\)

*Data on medical resource use*

Medical resource use data (hospitalisations, outpatient medical visits, home care visits and medical treatment) were collected at trial visits that occurred every 2 weeks for the first 2 months, after 4- and 6-months, and every 3 months for the remainder of the trial. Data were collected throughout the trial, irrespective of treatment compliance.

The following resource use data were collected on the Val-HeFT case report form: (i) hospitalisation data involving admission and discharge dates, primary reason for hospitalisation (using ICD-coding), an indicator as to whether a local investigator deemed the hospitalisation to be due to heart failure and transportation to the hospital; (ii) outpatient data involving the number of consultations; and (iii) concomitant cardiovascular medications, including name, dose, indication, and start and end dates of the treatment(s).

While the numbers of physician visits external to the clinical trial was collected on the Val-HeFT case report form, data revealed that the average number of provider visits was unexpectedly low. Therefore, as a proxy, the frequency of outpatient physician visits was imputed based on NYHA class. Patients with class II, III or IV heart failure were assigned one visit every 3 months, every 2 months and every month, respectively.
Costing

The analysis was conducted from the healthcare perspective and only included direct medical costs. To correspond with the period in which Val-HeFT was conducted, all costs were estimated for 1999 price levels (€1 = Dfl2.20371 = US$1.21489). If appropriate, discounting was applied at 3% per annum. Where needed, unit cost estimates from previous costing studies performed in The Netherlands were updated and corrected for cost increases using an average index for healthcare costs (http://www.cbs.nl). Inpatient and outpatient unit cost estimates (including variable and fixed costs, such as equipment, capital and overhead) for The Netherlands were obtained by the Institute for Medical Technology Assessment (iMTA). Further details on applied costing methodology can be found elsewhere. Table 2 shows the cost estimates for hospitalisations.

The number of outpatient physician visits per patient was imputed according to the baseline NYHA classification. The costs of outpatient physician visits (€63.53 per visit) were based on national estimates according to the Dutch guidelines for pricing in pharmacoeconomic analyses. Patients who were transported to the hospital by ambulance were assigned an ambulance transport at costs of €334.89 according to the specific guideline.

The costs for medication were based on average daily costs per drug class using official Dutch drug prices. Nine drug classes were identified (diuretics, digitalis, statins, anticoagulants, ACE inhibitors, beta-blockers, nitrates, calcium channel blockers and aspirin) and the average daily dose was determined using the 2000 Drug Facts and Comparisons. Medication costs were calculated by multiplying treatment duration with average daily costs per class. Daily costs of valsartan of €0.68, €1.36 and €2.01 were used for daily doses of 80 mg, 160 mg and 320 mg, respectively. Deaths that occurred outside the hospital were identified by death dates beyond 2 days of hospital discharge. The cost of a death outside the hospital was recalculated from the assumed US$1,000 in the US economic study, using purchasing power parities for the Dutch guilder in 1999 and an exchange rate for the guilder and Euro (€1 = Dfl2.20371). The cost estimates for hospitalisation in the Netherlands are shown in table 2.
**Table 1**  Patient characteristics at baseline of the Valsartan Heart Failure Trial (Val-HeFT)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Val-HeFT (n = 5,010)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (sd) (years)</td>
<td>62.7 (11.0)</td>
</tr>
<tr>
<td>Male sex</td>
<td>4,007 (80.0)</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>4,526 (90.3)</td>
</tr>
<tr>
<td>Black</td>
<td>344 (6.9)</td>
</tr>
<tr>
<td>Asian</td>
<td>140 (2.8)</td>
</tr>
<tr>
<td>CHF aetiology</td>
<td></td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>2,865 (57.2)</td>
</tr>
<tr>
<td>Idiopathic cardiomyopathy</td>
<td>1,560 (31.1)</td>
</tr>
<tr>
<td>Hypertension†</td>
<td>337 (6.7)</td>
</tr>
<tr>
<td>Other‡</td>
<td>248 (5.0)</td>
</tr>
<tr>
<td>NYHA classification§</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>3,095 (61.8)</td>
</tr>
<tr>
<td>III</td>
<td>1,813 (36.2)</td>
</tr>
<tr>
<td>IV</td>
<td>97 (1.9)</td>
</tr>
<tr>
<td>Concomitant medications</td>
<td></td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>1,750 (34.9)</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>4,644 (92.7)</td>
</tr>
<tr>
<td>Digitalis</td>
<td>3,374 (67.3)</td>
</tr>
<tr>
<td>Diuretics</td>
<td>4,282 (85.5)</td>
</tr>
<tr>
<td>Anti-arrhythmia agents</td>
<td>724 (14.5)</td>
</tr>
<tr>
<td>Left ventricular ejection fraction (mean) (sd)</td>
<td>27.6% (7.2)</td>
</tr>
</tbody>
</table>

CHF, congestive heart failure; NYHA, New York Heart Association; ACE, angiotensin-converting enzyme.

*Values are expressed as number (%) unless otherwise indicated.
†Data were missing for two patients.
‡Data were missing for one patient.
§Five patients had NYHA class I heart failure.
Table 2  Cost for hospitalisations in The Netherlands in 1999∗

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Cost estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart failure</td>
<td>€4,795</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>€3,916</td>
</tr>
<tr>
<td>Acute MI</td>
<td>€5,823</td>
</tr>
<tr>
<td>Sudden death with resuscitation</td>
<td>€494</td>
</tr>
<tr>
<td>Coronary angiography</td>
<td>€1,210</td>
</tr>
<tr>
<td>PTCA with stent</td>
<td>€4,208</td>
</tr>
<tr>
<td>PTCA without stent</td>
<td>€3,511</td>
</tr>
<tr>
<td>Heart transplant</td>
<td>€24,112</td>
</tr>
<tr>
<td>Stroke</td>
<td>€5,404</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>€2,543</td>
</tr>
</tbody>
</table>

MI, myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty. ∗Specific costing research done by the Institute of Medical Technology Assessment (iMTA), Erasmus University (data available on request) and based on literature.11,12

Statistical analysis

The analysis was conducted on an intention-to-treat basis. Because of the relatively large sample size, means were assumed to be normally distributed. T-tests were, therefore, applied to compare means between treatment groups.16 As further explained in annex 1, the t-test is an adequate test here. The χ² test was used to test the hypothesis that the proportion of patients not hospitalised at all during the trial was equal between groups.

Subgroups

Subgroup analyses were defined based on ACE inhibitor use at baseline, beta-blocker use at baseline, gender, age and NYHA classification. Our subgroup analyses corresponded with those reported previously on clinical outcomes.

Results

Clinical and health outcomes from the Val-HeFT study

The incidence of the combined endpoint of morbidity and mortality in the valsartan group – defined as a cardiac arrest with resuscitation, hospitalisation for heart failure on receipt of intravenous inotrop or vasodilator therapy for at least 4h – was lower than in the placebo group (relative risk (RR) = 0.87; 95% confidence interval (CI) 0.77-0.97).7 This was
predominantly due to 22.4% fewer heart failure-related hospitalisations (p = 0.002). Overall mortality was similar in the valsartan and the placebo group. The mean change in ejection fraction was significantly better in the valsartan group (4.0% vs. 3.2%; p = 0.001), and more patients improved in NYHA classification and fewer worsened relative to placebo (23.1% vs. 20.7% and 10.1% vs. 12.8%, respectively; both p < 0.001).

In 3,010 patients, the ‘Minnesota Living with Heart Failure’ questionnaire was administered to assess the impact of disease-specific quality of life. While quality of life remained virtually unchanged in the valsartan group, the placebo group showed a worsening of 1.9 points on average, which was statistically significant (p = 0.005).

**Resource use**

On average, heart failure-related hospitalisations per patient over the study follow-up 0.4 and 0.5 in the valsartan and placebo groups, respectively (table 3). This difference was statistically significant. Moreover, the number of all-cause hospitalisations per patient was significantly reduced (table 3). Since there were no differences in hospital admissions between groups for reasons other than heart failure, differences in all-cause hospitalisations reflect the differences found in heart failure-related hospitalisations. Inpatient days per patient with heart failure-related hospitalisation were significantly lower for valsartan. Significantly more patients in the valsartan group did not require heart failure hospitalisation during the trial (χ² test, p = 0.004). For all-cause hospitalisations, no statistical significant difference was found between the groups (χ² test, p = 0.224).

**Table 3** All-cause and heart failure-related hospitalisations, mean hospitalisations and inpatient days per patient, differences and corresponding p-values

<table>
<thead>
<tr>
<th></th>
<th>Valsartan (n = 2,511)</th>
<th>Placebo (n = 2,499)</th>
<th>Difference</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All-cause hospitalisations</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total number</td>
<td>2,856</td>
<td>3,106</td>
<td>–0.11</td>
<td>0.039</td>
</tr>
<tr>
<td>Hospitalisations per patient</td>
<td>1.14</td>
<td>1.25</td>
<td>–0.11</td>
<td></td>
</tr>
<tr>
<td>Inpatient days per patient</td>
<td>9.82</td>
<td>10.97</td>
<td>–1.15</td>
<td>0.066</td>
</tr>
<tr>
<td><strong>Heart failure-related hospitalisations</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total number</td>
<td>923</td>
<td>1,189</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospitalisations per patient</td>
<td>0.37</td>
<td>0.48</td>
<td>–0.11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Inpatient days per patient</td>
<td>3.51</td>
<td>4.81</td>
<td>–1.30</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Based on t-test
Direct medical costs

On average, additional costs for valsartan amounted to €1,055 for the entire follow-up period per patient (€535 per patient per year) compared with placebo. The major part of these additional costs was compensated by savings on other healthcare resource use (table 4). Primarily owing to a lower incidence of heart failure hospitalisations and shorter length of stay, the mean heart failure-related costs were €617 lower in the valsartan group than in the placebo group. Statistical analysis showed that these savings were significant (95% CI €267-968; p < 0.001). Total inpatient and outpatient costs resulted in incremental cost of €368, which should be weighted against clinical and health status benefits of valsartan compared with placebo.

Table 4  Economic impact of valsartan per patient with heart failure in The Netherlands, based on the Valsartan Heart Failure Trial (Val-HeFT)

<table>
<thead>
<tr>
<th>Resource</th>
<th>Valsartan</th>
<th>Placebo</th>
<th>Difference†</th>
<th>p-value‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart failure-related</td>
<td>€1,711</td>
<td>€2,328</td>
<td>–€617</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Other</td>
<td>€4,115</td>
<td>€4,131</td>
<td>–€16</td>
<td>0.961</td>
</tr>
<tr>
<td>Total inpatient cost</td>
<td>€5,826</td>
<td>€6,459</td>
<td>–€633</td>
<td>0.098</td>
</tr>
<tr>
<td>Death outside the hospital</td>
<td>€102</td>
<td>€103</td>
<td>–€1</td>
<td>0.902</td>
</tr>
<tr>
<td>Cardiovascular medication</td>
<td>€1,270</td>
<td>€1,322</td>
<td>–€52</td>
<td>0.016</td>
</tr>
<tr>
<td>Outpatient physician visits</td>
<td>€557</td>
<td>€558</td>
<td>–€1</td>
<td>0.851</td>
</tr>
<tr>
<td>Cost of valsartan</td>
<td>€1,055</td>
<td>€0</td>
<td>€1,055</td>
<td>—</td>
</tr>
<tr>
<td>Total inpatient and outpatient costs</td>
<td>€8,810</td>
<td>€8,442</td>
<td>€368</td>
<td>0.336</td>
</tr>
</tbody>
</table>

*Inpatient costs comprise costs for hospitalisations, ambulance transport and inpatient physician fees.
†Negative values indicate cost savings of valsartan compared with placebo.
‡Calculated using t-test.

Subgroup analyses

In patients not receiving ACE inhibitors at baseline (n = 366), valsartan treatment resulted in significant improvement in all-cause mortality (17.3% vs. 27.1%; RR = 0.67; p = 0.017) and significant difference in the composite combined mortality and morbidity endpoint (24.9% vs. 42.5%; RR = 0.56; p < 0.001). Moreover, the rates of first hospitalisation for heart failure were 13.0% and 26.5% for valsartan and placebo, respectively (RR = 0.47; p < 0.001). These findings were observed regardless of concomitant beta-blocker use. A 56% risk reduction in the total number of heart failure-related hospitalisations (and no difference in non-heart failure hospitalisations) due to valsartan led to substantial savings on healthcare
costs of €2,290 per patient (table 5). The total inpatient and outpatient cost per patient in the valsartan group was €1,311 less than the total cost in the placebo arm of Val-HeFT.

In a second subgroup analysis of patients using an ACE inhibitor at baseline but no beta-blocker (n = 3034), significant survival gains were not demonstrated. However, in this subgroup of patients the net incremental costs for valsartan treatment were only €171, primarily caused by relatively high cost-savings on heart failure-related hospitalisations (€853 per patient).

Analysis of age (above or below 65 years) resulted in lower net incremental costs of valsartan in the under 65 age group (€75 vs. €747). For men, who constituted the majority of patients, the incremental cost of valsartan was lower compared with women (€241 and €879, respectively). Treatment with valsartan in patients with heart failure classified as NYHA class II or III at baseline was associated with net incremental costs of €341 and €574, respectively. In a small subgroup of patients classified as NYHA class IV at baseline (n = 97), valsartan treatment was associated with total net savings of €939.

Table 5  Economic impact of valsartan per patient with heart failure in The Netherlands, based on the Valsartan Heart Failure Trial (Val-HeFT) study: subgroup analysis of patients without angiotensin-converting enzyme inhibitor at baseline

<table>
<thead>
<tr>
<th>Resource</th>
<th>Valsartan</th>
<th>Placebo</th>
<th>Difference</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart failure-related</td>
<td>€996</td>
<td>€3,286</td>
<td>–€2,290</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Other</td>
<td>€4,101</td>
<td>€4,162</td>
<td>–€61</td>
<td>0.948</td>
</tr>
<tr>
<td>Total inpatient cost</td>
<td>€5,097</td>
<td>€7,448</td>
<td>–€2,351</td>
<td>0.037</td>
</tr>
<tr>
<td>Death outside the hospital</td>
<td>€82</td>
<td>€140</td>
<td>–€58</td>
<td>0.070</td>
</tr>
<tr>
<td>Cardiovascular medication</td>
<td>€704</td>
<td>€676</td>
<td>€28</td>
<td>0.647</td>
</tr>
<tr>
<td>Outpatient physician visits</td>
<td>€575</td>
<td>€579</td>
<td>–€4</td>
<td>0.864</td>
</tr>
<tr>
<td>Cost of valsartan</td>
<td>€1,074</td>
<td>€0</td>
<td>€1,074</td>
<td></td>
</tr>
<tr>
<td>Total inpatient and outpatient costs</td>
<td>€7,532</td>
<td>€8,843</td>
<td>–€1,311</td>
<td>0.244</td>
</tr>
</tbody>
</table>

1Inpatient costs comprise costs for hospitalisations, ambulance transport and inpatient physician fees.
2Negative values indicate cost savings of valsartan compared with placebo.
3Calculated using t-test; 4indicates statistical significance.

**DISCUSSION**

The Val-HeFT study has shown a statistically significant decrease in hospitalisations for patients with heart failure with a subsequent significant reduction in average costs for heart failure-related hospitalisations of €617 per patient. This corresponds to a total net additional costs of
€368 per patient during 23 months of patient follow-up (approximately €192 annually) and €3,346 per hospitalisation averted. In patients not receiving an ACE inhibitor during the trial, valsartan was estimated to be cost-saving, with €1,311 lower total costs due to a statistically significant reduction in costs for heart failure-related hospitalisations of €2,290 (p < 0.0001). Our analysis was designed as a cost-effectiveness analysis, but the analysis resulted in cost-savings, which were not spelled out against known health gains in terms of hospitalisations averted.

In the Val-HeFT study design, valsartan or placebo was added to other heart failure therapy. Val-HeFT showed that, at moderate incremental costs, valsartan resulted in positive health gains overall and that valsartan turned out to be cost-saving in a group of patients not receiving ACE inhibitors at baseline. Therefore, in daily practice, valsartan may lead to cost-savings in ACE-intolerant patients. This corresponds with earlier findings and conclusions from other studies. Maggioni et al reported that the 7% of patients included in the Val-HeFT study not receiving an ACE inhibitor were likely to be ACE-intolerant. Corresponding to this, Bart et al confirm the reasoning that ACE intolerance is the most common reason for not using ACE inhibitors, with an estimated intolerance of approximately 10% of the cases. Previous percentages suggest that those patients excluded during Val-HeFT for receiving angiotensin receptor blockers at baseline constitute only a few percent of all ACE-intolerant patient eligible for Val-HeFT, and so the majority of ACE-intolerant patients may still have been included in the trial despite this explicit exclusion criterion.

In the Dutch reference pricing system for reimbursement, angiotensin receptor blockers were recently de-clustered from ACE inhibitors, despite the fact that these drugs have similar indications for lowering blood pressure, are based on similar mechanism of action, and results from clinical trial show comparable efficacies. Angiotensin receptor blockers may, however, be preferred in specific patients (i.e. with diabetes mellitus, heart failure or renal insufficiency) and when side-effects on ACE inhibitors (such as cough) occur. On a European level, recently valsartan, in addition to essential hypertension, was approved for registration in the treatment of patients with recent myocardial infarction with left ventricular systolic dysfunction and symptomatic heart failure. Owing to these developments and based on studies in recent years, guidelines for the management of heart failure now more often focus on the position of angiotensin receptor blockers (i.e. valsartan) in current treatment options. The current analysis of the Val-HeFT study also indicates that from an economic viewpoint valsartan may offer an attractive treatment option in CHF.

Our evaluation adds European information (The Netherlands) on the economics of the Val-HeFT study to an already previously performed
analysis for the USA. This is highly relevant as many national and regional factors influence the economic analysis, including differences in the system and cost prices.

Adjustments for between-country differences in practice patterns or patients characteristics were not carried out. Such adjustments would be difficult to make in practice and would rely heavily on assumptions. However, country adaptations based on clinical trials such as ours do represent an adequate tool to estimate the cost consequences of specific interventions. In general, calculations can easily be conducted using country-specific costs based on different assumptions. Despite these assumptions, imperfections can be found in the transferability of data from clinical trials between countries (i.e. demographic factors). Ideally, our analysis would be based on Dutch trial outcomes (effects) and costs. Therefore, our study should be interpreted carefully and estimated positive economic and clinical implications of valsartan use require confirmation in analysis of daily practice utilisation.

Economic evaluation of the Val-HeFT study adapted to the Dutch situation, with a favourable pharmacoeconomic profile for valsartan, indicates that drug prices alone do not provide a sufficient economic picture. Downstream cost-savings resulting from efficiency considerations can offer opportunities to control further the Dutch healthcare budgets and approach optimal treatment choices within such budgets.

In conclusion, valsartan provided benefits at modest costs in The Netherlands for patients with CHF. In patients not receiving an ACE inhibitor at baseline, valsartan turned out to be the dominant treatment strategy, with net cost-savings and health benefits. For the Dutch situation, it therefore seems justifiable, both from a clinical and an economic point of view, to at least treat ACE-intolerant patients with valsartan.

Acknowledgement

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References

Annex

Skewed Distribution of Hospital Admissions Complicates Cost Analyses; Pitfalls in Judging Cost Reductions

Robin de Vries
Cornelis Boersma
Maarten J. Postma


During the Valsartan Heart Failure Trial (Val-HeFT) study, the effect of the angiotensin-II-antagonist valsartan in addition to conventional therapy for heart failure was compared with placebo. In total, 5,010 patients were assigned to valsartan (n = 2,511) or placebo (n = 2,499). Important outcomes of this study are summarised as follows:

i. no difference in mortality;
ii. a higher percentage of patients with heart failure-related hospitalisations for placebo-treated groups during study follow-up (p = 0.004);
iii. No decrease in quality of life for valsartan-treated patients versus decrease in quality of life for placebo-treated patients (p = 0.005).

An important question following from these findings relates to the translation into economic outcomes and subsequent consequences. For example: does ‘more patients without hospital admission’ likewise translate in a decrease in total length of hospital stay or is this compensated by more admissions per admitted patient and/or longer length of stay per hospital admission? Does decrease in hospital admissions and/or length of stay also translate in less health care costs?

To answer similar questions, it is important to focus on the judgement of difference in health care resource use and costs between the intervention group and reference group of such clinical trials.

Analysis

By approximation, figure 1 shows the frequency-distribution of per patient number of heart failure related days of hospital admission of valsartan-treated patients during the 23 months study follow-up of Val-HeFT. A comparable distribution holds true for the placebo-treated group. The distribution found is typically for and often seen in the analyses of health
care resource use and costs based on clinical trials: the distribution is bimodal (two ‘peaks’) and skewed (long ‘tail’ to the right). In a pharmacoeconomic analysis, the distribution of costs is often skewed due to low percentages patients with relatively extreme high costs through e.g. medical complications, prolonged hospital stay or occurrence of adverse/side effects. In the example of the Val-HeFT study, the typical shape of the curve is on the one hand caused by an enormous group of patients without hospital admissions and/or no length of stay (79%, n = 1,974), and on the other hand a separate distribution of the length of stay of patients who were at least hospitalised twice, which results in the second ‘peak’. Obviously, the shape of the curve is anything but not following the shape of a normal distribution (‘Gauss-curve’).

The mean per patient length of stay from figure 1 corresponds with 3.5 and 4.8 for the valsartan-treated and placebo-treated groups respectively. How do we have to judge the difference found, in the light of the typical kind of distribution found (bimodal and skewed)? Is there a statistical significant difference between the means in both groups or in other words is the difference in per patient length of hospital stay between both groups really relevant or is this difference caused by chance? The t-test is the conventional statistic test for comparison of two means. Therefore, this test was also used for the economic analysis based on the Val-HeFT study for the United States (p < 0.001). Additionally, the t-test was also used for comparison of per patient costs for (length of) hospital stay: US$1,588 per patient versus US$2,010 per patient for valsartan and placebo, respectively (p = 0.005). Note that per patient hospital costs follow the same bimodal skewed distribution as length of stay (days of nursing care). Applying the t-test for means is based on the assumption that variances (as a measure for the spread of the distribution) are the same in both groups and the assumption that both means follow the normal distribution by approximation. As mentioned earlier, figure 1 suggests something different.

Conform the central limit theorem, means found for both the intervention and reference group in large studies as the Val-HeFT study, will by approximation be normally distributed. Therefore, despite the individual patient data which are not following the normal distribution, likely indicates that the t-test is an adequate test. This probably does not hold true for a subanalyses of the original study for a much smaller number of patients; e.g. a subanalysis was conducted on Val-HeFT data for patients with NYHA-class IV heart failure (n = 97; 42 in the valsartan group and 55 in the placebo group).

In case of small numbers of patients and skew distribution of costs, the use of the t-test becomes doubtful. As a rule of the thumb for the validity of
the central limit theorem $n > 30$ is generally used, but it is known that this
does not always hold true for asymmetric distributions which are typical
for cost-data.$^7$ Although, the t-test is known as robust – not all deviations
from earlier mentioned assumptions will have little effect – it is not possible
to exactly indicate when the t-test will no longer result in valid results.$^5,^6$

![Figure 1](image.png)

**Figure 1** Distribution of number of inpatient days per stay in the valsartan group of the Val-HeFT study (y-axis is logarithmic).$^5$

**Alternative tests**

In literature, different recommendations were done for analysing
skewed distributed data on health care resource use and costs. First and
foremost, the (natural) logarithmic transformation has been described
to overcome problems related to normal distributed distributions and
dissimilar variances. By taking the (natural) logarithm of the individual
observations, the sampling test will possibly better approximate the
normal distribution. However, applying the t-test on log-transformed
data entails another problem: instead of arithmetic means, geometric
means are compared. The geometric mean is the exponent of the mean of
logarithmic transformed data ($= e^{(\text{mean log data})}$) and is mostly situated close
to the median.$^5,^6$ In pharmacoconomics, we are mainly interested in the
(arithmetic) means. After all, mean costs per patient multiplied with the
number of patients finally determine total cost of health care.

Also non-parametric tests can be considered for comparison of health
care resource use and costs. Such methods do not make assumptions on
the underlying distribution. A well-known example is the Mann-Whitney-Wilcoxon-test.\(^5\) A great disadvantage of non-parametric tests can be found in the fact that it compares the location of the distributions instead of means. In case of skewed distributions, you actually are comparing medians.\(^6\) Next to this, there are different bootstrap-methods described for comparison of mean costs of two groups.\(^4,8\) Bootstrap-methods are mostly used to empirically estimate the sampling distribution.\(^9\) The validity here is, just as for the central limit theorem, dependent of the number of patients. Ergo, if the central limit theorem does not hold true due to small patient numbers, the bootstrap-method is in fact for the same reason not an alternative.

O’Hagan and Stevens\(^10\) in general argue that often used methods based on the normal distribution of bootstrap-methods are incorrect in analysing skewed data on health care and costs. They plead for using adequate parametric models. If cost-data would for example follow a log-normal distribution, than not the mean from the study but \(e^{(\text{mean} + \text{variance}/2)}\) would give the best estimation of the population-mean. Parametric models/methods indeed give the best outcomes if the exact underlying distribution is known, but these distributions are most of the time unknown.\(^5,6\) Next to this, data concerning costs for pharmacoeconomic analysis are in general combinations of different types of health care resource use (drugs, inpatient days, diagnostic tests, etc.) with their own distribution. Therefore, the distribution of total costs can hardly or not be described by a parametric model.

Briggs and others\(^11\) argue that it is in general improbable that use of means from the study will result in invalid conclusions and that use of parametric models only has added value in case of sufficient available data to estimate the real distribution. Next to this, they showed that using the earlier mentioned estimator \(e^{(\text{mean} + \text{variance}/2)}\) possibly results in misleading results when the real distribution slightly differs from the log-normal distribution.

**Recommendations**

In general, the t-test is a valid method for analysing means of health care resource use and costs in a clinical study. Use of parametric models is only preferred if the underlying distribution is exactly known or in case of an enormous number of patients which facilitates in an accurate estimation of the distribution. For relative small study populations one should be aware of the fact that real alternatives for the t-test are difficult to give.


