# Clinical and Cost Effectiveness of VentrAssist®LVAD as a "Bridge" to Transplantation for People with an End -Stage Heart Failure

**Is the use of VentrAssist ®LVAD Cost-Effective in Norway?**

Butta Dulo Defi


**Master thesis**

**The Institute of Health Economics Policy and Management**

**Faculty of Medicine**

**University of Oslo**

**May 2009**

# Acknowledgment

Many people have contributed to the realization of this work.

First of all I would like to thank Inger Natvig Norderhug (PhD) , Section Leader for the Specialist Health Services at the Norwegian Knowledge Centre for introducing me to this attractive topic of Health Technology Assessment. Thanks to those fine people whom I met during my stay for the internship at the centre. And particularly, Helene, Bjørn, Torbjørn, & Vida, for the nice discussion we held about the use of LVADs as a mechanical circulatory support for a deteriorating heart. I present my appreciation to all people who contributed towards my pleasant stay at the centre.

Secondly my sincere thank goes to my supervisor Eline Aas post doc at the Institute of Health Economics Policy and Management , University of Oslo, who unconditionally allowed me to raise all my inquiries regarding the technique of economic evaluation during our meeting for discussions. Her inputs during our first discussion encouraged me to track on this research question though I was uncertain about the availability of data material on the clinical use of VentrAssist®LVAD in Norway. Without her genuine guidance this work would have not been completed. Further, I would like to extend my heartfelt thanks to Vinod Mishra post doc at Health Professional Support Department, The RiksHospitalet, University Hospital in Oslo, who unreservedly showed his enthusiasm to assist me as a co- advisor in all along my work. I also thank Arnt E. Fiane, MD, PhD Associate professor, Head of Adult Section, Department of Thoracic and Cardio-vascular Surgery at Rikshospitalet for the usefull communications. He, together with Vinod Mishra, coordinated and arranged nice panel discussions were we met and discussed the clinical use of VentrAssist®LVAD in Norway.

Third, I am thankful to all my family in Oslo. My wife Shumiya Edris Bati has supported me by taking care of our beloved son Kenna during the lengthy study periods. Her tolerance and understanding has enabled me to achieve my study dream cut short while I was in my home country. My fellow friends in Oslo, people like Dr Med Kiniso B. Sado, Torben Midhaksa, Gudata

B.Tufa, and Shigido my younger brother, who live in Ottawa Canada are greatly acknowledged for their informal discussion and contribution for the success of this work.

I am indebted to Associate Professor Rune Flikke, for his continuous advice and encouragement since the undergraduate program study time at the Social Anthropologic Institute and until this moment.

Last, but not least, I would like to express my special gratitude to all fellow student friends, the administrative and research community at the Institute of Health Economics Policy and Management for best scholarly commitment they showed during the last two years. Thank you all.

Butta Dulo Defi

15 may 2009

# Abbreviations and Acronyms

| | |
|---|---|
| **ASX** | **Australian stock exchange** |
| **BNP** | **Brain natriuretic peptide** |
| **BRACE** | **Best result clinical and effectiveness** |
| **BTT** | **Bridge to transplant** |
| **CA** | **Clinical approval** |
| **CBA** | **Cost benefit analysis** |
| **CE Mark** | **Certification European Mark** |
| **CEA** | **Cost effectiveness analysis** |
| **CEAC** | **Cost effectiveness acceptability curve** |
| **CRT** | **Cardiac resynchronization** |
| **CT** | **Conventional therapy** |
| **CUA** | **Cost utility analysis** |
| **DRG** | **Diagnose related grouping** |
| **DT** | **Destination therapy** |
| **ECG** | **Electrocardiogram** |
| **EF** | **Ejection fraction** |
| **ESHF** | **End stage heart failure** |
| **FDA** | **Food and Drug Adiminstration** |
| **HTA** | **Health Technology Assessment** |
| **HTX** | **Heart transplantation** |
| **IC** | **Intensive care** |
| **ICER** | **Incremental cost effect ratio** |
| **ICU** | **Intensive care unit** |
| **ISHLT** | **International Society of Heart and Lung Transplantation** |
| **LVADs** | **Left ventricular assist devices** |
| **LV** | **Left ventricle** |
| **MI** | **Myocardial Infraction** |
| **NHB** | **Net health benefit** |
| **NMB** | **Net monetary benefit** |
| **NOK** | **Norwegian Crowns** |
| **NOKC** | **Norwegian Knowledge Centre** |

| | |
|---|---|
| **NYHA** | **New York Heart Association** |
| **NYHAC** | **New York Heart Association Classification** |
| **OMM** | **Optimal Medical Management** |
| **QALY** | **Quality adjusted life year** |
| **REMATCH** | **Randomized Evaluation of Mechanical Assistance in The Treatment of Heart failure** |
| **RVAD** | **Right ventricular assist device** |
| **SSB** | **Statistics Norway** |
| **VA** | **VentrAssist** |
| **VAD** | **Ventricle Assist Device** |
| **VCR** | **Ventracor** |

# Abstract

***Back ground***

End -stage heart failure is an increasing problem in the western (developed) countries[1]. It is a major health care issue whose frequency is alarmingly increasing. Heart transplantation has been a gold standard medical treatment for this problem. However, the shortage of organ donation due to the high demand for heart transplantation has led to the use of mechanical assist circulation.

Ventricular assist devices (VADs) have become alternative treatments for people with an end –stage heart failure (ESHF). Especially the Left Ventricular Assist Devices (LVADs) are recently introduced as a bridge to heart transplantation for people with an end-stage heart failure until a donor heart is available. The brand of a third generation VentrAssist ® LVAD has been in use in Norway. Economic evaluation of this new intervention is not yet assessed.

***Objective:*** To asses the cost-effectiveness of VentrAssist® LVAD as 'a bridge' to heart transplantation (BTT) for patients with an End-Stage Heart Failure (ESHF), when compared with the conventional medical management.

***Materials and Methods***: Data on the efficacy of the VentrAssist®LVAD is taken from a population based multicentre clinical trail studies, and from a Meta analyses study including the clinical use of VentrAssist ®LVAD. The Norwegian clinic is one of the multicentre clinics included in the study, and the cost data used in this study were taken from the Department of Thoracic and cardio-vascular Surgery the Rikshospitalet, university hospital. This cost data were projected from the Micro-costing study by Mishra et al 2004. The decision Tree Pro Health Care Model 2008 was used to estimate the optimal survival of people with an end-stage heart failure. The costs-effectiveness of using VentrAssist LVAD as a BTT and until one year post HTX was estimated.

***Results:*** This first hand cost-effectiveness study showed that VentrAssit®LVAD is clinically effective. VentrAssistLVAD increases the life of an end –stage heart failure patient by 0.04 with an incremental cost of NOK 0.251M per life year gained until HTX. And it increases life years post

HTX until one year by 0. 14 with an incremental cost of NOK 0.392 M per life year gained when compared with the conventional medical management.

Though the use of VentrAssist®LVAD increased the length of life for people who do not respond to the conventional medical therapy, its cost is much higher than the current willingness to pay ceiling suggested for the Norwegian health care system.

***Key words*:** End-stage heart failure, Health Technology Assessment, VentrAssist® LVAD, Cost-Effectiveness Analysis, Survival probability, Decision Analytic Model

# Table of Contents

# 1. Introduction

An end-stage heart failure is a severe heart disease that does not respond adequately to medical or surgical treatment. End stage heart failure has become an increasing problem in the developed nations across the world. It is a major healthcare issue, whose frequency is expected to continue to rise in the coming years due to the western world's aging population and increased survival rate from acute coronary events.

Annually about 20 million people at worldwide are affected by heart failure (SE Fauci et al 2008) [1]. This indicates that, the morbidity and death rate for people with an end –stage heart failure is increasing. The number of Norwegian who may experienced or have had an end-stage heart failure is estimated to be about 50,000- 100,000 (Helse nytt for alle 2008). [4] Yearly about 12000 – 15000 individuals in Norway have an acute heart failure (data from Nycomed) [1-2]. Thus heart failure at its end stage implies additional major health cost to patients, health care systems and the society as well. Although there are some treatment modalities which can be introduced for end-stage heart failure patients who do not respond to the conventional medical management, their effect, and the

economic impact of such interventions for the patient population in Norway are not assessed and documented.

Heart transplantation remains the most effective and reliable form of treatment for advanced heart failure unresponsive to medical therapy for patients under the age of 65 years. However, despite the increasing prevalence of heart failure, the usage of heart transplantation Worldwide is actually decreasing (a 31% decrease from 1994 to 2002) [1]. This is not only due to a shortage of suitable donors but also due to the improved results of medical therapy for advanced heart failure. The worsening supply/demand imbalance for donor hearts remains the stimulus for research and development of artificial hearts and Ventricular Assist Devices. The rationale for the introduction of prolonged assisted circulation (mechanical support circulation for the people with an ESHF is that, improved assist devices will be accepted as convincing alternatives to biologic replacement of the heart even in transplant- eligible patients and may help modify the supply / demand mismatch for cardiac replacement therapy.
Though there are international studies evaluating treatment costs of LVADs, this has not yet been done in Norway. However, the technology of VentrAssist®LVAD has been in use at the heart clinics (the Rikshospitalet University Hospital, Oslo), and promising clinical outcomes have been registered. Until now15 patients have used VentrAssist LVAD and good results have been registered both in terms of life extending and quality of life. The age range for the patients group is between 10 and 65. The mean age is 38.9 year according to the sources from the patient data registery of the Department of Thoracic and Cardio-Vascular section, Rikshospitalet the Oslo University hospital in Norway. However, in this study we used patients from different clinical trials. We considered 68 patients who used LVAD and 61 patients who used the Conventional medical management (REMATCH) [5]

The aim of this paper is to assess the cost-effectiveness of the VentrAssist ®LVAD BTT in comparison with the Conventional medical management for patients with an ESHF. The health effects of the interventions are measured by the natural units, i.e. the number of life years gained. In this particular case, the proportion of patients survived until HTX at the mean days of 167 while waiting for a donor hear and survival post HTX until one year. The other end point is the costs of the intervention to the health care service until heart transplantation and the follow up cost post transplantation until one year. The incremental cost effect ratios until heart transplantation and post transplantation until one year is calculated. The costs per life year gained of the alternative intervention until HTX and one year cost post- HTX will be analysed.

The paper is organised as follows; the epidemiological background and aetiology of an end-stage heart failure is presented in the second part. Third, the treatment options for the ESHF patients are described. Fourth, the literature reviews regarding the clinical efficacy of VentrAssist® LVAD are summarised. Fifth, the research question, which describes the objective of this study, is presented. Sixth, the rationale for the use of an economic evaluation technique which is the basis for this study will be briefed and all the concepts used in this particular study will be defined and explained as well. Seventh, the model and mechanism used in answering the research question is briefly described. Then, the method and material we used to solve the stated question for this particular study are presented. Further more, the effect measure used to estimate the cost-effectiveness of using ventrassist device when compared with the conventional medical management is elaborated. Eight, by explaining sensitivity analysis, which is the method of capturing uncertainty in the study outcome, the technique of probabilistic sensitivity analysis is briefly discussed and presented. Ninth, the result of this study is presented by using the incremental cost- effectiveness ratio. Finally, the whole study is critically assessed under the discussion by pinpointing the limitations of this cost-effectiveness study reults. Future task to be done in order to assess the cost utility of VentrAssist ®LVAD as BTT is indicated.

Finally, the policy implication of using VentrAssist® LVAD in Norway setting is presented as a conclusion.

# 2. Epidemiology

## *2.1* End- stage Heart Failure

End- stage heart failure (ESHF) is an abnormal physiological condition caused by many different diseases, such as coronary atherosclerosis, hypertension, myocarditis, valvular heart disease, and alcoholism, and each disease has a different incidence of heart failure (Douglas L .Mann 2007). [3] Furthermore, each disease may respond differently to standard therapy such as treatment with diuretics, cardiac glycosides, angiotensin-converting– enzyme inhibitors, and other vasodilators. Harrison's Principle of Internal Medicine the 17th edition, defines heart failure as ''*a clinical*

*syndrome that occurs in patients who, because of an inherited or acquired abnormality of cardiac structure and/ or function, develop a constellation of clinical symptoms that lead to frequent hospitalizations, a poor quality of life, and a shortened life expectancy*( Douglas L . Mann 2007: 1443)''. [3]

End stage heart failure is the condition in which the functional status of heart is characterized by a marked limitations and breathlessness at rest. Like most cardiovascular diseases in industrialized countries, end stage heart failure has become an increasing problem. As the population ages, the number of elderly patients with an end-stage heart failure is expected to rise to 70 million within 25 years (Douglas L: Mann 2007:1443) [3]. The life time risk of developing heart failure for people in the highly developed countries such as North- America and Europe are estimated to be one in five for a 40 – year-old people.[2]

## 2.2 *Prevalence of an End- stage Heart Failure*

Prevalence is a term used by epidemiologists (scientists who study diseases in populations) to describe how often a disorder occurs in a population. [7]

The overall prevalence of heart failure in adult population in developed countries is 2%. Nearly over 20 million people in the world, 6.5 million people in Europe and, 5 million people in the United States have congestive heart failure.
Whereas, approximately about 12000-15000 people per year are suffering from an end-stage heart failure in Norway. [2] The time magazine edited by the Norwegian physicians and specialists in Internal Medicine (Hjerte Forum) discloses that 2 in 10 of the Norwegians aged above 40 years have problems related to heart. [4]
The prevalence of heart failure follows an exponential pattern, rising with age, and affects 6-10% of people over the age of 65[1]. It is the leading cause of hospitalization for people over 65 years of age. In the future, the prevalence of heart failure is expected to increase, partly because the current therapies of cardiac disorders such as myocardial infarction (MI), valvular heart disease, and arrhythmias, are allowing patients to survive longer. Nevertheless, due to lack of systematic population-based studies about the prevalence of heart failure in emerging nations, very little is known with respect to the prevalence or risk of heart failure in most part of the world population.

## 2.3 Incidence

In epidemiology incidence is defined as the number of cases of disease, infection, or some other event having their onset during a prescribed period of time in relation to the population in which they occur.[7] Incidence measures morbidity or other events as they happen over a period of time. Literatures referring to population-based systematic studies show that the relative incidence of heart failure is lower in women than in men. However, women constitute at least half of the cases of heart failure because of their longer life expectancy.

## *2.4 Etiologies of an End-stage Heart Failure*

Etiology is the study of the cause of a disease, including its origin and pathogens. According to the Medical Dictionary - Free dictionary on line etiology is the branch of philosophy which deals with factors of causation or the factors associated with the causation of abnormal body states.
Major risk factors of an ESHF end are hypertension, myocardial infarction, Valvular heart disease, alcoholism and diabetes. Any condition that leads to an alteration of left ventricular structure or function can predispose a patient to developing heart failure. The major aetiologies' of heart failure are depressed ejection fraction EF (< 40%), preserved ejection fraction (> 40-50%), pulmonary heart diseases and high-output states. [1] Ejection fraction (EF) is the fraction of the total ventricular filling volume that is ejected during each ventricular contraction. The normal ejection fraction of the left ventricle is 65%. [1] The New York Heart Association Classification (NYHAC) on the basis of the functional capacity of an impaired heart categorized heart failure in to *four* groups (see table 1 on page 14). The ESHF end category III and IVaccording to the NYHAC is characterized with cardiac disease resulting in inability to carry on any physical activity without discomfort.[6] Patient at the fourth stage may exhibits symptoms of heart failure or the anginal syndrome, even at rest and if any physical activity undertaken discomfort is increased (Little Brown 1964 pp 114).[8]
According to e*medicine* from WebMD- the etiology (the disease processes) that require heart transplantation can be divided into the following categories. These are Idiopathic cardiomyopathy about 54%, Ischemic cardiomyopathy about 45% and congenital heart disease and other diseases about 1% (Mancini C, & Ganghar M, et al. 2006). [8]

## 3. **Diagnoses**

Clinical manifestation reveals that the symptoms of heart failure (chronic cor pulmonale are generally related to the underlying pulmonary disorder. Based on an investigation that may apply simple tests (e.g. urea, electrolytes, hemoglobin, thyroid function ECG, heart chest X-ray) help to establish the nature and severity of the underlying heart disease and detect any complications. Brain natriuretic peptide ( BNP) is elevated in heart failure and can be used as a screening test in breathless patients and those with edema (S.Fauci et al 2008:547). [1]

Table 1. The New York Heart Association (NYHA) functional classification

| **Heart Failure category** | **Functional classification** |
|---|---|
| **I.** | No limitation during ordinary physical activities |
| **II** | Slight limitations, eg dyspnoea on walking |
| **III.** | Marked limitation, symptoms easily provoked |
| **IV** | Breathlessness at rest |

**(New York Heart Association classification)**

## 4. Treatment

Once patients have developed structural heart disease, their therapy depends on their New York Heart Association (NYHA) functional classification. The NYHA classification is the widely used criterion for the identification of the functional capacity of heart for people who experiences heart problem. However, researches on cardiovascular diseases indicate that the NYHA classification system is notoriously subjective, and has large inter observer variability [1].

Most patients who have recently been categorized as class IV (refractory end-stage heart failure) are appropriately treated with compassionate end-stage of life care. Younger heart patients who have fulfilled the NYHA category IV classification would be eligible for transplantation though the exact criteria vary from centre to centre. However, experts revealed that precautions have to be made to the patient's physiologic age and the existence of co morbidities such as peripheral or cerebrovascular disease, obesity, diabetes, cancer, or chronic infection.

## 4.1 Conventional Medical Management

Literature identifies pharmacological / conventional interventions options as the Optimal Medical Management (OMM). This includes the use of drug therapy, diet and exercise. Diet Control lowering the salt intake per day and, physical exercises together with drug prescription are some of the early treatment options for people with heart failure.

The conventional medical treatment, using drugs appropriate for the specific type of heart disease depend on the type of the heart disease, and the available clinical diagnosis. If pharmacologic intervention fails to stabilize patients with end-stage heart failure, mechanical and surgical interventions may provide effective circulatory support. Heart specialists maintain that, prior to the onset of mechanical or surgical interventions; some patients may undergo cardiac resynchronization therapy.[8 ] The use of cardiac pacing to coordinate the impaired electrical activation and myocardial contraction is called cardiac resynchronization therapy ( Fuci et al 2008).[1] Randomized trials of cardiac resynchronization were demonstrated to improve left ventricular systolic function, exercise tolerance, quality of life, and reduction in re-hospitalization frequency of the patients (Douglas L Mann et. al 2007).[3] Re-synchronization also prolongs survival in patients with NYHA Class III or IV heart failure and left ventricular ejection fraction =or<35%.[1]

Cardiac resynchronization therapy (CRT) is a proven treatment for selected patients with heart failure-induced conduction disturbances and ventricular desynchronize. When used in combination with stable, optimal medical therapy, CRT is designed to reduce symptoms and improve cardiac function by restoring the mechanical sequence of ventricular activation and contraction. [1]

## 4.2. Heart Transplantation

HTX has been the optimal treatment for eligible patients, but the shortage of donor hearts limits this option. Mechanical and surgical interventions are the most common options for the treatment of people with an end-stage heart failure.

Some interventions include intra-aortic balloon counter pulsation, left ventricular assist device, and cardiac transplantation. Surgical techniques for orthopedic transplantation of the heart were devised in the 1960s and introduced in to the clinical field in 1967(Harrison chap 228: 1445).[1] Due to the technological advancement in the clinical field of internal medicine, the demand for heart transplants

were successfully met during the 1990s. Heart transplantation as a treatment option for the people with an end stage heart failure has attained a gold standard status, qualitatively. However, the shortage of organ donation has jeopardized this treatment option and the development of left ventricular assisted devices (LVADS) has eased the problem by buying time for penitents whose survival probability without it would have been low. According data from the registry of the International Society for Heart and Lung Transplantation (ISHLT) there are 4000 heart transplants worldwide that are leveled off annually because of lack of donor heart. [9] Heart transplant activity is expected to increase annually, but it will remain stable in the United States at about 2200 per year. [1] This apparent stability in the number of the heart transplant may be explained by the fact that the reporting of the case has become legally mandated in the United States and several countries have also started their databases. However, very little is known about the registry of heart transplant activity in the other countries. The outcome of heart transplantation is assessed by survival rate. It has been 83% for 1 year and 76% for 3 years post transplant respectively (Harrison chap 228 1456). [1] In his study of heart transplantation in patients with diabetes Leslie Miller MD at the Georgetown University found that the average survival rate was 85% with in the range of 365 days until transplantation and 80% post transplantation Miller 2006.[11] The effect of heart transplantation on non- ambulatory patient group based on time dependent proportional hazards model showed that 71% were transplanted with in the average waiting time of 167 days and 70% of those transplanted survived until one year. (NR Banner et al 2008)[12] .The quality of life for these patients is generally proven to be excellent as over 90% of patients in the International Society of Heart and Lung (ISHLT) registry returned to normal and unrestricted function after transplantation[13]. In Norway, the number, of heart patients who undergo heart transplantation per year (including the extra corporal/ assisted circulation) is about 30-40. [15]

Data from The Statistic Bureau in Norway showed that in 2008 there were 39 patients who under went HTX.[14 ] In recent study Hermansen et al( 2008) , made comprehensive study and estimated the potential number of people who need short term use of ventricular assist device( VAD). They used data from all patients admitted to intensive care unit (ICU) and continuous care unit (CCU). They found that about 12% of the patients admitted to the care units needed the use of ventricular assist device (VAD) [15] Aggregating the finding in Hermansen et al (2008), at the national level, 70 patients per year could be potential candidate for the use of VAD in Norway.[15]

## 4.3 Prolonged Assisted Circulation

The underlying principle for the introduction of prolonged assisted circulation (mechanical support circulation for the people with an ESHF is that improved assist devices will be accepted as valid alternatives to biologic replacement of the heart even in transplant- eligible patients. Currently, the technological advance in the field of internal medicine has enabled physicians to diagnose patients with end-stage heart failure or refractory heart failure. Literature shows that, Physicians are left with two options in deciding the medical care for an ESHF patient. Advising compassionate end of life care or choosing to recommend extraordinary life- extending measures. Patient type and age determine the option for the physicians and life –extending measure might be reasonable option for a younger patient without serious co-morbidities. Hunt in SE Fauci et al (2008) suggests that current therapeutic options are limited to cardiac transplantation (with option of mechanical cardiac assistance as a bridge to transplantation) or at least in theory the option of destination therapy as a permanent mechanical assistance of the circulation (SE.Fauci et al 2008: 1455). [1]

The modern era of mechanical circulatory support can be traced back to 1953 when cardiopulmonary bypass was first used in clinical setting to permit open- heart surgery (SE.Fauci et al 2008: 1456).[1] To date, among the treatment options for an end-stage heart failure, ventricular assist devices (VADs) are an emerging new technology, which may serve as a realistic therapeutic option once the complication rate is reduced .[16] The introduction of mechanical circulatory support for the failed heart was considered as an alternative to biologic replacement of the heart. However,( LVADs) the left ventricular assist devices) since their introduction as mechanical support are primarily used as temporary “bridges” to heart transplantation in heart patients who failed to benefit from medical therapy before a donor heart becomes available. Whereas these devices were used in the past almost exclusively as a bridge to transplant, today full-implantable VAD are also considered for destination therapy[19]. The implantable devices are compatible within the body during the hospital discharge, and offer the patient chance for life at home while waiting for a donor heart. Literatures in the field of medical technology confirm that there are several devices that have been emerging. However, their acceptability has been subjected to the approval from the U.S. Food and Drug Administration (FDA).[ 17 ] Currently there are only a handful devices which have attained a clinical acceptance (CA) mark and are in use for alternative treatment for people with an end stage heart failure. LVAD-VentrAssist is among those devices being in use to extend life of some patients with an end stage heart failure. [16]

Left ventricular assist devices (LVADs) are the most commonly used form of mechanical cardiac support, mainly as a bridge to transplantation. The results of mechanical support as a bridge to transplantation have shown significant success with most patients being supported for 3–6 months before heart transplantation with an overall post-transplant survival comparable to orthotropic heart transplantation, namely 50% 10-year survival and 30% 15-year survival. [21]

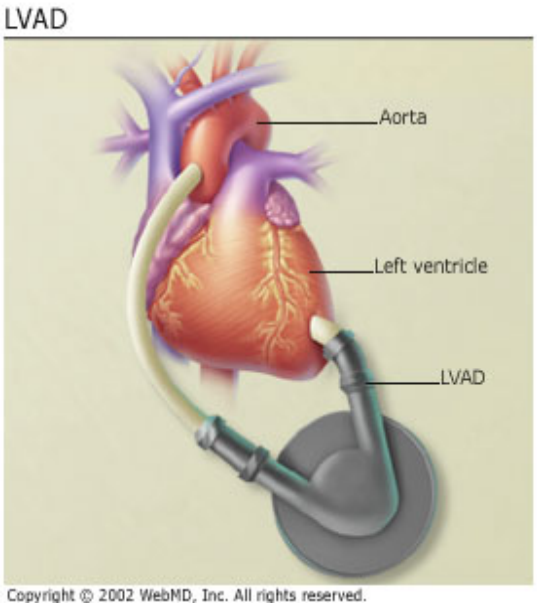
## 4.4 Literature Review of the Ventrassist® LVAD

Ventricular assist device (VAD) is a mechanical pump that helps the heart to pump blood through the body if it is too weak to do it self. The Ventrassist®LVAD does not replace the heart. Instead, it works with the patient's own heart to pump sufficient blood throughout the body. The VAD consists of a pump, a control system, and an energy supply. Some VADs including the VentrAssist rely on a battery for their energy supply; others use compressed air (pneumatic). The energy supply and the control system are located outside the body; the pump can be either inside or outside the body, however, the VentrAssist LVAD is inside the body.

The left ventricular assist device (LVAD) receives blood from the left ventricle and delivers it to the aorta (the large artery) that carries the blood from the heart to the rest of the body.

Ventricular assist devices were originally intended for a short term use to support failing hearts until donor hearts became available. It is sometimes referred to as "a bridge to transplant" .The VentrAssist ®Device is used to aid the pumping action of a weakened heart ventricle (a major pumping chamber of the heart). However, some ventricular assist devices are now used for long-term therapy for who are not candidates for HTX. The following is an example of an LVAD in use and taken from WebMD.

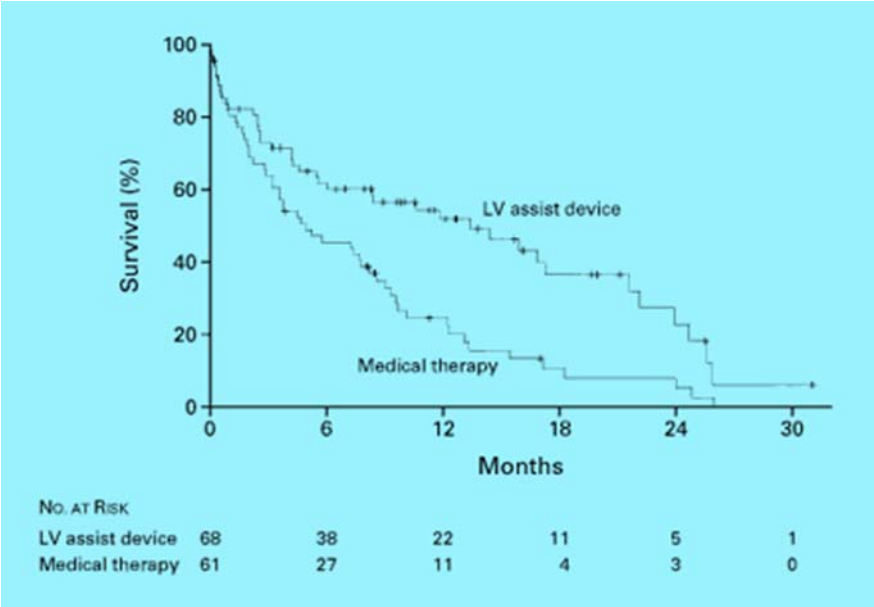
Fig 1 LVAD in use




VentrAssist®Device is a novel, third-generation, continues-flow LVAD designed to overcome earlier LVAD limitations such as size, noise, reliability and mechanical complexity. It is developed by the Ventracor Limited, Sydney, Australia. This device has been in use in many countries including Norway. A prospective, multicentre international clinical trial of the ventrassist left ventricular assist device has demonstrated the favorable efficacy and safety profile for use of the VentrAssist LVAD in BTT patients ( Donald Esmore Fracs et al: Journal of Heart Lung Transplant June 2008).[6] The first implant of the VentrAssist occurred in 2003 with an updated implant report published in 2006. According to Ventracor Limited (ASA: VCR) report of March 2009 US Bridge to Transplant (BTT) trial of ventrAssist® has reached successful completion. [19] The increasing prevalence of an end stage heart failure has stimulated the ongoing development of Left Ventricular Assist Device (LVADs) for both bridges to transplant (BTT) and destination therapy (DT).

The survival curve for the left ventricular assist device and for the conventional therapy is presented in the figure 3. However, this figure shows with use of an old 1st generation pump Heart Mate XV and not VentrAssist LVAD 3$^{rd}$ generation pump. Morover, Patients in the US are not comparable with that of the Norwegians. The curve includes patients who used LVAD as a destination therapy and depicts the feasible life extended in comparison with the conventional therapy. It is based on the

Kaplan Meier Analysis of survival probabilities for heterogeneous groups of patients experiencing end stage heart failure with different categories of New York Heart Association classification. It covers a total period of over 2 year's time and we used this curve in order to capture the early survival rate for patients who are waiting for a donor heart.




Taken from：

The New England Journal of Medicine

Long-Term Use of a Left Ventricular Assist Device for End-Stage Heart Failure
*N Eng l J Med 2001; 345:1435-1443,*
*Nov 15, 2001*

Figure2. Kaplan–Meier Analysis of Survival in the Group That Received Left Ventricular (LV) Assist Devices and the Group That Received Optimal Medical Therapy. Crosses depict censored patients. Enrollment in the trial was terminated after 92 patients had died; 95 deaths had occurred by the time of the final analysis.

## 4.5 Clinical Efficacy of VentrAssist® LVAD

The Department of Health define clinical effectiveness as: "*the extent to which specific interventions, when deployed in the field for a particular patient or population, do what they are intended to do – i.e. maintain and improve health and secure the greatest possible health gain from available resources*."[19] Moreover, to minimize uncertainty an intervention has to produce health

benefits and this have to be shown practically being capable of producing worthwhile benefit (efficacy and cost effectiveness).

Literatures on mechanical circulatory support for failed heart have confirmed that Ventrassist®LVAD has a particular advantage for the destination therapy patient (Esmore D et al 2007).[15] Left ventricular assist devices can be used as a destination therapy for an end-stage heart failure patients who are not eligible for transplantation. Esmore et al 2007 showed that with its silent function, small size, low rates of infection and thrombosis, the 3rd generation VenrAssist®LVAD has proven its clinical efficacy with similar rate of adverse side effects in line with the other about 30 existing assist devices currently in use. Moreover, the literature further confirms that, this Australian based third generation device is effective with a theoretically long life, thus providing excellent quality of life for the patient with an ESHF. However, some more controlled randomized trial studies are ongoing and are previously not published. As controlled randomized trials are the standard clinjcal studies so far used for approval of clinical efficacy of health interventions, we expect the clinical use of VentrAssist would be warranted by such a conventionally accepted measure of efficacy.

The validity and reliability of the clinical outcomes of VentrAssist®LVAD is less documented and it is limited to the publication of Randomize Evaluation of Mechanical Assistance in the Treament of Heart Failure (REMATCH).[5] The REMATCH trial in 2001 documented an improved survival in non-transplant candidates ESHF.

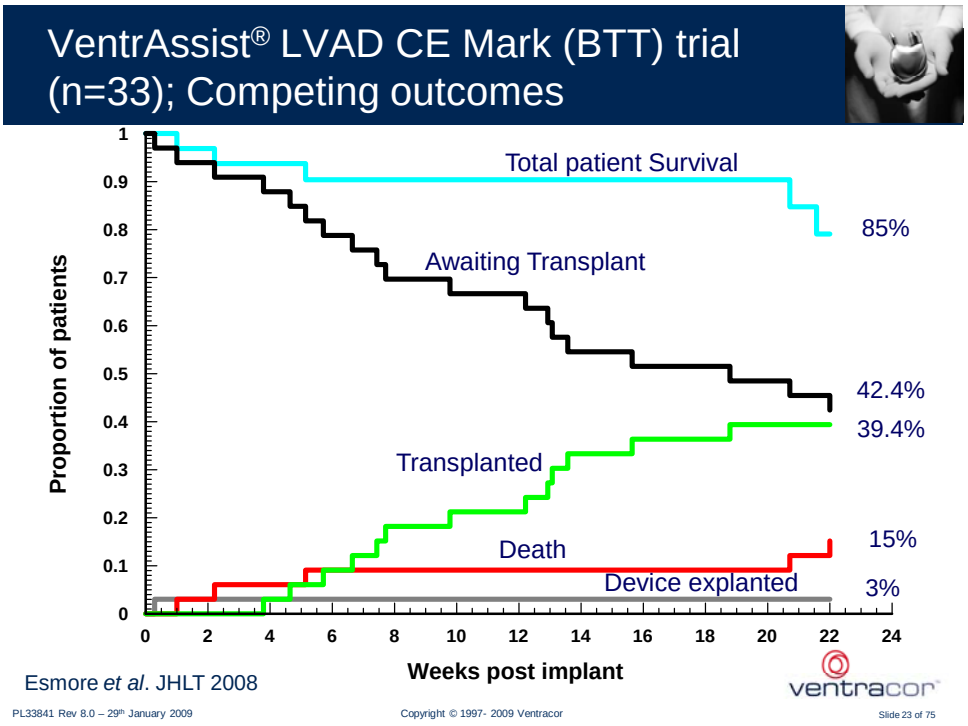


Fig. 3 **VentrAssits LVAD certification of uropean Mark (CE)**

Based on the data from an international, multicentre clinical trial, the above curve depicts the use of VentrAssst –LVAD as a CE Mark trial in Europe, Australia and USA. The primary efficacy outcome measure (survival until transplant or transplant- eligibility) was achieved by 83% of patients implanted with VentrAssist. According to D. Esmore et al 2008, these results compare favorably with the other LVADs results of published reports of 65-70%.[6]

Table 2: Summary of survival data from different clinical trials, Conventional therapy vs. Alternative therapy

| **Study year** | **Intervention** | **Outcome Measure** | | **P value** |
|---|---|---|---|---|
| | | Survival until Htx | One year survival | |
| D Esmore et al Nov 2008 | Alternative (VentrAssist LVAD) | 0,83 | 0,78 | Non sig |
| NR Banner et. al Dec 2008 | Conventional | 0,71 | 0,70 | sig |
| D Esmore et al 2007 | Alternative(LVAD) | 0,75 | 0,60 | sig |
| Miller et al 2006 | Conventional | 0,85 | 0,8 | Non sig |

Survival until HTx includes all patients transplanted and waiting Htx.

*Aveage waiting time until Htx is 167 days

## 4.6 Adverse Effects

LVAD implant surgery carries risks of severe complications. Potential complications include bleeding, development of blood clots, respiratory failure, kidney failure, infection, stroke, and device failure. [23] Physicians or surgeons in charge of operation rooms are accountable for patients to inform and tell them more about the risks associated with ventricular assist devices. VAD should firstly be used only in patients who are eligible for heart transplants or secondly for those patients who have severe ESHF and are not candidates for heart transplants. In the second cases, VAD mostly are used as a DT.

Poor candidates for VAD include people with irreversible kidney failure, severe liver disease, blood clotting disorders, and severe lung disease infections that do not respond to antibiotics.

# 5 The Research Question

## 5.1 Is the use of VentrAssist® LVAD as a bridge to heart transplantation for an End -stage Heart Failure (ESHF) patient's a Cost-effective option in Norway

It has long been recognized that health care, like other aspects of life, faces the problem that the resources available to spend are scarce to meet all demands. Decisions about what services to provide, to whom, where and when, usually have resource implications. Pursuing one course of action such as offering a VentrAssist ® LVAD for an end-stage heart failure patient at a given frequency means that other possible decisions were not made regarding the treatment of an end-stage heart failure patient. Hence, making such decisions entail an opportunity cost of using scarce resources. In publicly funded health care system, with a limited budget, or in an insurance-based system where premiums have to be competitive priority making have implication for health.

Considering the current financing policy of the Norwegian health care system for the specialist health care services, this paper bases its analysis on the existing literature reviews internationally, and some empirical data from the Norwegian setting. The research aims to assess the cost effectiveness of Ventrassist®LVAD, as a BTT when compared with the conventional medical therapy. Literature on the clinical use of VentrAssist LVAD the VentrAssist has shown that, survival rate of an end-stage patents that used the device increased significantly when compared with those patients groups of the conventional medical treatment. Hence, it is necessary to compare the use of LVAD with the conventional medical treatment with regards to not only current survivals, quality of life, and complication metrics, but also relative costs between the two treatments. Demographically this study intends to evaluate currently available VentrAssist ®LVAD used as a "bridge" to transplantation for people between 10 , and 65[9] years who are suffering from end-stage heart failure. The heterogeneity across the study population is one of the major issues which we assume will have significant variation in the study results.

Theoretically, the Norwegian health care policy is based on the social welfare approach. The policy objective is to finance the health care programs according to the severity of the disease and their health improvement. The health improvement is measured by natural units. In this case, maximizing

the length of life for ESHF patient who do not respond to the conventional medical treatment would be the prime objective of the policy. Maximization of health at a reasonable cost is the other policy objective stated in the Norwegian financing policy of the health care system. Hence, it is arguable that there is a tradeoff between health maximization, priority of severity and cost containment and fairness. Said in another way, efficient service and quality services based on the principle of prioritizing severity is the central focus of the Norwegian Health Care System.

## 5.2 Perspectives of the Study

In any program evaluation or health technology assessments view points are important in order to value the outcome of using any pharmaceutical and medical equipments. In health care services view points or perspectives of the providing institution, patients, third party payers, government and society are used to undertake a cost effectiveness analysis or cost utility analysis of a given health program.

For a given health care intervention to be cost- effective or worthwhile, the aims or objectives set to achieve are crucial factors. To analyze the clinical and cost effectiveness of VentrAssist®LVAD for ESHF patients as BTT, we have chosen the health care provider (hospital) perspective. We limited our perspective to the health care provider due to the fact that, this study is based on the data from the health care provider only. The gold standard cost effectiveness analysis should include the greater wider prospective which is the societal perspective.

The societal perspective considers additional costs that are not relevant to the hospital. A good example is the lost productivity. Lost wage from work due to illness would be relevant for the societal perspective. We imagine people with an ESHF are already a burden to the society and their costs are societal. A societal perspective incorporates all the costs and benefits regardless of who incurs or obtains them. Literatures in the economic evaluation of health care programs consider the societal perspective as wider and more complex perspectives. More restricted perspectives may mask the fact that costs are simply being shifted to another sector rather than being saved. The Norwegian health care policy is also in line with the broader societal perspective when putting the decision rule in prioritizing two competing and life prolonging health care interventions.

# 6. Economic Evaluation

In assessing the economic impact of health care interventions different techniques of economic evaluations methods are employed. In what follows we present the definition of economic evaluation and then elaborate those techniques that are in use by health care policy analysts depending on his/her interest of analysis.

Economic evaluation is 'a *comparative analysis of the costs and outcomes of therapy involving the proposed drug and therapy relating its main comparator(s). The concept covers cost utility analysis, cost effectiveness analysis, cost benefit analysis and cost minimization analysis as an umbrella term'. (*Drummond et al 2005*)*[27]. Economic evaluations have emerged as a set of research methods to define the economic burden of diseases. The expected utility theory asserts that: when choosing between two things, our preferences should minimize risk and maximize safety. Likewise, evaluation of any new program is subject to assessing the quality outcome of the program in comparison with the existing or the conventional one.

In economic evaluation the unit for measuring the benefit of health care is the key feature that distinguishes the different techniques of economic evaluation. The brief overview of each technique based on the Drummond et al 2005 is given as follows.

## 6.1 Cost Benefit Analysis

Monetary valuation of any program in general and that of health care programs in particular is the fundamental feature that distinguishes the technique of economic evaluation. Cost benefit analysis (CBA) is the way in which we give value judgment to certain health interventions. Cost benefit analysis enable us to make a direct comparison of programs under scrutiny to see the incremental costs with their effects in a commensurable units of measurements. Units of monetary measurements such as USD, Euro, and NOK are used to value health benefit. However, measuring health benefit in monetary value has several theoretical underpinnings (Drummond et al 2005). [27]

## 6.2 Cost Effectiveness Analysis

Cost effectiveness analysis (CEA) can be defined as a type of economic evaluation which assess the costs and effect of two or more health interventions under scrutiny. Drummond et al 2005 defined it as one form of full economic evaluation where both costs and consequences of health programs or

treatments are examined (Drummond et al 2005: 103). [27] Drummond et al (2005) further emphasized that CEA is a type of program evaluation in which the incremental cost of a program from a particular viewpoint is compared to the incremental health effects of the programs. The analysis measures health effect in natural units such as life years gained both in quantity and quality, and heart infraction avoided. Quality adjusted life years have become the common effect measure. Important considerations when designing a cost-effectiveness analysis include the audience, the perspective, the type of health effects, and the time horzon. The patient population and the setting together with the details about the two or more competing interventions are equally important.

## 6.3 Cost Utility Analysis

Cost utilitiy is a form of CEA where the effects or outcome of health interventions are measured in a common metric based on people's utility levels or preferences over different health states. (Tsuchiya et al 2007) [28]

The focus of cost utility analysis in health economics is the quality of the health effect produced or forgone by health programs or treatments. The analysis converts effects into personal preferences (or utilities) and describes how much it costs for some additional quality gain (e.g. cost per additional quality-adjusted life-years or QALYs). See the definition of QALYs below. Cost utility analysis allows broad comparisons across widely differencing programs. In health care interventions, cost utility is used as an analytic tool to provide method to attach values to the outcomes of two or more competing interventions so as to give more weight to the most important outcomes.

In general Cost benefit analysis is grounded in welfare economic theory and it assesses whether a program is worthwhile without reference to any external standard. The main concern for a cost benefit analyst is to see if a given budget could be enough to accommodate the new program. Cost effectiveness and cost utility analyses assume that the decision maker seeks to maximize achievement of a defined objective by making use of a constraint budget. Economic evaluation of new technologic health care interventions by and large reveal that most new interventions are more expensive and more effective than the usual ones. Hence, some Health Economics Literatures seem to neglect the issue of cost minimization and opt for looking at, if a given intervention has better consequence when compared with the other which is usually termed as a comparator.

## 6.4. Health outcome

Health outcome from a given intervention can be measured by using natural units such as; number of pain or depression free days, number of myocardial (MI) averted, death postponed by days, months or years. When measuring health outcome for the treatment of patients with an end-stage heart failure, the length of life extended until a donor heart is available and life year gained post HTX until one year is used. QALYs (Quality adjusted life years) are used in order to measure the health outcome of a given intervention.

Quality – adjusted life years (QALYs) are a measure of health outcome which assigns to each period of time a weight, ranging from negative infinity (or negative one for transformation) to 1, corresponding to the health- related quality of life during that period. '*A weight of one 1 corresponds to optimal health, and a weight of 0 corresponds to a health state judged equivalent to death when aggregated across time period*.'(Tsuchiya et al 2007) [28]

Willingness to pay is a method of measuring the value an individual place on a good, service, or reduction in risk of death in illness by estimating the maximum amount of money one would pay in order to obtain the good or services one needed.

## 6.5 Prerequisites for Economic Evaluation

As any economic resources, health- care resources are limited. The consumption of resources by a patient means that somewhere, some time, resources are unavailable for some other health-care purpose. All the resources used in the provision of a given health -care are those which constitute the cost of an intervention. The measure of cost is the value that is forgone when resources are used for one purpose rather than the next best use. Such value of resource used in the next best use is often known as the *opportunity* cost of the resource (Huninkk et al 2001). 29]

Identifying, quantifying and measuring of the costs and the consequences associated with health intervention under study will be the underlying process in an economic evaluation. This helps an analyst to determine the value of health technologies, treatments and policies to manage patients. Identification is the way in which a health state changed, resource saved and other value created from the intervention is described. Identification of resource used for intervention say some thing about the impact of intervention on the patient, family, health sector and societal productivity as well. The perspective of an economic evaluation is the fundamental basis for identification of the

resource consumed or used for particular intervention. Quantification is the way we measure the consequences or health effects obtained from an intervention. The perspectives of an analysis determine the effects to be measured and mostly health care sectors are the immediate arena to quantify the resource used for certain interventions.

Valuation is the way in which we judge the value of resource used or saved when implementing a given interpenetration. Opportunity cost is abetter concept which can explain valuation. Opportunity cost is the health benefit lost because the next best alternative was not selected. Costs considered and estimation of the costs used for intervention using different units is the way we can value the cost of a specific intervention. The techniques of CEA and CBA in economic evaluation are tools we use to judge the value of resource used or saved. Perspective of the analysis have pivotal role in weighing the value judgement we give to a given intervention. Diagnoses related grouping (DRG) can be used for valuing the cost to be devoted for an intervention.
DRG also called diagnoses related grouping is the system which classifies in-hospital patients in to approximately 500 different groups. Theoretically each group of patients represents the same need of medical and surgical procedures during their hospital stay. The method of micro-costing that estimate each component of resource used for an intervention such as number of hospital stay by ward and drug, laboratory tests, medication, administration and operation constitutes the basis for DRG pricing. Micro-costing is the process of settling health care service costs based on the duration and motion of a patient under treatment.

## 6.6. The Incremental Cost Effectiveness Ratio (ICER)

Incremental Cost Effect Ratio (ICER) is the ratio (value) of a change in a cost divided by the change in effect when comparing a comparator with its alternative intervention. It is commonly used in presenting the result of CEA and CUA. The incremental cot effectiveness ratio measures the incremental prices of obtaining a unit health effect from an intervention in comparison to the alternative (comparator).

If $C_0$ and C1 are the cost of comparator and intervention respectively, and $E_0$ and E1 are the effects;

$$ICER = C_1\text{-}C_0 / E_1\text{-}E_0 \quad \text{---------- (1)}$$

The drawbacks of the ratio as explained by Drummond et al 2005 Chap 1&2, is that it does not explain about the size of the treatments under scrutiny.

The net health benefit (NHB) is a concept taken from the economist using when discussing about net benefit of a certain program. The inequality in the value of an assumed willingness to pay for a certain program multiplied by the change in an effect of the program minus the change in cost is called the NHB – net health benefit. If the willingness to pay times the change in effect minus the change in cost of the programs under consideration is greater than zero the program is deemed cost effective. If NHB is the net health benefit and '$\Delta E$' is an effect from the intervention, '$\Delta C$' is cost, and 'Rt' is the willingness to pay; then

$$NHB = \Delta E-(\Delta C/Rt) > 0 \quad \text{---------- (2)}$$

For a given intervention to be cost-effective, in principle NHB has to be greater than zero.

Cost effectiveness plane is used to judge the cost and the effect of two competing health care interventions. On the cost effectiveness plane, the x- axis is the effect and the y-axis is the cost.

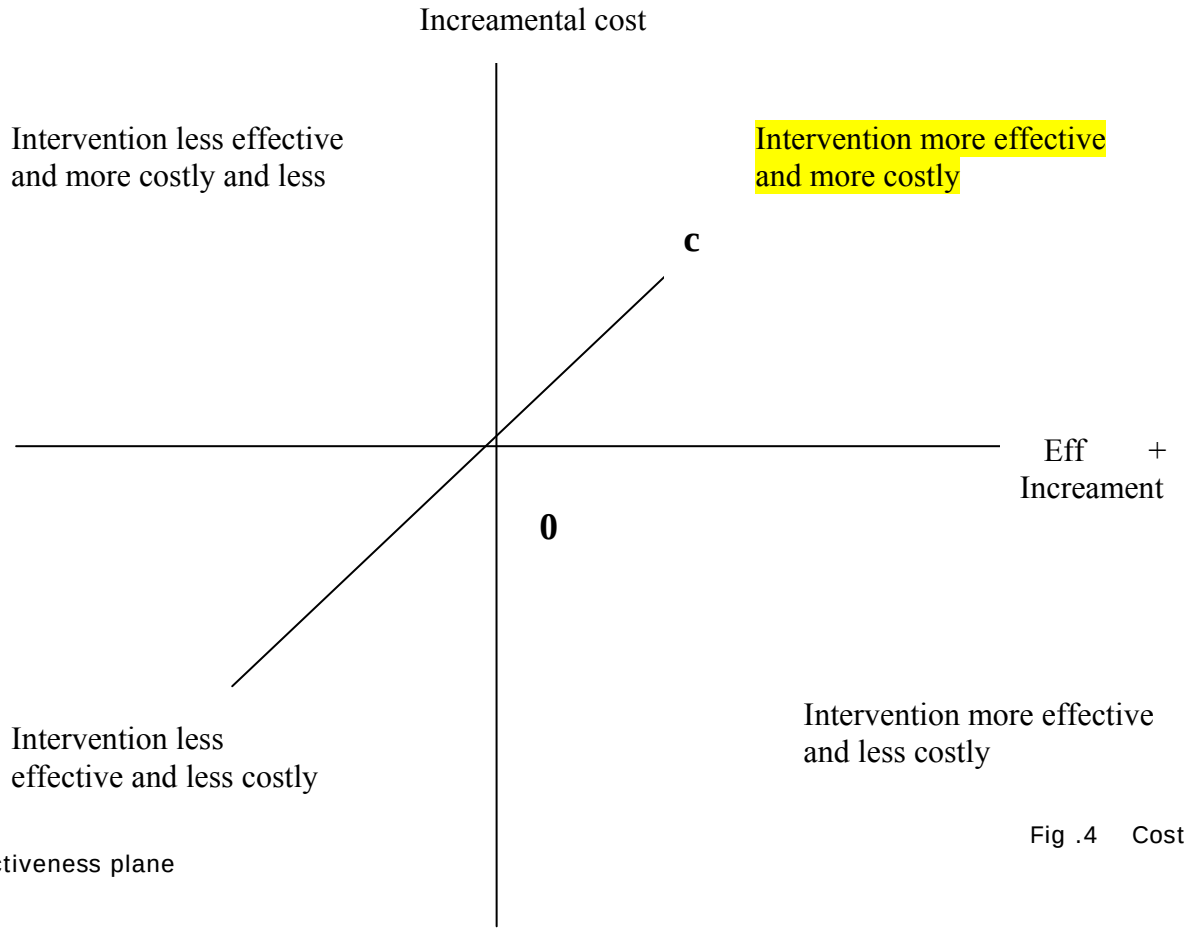



Fig .4 Cost effectiveness plane

Fig 4

# 7. Model and Material

## 7.1 The Model

The model for the treatment of ESHF patient is based on the assumption that: At the onset of the intervention the patient is treated with the conventional medical management. If the medical condition is complicated, and the degree of heart failure is in the New York Heart Association Classification (NYHAC) III or IV, the patient is switched to the alternative therapy. Complicaation can be explained as any adverse effects accosiated with interventions. In the conventional + VentrAssist arm the model assumed that some patients may recover from severe heart failure and continue with the medical treatment. The alternative strategy is ensue when all the manses's under the conventional medical therapy are exhausted and proven to be non responsive. In the model the symbol □ is the decision node and ○ is the chance node.

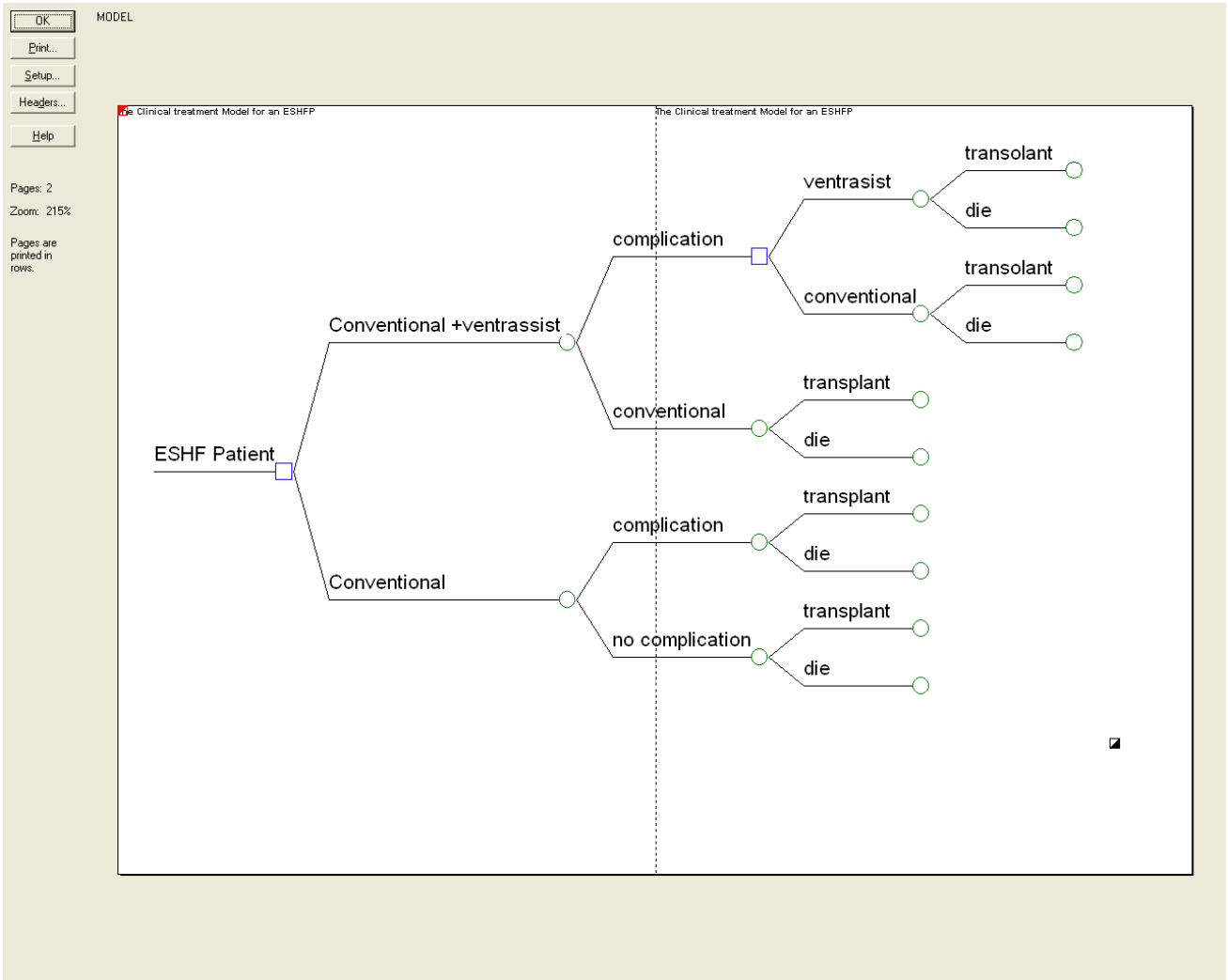



**Fig.5 Model showing treatment courses for an end stage patient.**

The model shows that, the patients who used the alternative therapy would not survived if they do not get VentrAssist ®LVAD that assists the heart to pump the essential blood to the rest part of the body. The application of the model is described with the Decsion Tree Pro Health Care. See Fig 12.1 on the appendix for the detail.

## 7.2 The Decision Tree pro Health Care Model 2008

Decision tree is a graphical representation of a decision which incorporates alternative choices of uncertain events with their probabilities and outcomes. [29]

We assume that clinical decisions like any other decisions are not completely free from value judgments. In most cases, clinical decisions between alternative strategies are not only used to estimate the probability out comes, but also the associated value judgments about how to weigh the benefits against the harms. In assessing the clinical and cost-effectiveness of VentrAssist device as a bridge to heart transplantation we used the Decision Tree Pro Health Care Model 2008. We compared the *optimal* survival probability of an alternative intervention with that of the conventional treatment until HTX. The mean survival day we assumed was 167 days HTX. Waiting time varies from center to centre and the Norwegian cenre has lower waiting time due better access to donor heart (expert view). [10]

## 7.3. Effect **Measure**

The health effects were measured in terms of life years gained and the cost associated with it. The quality of an effect measure used in assessing the clinical outcome of a given intervention is the building block in order to perform a better economic evaluation of the intervention. The effect measures we used when assessing the clinical efficacy of VentrAssist®LVAD as a BTT are life years gained (extended) to HTx and post HTx until one year as primary effects, and the costs associated with the use of VentrAsist ®LVADas a secondary effect. Explicitly, the effect measure is explained as which option or strategy is maximizing the *optimal* survival and which one is minimizing the costs for the treatment of people with an ESHF when waiting for donor heart.
We used the clinical data from the multicentred population based trials with an intention to treat principle. Medical Experts have the view that, given the shortage of data which compared the clinical efficacy of the conventional medical management with that of a 3rd generation LVADs such

as the VentrAssist, the introduction of LVADs as a BTT is clinically effective. The length of survival time is measured by the number of days and the mean days of waiting for heart transplantation considered in this particular study is 167 days. The standard deviation was 135 days; minimum 4 days and, maximum 468days (Esmore et al 2007**)** [18]. However, according to the information from the Rikshospitalet, Department of Thoracic and Cardio-vascular Surgery, the mean waiting days in Norway is about 100 days. This is because; Norway has better access to donor heart. [8] The study data is based on population based multicentre clinical trials and the randomized controlled clinical trial studies are expected to be published in the coming two or three years (report from the Norwegian Knowledge Centre for Health services 2008).[30]

## 7.4 Clinical Data

Data production for this study has been challenging .This is because; there is no standard data base where one can find the clinical efficacy of the conventional medical management for the treatment of end stage heart failure people that can be comparable directly with the alternative intervention-the ventrAssist device. Neither was it possible to find enough data regarding the clinical effectiveness of these two interventions under scrutiny as direct comparators. Systematic literature searches were performed in order to assess the clinical efficacy of using the conventional medical management and the use of Ventricular Assist Devices for the treatment of people with an end-stage heart failure. The search included clinical outcomes of all the conventional medical managements, and the use of assisted circulation. We searched for all published and unpublished materials. To this end, *eighteen* electronic data bases including, Pub Med Cochrane Library, Medline, and Embase up to January 2009 were assessed in order to capture the survival curve for patients who have been implanted Ventricular Assist Devices. Our search results for a randomized controlled trial studies for the third generation LVADs were limited to the HeartMate. HeartMate is a third generation Left Ventricular Assist Device commonly used in the Untied States of America. We found one study which compared the survival of the patient group that received left ventricular assist devices and the group that received the conventional medical therapy. [5] The numbers of patients at risk were 68 and 61 for the LVAD and the conventional medical therapy respectively (Fig 4 above). Six months survival was 38 out of 68 for the LVAD and 27 out of 61 for conventional medical therapy. This shows that there is about 12% difference in the survival probability between the two groups. The survival curve shows that, LVAD has a better survival rate when compared with the conventional medical therapy despite some side effects such as bleeding, development of blood clots, respiratory failure, kidney failure that may be related to the device failure.[ 23]

Tabel 3 Probabilities used for the estimation of clinical survivals until Heart tansplanatation

| Variable name | Descriptions | value | Source |
|---|---|---|---|
| P_C_Comp | probability of Conventional Complication | 0,2 | Miller et al 2006 |
| P_C_Comp_Transp | Probability of Conventional Complication Transplant | 0,71 | NR Banner et. al Dec 2008 |
| P_C_Non_Comp_Transp | Probability of Non _complication Transplantation | 0,8 | Miller et al 2006 |
| P_V_Comp | Probability of Ventrassist Comlication | 0,3 | Miller et al 2007 |
| P_V_Comp_V | Probability of Ventrassist Complication Ventrassist | 0,9 | Expert views(Arnt Fiane |
| P_V_Com_Transplant | Probability of Ventrassist Complication Transplant | 0,83 | D Esmore et al Nov 2008 |
| P_V_C_M | Probability of Ventrassist Complication Medication | 0,1 | Expert views(Arnt Fiane) |
| P_V_Non_Comp_Transp | Probability of Non-Complication Transplantation | 0,85 | Expert views(Arnt Fiane) |

Tabel 4 . Probabilities used for the estimation of clinical survival until one year

| Variable name | Description | Low | High | Outcome measure One Year survival | Source |
|---|---|---|---|---|---|
| P_C_Comp | probability of Conventional Complication | 0,005 | 0,25 | 0,2 | Miller et al 2006 |
| P_C_Comp_Transp | Probability of Conventional Complication Transplant | 0,65 | 0,75 | 0,7 | Miller et al 2007 |
| P_C_Non_Comp_Transp | Probability of Non _complication Transplantation | 0,6 | 0,85 | 0,8 | D. Esmore et al 2008 |
| P_V_Comp | Probability of Ventrassist Comlication | 0,025 | 0,35 | 0,3 | Miller et al 2007 |
| P_V_Comp_Med_Transp | Probability of Ventrassist Complication Medication Transplanatation | 0,56 | 0,8 | 0,71 | N Banner et al 2008 |
| P_V_Comp_V | Probability of Ventrassist Complication Ventrassist | 0,68 | 0,95 | 0,9 | Expert views(Arnt Fiane) |
| P_V_Com_Transplant | Probability of Ventrassist Complication Transplant | 0,7 | 0,85 | 0,83 | D esmore et al 2008 |
| P_V_C_M | Probability of Ventrassist Complication Medication | 0,0054 | 0,15 | 0,1 | Expert views (Arnt Fiane) |
| P_V_Non_Comp_Transp | Probability of ventrassist Non-Complication Transplantation | 0,58 | 0,87 | 0,85 | Expert views(Arnt Fiane)) |

Moreover, the search yielded also some ongoing randomized controlled trial studies for some of the third- generation LVADs including the VentrAssist device (report from Kunnskapssenteret 2008).[24] Clinical studies that compared the general survival outcome of the oconventional medical management against that of VentrAssist®LVD have been used in order to substantiate the clinical trial data used in this preliminary study of assessing the clinical and cost-effectiveness of VentrAssist®LVAD. The mean number of waiting days is 167 in the Certification for European mark (CE Mark) trial of VentrAssist device. [18] Moreover, Panel discussions with the Department of Thoracic and Cardio-vascular section at Rikshospitalet, and University of Oslo were made. The panel discussions were based on the expert views. This helped us to establish the clinical efficacy of VentrAssist ®LVAD as a BTT for the treatment of people with an ESHF patients. Further searches were made for all the Conventional medical managements and the use of assisted circulation. Systematic search for the use of Assisted Mechanical Circulation was performed. All searches confirmed that LVAD third generations including VentrAssist®LVAD are better options for the treatment of ESHF, not only as BTT, but also as DT especially for pediatric patients. [26]

## 7.5 Cost Data

The major costs associated with the treatments of ESHF patients have been identified in to *five* components for the sake of simplicity. These are categorized as examination costs, medication costs, operation costs , personnel costs and follow up costs for the conventional medical management and the corresponding categories for the alternative intervention (VentrAssist®LVAD) are pre VentrAssist ®LVAD, medication, operation( implantation), personnel and follow up costs. Tabels appendix Examination costs include the entire test that a patient under go including specialist consultations. Medication costs are those costs related to the purchase of prescribed medicines which a heart failure patient uses during treatments. As indicated in the tables and appendix, medication costs of the conventional medical treatment is higher than that

of the alternative treatments. This is due to the fact that patients who implanted VentrAssist®LVAD use less medications as the device assist the heart to pump the blood. Personnel costs are those costs related to the movement of a patient in the ward. Nursing, physiotherapy and all other costs associated to the physical and social services that are rendered to a patent during hospitalization. Operation (implantation) costs comprise all the costs related to the surgical room. Surgeons costs, assistant nurses, and surgery equipments. Follow up costs are all medical and other services costs used after the patient is discharged. The follow up for the both interventions are assumed to be comparable if there is no complications which require special attention.

Cost accuracy is far from perfection, but it is '*important not to make the perfect the enemy of the merely good' (*Drummond et al 2005:71). [27]. Cost data we used for this study is based on the micro-costing study done at the Riks Hospitalet, the University Hospital in Oslo. Hence, our assumption of valuation is limited to the hospital perspective. In the micro-costing study each component of the resource use such as laboratory tests, each days of stay by ward and drugs are identified and estimated so as to drive a unit cost for each component. Four levels of precisions have been discussed in the Drummond's et al (2005). These are Micro-costing, Case mix group, Disease specific per diem or daily costs and Average per Diem. Micro-costing is the most precise where as the Average per diem cost is the least precise level of cost estimation ( Drummond et al 71 box 4.6). In Micro-costing method each component of resource use is identified and estimated properly. Micro-costing is a process of settling a health care service costs based on the duration and motion studies of a patient under treatment. Such costing is the basis for obtaining total direct cost incurred in order to provide necessary service to a patient. Hence the information generated by micro-costing enables better accuracy for decision-making purposes (Mishra et al 2004:23) [32]. Costs for the conventional and alternative interventions are given in the tables 3 and 4 below.

Table 5 Cost parameters and estimation used until Heart transplantation

| Name | Description | Value | Source |
|---|---|---|---|
| a | Pre-ventrasssit medic | 157810 | Estimation based on Micro-costing |
| b | Medication+compl cost | 36303 | Estimation based on Micro-costing |
| c | Operation cost+device cost | 3527380 | Estimation based on Micro-costing |
| Conven | Cost of conventional _Transplant | 943449 | Estimation based on Micro-costing |
| C_conven_death | (a+b+d) | 2564268 | Estimation based on Micro-costing |
| C_Conven_Tx | (a+b+d+e) | 943499 | Estimation based on Micro-costing |
| C_nonComp | Cost of non complication | 27207 | Estimation based on Micro-costing |
| C_V_Coml_Transolant | (a+b+c+d+e) | 4 886 437 365 | Estimation based on Micro-costing |
| C_V_Copm_death | a+b+c+d | 3 900 801 165 | Estimation based on Micro-costing |
| med | Medication cost | 36303 | Estimation based on Micro-costing (Mishra et al 2004) |

Costs in NOK1000

Table 6 Cost parameters and estimations used for one year model

| Variable Name | Description | Low | High | Cost per patient | Source |
|---|---|---|---|---|---|
| a | Pre-ventrasssit medic | 37366 | 356709 | 157810 | Estimation based on |
| Conven | Cost of conventional _Transplant | 472915 | 3198039 | 943449 | The Mirco-costing |
| C_conven_death | (a+b+d) = cost of conventional death | 472915 | 2972580 | 832439 | study |
| C_V_Coml_Transolant | (a+b+c+d+e)= cost of Ventrasist complication l transplant | 1497751 | 4122708 | 3246943 | |
| C_V_Copm_death | a+b+c+d= cost of ventrasist complication death | 1023512 | 3852256 | 2564268 | |
| d | Cost of personnel for alternative treatment cost+comp | 1064240 | 3901330 | 2284300 | |
| e | Follow up cost for alternative treatment | 53973 | 361204 | 111600 | |
| med | Medication cost for alternative treatment | *8594* | 82504 | *36303* | |

Costs are in NOK1000

# 8. Sensitivity Analysis

Survival probability and cost associated for the interventions are estimated by the Decsion Tree pro health care model as presented above. However, Macro simulation models such as Decision Tree and Markov cohort models which are used to simulate cohort or group of subjects are subject to a number of limitations (Mariyam Huninken pp 339). [29]

Variability and uncertainty in a clinical and cost –effectiveness analysis of health intervention under study can be attributable to: unpredictability across sub groups under study, changeability in the population, uncertainty due to random events, parameter uncertainty and Model structure uncertainty. Although we believe that all the factors of variability and uncertainty we mentioned above have their part in contributing to the change in our study outcome, our sensitivity analysis is aimed at testing of variability in ICER across the interventions complication of clinical outcomes population and parameter uncertainty. Sensitivity analyses can be conducted in two ways. Deterministic sensitivity is a non parametric approach, where as, probabilistic sensitivity analysis assumes sample distribution in a parametric way. In this study we performed the probabilistic sensitivity analysis (PSA) by using of a Monte Carlo simulation technique. Monte Carlo simulation recalculates a model multiple times and updates any number of parameters between model recalculation. It assigns values that are randomly sampled from a probability distribution. We used the Beta distribution for the clinical (survival) sampling and the Gamma distribution for the costs distribution associated with the treatment of an end –stage heart failure patients.

## 8.1 Probablistic Sensitivity Analysis

In probabilistic sensitivity analysis all parameter uncertainties can be incorporated into an analysis. Parameter values are sampled from the probability distributions rather than a simple range defined by upper and lower bounds. The technique places greater weight on the likely combinations of the parameter values. The simulation out come quantify the total impact of uncertainty on the model.

This is due to the fact that people who have experienced an end-stage heart failure and considered in this study are heterogeneous .Their heterogeneity lies on their age, sex, risk factors, and prior events in which they found themselves.

Our assumption in testing of the uncertainty due to parameter arises from the fact that our study of the subjects under the intervention group ( VentrAssist) is characterized by hetrogenity of patients with respects to complications due to mechanical or biological side effects that may arise from the use of LVAD. In order to estimate the uncertainty and variation of the study result we employed a probabilistic sensitivity analysis by using Monte Carlo simulation method.

Tabel .7 Summary of the cost effectiveness concept used in this study

| | |
|---|---|
| Study type | Cost effectiveness analysis |
| | |
| Audiences | Researchers, hospitals, and health policy makers |
| | |
| Perspective | Hospital ( health care sector) |
| | |
| Health effect | Life year gained Cost per life year gained |
| | |
| Patient population | End stage heart failure patients between 10 65 years old |
| | |
| Time horizon | 167 days for HTX and 1 year for post HTX |
| Setting | Norway |

# 9. Results

This study showed that the clinical efficacy of ventrAssist is 83% and that of the conventional medical therapy is 74% for an ESHF who is waiting heart transplantation. When converted to life years gained it will be 0, 83*167/ 365= 0, 38 for ventrAsist ®LVAD until HTX and 0.74*167/365 = 0, 34 for conventional medical management. The intervention with VentrAssist®LVAD has increased life years until HTX by 0, 04 with an increamental cost of NOK0.251M when compared with the conventional medical management. Survival until one year is shown to be 80% for alternative therapy (the VentrAssist®LVAD) and 66% for the conventional medical management respectively. In terms of life years gained; 0,80*365= 0,8 for VentrAssist until one year post heart transplanatation and 0.66*365= 0,66 for the conventional medical management . In comparison with the conventional medical treatment, the alternative intervention has increased life years gained by 0, 14 with an increamental cost of NOK0.392M until one year post transplantation.

In addition to serving as a BTT, LVAD substitutes HTX that resulted as a shortage of organ donors or HTX which are not practical due to some clinical complications. Compared with the conventional medical treatment which is the *optimal* medical management, VentrAssist®LVAD improved life expectancy. And particularly death at the younger age is reduced- due to high standard of safety measures introduced to minimize hazards (Clegg et al 2005). [31]

Table 8 The incremental cost effectiveness ratio (ICER) until heart transplantation (HTx)

| Treatment Strategy | C[1] | E[2] | C/E[3] | ΔC[4] | ΔE[5] | ICER[6] |
|---|---|---|---|---|---|---|
| CT[7] | 503 | 0,34 | 1479 | | | |
| CT+VentrAssist[8] | 754 | 0.38 | 1984 | 251 | 0.04 | 6275 |

[1] Cost of conventional
[2] Effect
[3] Cost over effect
[4] Change in cost
[5] Change in efect
[6] Increamental cost-effectiveness ratio
[7] Conventional treatment
[8] Alternative treatment

As can be seen from the table 8 above, the base line cost was NOK0.503M. The cost of alternative treatment was NOK0.754M. The effect measured by life year gained from strategy (CT) was 0, 34 and that of the alternative strategy was 0, 38 until heart transplantation. The change in effect is 0, 04. The Increamental cost effectiveness ratio (ICER) is 0.754M-0.503M/0, 38-0.34 = 0.251M/0.04 = NOK6.275M.

The net health benefit of an alternative intervention until HTX is 0.04-0.251M/0.5M=- 0 .46. The net health benefit of the alternative intervention is less than that of the conventional intervention by 0.46

Table 9 the incremental cos-effectivenes ratio (ICER) until one year

| Treatment Strategy | C | E2 | C/E3 | ΔC 4 | ΔE5 | ICER6 |
|---|---|---|---|---|---|---|
| CT7 | 698 | 0.66 | 2896 | | | |
| CT+VentrAssist8 | 1090 | 0.80 | 1362 | 392 | 0.14 | 2800 |

From table 9 above, the baseline cost is NOK0.698M while, the cost of alternative is NOK1.09M. The change in cost for the treatment of one year post HTX is NOK0.392M. The change in effect is 0.14. The ICER is NOK2.8 M per life year gained until one year post HTX.

The threshold value in Norway is estimated to be 0.5 mills. NOK/ Life year gained (expert views or suggested estimate based on the expert views)

One year Net health benefit (NHB) from the use of VentrAssist®LVAD will be 0.14 -0.392M/ 0.5M

= -0. 6. This means the net health benefit of alternative intervention is less than that of the conventional intervention by 0.64.

[1] Cost of conventional
[2] Effect
[3] Cost over effect
[4] Change in cost
[5] Change in effect
[6] Increamental cost-effectiveness ratio
[7] Conventional treatment
[8] An lternative treatment

In order to estimate the uncertainty and variation of the study result we employed the probabilistic sensitivity analysis by using Monte Carlo simulation method. The probabilistic sensitivity analysis shows that there is a significant variation in increamental effectiveness distributions of the life years gained between the two interventions. The range varies from -0.172 to 0.048 as shown in the graph below. (Fig 6)

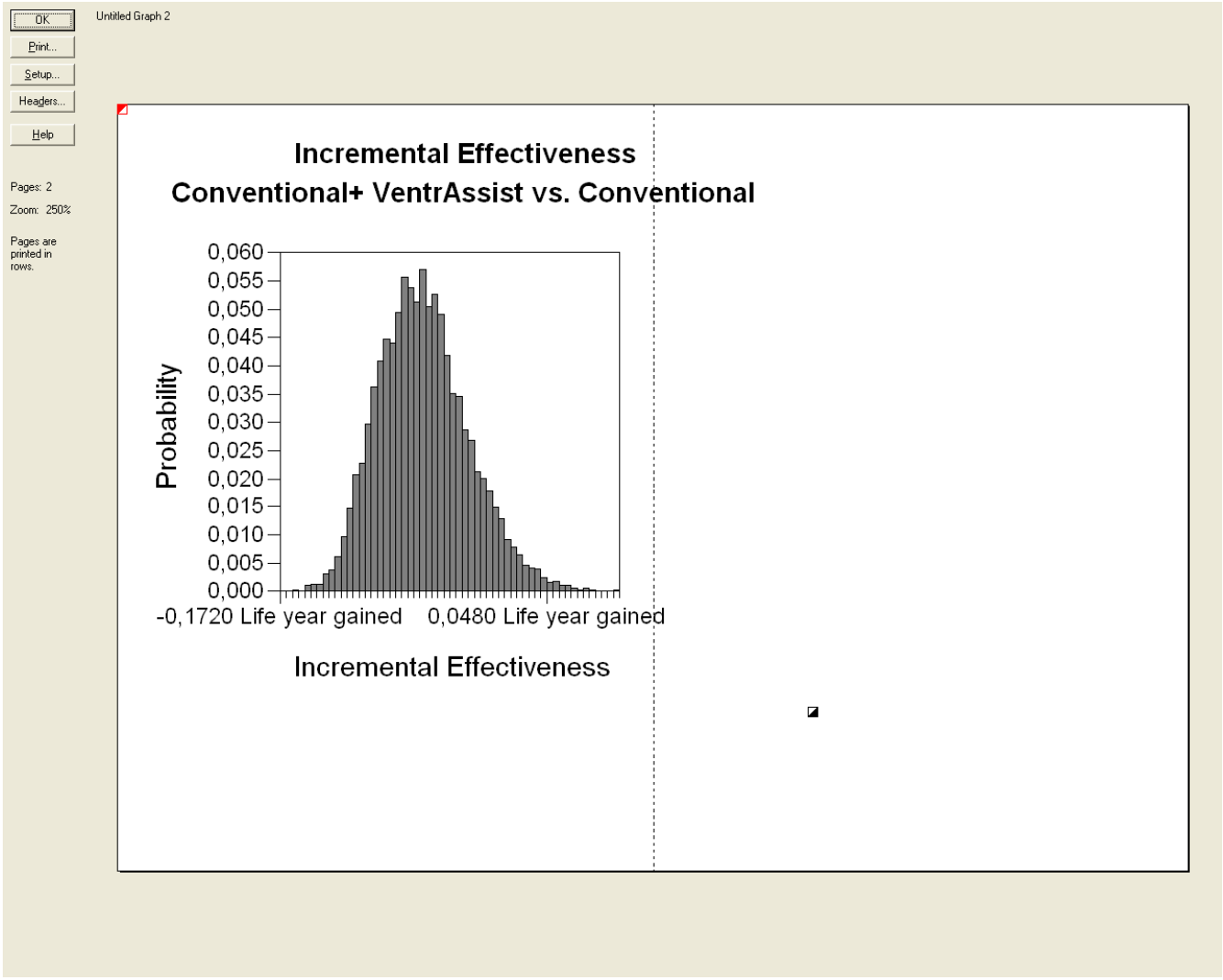



Fig 6 Effectiveness Distribution graph.

Distribution graphs in cost-effectiveness simulations helps to determine the uncertainty about the sign of the increamenta effectiveness. The increamental distribution graph compares the alternative intervention with the baseline (conventional intervention). As can be shown from the graph above, the increamental effectiveness ranges between -0.172 life year gained to 0.048 life years gained. Interpretation of scatterplots, acceptability curves, and net health benefit graphs have to consider the ICER distribution graph in context so as to explain the sign of increamental effectiveness.(Briggs and Polsky 2001).[35]

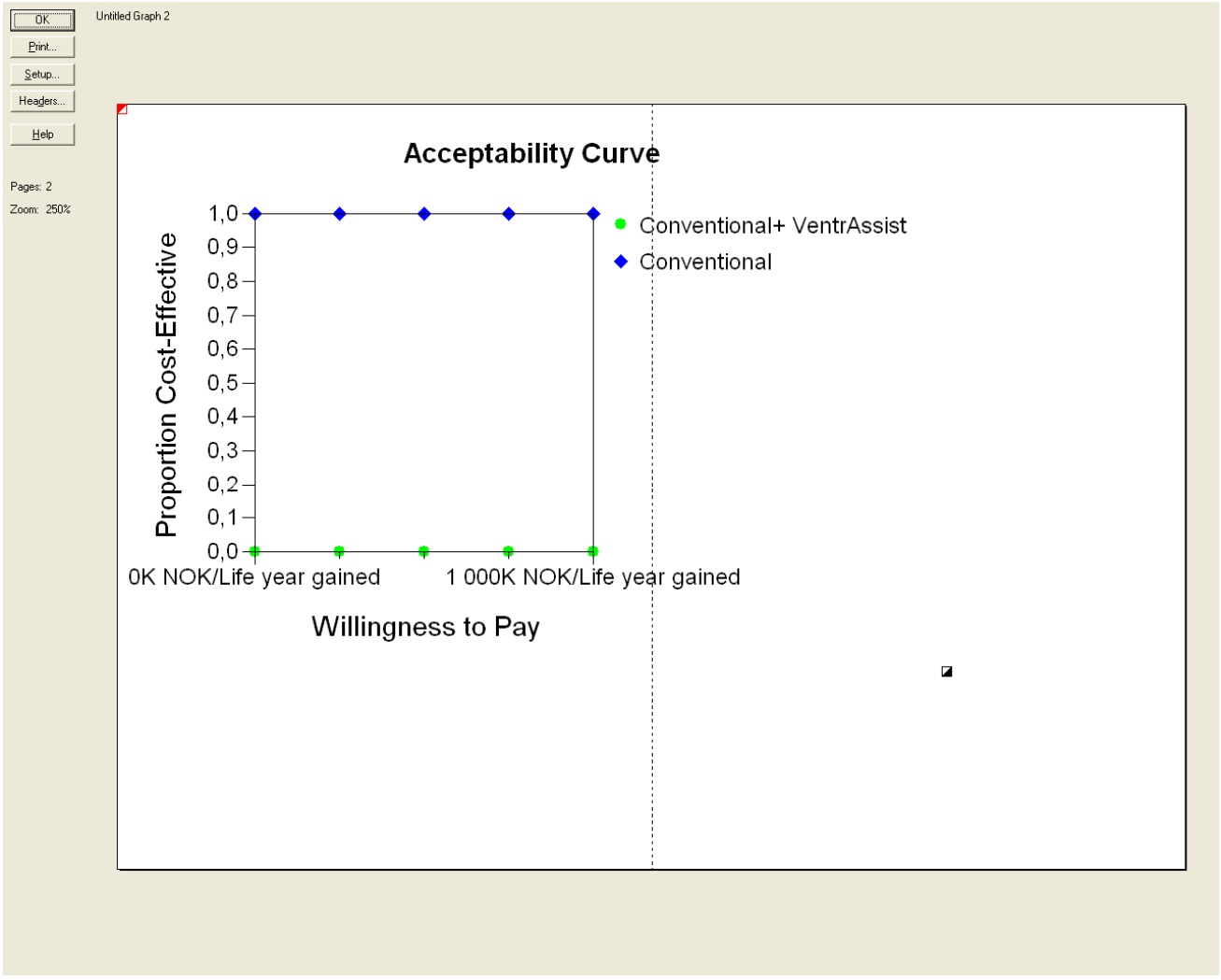
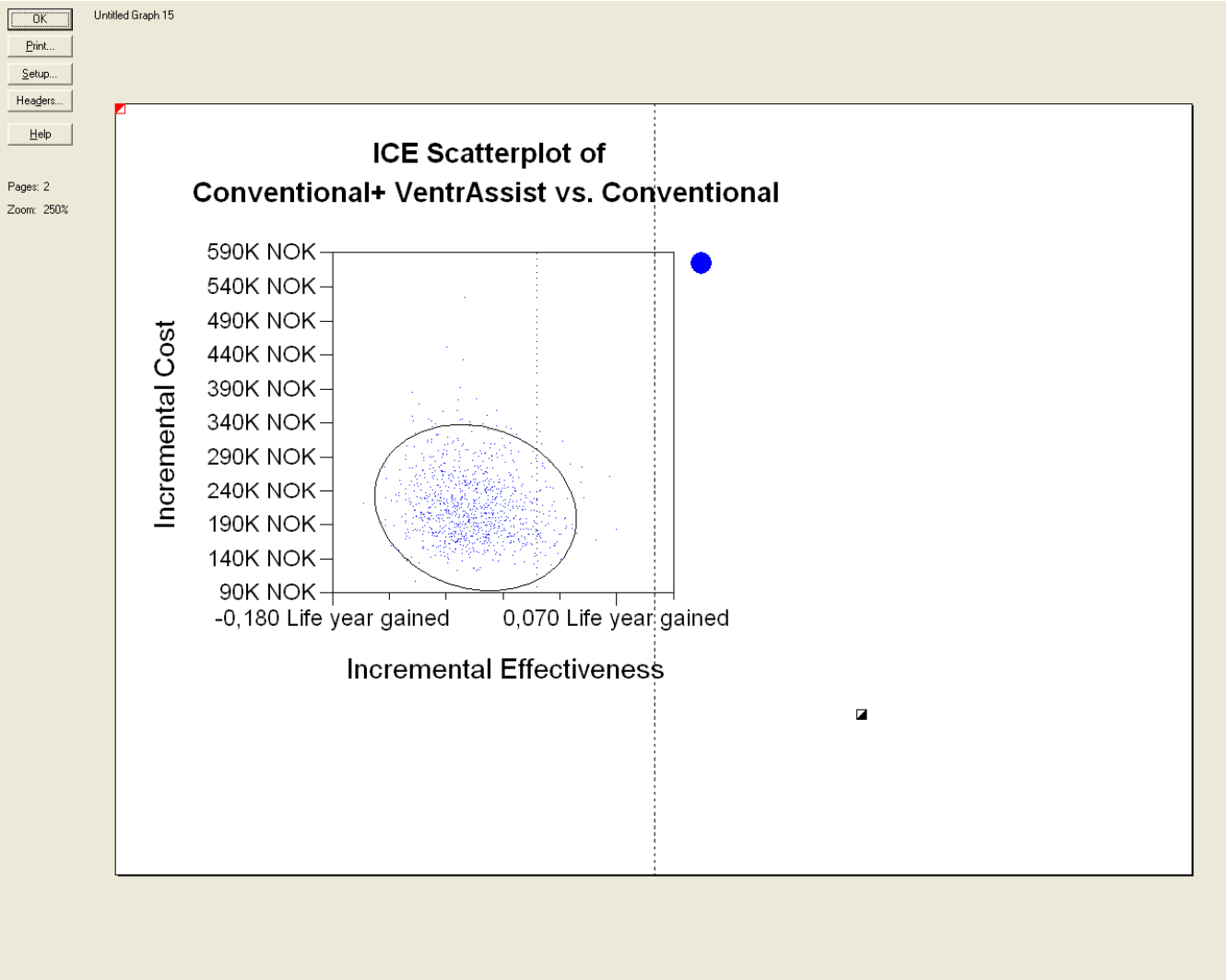



Fig 7 Cost-effectiveness acceptability curve

The cost-effectiveness acceptability curve shows that, the proportion of cost-effectiveness for conventional + VentrAssist intervention is below zero at the willingness to pay of NOK1M/ life year gained. This is so for both interventions until HTX and post HTX until one year. The interpretation

is the probability that the comparator's (Conventional+VentrAssist) most effective option within the ICER threshold is far from optimal cost-effectiveness.

Fig 8 ICE Scatterplott of Conventional+VentrAssist Vs Conventional until One year




The scatter plot points represent the spreding of the alternative (comparators) increamental cost and increamental effectiveness relative to the conventional therapy (baseline).[33] The incremental cost-

effectiveness ratio increased from -0,180 life year gained to 0,070 life year gained with significant increamental cost. The region of cost effectiveness is not significant

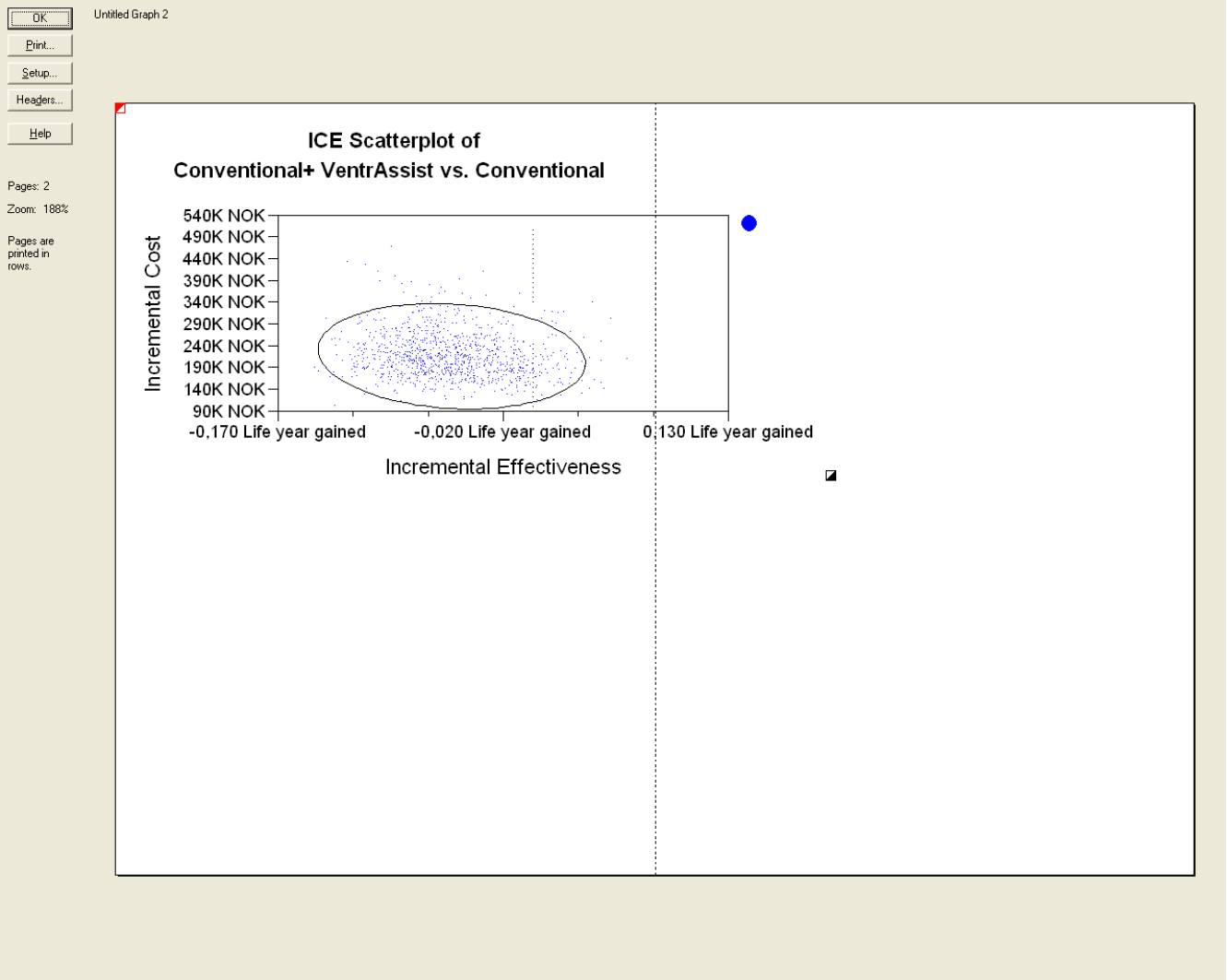



Fig 9 ICE Scatterplot Conventional+Ventrassist vs. Conventional until HTX

The points in the scatterplot show the alternative intervention's (conventional+VentrAssist) increamental cost and increamental effectiveness relative to the base line. The increamental effectiveness of conventional intervention is not visible in the plot. The origion represents the ICER scatterplot for the conventional intervention. The scatterplot indicates that the alternative intervention is far from being optimally cost- effective option.

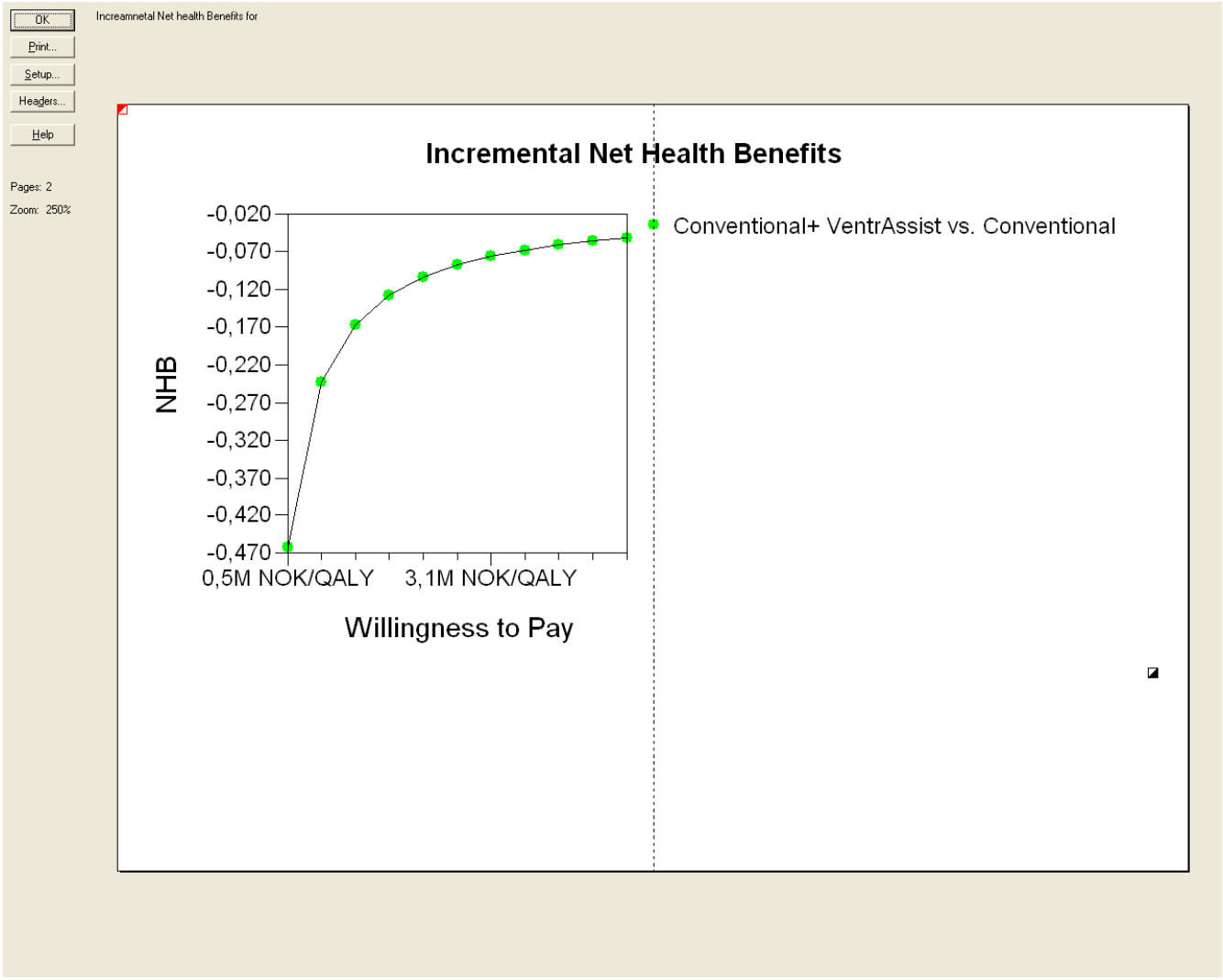



Fig 10 Increamental NHB for One year

Increamental net health benefit like increamental cost effectiveness ratio is a function of willingness to pay[34]. PSA out put shows that the NHB of an alternative intervention is negative. The threshold value at which the alternative intervention will have a positive NHB is very high and it is

impossible to reach this threshold line at the present NHB from the intervention. Introducin an intervention with a negative NHB is a loss to the health care providers.

## 10. Discussions

Our findings are subject to the availability of both clinical and cost data. The effect measure used in this model is not complete as it lacks the quality of life obtained along with the longevity of life gained by an alternative intervention. We believe that in order to asses the quality of life gained by treating an ESHF patient over a span of time through implantation of the ventrAssist@ LVAD, making an assessment by using cost utility method in order to measure the quality of life from the health utility based on the patient data is important. Using cost utility technique and measuring the quality adjusted life year (QALY) gained from the introduction of Ventrassist@LVAD may report improvement of the health effect gained from VeantrAssist.
Units of measurments such as USD, Euro, and NOK are bused to value health benefit. However, measuring health benefit in monetary unit has several theoretical underpinnings (Drummond et al 2005). [27] Quality adjusted life years and net health benefits are used to measure the health consequence of a given intervention

One of the main challenges for the publicly financed health care services is the setting g of priorities among the competing health care programs. Priority setting among two competing health care programs is contingent to the objective of the health care financing body. An analysis done for a public program might consider only the health outcomes experienced by the intervention's beneficiaries and the cost paied by the intervention. This may undermine the broader societal resource use. Literatures of the cost effectiveness analyses revealed that resource allocation decisions often are made in the context of diverse views and preferences (Myriam Hunink and Paul P.Glasziou et al 2001).[29] This paper assessed, the clinical and cost-effectiveness of VentrAsist® LVAD as a BTT from health care perspective. The result indicated that VentrAssist Device is clinically effective and its cost is high to the health care sector. The broader societal perspective is mostly preferred for an economic evaluation which employs cost effectiveness analysis. However, our analysis in this study is limited to the health care perspective as we lack sufficient data on

informal care costs and morbidity costs that constitute the basis for productivity loss in the society.

In this study, the data for the analysis of costs from the hospital perspective is based on the micro-costing study done at the Rikshospitalet University hospital in Oslo. The micro- costing study, done by Viond Mishra et al (2004)[32] was taken from the actual hospital costs of the year 2000. It is adjusted to the year 2008 price index, based on the Norwegian consumption index. Micro-costing provides much more accurate information about the cost of individual patient care than the more generalized, top-down case-mix costing method (Mishra et al 2004).[32]

Though VentrAssist@LVAD extends life for people with an ESHF who do not have chances of survival under the conventional medical regimen, it is not cost-effective. This paper warrants a further investigation on the health utility of the program by using of the standard utility measurement instruments such as EQ-5D, the 15D .The health utility study need to include different patient groups, the paediatrics and the older patient population . We recommend that such comprehensive health utility assessment which reports the quality of patents life after the usage of VentrAssist® LVAD may improve the cost- effectiveness of the program, given the willingness to pay for the severely ill with potential health improvement is also enhanced in accordance with health technology improvement.

Health economists generally advocate adopting the broader societal viewpoint when possible. This is because data can usually be disaggregated and the analysis carried out from a number of viewpoints. [35]. Also, the additional cost of adopting a broader perspective at the outset of a study is probably less than the cost of attempting to gather additional information later. Researchers should therefore identify key potential decision makers (government, purchaser, or provider) at the outset and be able to show that the research question posed will meet the needs of all key groups. This research is anticipated to address the health care policy makers and the providers as the potential decision makers with respects to financing the use of VentrAssist ®lVAD as an alternative intervention for the treatment of people with an ESHF while they are waiting donor heart. The mismatch between the demand for donor heart and the supply for it has been the rationale for the technological development of assisted mechanical circulation. Despite the lack of sufficient randomised controlled trial studies LVADs have proven to be clinically efficacious. We used the clinical data from the multicentred population based trials with an intention to treat principle. Medical Experts have the view that, given the shortage of data which compared the clinical efficacy of the conventional medical management against that of a 3rd generation LVADs such as the VentrAssist, the

introduction of LVADs as bridge to transplantation is clinically effective. We believe that with the absence of cost utility analysis the use of the 3rd generation VentrAssist ®LVAD either as a bridge to transplantation or destination therapy may be questionable. The clinical effect of 3rd generation VentrAssist ® LVAD that is substantiated with cost utility analysis study thereby measuring the quality adjusted life year gained from the use of VentrAssist ®LVAD is non-existent. By using patient level data applying the standard generic instruments designed for health state measurements such as Health Utility Index (HUI), EQ-5D, and 15D may help to assessing the health utility of VentrAssist®LVAD. Therefore, we recommend conducting of such health utility estimation for VentrAssist®LVAD with sufficient number of patients. Patient population variations such as individual characteristics need to be accounted for. General population preferences which often referred to as community preferences are favoured for cost effectiveness design to inform broader resource allocation decisions(Dolan and Olsen 2002)[35]. This is in harmony with the societal perspective which is intended to represent the public interest rather than the interest of any particular group. In Hunink et al 2001:267 [29] it is suggested that the general population preferences based on unbiased, broad community of people who are well informed about the health state in question are the most defensible choice. However, we believe that, the sources of preference in assessing and determining the quality adjusted life years gained from the intervention of VentrAssist®LVAD should relay on the patient's preferences as we are comparing two different interventions for the same patient group – that is an end-stage heart failure patients. The main drawback of using patient preferences could be that patients have the ability to discriminate among the varieties of health sates they have experienced and the analysis would not be comparable to analyses using the general population preferences. [35]

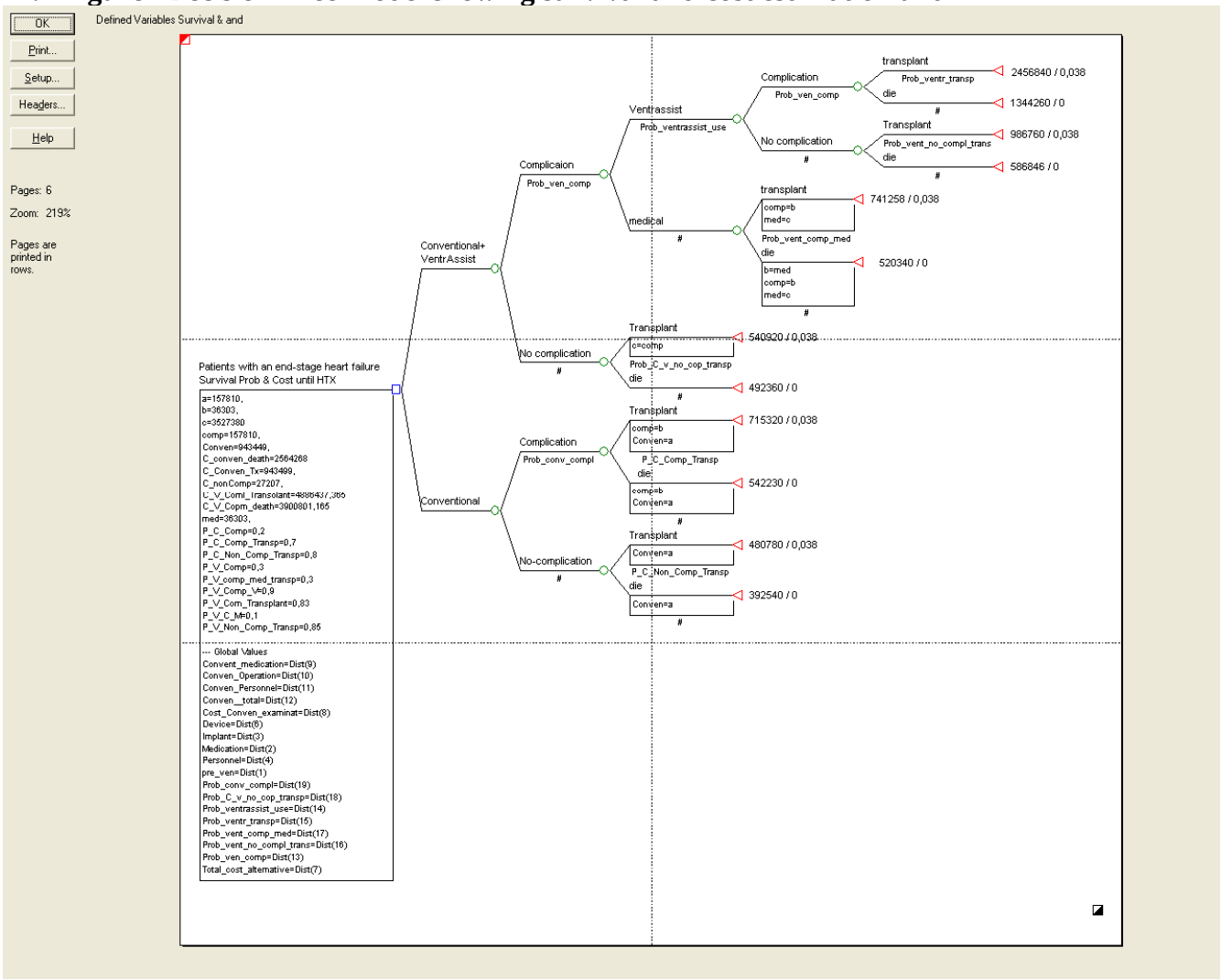
## 10.1 Policy Implications

New treatment options with the VentrAssist ® LVAD for people with an ESHF give good clinical results. Lack of alternative treatment options coupled with the shortage of organ donation has increased the attention of the possibility of developing a specialist services for the treatment of an ESHF people within the Norwegian health care setting. The Norwegian health care system is characterized by its national or socialized health care system. Such systems are operating under

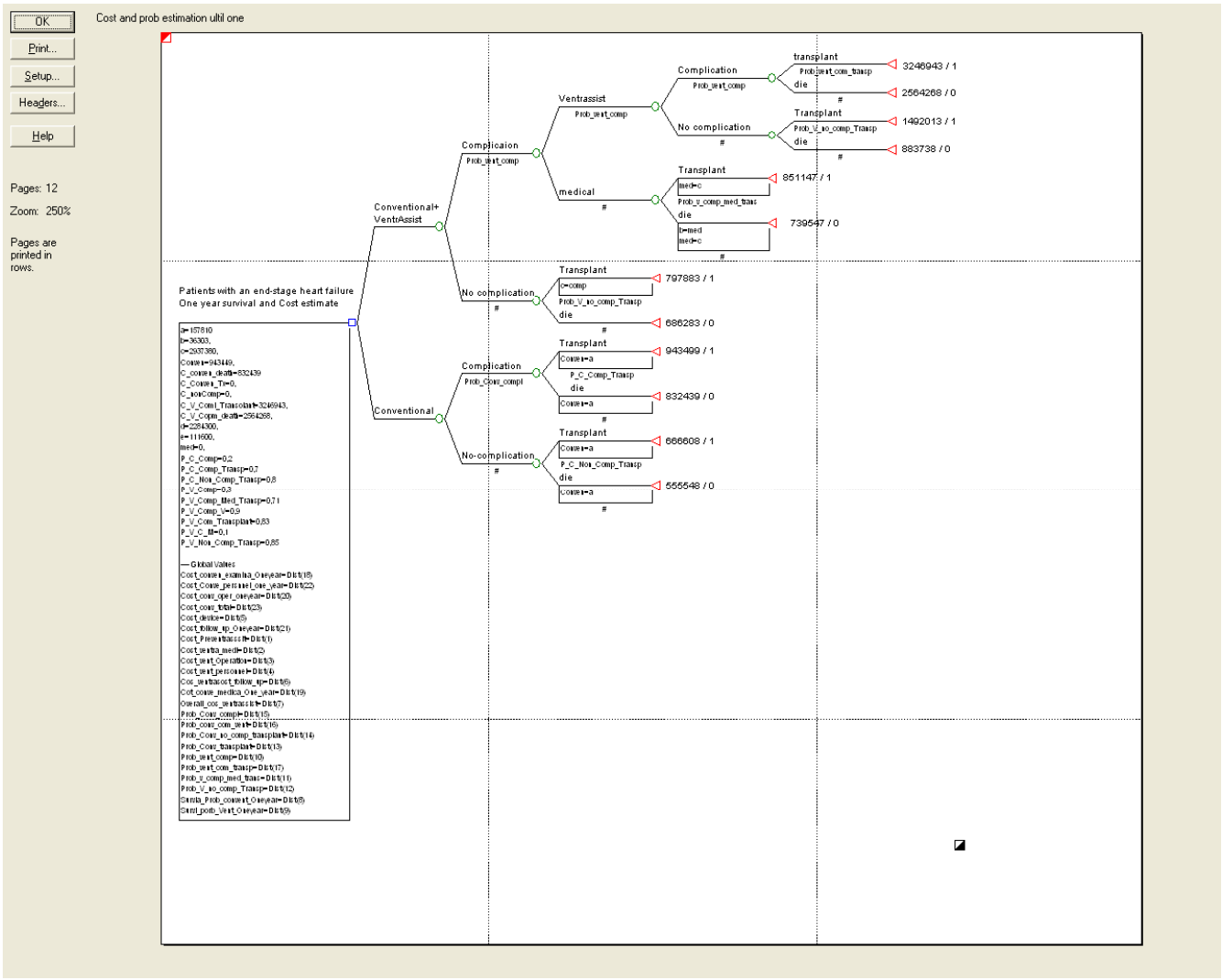
regulation by objective in order to encourage a rational distribution and use of health care technologies. In contrary to this is the liberal or market based health care systems that are more likely to relay on regulation by incentive (Haan and Rutten 1987 in Drummond et al 2005: 350).[27] In response to the objective of maximizing *optimal* health care for all citizens with giving priority to severiety of disease, and given the cost of using LVAD- the ventrAssist device to prolong the life of ESHF patients, planning of specialist facilities at the national level for specific technologies may be an option in addressing the health care services for those who are at risk. Perhaps, by deciding on the number and location of the specialist facilities like heart transplant centers and separating the financing source from the general block grant could be feasible until the health effect of VentrAssist®LVAD increases and its cost decreases by significant proportion.

# 12. Appendices

## 12.1 Figure1 Decision Tree Model showing survival and cost estimation until HTX




**12.1 Figure 1**




12.2 **Figure 2 Decision Tree Model showing survival and cost estimation until one year**

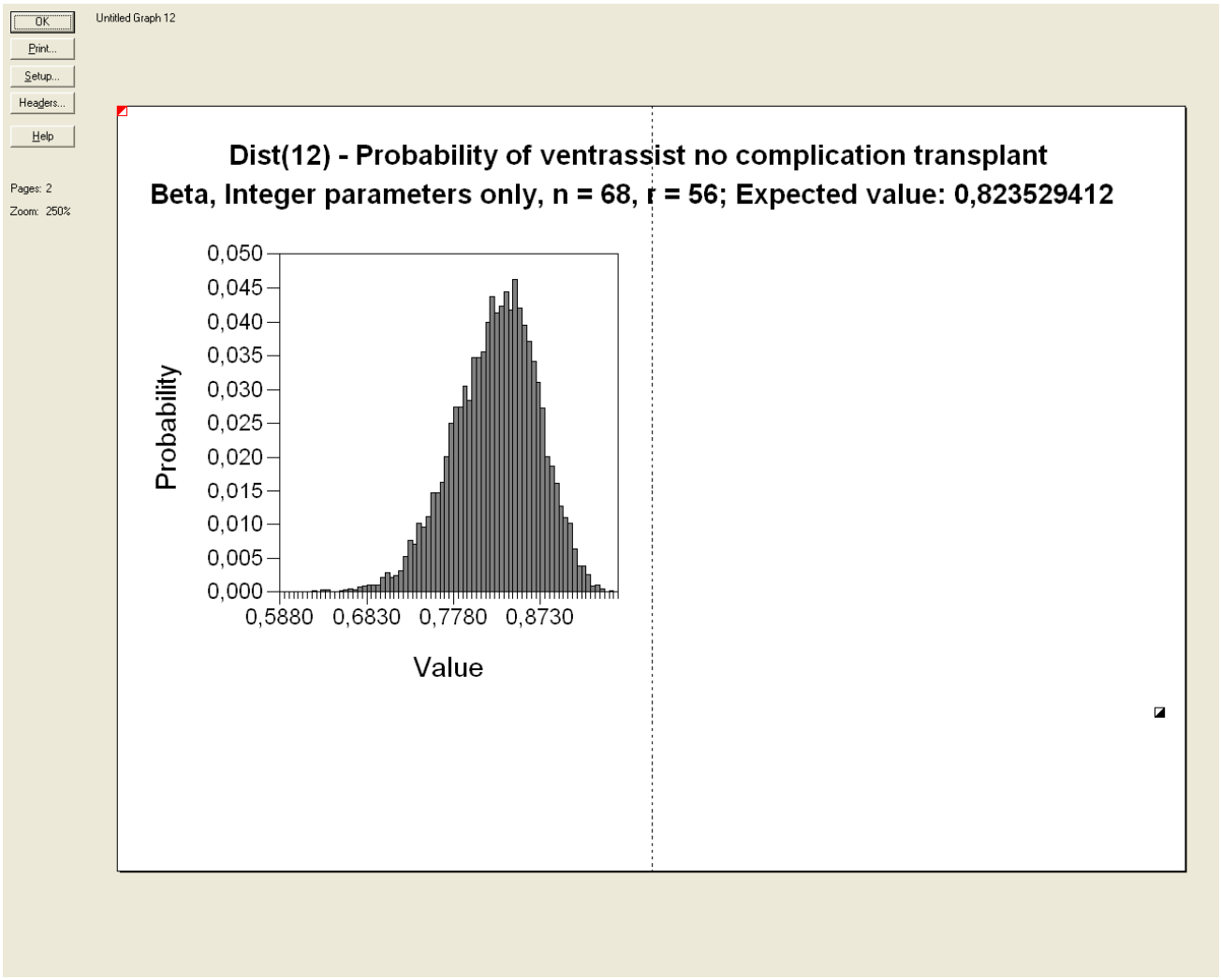
12.3 (Tabel 1) Cost components etimates used for Cost estimate of the Conventional Treatment median range in bracket

| Components | Cost in NOK | Event rate | Total cost(median) | Source |
|---|---|---|---|---|
| | | Per patient | | |
| Median lab Examination | 13604 | 2 | 27207 (20285-383763) | Mishra et al 2004 |
| Median Medication | 221361 | 2 | 442722 (292596-1177139) | |
| Median operation | 85062 | | 85062 (41332-551832) | |
| Median personnel | 92483 | 3 | 277448 (86987-1085068) | |
| Median follow up | 55530 | 2 | 111060 (52000-384000) | |
| Overall costs | | | 943449 (472915-3198039) | |

12. 4 (Table 2) Cot components estimate used for the Alternative Treatment median range in bracket

| Component | Cost in Nok | Event rate | Total cost(median) | Source |
|---|---|---|---|---|
| | | Per pasient | | |
| Median pre-ventrassist implant assessment | 78905 | 2 | 157810 (37366-356709) | Mishra et al 2004 |
| Median medication | 12101 | 3 | *36303 (8594-82504)* | |
| Median implant operation | 2347380 | 1 | *2347380 (1497751-4122708)* | |
| Median personnel | 571075 | 4 | *2284300 (1064240-3901330)* | |
| Device | 590000 | 1 | *590000* | |
| Median follow up | 37200 | 3 | *111600 (53973-361204)* | |
| Overall costs | | | 4894651 | |
| | | | *(3251924-8824455* | |

Fig 12.5 Probability of expected survival Variation with in a given Intervention



12.6 Tabel 3 Parameters used to estimate costs and survival probabilities.

| INDEX | NAME | DESCRIPTION | PARAMETRS/INFO |
|---|---|---|---|
| 1 | Cost_Preventrasssit | Cost of examination | Gamma, alpha = (177472,6621^2)/(93227,5272^2), lambda = 177472,6621/(93227,5272^2); Expected value: 177472,6621 |
| 2 | Cost_ventra_medi | pre_ventrasist Cost of ventrasssit | Gamma, alpha = (40937,52868^2)/(21582,90006^2), lambda = 40937,52868/(21582,90006^2); Expected value: 40937,52868 |
| 3 | Cost_vent_Operation | medication Cost of ventrassist operation | Gamma, alpha = (2873646,208^2)/(761492,6344^2), lambda = 2873646,208/(761492,6344^2); Expected value: 2873646,208 |
| 4 | Cost_vent_personnel | Cost of ventrasist personnel | Gamma, alpha = (2383789,988^2)/(824077,3315^2), lambda = 2383789,988/(824077,3315^2); Expected value: 2383789,988 |
| 5 | Cost_device | Cost of device | Gamma, alpha = (295473,8155^2)/(125803,6898^2), lambda = 295473,8155/(125803,6898^2); Expected value: 295473,8155 |
| 6 | Cos_ventrasost_follow_up | Cost of ventrassist follow up until one year | Gamma, alpha = (159713,9364^2)/(93266,27777^2), lambda = 159713,9364/(93266,27777^2); Expected value: 159713,9364 |
| 7 | Overall_cos_ventrassist | Overal cos of ventrasist until one year | Gamma, alpha = (5424048,592^2)/(1675847,858^2), lambda = 5424048,592/(1675847,858^2); Expected value: 5424048,592 |
| 8 | Survia_Prob_convent_Oneyear | One Year survival probability for Conventioinal Treatment | Beta, Integer parameters only, n = 61, r = 40; Expected value: 0,655737705 |
| 9 | Survi_porb_Vent_Oneyear | One Year survival probability for alternative intervention( Ventrasist)Treatment | Beta, Integer parameters only, n = 68, r = 54; Expected value: 0,794117647 |
| 10 | Prob_vent_comp | Probability of ventrassist no complication | Beta, Integer parameters only, n = 68, r = 20; Expected value: 0,294117647 |
| 11 | Prob_v_comp_med_trans | Probability of ventrasist complication medication transplant | Beta, Real-numbered parameters, alpha = 68, beta = 7; Expected value: 0,906666667 |
| 12 | Prob_V_no_comp_Transp | Probability of ventrassist no complication transplant | Beta, Integer parameters only, n = 68, r = 56; Expected value: 0,823529412 |

| | | | |
|---|---|---|---|
| 13 | Prob_Conv_transplant | Probability of conventional transplant | Beta, Integer parameters only, n = 61, r = 38; Expected value: 0,62295082 |
| 14 | Prob_Conv_no_comp_transplant | Probability of Conventional no complication transplant | Beta, Real-numbered parameters, alpha = 61, beta = 43; Expected value: 0,586538462 |
| 15 | Prob_Conv_compl | Probability of Conventional complication | Beta, Integer parameters only, n = 61, r = 8; Expected value: 0,131147541 |
| 16 | Prob_conv_com_vent | Probability of conventional copliation ventrasist | Beta, Integer parameters only, n = 68, r = 61; Expected value: 0,897058824 |
| 17 | Prob_vent_com_transp | probability of ventrassist compliaction transplant | Beta, Integer parameters only, n = 68, r = 57; Expected value: 0,838235294 |
| 18 | Cost_conven_examina_Oneyear | Cost of Conventional examination until one year | Gamma, alpha = (123391,415^2)/(126619,0326^2), lambda = 123391,415/(126619,0326^2); Expected value: 123391,415 |
| 19 | Cot_conve_medica_One_year | ost of Conventional medication until One year | Gamma, alpha = (604152,655^2)/(293967,0726^2), lambda = 604152,655/(293967,0726^2); Expected value: 604152,655 |
| 20 | Cost_conv_oper_oneyear | Cost of operation | Gamma, alpha = (201616,65^2)/(173881,2888^2), lambda = 201616,65/(173881,2888^2); Expected value: 201616,65 |
| 21 | Cost_follow_up_Oneyear | Cost of follow up until one year | Gamma, alpha = (170172,3^2)/(110100,3128^2), lambda = 170172,3/(110100,3128^2); Expected value: 170172,3 |
| 22 | Cost_Conve_persnnel_one_year | Cost of personnel until one year | Gamma, alpha = (448119,03^2)/(329903,3547^2), lambda = 448119,03/(329903,3547^2); Expected value: 448119,03 |
| 23 | Cost_conv_total | Overall cost of conventional Treatment until one year | Gamma, alpha = (1436417,07^2)/(904958,9151^2), lambda = 1436417,07/(904958,9151^2); Expected value: 1436417,07 |

# 13. Reference Lists:


1. Anthony S. Fauci et al 2008, Harrison's Principles of Internal Medicine Edition: 17, illustrate Utgitt av McGraw-Hill, 2008 Original fra University of Michigan Digitalisert 25. jul 2008 ISBN 0071476911, 978007147691 2650 sider

2. LandsforeningenforHjerteogLungesykewww.apotek1.no,/ 12.03.09)
http://www.nycomed.no/no/Menu/Terapiomraader/Terapiomraader1/Hjerte-kar/

3. Douglas L Mann et al 2007, Braunwald's Heart Disease: A Text book of Cardiovascular Medicene Forlag: Saunders Utgitt**:** 2007-11-16 Utgave: 8 Innbinding**:** Hardbac Sider 2304Språk**:** English EAN/ISBN13**:** 9781416041061 Dewey: 616.1

4. Helse nytt for alle 2008: Nasjonalforeningen for folkehelsen: Hjerte og Karsykdom

5. REMATCH Long-Term Use of a Left Ventricular Assist Device for End-StageHeart Failure
*N Engl J Med 2001; 345:1435-1443,*
*Nov 15, 2001*

6. D. Esmore et al 2008; Journal of Heart Lung Transplant; 2008 Jun; 27(6):579-88. Epub 2008 Apr 23: The Alfred Hospital, Melbourne, Australia.

7. http://medical-dictionary.thefreedictionary.com/etiology Medical Dictionary- The Free Dictionary by FARLEX/ 15.06.2008

8 New York Heart Association, inc , Diseases of the Heart and Blood Vessels: Nomenclature and Criteria for Diagnosis, 6th ed. Boston, Little Brown, 1964, pp 114

9. Electrophysiology of the Heart**.** *Edited by B Taccardi, and G. Marchetti.* New York, New York, Pergamon Press, 1965, 344 pages,

10 Arnt Fiane, MD, PhD Associate professor Head of Adult Section Department of Thoracic and Cardio-vascular Surgery; Oslo University Hospital Rikshospitalet, Norway

11 Lesile Miller 2006 Heart transplantation in Patients with diabetes; Georgetown University and Washington Hospital Center: *Circulation.* 2006; 114:2206-2207.) © 2006 AmericAssociation,Inc

12 NR Banner et al 2008 Effect of heart transplantation on survival in ambulatory and decompensated heart failure**:** Clinical Effectiveness Unit, The Royal College of Surgeons of England, London, United Kingdom.

13. The Journal of Heart and Lung Transplanatation Volume 27 issue 6, June 2008 ,Pages 579- 588 www.emedicine.medscape.com/ article 429816-Overviewe

*14* Statistics Brueau in Norway www.ssb.no/ helse/ dødelighet/ 24.02.2009

*15* SE Hermansen 2008, Scandinavian Cardiovascular Journal 42(2) 118 -24: Department of Cardiothoracic and Vascular Surgery University Hospital North Norway, Tromsø

16 D.S. Esmore, D. Kaye and R. Salamonsen et al., First clinical implant of the VentrAssist left ventricular assist system as destination therapy for end-stage heart failure, J Heart Lung Transplant 24 (2005), pp. 1150–1154.

17 *US Food and Drug Administration: Department of Health and Human Services.*

http://www.fda.gov/hearthealth/treatments/medicaldevices/vad.html/ *12.03.08*

18. D. Esmore, P. Spratt and R. Larbalestier et al., VentrAssist left ventricular assist device: Clinical trial results and clinical development plan update, Eur J Cardiothoracic Surg 32 (2007), pp. 735–744.

19. D. Esmore et al 2008; Journal of Heart Lung Transplant; 2008 Jun; 27(6):579-88. Epub 2008 Apr 23: The Alfred Hospital, Melbourne, Australia.

20 Statistics Brueau in Norway www.ssb.no/ helse/ dødelighet/ 24.02.2009

21 L.W. Miller, F.D. Pagani and S.D. Russell et al., Use of a continuous-flow device in patients awaiting heart transplantation, N Engl J Med 357 (2007), pp. 885–896

22 The Health and Social Affairs Sector In Norway: Department of Public health services **,** *An overview (I-0990 E)*

23 W.E. Pae, J.M. Connell and A. Adelowo et al. 2007, does total implant ability reduce infection with the use of a left ventricular assist device?: The Lion Heart experience in Europe, Journal Heart Lung Transplant 26 (2007), pp. 219–229.

24. A.E. Ibrahim, B.W. Duncan and E.D. Blume et al., Long-term follow-up of pediatric cardiac Patients requiring mechanical circulatory support; Ann Thorac Surg 69 (2000), pp

25 J.Yager, G . Felker 2209; Left ventricular assist devices as destination therapy for end-stage heart failure
*American Heart Journal*, Volume 148, Issue 2, Pages 252-253

26,. Effect of heart transplantation on survival on ambulatory and decompensate heart failure; Clinical Effectiveness Unit, *The Royal College of Surgeons of England, London, United Kingdom*

27, Drummond et al 2005 Methods for Economic Evaluation of Health Care Programs

*Third edition: Oxford Unoversity Press*

28. Tsuchiya et al 2007 Measuring and Valuing Health Benefits for Economic Evaluation.
*Oxford University Press*

29. . Myriam Hunink and Paul P. Glasziou et al 2001, *Decision making in health and medicine: Integrating evidence and value; Cambridge university press*

30 . Nasjonalt kunnskapssenteret for helsetjenesten Implanterbar hjertepumpe (LVAD) ved avansert hjertesvikt
Metodevarsel nr 4. Oktober 2008

31 A.J. Clegg, D.A. Scott and E. Loveman et al., The clinical and cost-effectiveness of left ventricular assist devices for end-stage heart failure: a systematic review and economic evaluation, Health Technol Assess 9 (2005), pp. 1–148.

32. Mishra et al 2004. *A Micro costing approach to determining in patient hospital cost*

*33* . Aaron stinnett and john Mully; medical Decsion Making supply 18:S68-S80)

34. Briggs and Polsky 2001 Quantfying stochastic uncertnity; *Expert Rev Pharmacoeconomic* Out Re 1(1) www.futue drugs .com

35. Dolan and Olsen 2002 Distributing health care: *Economic and ethical issues Oxford University Press*