Cost-Utility Analysis of replacing photodynamic therapy with verteprofin by anti-VEGF treatment with ranibizumab on patients with predominantly classic neovascular age-related macular degeneration

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15th of May 2007

FOREWORD

Vision has a major influence on quality of life, and is perhaps even more important for the elderly, for whom mobility and the opportunity to adapt to new situations can be restricted. Age-related macular degeneration (AMD) is the most common cause of severe vision loss in the elderly population in the developed world. As the general Norwegian population is getting older, the prevalence of AMD will rise, resulting in an increased burden on patients and society. The anti-VEGF treatment with ranibizumab has shown considerable efficacy with respect to improvement of visual acuity among patients with neovascular AMD. However, there is also a cost side related to this treatment. Uncritical implementation of promising, but costly new treatments will have consequences in other parts of the health care system, which operates under scarce resources and seeks optimal allocation of its resources. Economic evaluation of health care programmes may be a useful tool for decision-makers who strive for optimal resource allocation. Based on the issue of priority setting in the health care sector, the aim of this study was to explore whether the costs of replacing the conventional PDT treatment by treatment with ranibizumab on AMD patients can be justified by the improvement in efficacy.

Acknowledgements

I would like to acknowledge the following for providing valuable information: Hanne Birkeland, Bettina Kinge, David M.Brown, John Engebretsen, Freddie Henriksson, Grethe Lyngedal and Ragnheidur Bragadottir.

My supervisor was Ivar Sønbø Kristiansen, MD PhD MPH, at The Institute of Health Management and Health Economics, University of Oslo.

ABBREVIATIONS AND ACRONYMS

AMD	Age-related macular degeneration
CNV	Choroidal neovascularization
RPE	Retinal pigment epithelium
RAP	Retinal angiomatic proliferation
PDT	Photodynamic therapy
VEGF	Vascular endothelial growth factor
Fab	Fragment, antigen binding
Fc	Fragment, crystallizable
VA	Visual Acuity
EDTRS	The early treatment of diabetic retinopathy study
TAP	Treatment of Age-related Macular Degeneration with Photodynamic Therapy
ANCHOR	Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-related Macular Degeneration
MARINA	Minimally classic/occult Trial of the Anti-VEGF Antibody Ranibizumab in the treatment of Neovascular Age-related Macular Degeneration
CUA	Cost utility analysis
ICER	Incremental cost-effectiveness ratio
QALY	Quality adjusted life time
HrQoL	Health related quality of life
CBA	Cost benefit analysis
CEA	Cost effectiveness analysis
TTO	Time trade off
SG	Standard gamble
NABP	The Norwegian association of the blind and partially sighted
NMA	The Norwegian medicines agency
NOK	Norwegian kroner
NPV	Net present value
RCT	Randomized controlled trials
PIER	Phase IIIb, multicenter, randomized, double masked, sham injection-controlled study of the efficacy and safety of ranibizumab
PRONTO	prospective OCT imaging of patients with neovascular AMD treated with intra-ocular lucentis
FOCUS	RhuFab v2 Ocular treatment combining the use of visudyne to evaluate safety
(number)	Reference
word[a]	Footnote

ABSTRACT

Background: Age-related macular degeneration (AMD) is the leading cause of severe vision loss in the developed world. Through clinical trials, treatment with ranibizumab has proved to be more effective than photodynamic therapy with verteporfin for AMD. The high price of ranibizumab, however, has raised questions about its cost-effectiveness.

Methods: Three treatment options were considered in a cost-utility analysis adopting a health care perspective. A decision analytic model was developed to assign patients to four different health states over a 2-year time period. The model inputs were efficacy results of the treatment options in terms of probabilities, costs related to treatment options and vision loss. Costs were expressed in 2007 Norwegian Kroner (NOK), and the health outcome was measured in quality adjusted life years (QALYs). Quality of life weights were taken from a study associating time trade-off utility values with visual acuity levels, while the use of health care was based on expert judgment

Results: When indirect costs were disregarded, the two-year costs of verteporfin, 0.3 mg and 0.5 mg ranibizumab were NOK 198,500, NOK 314,500 and NOK 437,000, respectively with corresponding QALYs of 1.34, 1.50 and 1.51. The incremental costs of replacing verteporfin by 0.3 mg and 0.5 mg ranibizumab were NOK 116,000 and NOK 122,500 with incremental QALYs of 0.16 and 0.015. The incremental cost-effectiveness ratios were NOK 739,500 and NOK 7,976,000, respectively.

Interpretation/conclusion: The results of this study indicate that neither treatment with 0.3 mg ranibizumab nor treatment with 0.5 mg ranibizumab is cost-effective as replacement of the conventional PDT treatment when NOK 425,000 is defined as the threshold for incremental costs per QALY. This conclusion may change if it were documented that two year treatment with ranibizumab has benefits beyond the treatment period. The treatment option with 0.3 mg ranibizumab would be cost-effective if the drug costs per dose of ranibizumab were reduced from NOK 9,190 to NOK 6,900 (excl. VAT).

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1. INTRODUCTION

Age-Related macular degeneration is a disease associated with aging that gradually destroys the macula, which is responsible for the sharp, central vision. It is the leading cause of severe vision loss amongst the elderly population in the developed world. In epidemiological studies, an age of 50 years old is arbitrarily chosen as the minimum age for the diagnosis of AMD (1). The exact cause of the disease is unknown. However, the prevalence increases with higher age, and there are also identified certain risk factors including female sex, Caucasian origin and cigarette smoking (2). Additionally, it is suggested that the immune system has an important role in AMD (3).

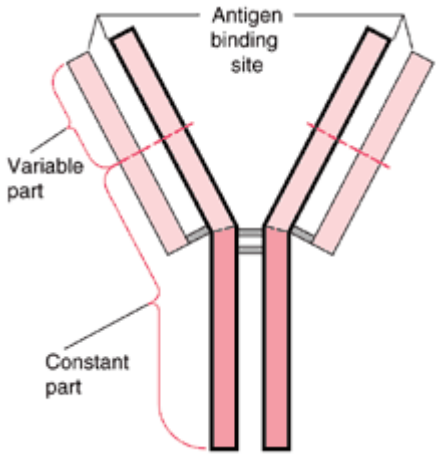
1.1 Antibodies

The immune system is supposed to play an essential part in both the development of AMD, but also in the anti-VEGF treatment of AMD with ranibizumab. Because of this, it is necessary to describe some basic principles of immunology, especially related to the function of the antibodies. The function of the immune system is to defend the body against pathogens. Pathogens are biological agents that can cause illness or diseases to the body. The pathogens contain antigens[1], which stimulate the body to initiate an immune response. A normal immune response consists of recognizing a foreign antigen, mobilize forces to defend against it, and then attacking it (4). The immune system contains many different parts with highly specific functions, which in combination form an effective defence mechanism that protects the body. However, in relation to AMD and the treatment with ranibizumab, it is the antibodies that are of most importance. Hence, I will put emphasis on the function of the antibodies in this part of the paper.

[1] Any substance that can stimulate an immune response is called an antigen.

The antibodies, also called immunoglobulins, are large Y-shaped proteins that are used by the immune system to identify and neutralize pathogens (Fig. 1).

Figure 1: Basic structure of an antibody



The antibodies consist of two fragments; the Fragment crystallisable (Fc) region and the Fragment antigen binding (Fab) region. The Fc region[2] is a constant part derived from the stem of the Y, and consists of two heavy chains of amino acids. This part determines the class of the antibody (IgG, IgM, IgD, IgE or IgA) and binds to receptors, such that an immune response is initiated. The Fab region[3] is a variable part that binds to specific antigens. This part varies among the antibodies depending on which antigen it is targeting (4).

[2] Illustrated as the constant part in figure 1.

[3] Illustrated as the variable part in figure 1.

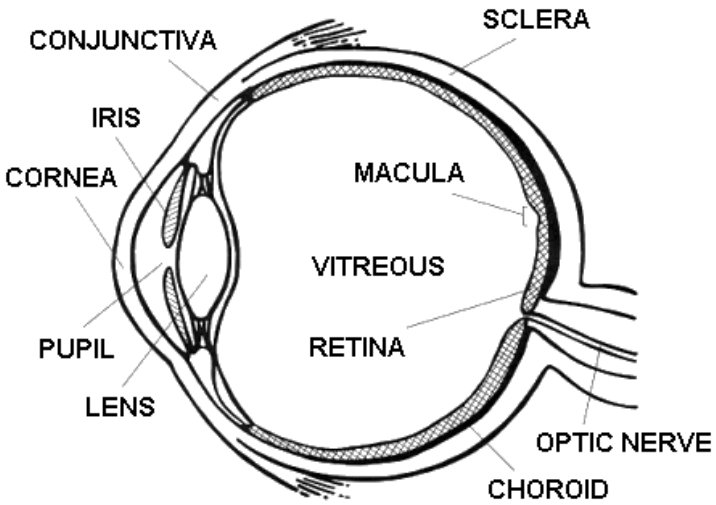
The identification process is done by the antibody recognizing certain targets, the antigens, and then binding to that specific antigen. After binding to the antigen, the antibodies bind to specific cellular receptors, so that other parts of the immune system can activate an appropriate immune response, and destroy that given antigen. The binding of antibodies to antigens can also neutralize the antigens directly, as it prevents the antigens to bind to the receptors they need to promote their type of illness.

1.2 Anatomy and Physiology of the Eye

AMD is a retinal disorder which affects the macula. The retina is a multi-layered sensory tissue on the inner surface of the back of the eye. It contains millions of photoreceptors that capture light rays and convert them into electrical impulses that are carried to the brain by the optic nerve. In the brain these electrical impulses are again turned into images. There are two types of photoreceptors in the retina: rods and cones. The cones are responsible for high-resolution and color vision (1). The cones are contained in an area of the retina called macula lutea, and function best in bright light. In the centre of the macula lies a pit called fovea centralis, which contains the highest density of cones. The preponderance of cones over rods in this area, make the fovea responsible for our sharp central vision. Hence, when we focus on a detail, the muscles in the eye focus the image of the detail to the fovea centralis (5). The rods are spread throughout the retina, and are responsible for the peripheral vision and the night vision. Because AMD is a disorder that affects the macula, patients will lose their sharp central vision, while their peripheral vision is maintained. However, in severe cases of central visual loss, the condition can be compared to being blind, as the patients are incapable of reading, recognizing people, movement on their own, etc. AMD is classified as a retinal disorder (4), and it is therefore necessary to describe some details of the structure of the retina and its function.

The retina consists of several distinct layers, which form the back of the eye. The inner retina is adjacent to the vitreous and the outer retina is adjacent to the choroid (Fig. 2).

Figure 2: Anatomy of the eye



Age-related changes that predispose a person to AMD, occur in the outer retina. The outer retina includes the outer segments of the photoreceptors, the retinal pigment epithelium (RPE) and Bruch's membrane (Fig. 3). The adjacent choriocapillaris, the capillary layer of the choroid, is the vascular system that feeds the outer retina. These structures, collectively called Ruysch's complex, provide an optimal environment for retinal function, that provides vision of high resolution, color vision, peripheral vision and vision at dusk (1).

Figure 3: Normal fundus – interior surface of the eye

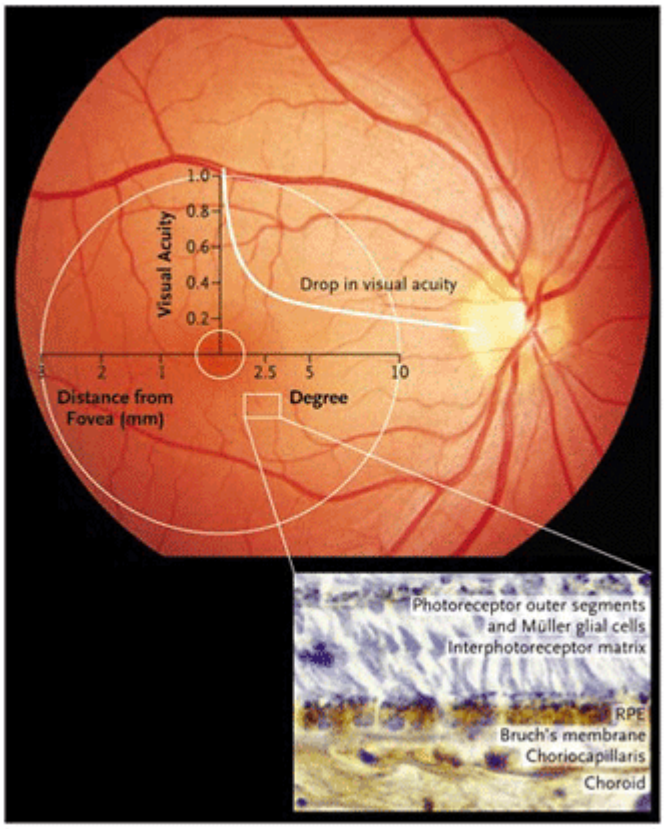


Figure 3: The outer circle shows macula lutea, while the inner circle represents fovea centralis. The inset shows the outer layers of the retina. The graph visualizes a coherence of the distance of a scar from the fovea, caused by AMD, and the drop in visual acuity (1).

The photoreceptors are specialized types of neurons that convert light into nerve signals, as electrical impulses. This is done by a change in the cells membrane potential when they absorb light (photons). These signals are sent to other neurons, ultimately sent to the brain by the optic nerve, and produce images.

The RPE is a pigmented[4] cell-layer, which has a central element in the pathogenesis of AMD. The RPE cells derive their name from the numerous melanosomes[5] within their cytoplasm. The most important functions of the RPE are to regenerate bleached

[4] A pigment is a material that changes the color of light it reflects as the result of selective color absorption.

[5] A melanosome is an organelle containing melanin, the most common light-absorbing pigment in the body.

visual pigments; formation and maintenance of the extracellular matrix[6] in Bruch's membrane, and transportation of fluids and ions between photoreceptors and the choriocapillaries (1). The RPE is also phagocytic[7] system that is essential to the renewal of photoreceptors. However, residues from this process are also a burden on the RPE cells as the metabolic waste is accumulated over a lifetime resulting in conditions that can promote the development of AMD (1).

Bruch's membrane consists of three layers, and lies between the RPE and the choriocappilaries. Its function is to transport substances between the RPE and the choriocappilaries, to maintain the survival of the RPE-cells. As a person is getting older this membrane calcifies and becomes thicker. As a result of this, the permeability of the membrane decreases, and basal laminar deposits and membranous debris is kept within the membrane. This leads to the formation of drusen, a common sign of early AMD. The decreased function of Bruch's membrane also results in diminished cell adhesion and anoikis. Anoikis is a form of apoptosis[8] resulting from incorrect cell adhesion. This results in extracellular deposits around Bruch's membrane, which may lead to local inflammation. This inflammation, again promotes the development of AMD (1).

Ruysch's complex receives its blood supply from the choriocappilaries, which has extensive fenestration to Bruch's membrane. Ruych's complex demands high levels of oxygen compared to the inner retina due to the photoreceptors that consume more than 90% of this oxygen. With increasing age, the lumina of the choriocappilaries and the choroidal thickness are reduced. This, together with a thinning or destruction of

[6] Extracellular matrix is any material of a tissue that is not a part of any cell.

[7] Phagocytosis is an immune response to control inflammation.

[8] Apoptosis is a type of deliberate programmed cell death in multicellular organisms.

the RPE, can result in a hypoxic environment[9] in Ruych's complex. The hypoxia increases the secretion of growth factors such as vascular endothelial growth factor (VEGF)-A within Ruych's complex. The VEGF-A causes the development of choroidal neovascular membranes, which result in the formation of new abnormal blood vessels. Leakage from these vessels are the main pathogenesis of neovascular AMD (1).

1.3 Forms and Stages of AMD

AMD can be divided into various forms and stages. The two clinical stages of AMD are categorized as early, in which visual symptoms are inconspicuous, and late, in which severe vision loss is usual. The early stage of AMD is always the atrophic form of the disease, while the late stage can be either categorized as atrophic or neovascular (1). This paper concerns treatment on neovascular AMD, and it will be emphasized on this condition. Another important feature of AMD is that the disease does not necessary appear in both eyes, but can appear in one eye independently of the other. The different forms of the disease, atrophic and neovascular, can vary between the eyes, but also within each eye (1).

1.3.1 Atrophic AMD

The atrophic, or dry form, of AMD is the most common, and constitutes about 90% of all cases of AMD (6). This is a condition characterized by a slowly progressive decline in central vision, which can develop over decades. Dry AMD is characterized by the appearance of drusen that build up in Bruch's membrane or by hyperpigmentation or hypopigmentations of the RPE (1). These phenomena can result in an atrophy[10] of the RPE that causes a loss of central vision. Drusen are tiny

[9] Hypoxia means shortage of oxygene.

[10] Pathologic athrophy is a decrease in the size of a body organ or tissue, caused by a disease, injury, or lack of use.

yellow or white accumulations of extracellular material, which can vary in numbers and size. The size of the area on the RPE affected by hyper- or hypopigmentation does also vary to a large extent. The development of drusen, hyper- or hypopigmentation is a normal part of the aging process. However, increased size and numbers of drusen, and/or area of pigmentation on the RPE, implicate an increased risk of the condition developing into the late stage, or to the much more serious neovascular form (1). Currently, there are documented no effective treatments for dry AMD, but it is important to follow up these patients to see how the disease develops. A patient will have benefits of early treatment, if the condition develops from atrophic to neovascular AMD.

1.3.2 Neovascular AMD

The neovascular, or wet, form of AMD is a much more aggressive form of the disease. Even though it affects only approximately 10% of the patients with AMD, it is responsible for about 90% of the cases leading to severe vision loss (6). Without any treatment of this condition, patients will experience a severe and rapid decline in central vision, during a period of time between 3-24 months (6). The wet form of AMD is characterized by the growth of new, abnormal blood vessels within or under the macula. Leakage from these vessels, termed neovascularization, results in scar formation in the macula and/or RPE detachment from Bruch's membrane, which again is responsible for the vision loss. If the new blood vessels originates, and penetrate the RPE from the choroid under the macula causing neovascularization, it is termed choroidal neovascularisation (CNV) (7). Neovascularization, originated in the retina, that extends to subretinal space is called retinal angiomatous proliferation (RAP) (8). CNV and RAP are also classified by fluorescein angiograpgy[11] into angiopraphic patterns termed "classic" and "occult", which are associated with different degrees of aggressiveness related to vision loss and response to treatment

[11] Angiography, or arteriography, is a medical imaging technique in which an X-ray picture is taken to visualize the inner opening of blood filled structures.

options (7). Often, the lesions are a mix of these two patterns, classified as predominantly classic and minimally classic. Predominantly classic means that the classic part of the entire lesion is more than 50%, while minimally classic means that the classic part of the lesion is below 50% of the lesion (9). When related to possible treatments options, it is also of importance where the lesions are located in the macula. Subfoveal CNV is located beneath the fovea, while extrafoveal CNV is located beside the fovea.

2. EPIDEMIOLOGY

AMD is the leading cause of severe vision loss in the developed world among people 50 years of age and older. This vision loss is mainly due to the neovascular form of the disease, which accounts for about 90% of these cases. Few epidemiological studies of AMD are done in Norway, but there is no reason to believe that the incidence and prevalence rates in Norway differ greatly from other similar populations. The reason for this is that the main risk factor of getting AMD is increasing age, as both the incidence and prevalence rates increase with higher age. The Oslo Macular Study (10) have also concluded that the prevalence of neovascular AMD in the Oslo area is similar to results achieved in epidemiological studies on other populations. Hence, I have extrapolated data from epidemiological studies done in the US to describe the incidence- and prevalence rates of AMD in Norway. A meta-analysis of population-based data performed by the Eye Disease Prevalence Research Group (11) estimated the prevalence of neovascular AMD on white participants aged over 40 years old, with age-specific prevalence rates[12]. Compared to numbers from the US Census 2000 Population[13], this resulted in a prevalence of neovascular AMD to be 1.19% among the white population aged 40 years and older in the US. Based on data from Statistics Norway[14], this indicated a prevalence of neovascular AMD in Norway to be about 26,130 persons in 2006.

The yearly incidence of neovascular AMD in Norway was also extrapolated from data from the US. An article by Brown et al. (12) used the Beaver Dam Eye Study (13) and the Eye Disease Prevalence Research Group (11) to estimate the yearly

[12] See appendix 1

[13] http://www.nei.nih.gov/eyedata/tables.asp

[14] See appendix 2

incidence of neovascular AMD in Canada to be 5.26 per 10,000 inhabitants. Extrapolated to the Norwegian population this means about 2,440 new cases of wet AMD in Norway per year[15].

A population prediction 20 years from now, predicted by Statistics Norway, indicated a prevalence of AMD to be about 31,920, which means an increase of approximately 22% in the prevalence of today. This indicates a yearly incidence of AMD to be about 2,775 persons in 2027.

[15] Based on a Norwegian population of 4,640,219 per 1st of January 2007 (Statistics Norway)

3. TREATMENT OPTIONS

There are currently no effective treatments of dry AMD. However, a clinical trial called The Age-Related Eye Disease Study, AREDS (14), sponsored by the US National Eye Institute, suggests that the use of antioxidant vitamins and Zinc could slow down the progression of dry AMD to more advanced states. For wet AMD, there are several types of treatments, whose effectiveness are dependent on how the condition is classified. This analysis focused and compared two of these treatments, namely the photodynamic therapy with verteporfin[16], and the anti-VEGF therapy with ranibizumab[17]. The experiences with treatments of wet AMD until the introduction of ranibizumab, were that the prior treatments only tended to slow down the processes of the vision loss, while ranibizumab also has shown improvement in the vision of the patients treated. In this paper I have used the visual acuity scale as the measurement of sharp, central vision, as this is a common clinical measurement of visual function.

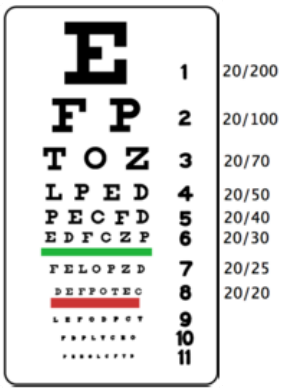
3.1 Visual Acuity Scale

Measurement of the visual acuity has often been performed by using the Snellen chart (Fig.4). The patient covers one eye, and starts reading form the top. The smallest line the patient is able to read represents the visual acuity of that eye. Both eyes are tested, and the visual acuity is defined by the best functioning eye

[16] Visudyne® is the commercial name for verteporfin.

[17] Lucentis® is the commercial name for ranibizumab.

Figure 4: The Snellen chart



Normal sight has the value of 20/20 on the visual acuity scale, which means being able to read line 8 in the figure, at the distance of 20 feet. A value of 20/40 indicates that the person is only capable of reading a line at 20 feet, which a person with normal sight is able to read at 40 feet. A person is considered legally blind if the best corrected visual acuity is defined as 20/200 or less (4). Today, EDTRS charts are widely used for measuring visual acuity (Fig. 5).

Figure 5: The EDTRS chart

The principles are the same as the Snellen chart, but there are made adjustments in the design of the chart to correct for some methodological deficiencies that the Snellen chart has been critized for. Hence, the EDTRS chart is claimed to give a more accurate measurement of visual acuity than the Snellen chart (15). Based on these charts, visual acuity can be measured according to the number of letters or lines gained/lost by the patient.

3.2 Photodynamic Therapy with Verteporfin

Until the introduction of anti-VEGF therapy, photodynamic therapy (PDT) with verteporfin was the treatment option that provided the best clinical results on AMD patients with subfoveal neovascularisation. The limitation of this treatment is claimed to be that it only slows down the progression of the disease, with no improvement of the sight of the patients. Another limitation is related to the fact that PDT treatment has only been proved effective on predominantly classic CNV (16). The Sintef Report 3/2000 (6), estimated that about 40% of the patients with wet AMD is receptive to PDT treatment.

PDT treatment was introduced during the 1980's for treatment of cancer. It uses different kinds of light-activated drugs to treat a wide range of medical conditions. Any disease in which there is fast-growing tissue, abnormal blood vessels included, can potentially be treated with this technology. PDT with verteporfin was the first pharmacological treatment approved for subfoveal CNV as a result of AMD (17).

PDT treatment with verteporfin is a two-step process involving an intravenous injection of verteporfin, usually through a vein in the arm of the patients, with a subsequent activation of the drug by light at wavelength 689 nm, delivered by a non-

thermal laser. The injection lasts for about 10 minutes, the patient then waits for about 15 minutes while the drug is absorbed in the endothelial cells of the abnormal blood vessels causing AMD. The photoactivation lasts for exactly 83 seconds[18], and generates short-lived reactive oxygen species that cause localised damage to the CNV endothelial cells. This leads to the destruction of the abnormal blood vessels, with minimal damage to the overlying retina (17).

PDT with verteporfin is typically given about every 3 months and as many times as needed to prevent regrowth of the abnormal vessels. For most people, this involves 6 to 7 treatments over 2 to 3 years. The treatments are normally performed in a doctor's office on an outpatient basis. In average, treatment is required 3.4 times the first year and 2.1 times the second year (18).

3.3 Anti-VEGF Therapy with Ranibizumab

Angiogenesis[19] is a key aspect in neovascular AMD, and substantial evidence has indicated that VEGF-A is a major mediator of angiogenesis and vascular leakage in wet AMD (19). VEGF-A is the prototype member of a gene family that also includes a sub-family of other growth factors such as VEGF-B, VEGF-C, VEGF-D and the placenta growth factor. These are signalling proteins, whose activities mainly are restricted to the cells of the vascular endothelium[20]. VEGF-A exists in several isoforms generated by alternative mRNA splicing. All these isoforms, which are separated by the number of amino acids they contain, may enhance the pathological angiogenesis of neovascular AMD by binding to receptors on the endothelial cells and stimulating cellular responses that cause the formation of new blood vessels.

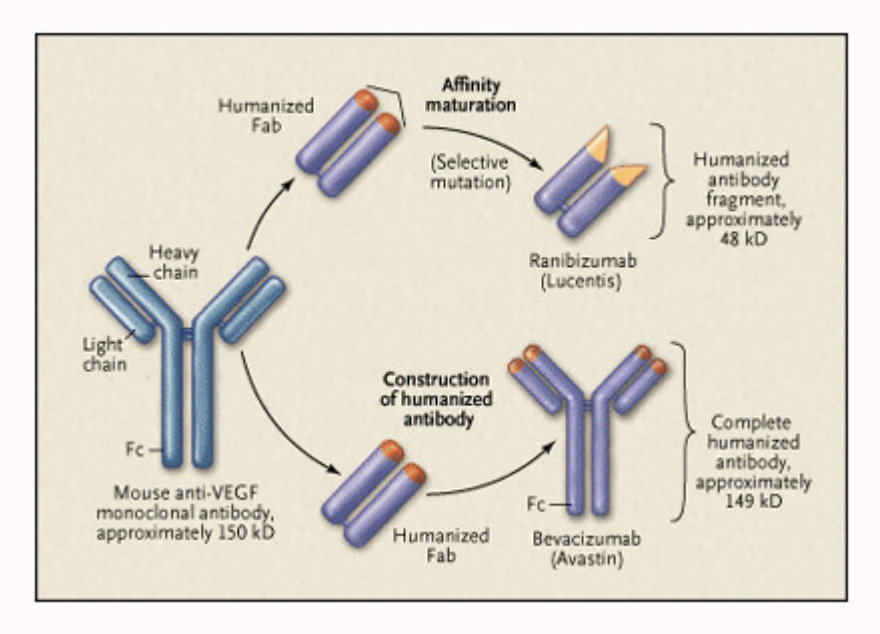
[18] http://www.visudyne.com/info/treating/photodynamic-therapy.jsp

[19] Angiogenesis is the physiological process involving the growth of new blood vessels from pre-existing vessels.

[20] The endothelium is the layer of cells lining the interior surface of blood vessels..

Ranibizumab, the antibody fragment in Lucentis®, is a high affinity[21] Fab that binds to all isoforms of VEGF-A. This results in a neutralization of VEGF-A because it blocks VEGF-A from binding to its receptors (19). Ranibizumab is produced in Echerichia coli cells deriving from a mouse anti-VEGF monoclonal antibody, and are genetically engineered through a process of selective mutation to increase its affinity for binding and inhibiting the growth factor (20) (Fig. 6).

Figure 6: Production process of ranibizumab

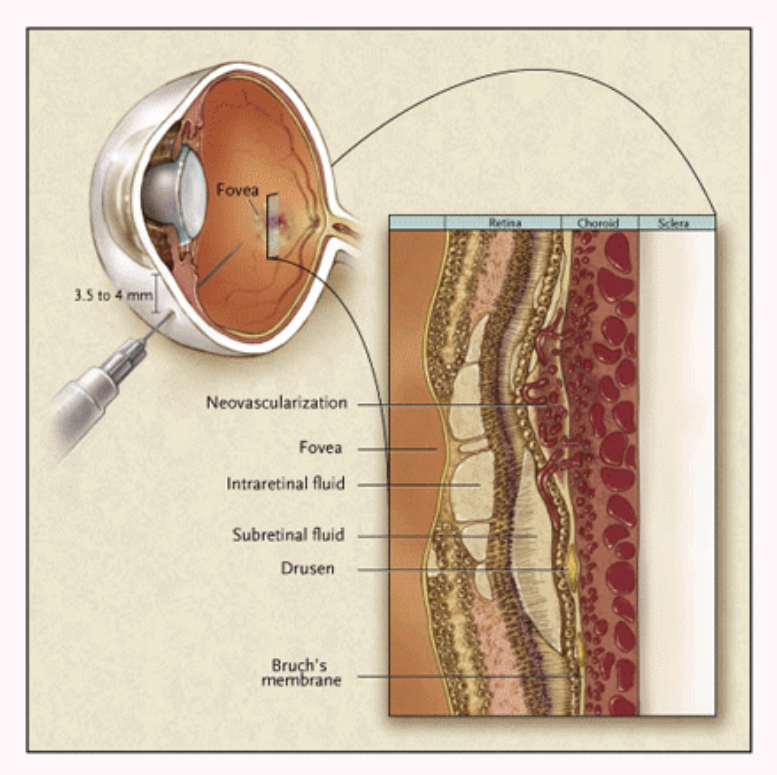


Treatment with ranibizumab was approved for use on AMD patients in June 2006 by the FDA in the USA, while the treatment in Norway was approved in March 2007. Some clinics, however, have got exemption for performing this treatment before the Norwegian approval, e.g Retinaklinikken in Oslo, which started this treatment as early as October 2006.

[21] Affinity is the binding strength of a single antibody (www.wikipedia.org).

The treatment consists of an intravitreal injection of ranibizumab (Fig. 7). Prior to the injection the patient should self-administer anti-microbial drops 4 times daily for 3 days before and following each injection. The injection procedure should be carried out under sterile conditions, and an adequate anaesthesia and a broad-spectrum topical microbicide[22] should also be administered prior to the injection. The injection needle is inserted in the vitreous cavity, and the site of the injection should be rotated for subsequent injections. Lucentis® are delivered in vials containing 3.0 mg of ranibizumab in a 0,3 ml solution, and are recommended for use at a monthly basis[23].

Figure 7: Intravitreal injection of ranibizumab



[22] A microbicide is any compound or substance whose purpose is to reduce the infectivity of microbes

[23] Based on the Official EU Prescribing Information of Lucentis®

3.4 Other treatments

Another treatment that has been widely used on AMD patients, is the conventional laser treatment aiming to destroy the abnormal blood vessels. However, this treatment can only be used on extrafoveal CNV as the laser also destroys the macula. In addition to being restricted to few patients (about 15% of the cases) it has been documented that successful laser treatment often followed by a subsequent subfoveal CNV (21).

There are also several treatments that are under consideration, and which effects are being under study. Some of them are: surgical movement of the macula; radiation therapy on the macula; thermo therapy of the macula; and transplantation of retinal cells.

4. ECONOMIC EVALUATION

A full economic evaluation can be defined as *the comparative analysis of alternative courses of action in terms of both their costs and consequences* (22). Economic evaluations are useful tools to make "right" decisions in situations where resources are scarce, and can be applied in a lot of different settings. Hence, it is important to describe what perspective the analysis is based on. The basic tasks of any economic evaluation is to identify, measure, value and compare costs and consequences of the alternatives being considered in an incremental analysis, which means that the difference in costs is compared with the difference in consequences (22). Full economic evaluations are often classified into three different approaches: Cost-Benefit Analysis (CBA), Cost-Effectiveness Analysis (CEA) and Cost-Utility Analysis (CUA). In short, these methods are primary distinguished according to how the consequences are being measured. Because, this paper is a CUA, I will describe the basic concepts of this method.

4.1 Cost-Utility Analysis

In CUA, the incremental cost of a programme from a particular viewpoint is compared to the incremental health improvement attributable to the programme, where the health improvement is measured in quality-adjusted-life-years (QALYs) gained. The results are expressed as a cost per QALY gained (22).

CUA has its background in utility theories describing rational behaviour under uncertainty, which means maximising individual utilities. Because of this, a central topic of this kind of economic evaluation is that it highlights the role of consumer preferences (utilities) in valuing the outcome. Another important aspect of CUA is that the outcomes are measured on an interval scale and made generic (22). This makes it possible to compare the benefits of different programmes within the health care sector across diagnosis, patient groups etc. The CUA are, however, dependent on

being compared to an external standard to assess whether a specific programme is worthwhile or not. These external standards are often budget constraints or threshold cost-effectiveness ratios, used by the decision makers to maximize the benefits with a given budget. (22). The most comprehensive use of cost-effectiveness ratio is to analyse the incremental cost-effectiveness ration (ICER), which is the ratio between the difference in cost and the difference in benefits of two interventions. This is illustrated by equation 1, where c=costs and E=health benefits.

Equation 1:

$$ICER = \frac{C_2 - C_1}{E_2 - E_1}$$

The cost analysis in a CUA is dependent on which perspective is chosen for the analysis. It is often preferred that the analysis is performed from a societal perspective, which means that all costs and health consequences shall be captured irrespectively of who pays or who benefits (23). The costs to be included in such a perspective are all relevant resources consumed by implementing the relevant health care programme[24], and can be divided into the following cost items: health sector costs; costs on other (public) sectors; patient/family (time) costs and productivity losses. After identifying the relevant costs, the cost analysis consists of measuring the quantities of resources used and valuing them by assigning unit costs or prices (22). The final cost of the health care programme is then measured in monetary units.

The most commonly used measurement of health outcomes in CUA are the QALY. The advantage of the QALY as a measure of health outcome is that it can simultaneously capture gains from reduced morbidity (quality gains) and reduced mortality (quantity gains), and combine these into a single measure (22). It combines

[24] Opportunity costs

health related quality of life (HRQoL) with a time perspective, and can be expressed with the following equation, where H = HRQoL and T = expected lifetime with H.

Equation 2:

$$QALY = H \times T$$

To be able to operationalize this equation, the difficult part is related to how the HRQoL is weighted. There are various methods for measuring the quality of life aspect, which means measuring individual preferences for different health states. Two of the most commonly used techniques for this purpose are the time trade-off method (TTO) and the standard gamble method (SG). In addition there are developed various generic descriptive systems for health, that assign preference scores to different health states according to how well the individual functions in different dimensions like, e.g mobility, self-care, pain, vision etc. Examples of such generic descriptive systems are EQ-5D, SF-6D and Health Utilities Index (HUI-II and HUI-III). To satisfy the QALY concept, the quality weights must meet the following three requirements: (22)

1) be based on preferences

2) be anchored on perfect health (H=1) and death (H=0)

3) be measured on an interval scale

Following from this, the QALY concept is a measure of health gains that can be compared across diagnosis. It also considers the duration of time that individuals spend in the different health states.

5. RESEARCH QUESTION

What is the incremental cost and health benefit of replacing PDT with verteporfin by anti-VEGF treatment with ranibizumab for patients with predominantly classic neovascular AMD in Norway from a health care perspective over a time period of 2 years?

The core issues of the economic evaluation are listed in the table below.

Table 1: Core issues in the economic evaluation

Issues	
Comparators	PDT with verteporfin, anti-VEGF treatment with ranibizumab
Perspective	Health care
Patient group	A Norwegian population in the age group 70-80 years old
Evidence of effectiveness	2 different phase III clinical trials; ANCHOR and TAP
Duration of treatment	2 years
Type of economic analysis	CUA performed within a decision tree modell
Utilisation of health states	Based on published article Brown et al 2005
Unit costs	Market prices, fee schedules, wage rates in the public sector
Quality of life measure	QALYs
Time horizon	2 years
Discount rate	4%
Sensitivity analysis	One-way

6. METHODS

To get an answer to my research question I developed a decision analytic model and performed a CUA. The model was designed and conducted in the software programme TreeAge. The inputs of the model, that is data regarding costs, effectiveness and utilities are derived from published articles, expert opinions and own estimates.

6.1 Despription of the Decision Analytic Model

The decision analytic model was performed as a decision tree. The model simulates three strategies: treatment with 0,5mg ranibizumab; treatment with 0,3mg ranibizumab and photodynamic therapy with verteporfin over a 2-year time period. The model starts with patients with an average of 75 years old, suffering from predominantly classic AMD with a visual acuity (VA) of 20/80. The age of 75 years old was chosen based on the baseline characteristics of the study population of the TAP-study (74.9 years) (16) and the ANCHOR study (76.0 years) (24). It was assumed that the patients were in perfect health apart from the AMD diagnosis, so that all changes in HRQoL were due to changes in visual acuity caused by AMD. From the initial state, I have assigned the patients to end up in 4 different health states according to VA. These health states were defined to be:

(1) VA $\geq$ 20/40

(2) 20/40 > VA $\geq$ 20/80

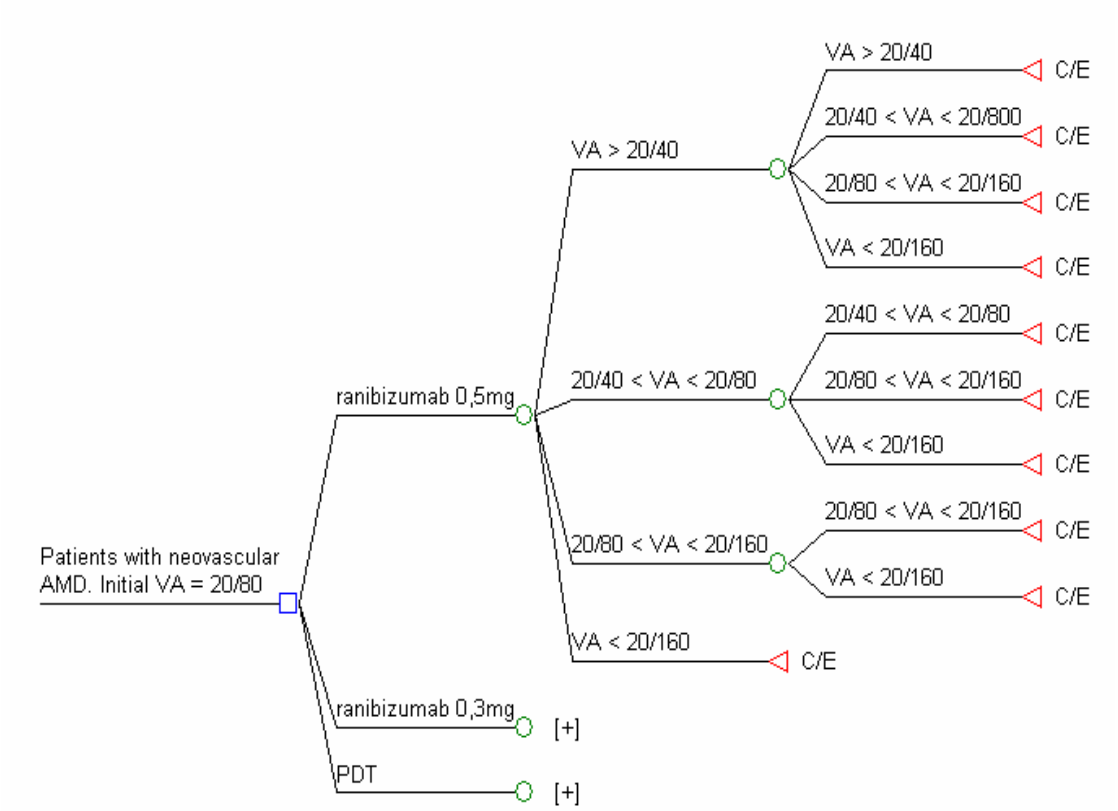
(3) 20/80 > VA $\geq$ 20/160

(4) VA < 20/160

I have estimated probabilities of ending up in each state over the time interval, and each state has also been assigned specific costs and quality of life values. The model

follows the patients for two years, and it is assumed that potential improvement of sight is obtained during the first year. This means that the patients only will maintain or lose vision during year 2. The structure of each main branch of the decision tree, representing the different treatment options, is identical. A simplified version of the decision tree is shown in Figure 8.

Figure 8: The decision analytic model



6.2 Literature Search

The first process of conducting the study was to perform a literature search to get an overview of relevant aspects for my study. I have prioritized my literature search on published articles in the PubMed database containing at least one of the following keywords: *age-related macular degeneration; AMD; VEGF; Ranibizumab; Lucentis;*

Photodynamic therapy; PDT; Verteporfin; Visudyne; epidemiology; prevalence; incidence; costs; cost effectiveness; cost-utility analysis; CUA.

One major inclusion criterion for choosing which articles to focus on was how the efficacy results in the articles were proved. Related to efficacy, only articles based on randomized controlled trials (RCT) were considered. For articles describing the effectiveness of ranibizumab, I have emphasized articles presenting the clinical results of the ANCHOR-(24) and the MARINA studies (25), both phase III clinical trials. The ANCHOR study is a comparison of the effectiveness of ranibizumab versus verteporfin in treatment of predominantly classic neovascular AMD, while the MARINA study is describing the effectiveness of ranibizumab on either minimally classic or occult CNV compared to sham injection. These two articles were published in a series of articles describing AMD in The New England Journal of Medicine. On the more general description of AMD, and the mechanism of disease I emphasized another article in this series, by deJong, P.T.V.M. (1).

When it comes to articles related to the effectiveness of PDT with verteporfin, I have chosen to include different reports from the TAP study group (16;18;26). This study group has published several reports regarding effectiveness of PDT on different subgroups of AMD, and also long-term effects of PDT treatment based on RCTs. For the best comparison to the ANCHOR study, I emphasized the TAP Report No. 8 (26), which described the efficacy of PDT on predominantly classic CNV over a 5-years time horizon.

In the data regarding the epidemiology of AMD, I have used articles based on the Beaver Dam Eye Study (13) as reference case because there are few studies related to the epidemiology of AMD in Norway. The extrapolation of data from the US was

supported by The Oslo Macular Study (10) and the SINTEF Report nr. 3/2000 (6), which conclude that the prevalence and incidence of AMD in Norway have similarities to those of similar populations. Because populations of Caucasian origin seems to have increased risk of developing AMD (11), I have only considered the prevalence- and incidence rates of the white population in the US when extrapolating to Norwegian conditions.

Utility values for the different levels of visual acuity were derived from a study by Brown et al.(27). This study is referred to by many other articles describing quality of life aspects regarding AMD, and has measured utility values associated with visual acuity levels based on a TTO method.

6.3 Probabilities

As mentioned in the context of the literature search, the efficacy of treatment with verteporfin and ranibizumab was based on respectively the TAP Reports and the ANCHOR trials[25]. The efficacy results from these clinical trials are reported in either lines gained/lost at a Snellen chart, or letters gained/lost on an EDTRS chart, where 5 letters on the EDTRS chart equals 1 Snellen line. Related to VA, losing15 letters or 3 lines represent a doubling of the visual angle (28), e.g going from a VA of 20/40 to 20/80. The primary outcomes in TAP and ANCHOR were proportion of patients losing fewer than 3 lines / 15letters. With these requirements, I have translated the results from the TAP reports and the ANCHOR study[26] , to probabilities of being in one of the four states after one year of treatment, with an initial VA of 20/80. This

[25] See appendix 3

[26] See appendix 4

translation was made by dividing the proportion of patients into groups of change in VA. These groups were:

1. VA gain ≥ 3-lines /15 letters
2. 0 ≤ VA gain < 3-lines /15 letters
3. 0 < VA loss ≤ 3-lines / 15 letters
4. VA loss < 3-lines / 15 letters

The proportions of these groups were then used to estimate the probabilities of being in one of the defined health states after one year of treatment when the initial VA was set to be 20/80. The proportion of patients in group 1 was equal to the probability of ending up in health state 1, the probability of being in health state was equal to the proportion of patients in group 2 etc.

The transition probabilities with treatment of 0.5 mg ranibizumab were estimated from the ANCHOR study, supplied with the subgroup analysis. Because the subgroup analysis did not include treatment with 0.3 mg ranibizumab, I estimated these probabilities on the assumption that treatment with 0.3 mg of ranibizumab followed the same distribution as treatment with 0.5 mg of ranibizumab. Because the published data of treatment with ranibizumab is restricted to the 1-year results, I also had to estimate how these data would be after 2 years. After a consultation with David M. Brown, MD, the main author of the article describing the results of the ANCHOR trials in The New England Journal of Medicine (24), I estimated the 2-year results based on his expert opinion. He reported that the 3-line gainers were quite constant at 24 months, and a decline in patients losing fewer than 3 lines of 4-5 % for all treatment options. From this information I estimated the 2-year efficacy results of treatment with ranibizumab. When it comes to the clinical results of PDT treatment, I found that these results differed substantially between the TAP reports and the ANCHOR trial even when the results derived from patients with

predominantly classic CNV. Because of this, I used the mean of the results from these trials. However, I used the same assumptions regarding the coherence between the 1-year and 2-year results as I did with ranibizumab. The probabilities used in the model are listed in appendix 4.The upper and lower bounds are determined by a 95 % confidence interval as reported in TAP (16) and ANCHOR (24), and calculated in Microsoft Excel. The max limit of the upper and lower bound was set to 0 and 1, because the values are probabilities.

6.4 Costs

In a societal perspective, all costs are included in the economic evaluation. I have excluded all indirect costs related to productivity losses and time consumption by e.g. family members and volunteers. Hence, the perspective of the CUA was narrowed to a health care perspective. From a health care perspective, costs related to adverse effects and injuries caused by impaired vision were excluded. All the excluded costs were due to limitations of available data.

The costs that were identified, measured and valued in my model was drug costs of ranibizumab and verteporfin, other costs related to giving the treatments, costs of physician visits, costs of vision aids related to levels of visual acuity, costs of nursing care (homecare) and costs related to rehabilitation. In general, the limitation of available data was substantial in the cost analysis. As a result of this, the costs were estimated to a greater extent on assumptions. All costs were measured in Norwegian Kroner (NOK), and presented in Table 2 (p. 40). The ranges of the upper and lower bounds were determined by the base case value +/- 20 %.

6.4.1 Drug Costs

The unit cost of verteporfin was defined as the price of one single dose of verteporfin (15 mg), with the assumption of one dose used per treatment. This cost was derived

from the Norwegian Medicines Agency (NMA)[27], where maximum pharmacy sales price[28] was subtracted 25% VAT, resulting in a unit cost of NOK 9,790. The frequency of treatment with verteporfin was 3.4 treatments the first year, and 2.1 treatments the second year (18). The upper and lower of the frequency in the first year were set to 5 and 2.5, while these bounds were set to be 3.5 and 1 in the second year.

Because treatment with ranibizumab can be given in doses of 0.3 mg and 0.5 mg, the unit cost of ranibizumab was defined to be the price of 0.1 mg ranibizumab. One single dose of Lucentis®, sold by pharmaceuticals, contains 0.3 mg of ranibizumab in a vial. The unit cost was found through the NMA price database and divided by 3, under the assumptions that patients can be accumulated so that "left-over" from one injection can be transferred to the next treatment. The unit cost of 0.1 mg of ranibizumab was NOK 3,063. The frequency of treatment with ranibizumab was on average 11 per year, derived from the ANCHOR study (24). The upper and lower bound of the frequency was set to be 14 and 6.

6.4.2 Other Treatment Costs

Estimating other treatment costs related to tests, investigations, use of medical equipments, nurses, overhead costs etc. were attached with great uncertainties as there were no available data on the exact costs of these components. Hence, these costs were estimated on the basis of an expert opinion provided by the pharmaceutical company Novartis, which is selling both drugs in Europe. As the tests and investigations are somewhat identical in the two treatments, the main difference in costs was related to the laser treatment given in PDT treatment. The unit costs of one treatment of the different strategies were assumed to be NOK 4,500 for PDT treatment, and NOK 3,500 for treatment with ranibizumab.

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[27] http://www.legemiddelverket.no/custom/templates/gzInterIFrame____1547.aspx

[28] In Norwegian: Apotekenes utsalgspris (AUP)

6.4.3 Costs of Physician Visits

Under the assumption that both treatment with ranibizumab and PDT lasts for approximately one hour, the unit cost was set to be one hour of consultation at a specialist in ophthalmology. Fee schedules from the Norwegian Medical Association[29] were used to estimate this unit cost to be NOK 491 (excl. the patient's charge of NOK 265).

6.4.4 Costs of Vision Aids

Because the need of vision aid is closely related to visual acuity, the costs of vision aids differ between the health states in my model. Each state was assigned costs that were estimated based on an expert opinion by John Engebretsen at MultiOptikk AS, Oslo. The estimated costs were calculated based of the average need of relevant vision aids within the different health states. The costs were added up based on approximate market prices of the different vision aids. Costs related to vision aids that were assumed to be relevant for all health states were excluded. Hence, the costs related to health state 1 (VA≥20/40) was set to 0. All vision aids that is supposed to be returned after the use of a patient were assigned annual costs, estimated by equation 3, where E=equivalent annual cost, n=the useful life of the equipment, r=discount rate, K=purchase price, with the assumption of no resale value.

Equation 3:

$$K = E\frac{1-(1+r)^{-n}}{r}$$

The lifetime of the products was set to be 5 years, and a discount rate of 4%, in line with guidelines from the Ministry of Finance[30]. was used in the estimations In cases

[29] http://www.legeforeningen.no/assets/Normaltariffen_2006.pdf

[30] http://www.regjeringen.no/upload/FIN/Vedlegg/okstyring/Veileder_i_samfunnsokonomiske_analyser.pdf

where not all vision aids were returned because of special customisation for the patients, the return rate was assumed to be 50%.

6.4.5 Costs of Home Care

This cost component consists of the costs related to need of homecare of the patients. I assumed that these costs were only relevant for patients in the health state with VA < 20160. However, there are great differences in the need for care within this group, resulting in large variations of what services they consume, and therefore also considerable uncertainties in the actual costs between the patients. Unfortunately, I was not able to find available data on what proportion of resource use AMD patients consumed of such services. I assumed that they consumed 5 hours of homecare per week in general, divided on three visits per week. The unit cost was set as 1 hour of "effective care", and was estimated from the wage rate of home nurses in the public sector. I used a price-model from the sector for care and social welfare in the municipality of Oslo[31] to estimate the mean cost of one 1 hour of care (NOK 314) when day-shifts and evening-shifts were considered, under the assumption that 65 % of the time spent by home nurses was related to actual treatment of patients. This estimate was supplied with unit costs per visit (NOK 54) and administrative costs per month (NOK 215) derived from the same price-model. These unit costs together resulted in total costs of one year of home care per patient to be NOK 92,617. Because I assumed that patients were in perfect health apart from the AMD diagnosis, I concluded that it was sufficient with home care. Hence, costs related to being institutionalized at nursing homes were excluded.

[31] http://cpub.www.helse-og-velferdsetaten.oslo.kommune.no/getfile.php/helse-%20og%20velferdsetaten%20%28HEV%29/Internett%20%28HEV%29/Dokumenter/dokument/omsorg/bakgrunn_for_pris_brukervalg.pdf

6.4.6 Costs of Rehabilitation

These costs are made up by courses arranged by the Norwegian Association of the Blind and Partially Sighted (NABP) for people with severe vision impairment, and will only affect the patients in the health state defined as VA < 20/160. An expert opinion from the NABP estimated these cost to be NOK 91,700 per person, which covers participation and transport. The courses offered by the NABP are provided once per person.

Table 2: Cost components used in the model

Name of model parameter	Description	Base case value	Lower bound	Upper bound	Sources
cRan05	Drugcost 0.5mg Lucentis	15 315	12 252*	18378*	NMA
cRan03	Drugcost 0.3mg Lucentis	9 189	7 351*	11027*	NMA
cPDT	Drugcost Visudyne	9 790	7 832*	11748*	NMA
cOTCRan	Other treatment costs Lucentis	3 500	2 800	4 200	Expert opinion
cOTCpdt	Other treatment costs visudyne	4 500	3 600	5 400	Expert opinion
cPhysVis	Cost of physician visit	491	393	589	Fee schedules from the Norwegian Medical Association
cVAids2080	Cost of vision aids in state 2	3 144	2 515	3 773	Expert opinion, student opinion
cVAids20160	Cost of vision aids in state 3	7 186	5 749	8 623	Expert opinion, student opinion
cVAids20160worse	Cost of vision aids state 4	16 620	13 296	19 944	Expert opinion, student opinion
cRehab	Cost of rehabilitation, state 4	91 700	73 360	110 040	NABP
cHome	Cost of home care, state 4	92 617	74 094	111 140	The sector for care and social welfare, municipality of Oslo

*For illustrative purposes

6.5 Quality of Life

The benefits of the two treatments compared are measured in QALYs. Data on HRQoL weights are based on the results from an article published by Brown et al.(12). The article has used a TTO-model to associate utility values with visual acuity levels of the better seeing-eye[32]. However, the visual acuity levels presented did not match exactly to the states in my model, so it was necessary to make some adjustments to make the data fit my model. The quality of life weights used in my model are therefore based on mean values taken from the article. I also assumed that the worst visual acuity level was limited to 20/800 which equals the term "counting fingers" in the article. The upper bound of utility value is set to be 0.97, and not 1.0 because it is assumed that a positive AMD diagnosis will represent some fear of future vision loss (12). As the base case values were estimated by the mean of the utility values in the VA range, the upper and lower bounds were defined by the highest and lowest utility value in the same range. The quality of life weights are listed in Table 3.

Table 3: HRQoL weights

Name of the model parameter	Description	Base case value	Lower bound	Upper bound	Source
q2040	VA ≥ 20/40	0.85	0.80	0.97	Brown et al.(10), student assumptions
q2080	20/40 > VA ≥ 20/80	0.76	0.72	0.80	Brown et al.(10), student assumptions
q20160	20/80 > VA ≥ 20/160	0.69	0.66	0.72	Brown et al.(10), student assumptions
q20160worse	VA < 160	0.59	0.52	0.66	Brown et al.(10), student assumptions

[32] See appendix 5.

6.6 Cost-effectiveness Threshold

Cost-effectiveness thresholds represent the maximum amount society is willing to pay for a unit of health benefit (23). This study used QALYs to express health benefits. An article by Kristiansen and Gyrd-Hansen (29), has discussed the need for setting a tentative threshold for the soctiety's willingness to pay for health benefits, which can be used by decision-makers in the health care sector when prioritizing health care programmes. The Norwegian Department of Finance has suggested this threshold to be NOK 425, 000 per QALY (30). Hence, I have used this threshold in the analysis of the results.

7. RESULTS

7.1 Costs and Health Consequences

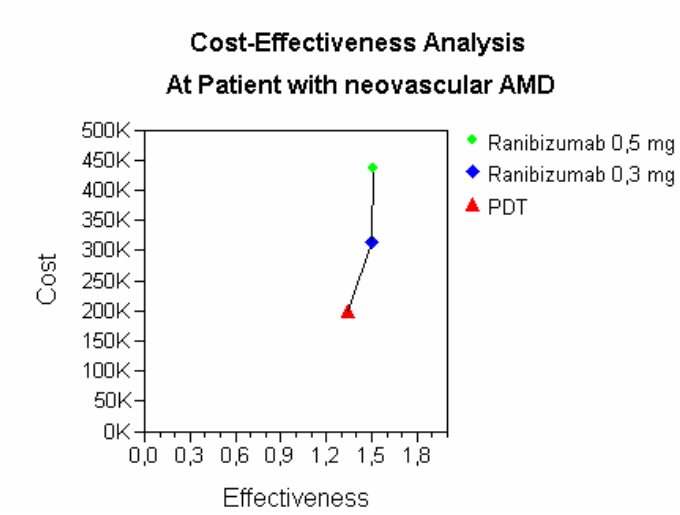
The expected total costs over 2 years of treatment with PDT per patient were NOK 198,500 with a total expected health gain of 1.34 QALYs. The incremental costs of treatment with 0.3 mg ranibizumab were NOK 116,000 with an incremental health gain in QALYs of 0.16, resulting in an ICER of NOK 739,500. This means that treating about 6.25 patients with 0.3 mg ranibizumab for 2 years instead of PDT, will have the health gain of 1 QALY, which represents a health gain equal to bringing 1 person from death to perfect health. The ICER of treatment with 0.5 mg ranibizumab gave an ICER of NOK 7,976,500. The main findings, when two years of costs and two years of QALYs were considered for the three treatment options, are presented in Table 4. The results are calculated by TreeAge, which operates with more decimals in the calculations than what is presented in the table. All costs are rounded off to the nearest amount in NOK 500.

Table 4: Main Results. All costs in Norwegian Kroner (NOK) with a discount rate of 4 %.

Strategy	Two year costs	Incremental costs	Two year QALYs	Incremental QALYs	ICER
PDT	198 500	0	1.34	0	0
0.3mg Lucentis	314 500	116 000	1.50	0.16	739 500
0.5mg Lucentis	437 000	122 500	1.51	0.015	7 976 500

These results are visualized in Fig. 9, which shows the cost-effectiveness plane for the treatment options, with the slope of the lines indicating the ICER.

Figure 9: Cost effectiveness plane of the treatment options



Assuming an incidence of 2440 new cases of neovascular AMD per year, with 40% of these receptive to PDT-treatment (6) the annual costs on the health care sector will be NOK 98,776,000. Under the same assumption the economical burden on the health care sector will be NOK 156,426,000 per year for treatment with 0.3 mg ranibizumab and NOK 217,468,000 for treatment with 0.5 mg ranibizumab.

7.2 Costs of Severe Vison Loss

If a VA < 20/160 is used as a definition of severe vision loss/blindness, costs related to this condition were calculated by the parameter values regarding costs of vision aids related to a VA < 20/160, costs of home care and costs of rehabilitation. Because the costs of rehabilitation are a one time expense when reaching this condition, the

results were presented in mean annual costs[33] and total costs[34] with a time horizon of 1, 2 and 5 years with a discount rate of 4%.

Table 5: Annual costs related to severe vision loss/blindness

Time period	Annual costs	Total costs
1 year	200 937	200 937
2 years	162 096	305 730
5 years	134 839	600 278

7.3 Sensitivity Analysis

A one-way sensitivity analysis was performed on all parameters in the model[35], showing that the drug costs of ranibizumab and the frequency of treatments with ranibizumab are the variables having the greatest impact of the results. The lower bound, indicating a 20% reduction of the drug price of ranibizumab, makes treatment with 0.3 mg ranibizumab borderline cost-effective compared to PDT, with an ICER of NOK 486,091. If the frequency of treatments with 0.3 mg ranibizumab is reduced to 6 treatments per year (lower bound) with the same effectiveness as those described in ANCHOR, this treatment will dominate PDT treatment, meaning that it is less costly and more effective. At a price of about NOK 6,900 per dose of Lucentis® (excl. VAT), the ICER of treatment with 0.3 mg of ranibizumab would be within the threshold of NOK 425,000 implicating that replacing PDT treatment by ranibizumab injection would be a cost-effective strategy. This is illustrated in Fig. 10, where the horizontally dotted line is representing the ICER threshold and the vertically dotted

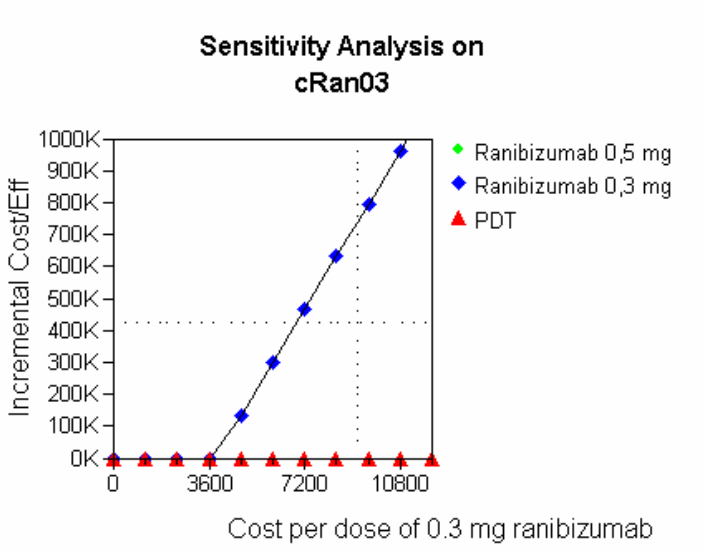
[33] Annual costs in the 5-year time horizon were calculated from equation 3.

[34] In net present value (NPV)

[35] See appendix 6

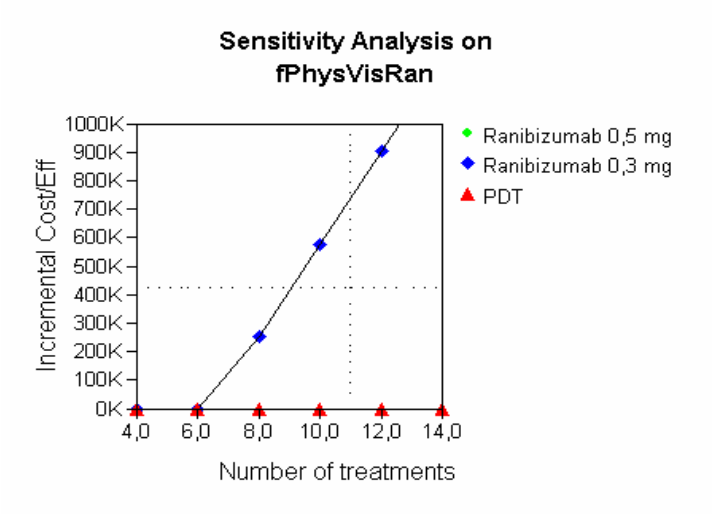
line is representing the current drug cost of 0.3 mg ranibizumab. At the point where the blue line, representing treatment with 0.3 mg ranibizumab, crosses the horizontally dotted line, the treatment is considered cost-effective compared to the threshold. With a drug price of Lucentis® of about NOK 3,600 per dose, PDT treatment will be dominated. This is indicated by the point in which the blue line crosses the red line, which represents PDT treatment, lying on the x-axis.

Figure 10: Incremental cost-effectiveness versus drug cost of ranibizumab



The one-way sensitivity analysis of the frequency of ranibizumab treatment was performed and illustrated in the same way in Fig. 11, with ICER threshold as the horizontally dotted line, and the average number of treatment with ranibizumab, from the ANCHOR study, as the vertically dotted line.

Figure 11: Incremental cost-effectiveness versus frequency of treatment with ranibizumab



Assuming no change in efficacy from reduced frequency of treatment with ranibizumab, the average number of treatments with 0.3 mg ranibizumab must be reduced from 11 (base case) to about 9 per year for the treatment to be considered cost-effective compared to the ICER threshold. If the treatment frequency is reduced to about 6 per year, PDT treatment will be dominated. Treatment with 0.5 mg ranibizumab is not depicted in any of the graphs because the ICER is far above NOK 1,000,000, which is the highest value on the y-axis.

8. DISCUSSION

The ICERs calculated in the model showed results concluding that replacement of PDT with ranibizumab is not considered cost-effective in a health care perspective, under the base case assumptions. With base case assumptions, the incremental cost per QALY with ranibizumab 0.3 mg instead of PDT was about NOK 740,000 while it was about NOK 8 millions by increasing the ranibizumab dose to 0.5mg. This implies that the use of ranibizumab may not be considered cost-effective in a Norwegian context. However, this conclusion must be seen against the limitations of the study and the interpretation of the results before it can be applied in a decision-making context. The conclusion is also dependent on the perspective of the study. Because of the exclusion of indirect costs, this study was performed in a health care perspective, regarding costs and consequences related to the health care sector. If the CUA was applied in a broader societal perspective the results may be different. It is fair to assume that patients suffering from the lowest levels of visual acuity will put demand of considerable resources on family members or other volunteers related to time costs. Because the effectiveness of treatment with ranibizumab is significantly better than PDT treatment (24), this will result in higher costs of PDT treatment because of a higher frequency distribution of patients ending up in the most resource consuming states, that is those with lowest visual acuity. According to the aspect of productivity losses, people that not yet are retired could also get neovascular AMD. This will also increase the costs on those with the most severe vision loss, due to e.g. early retirement or special arrangements at the work place. Hence, the results in a societal perspective might make treatment with ranibizumab more cost-effective compared to treatment with PDT than the results achieved in a health care perspective

8.1 Methodological Limitations

Using anti-VEGF treatment with ranibizumab on AMD patients is a relatively new kind of treatment. Because of this, the long-term effects are uncertain, as the

published results are restricted to the efficacy results of one year of treatment. Based on an expert opinion I assumed the two-year results to be quite constant as the one-year result. How the efficacy of treatment with ranibizumab will be beyond two years of treatment are attached with uncertainties and might have considerably effects related to the cost-effectiveness of the treatment options. The TAP report No. 8, presented the long-term effects (5-year results) of PDT treatment, concluding that the visual acuity outcomes were stable from 2 to 5 years. If the long-term effects of ranibizumab treatment provide benefits beyond 2 years compared to PDT, this means that the effectiveness of ranibizumab compared to PDT are underestimated in terms of QALYs gained. This scenario will make treatment with ranibizumab more cost-effective over a prolonged time perspective. If the long-term effects of ranibizumab indicate that the efficacy results decline over the time horizon towards the long-term effects of PDT, this will have an opposite effect on the ICERs of ranibizumab.

The costs and consequences of adverse events, both ocular and non-ocular, were excluded in the study. The ANCHOR study and the FOCUS[36] study have reported an increased risk of serious adverse ocular[37] and non-ocular[38] events with higher dosage of ranibizumab treatment. The differences were, however, not statistically significant. The more common ocular adverse events that were more frequently in the ranibizumab-treated groups compared with PDT included mild to moderate inflammation, conjunctival hemorrhage, increased intraocular pressure, eye pain and vitrous floaters. Treatment of the adverse effects will imply increased costs of treatment with ranibizumab. In addition, the QALYs gained from ranibizumab injection could be overestimated as the adverse events would have negative impact

[36] A phase I-II, randomized, single masked study evaluating the safety, tolerability and efficacy of ranibizumab in combination with PDT compared to PDT alone (7).

[37] Uveitis and endolphthalmitis (7).

[38] Cerebral vascular events and myocardinal infarctions (7).

on HRQoL. Hence, the exclusion of costs and consequences related to adverse effects will overestimate the cost-effectiveness of treatment with ranibizumab. It is also worth mentioning that in the same way as long-term efficacy of treatment with ranibizumab is uncertain, so are the long-term effects related to the adverse events. Costs related to injuries caused by vision loss were also excluded in the model. Including these costs will disfavour treatment with PDT because of the higher proportion of patients ending up in the health state with lowest VA. All these costs were excluded because of the limitation of available data. In the costs related to physician visits, the patient's charge of NOK 265 was excluded. However, the sensitivity analysis showed that the parameter describing the costs of physician visits had minor impacts on the results of the study.

Another methodological limitation is regarding uncertainties in the parameter values. The results of the study are based on a decision analytic model were all the inputs are assigned parameter values. Hence, variations and uncertainties in these parameter values will affect the main results. Input data, especially regarding the costs, are attached with great uncertainties and variations. This was a result of lack of available data, which made these inputs to a large extent to be based on assumptions and estimated guesses. However, the sensitivity analysis implicated that the variables with greatest impact of the results were the drug price of ranibizumab and the frequency of treatments with ranibizumab. These two variables are among those that are attached with least uncertainties, as the drug price is given by NMA, and the average number of treatments with ranibizumab is based on randomized controlled trials (RCT).

There is also reason to comment on the different health states used in the model. These states were used in an attempt to assign costs related to different degrees of vision loss. The health states are divided according to levels of visual acuity. However, the variations of visual acuity within each health state can be substantial,

leading to great differences in the need for care, vision aids etc. This will again have consequences on the cost side, resulting that costs of being in each of the health states must be regarded as values with possible large uncertainties.

The health benefits of this study were based on efficacy results of RCTs, from the ANCHOR-study and the TAP-studies. Even though RCTs provide the best type of information on which to base an analysis (31), there are some limitation in my study regarding the probabilities used in the model. This is related to the fact that I had to adapt the efficacy results to fit into my model. Both studies reported the primary outcomes in proportion of patients losing fewer than 15 letters/3 lines of visual acuity. Supplied with subgroup analysis these proportions were used to find the probability of ending up in the 4 different health states when an initial VA of 20/80 was assumed. However, the distribution of patients with different VA within each state is uncertain. This might have considerable consequences because resources consumed by the patients are closely related to the level of visual acuity, so also with the health benefits in terms of QALYs. Hence, the actual costs and health benefits related to each health state would differ depending on the distribution within the different health states. If the distribution within a certain health state is skewed towards a health state with higher visual acuity, the actual costs will be lower, while the health gain in QALYs will be higher than what the model predicts. The opposite, with increased costs and decreased health gains, will be the case if the distribution is skewed towards a health state with a lower VA. Another limitation regarding the probabilities was that the two-year results of the ANCHOR study are not published, leading to the probabilities of year two in the model to be estimated based on an expert opinion.

Because the patient group that entered into my model was set to be people with neovascular AMD between 70-80 years old, with a mean age of 75, the assumption of

the initial health state of patients being in perfect health apart from the AMD diagnosis is unlikely to hold. This assumption was chosen in an attempt to measure and value quality of life aspects strictly related to visual acuity. However, it is fair to assume that people in this age group also would suffer from other disorders or disabilities. As a result of this, the incremental costs related to nursing care might be overestimated in the analysis because some proportion in this age group already will receive nursing care based on other medical conditions. This will be in disfavour of PDT treatments that have most patients in the health state that receives nursing care. However, the costs of being institutionalized at nursing homes are excluded. This might be a considerable cost item that would have the opposite effect, in being favourable for the cost-effectiveness outcome of PDT treatment. The age of the patient group would also expect that costs and consequences of mortality are likely to be of relevance. These aspects were excluded in the model because there were no empirical data to document a significant difference in mortality between the treatment options considered.

The limitations regarding uncertainties in the long-term effectiveness of ranibizumab, and also the coherence between treatment frequency and efficacy, are probably among the most import aspects when considering ranibizumab injection to be a cost-effective treatment option compared to PDT. Hence, there is a need for more certain data on these aspects to achieve more certain results that be used in a decision making context to draw conclusions regarding the cost effectiveness of ranibizumab compared to PDT.

8.2 Findings of Other Cost-Effectiveness Studies

It was not found any other studies comparing the incremental costs and incremental health benefits of PDT replacement by treatment with ranibizumab on AMD patients. This is probably because of ranibizumab's first approval for use was such short time

ago, and that the published efficacy results of ranibizumab treatment are restricted to the one-year results.

Prior cost-effectiveness studies on PDT primarily use placebo as a comparator (e.g. TAP-studies). As economic evaluations involve comparative analysis of alternative courses of action(22), my study can not be used to decide whether PDT treatment is cost-effective by itself. Hence, comparisons with such studies are not appropriate. However, since PDT treatment is the conventional treatment of neovascular AMD, it must be assumed that it is considered cost-effective in the sense that the treatment is widely adopted.

Published cost-effectiveness studies on ranibizumab are very limited. The few articles related to cost-effectiveness and ranibizumab/Lucentis®, are using bevacizumab/ Avastin® [39] as comparator. This comparison is currently a hot prospect in the treatment of neovascular AMD. Ranibizumab is the antibody fragment derived from the complete humanized antibody, called bevacizumab (20). As a result of this, bevacizumab have similar medical effects as ranibizumab in the interaction with VEGF. However, bevacizumab is not designed for intravitreal use, but for intravenous treatment of colorectal cancer, and for this reason the drug price of bevacizumab is much lower than ranibizumab per mg. The reason for the low drug price of bevacizumab compared to ranibizumab is due to each single dose is purchased in a larger volume. A single dose of Avastin® contains 100mg of bevacizumab in a 4 ml vial, while Lucentis® is sold in doses of 0.3 ml containing 0.3 mg of ranibizumab. From the price database of NMA, the price of Avastin is NOK 2,851 per dose while the price of Lucentis is NOK 9,189, excl.VAT. Because of the large volume of Avastin, one single dose can be used to treat more patients because

[39] The commercial name for bevacizumab is Avastin®.

of the small volume needed in intravitreal injections. As a result of this the drug price of bevacizumab is 40-50 times lower than the drug price of ranibizumab (32). This major difference in drug prices have resulted in bevacizumab being used off-licence in AMD-treatment. There are, however, moral and ethical dilemmas with such off-licence use, because bevacizumab is not approved for intravitreal injections. In addition the efficacy and safety results for intravitreal use have not been targeted by randomized controlled trials. Published articles comparing bevacizumab to ranibizumab suggests that it is unlikely that ranibizumab will be cost-effective treatment option with the current drug prices (20;32;33) . The Norwegian Knowledge Centre for the Health Services is currently doing a study comparing ranibizumab and bevacizumab.

8.3 Discussion of Results

The efficacy results of treatment with ranibizumab are based on monthly intravitreal injections. However, in practice the average treatment frequency is reduced. The ongoing PIER and PRONTO studies are investigating the results of less frequent treatments with ranibizumab (7). It is suggested that fewer treatments might obtain similar efficacy results as those described in the ANCHOR and MARINA studies. There are, however, not been published any results regarding the impact on efficacy from frequency reduction. Because the total treatment costs, both related to drug costs and other treatment costs, represent a major variable in estimating the cost effectiveness of ranibizumab, the results from PIER and PRONTO might have considerable effects when determining if ranibizumab is a cost effective treatment option. The lack of data from PIER and PRONTO made me use the study treatment described from ANCHOR when documenting the effectiveness of ranibizumab. The efficacy results in ANCHOR were based on an average of 11.1 treatments with ranibizumab given to each patient per year. When it is argued that the number of treatments with ranibizumab in clinical practice can be reduced, it is also important to notice that the impact of this reduction on the effectiveness of the treatment is

uncertain. The results of the sensitivity analysis indicated that a frequency reduction in the average number of treatments with ranibizumab from 11 to 9 per year, would make treatment with 0.3 mg ranibizumab cost-effective compared to PDT treatment when no reduction in efficacy is assumed. The cost-effectiveness of ranibizumab must also be seen, as mentioned earlier in the discussion, in relation to how the long-term effects of treatment will be.

From the sensitivity analysis the drug cost, and the number of treatments with ranibizumab were the variables with the greatest impact of the ICER. However, there was also an indication that the effectiveness of PDT in the first year could be of importance. If the effectiveness of PDT is reduced, in this case meaning that the all the base case probabilities attached to PDT treatment is replaced by the lower bounds, the results gave an ICER of replacement with 0.3 mg ranibizumab to be NOK 308,896, which must be considered cost-effective. This result, however, must be considered as a worst case scenario of PDT treatment, because the accumulated reduction in all these probabilities[40] will be transferred to the probability of ending up in the worst health state, with VA < 20/160. This is because the probability attached to the worst health state is denoted, #, in the TreeAge model, which means that this probability is calculated by subtracting the other probabilities from 1[41]. This situation being the case must be considered unlikely, when compared to the RCTs, because it indicates a proportion of patients losing fewer than 3-lines/15 letters to be 43.5%. The proportion of patients losing fewer than 3-lines/15 letters of VA are the primary outcomes of both the ANCHOR- and TAP studies. The ANCHOR study has reported this proportion to be 64.3% while TAP Report No.8 has reported this proportion to be 67%[42]. The one-way sensitivity analysis gave an ICER for 0.3 mg ranibizumab

[40] Name of parameters in the model: p2040PDT, p2080PDT, p20160PDT.

[41] # = (1-p2040PDT-p2080PDT-p20160PDT)

[42] This proportion is based on results after 2 years. The 1-year results must be assumed to be even higher.

treatment to be in the range of NOK 512,000 -533,500 when the base case probabilities where changed one at the time in the parameters attached to probabilities in PDT treatment. .

The results of this study are based on patients with predominantly classic neovascular AMD. This is an aggressive form of the disease, as it is associated with more severe and more rapid vision loss compared to the minimally classic and occult forms (24). PDT treatment with verteporfin has proved to be effective on predominantly classic CNV and occult (with no classic) CNV compared to no treatment (34). The treatment with ranibizumab, however, is also providing benefits to patients with the minimally classic form of AMD (25), with the result that more patients are receptive to treatment with ranibizumab than treatment with verteporfin.

8.4 Policy Implication and Conclusion

The conclusion of this study is that, with the current price of Lucentis® and an average treatment frequency as described in the ANCHOR-study, replacing PDT treatment by ranibizumab on patients with neovascular AMD is not cost effective when the threshold is set to NOK 425,000 per QALY gained. There is, however, a need of documenting the long-term effects of treatment with ranibizumab, and also documenting the relationship between number of treatments given and efficacy, when considering the cost effectiveness of ranibizumab. Treatment with 0.3 mg ranibizumab appears to be a cost-effective treatment if the price per dose were reduced to about NOK 6,900 (excl. VAT).

9. APPENDIX

Appendix 1: Prevalence of AMD in the US

Table 4. Estimated Prevalence of Neovascular Age-Related Macular Degeneration in the United States by Age, Gender, and Race/Ethnicity

Age, y	No. of Cases (in Thousands)		Total US Population*	
	White Participants	Black Participants	No. of Cases (in Thousands) (95% CI)	Prevalence per 100 Individuals (95% CI)
Female Participants				
40-49	NA	13	13 (10-16)	0.06 (0.05-0.07)
50-54	10	5	20 (17-23)	0.22 (0.18-0.25)
55-59	9	4	18 (16-19)	0.25 (0.23-0.28)
60-64	12	4	20 (19-22)	0.36 (0.33-0.39)
65-69	21	4	30 (27-33)	0.59 (0.53-0.65)
70-74	45	5	54 (49-60)	1.10 (0.98-1.21)
75-79	90	4	99 (88-109)	2.25 (2.02-2.49)
≥80	556	8	570 (479-662)	9.31 (7.82-10.81)
Subtotal	**743**	**47**	**824** (731-916)	1.29 (1.15-1.44)
Male Participants				
40-49	NA	7	7 (2-12)	0.03 (0.01-0.06)
50-54	15	2	20 (14-26)	0.23 (0.17-0.30)
55-59	14	2	18 (15-21)	0.28 (0.24-0.33)
60-64	17	2	21 (18-24)	0.41 (0.35-0.47)
65-69	26	2	30 (25-35)	0.68 (0.58-0.79)
70-74	44	2	47 (40-54)	1.21 (1.90-2.53)
75-79	64	1	67 (58-77)	2.21 (1.90-2.53)
≥80	178	2	181 (137-226)	5.92 (4.47-7.37)
Subtotal	**358**	**20**	**391** (346-440)	0.71 (0.62-0.79)
All Participants				
40-49	NA	**20**	**20** (15-26)	0.05 (0.03-0.06)
50-54	**25**	**7**	**40** (33-46)	0.23 (0.19-0.26)
55-59	**23**	**6**	**36** (33-39)	0.27 (0.24-0.29)
60-64	**29**	**6**	**41** (38-45)	0.38 (0.35-0.42)
65-69	**47**	**6**	**60** (55-66)	0.63 (0.57-0.69)
70-74	**89**	**7**	**101** (92-111)	1.15 (1.04-1.25)
75-79	**154**	**5**	**166** (152-180)	2.24 (2.05-2.43)
≥80	**734**	**10**	**751** (650-853)	8.18 (7.07-9.29)
Total	**1101**	**67**	**1215** (1113-1320)	1.02 (0.93-1.11)

Abbreviations: CI, confidence interval; NA, not applicable.
*Estimates for the prevalence of advanced age-related macular degeneration in the total US population (based on the US Census 2000) include estimates for Hispanics and other races/ethnicities (ie, Asian, Native American, Alaska Native, Hawaiian and other Pacific Islander, and any other race/ethnicity) and those designating more than 1 race/ethnicity on the US Census 2000 form. These estimates were derived using the modeled age- and gender-specific rates for black participants. The age- and gender-specific estimates for the prevalence of advanced age-related macular degeneration (defined as having neovascular or geographic atrophy age-related macular degeneration in either eye) derived in this way are available at Web site: http://www.nei.nih.gov/eyedata/.

Table 2. Prevalence Rates for Advanced Age-Related Macular Degeneration (AMD) and Presence of Drusen of 125 µm or Larger in Diameter by Age, Gender, and Race/Ethnicity

Gender and Age, y	Prevalence per 100 Individuals (95% CI)			
	Any AMD	NV AMD	GA AMD	Drusen ≥125 µm*
White Participants				
Females				
40-49	NA	NA	NA	1.41 (1.24-1.60)
50-54	0.20 (0.17-0.24)	0.14 (0.10-0.19)	0.11 (0.09-0.13)	2.52 (2.29-2.78)
55-59	0.22 (0.20-0.24)	0.16 (0.14-0.19)	0.12 (0.11-0.13)	3.70 (3.41-4.00)
60-64	0.35 (0.33-0.39)	0.26 (0.20-0.30)	0.19 (0.17-0.21)	5.39 (5.03-5.78)
65-69	0.70 (0.64-0.76)	0.51 (0.45-0.59)	0.37 (0.34-0.40)	7.81 (7.30-8.34)
70-74	1.52 (1.41-1.64)	1.09 (0.96-1.24)	0.81 (0.74-0.88)	11.17 (10.39-12.00)
75-79	3.44 (3.22-3.69)	2.40 (2.14-2.70)	1.85 (1.72-1.99)	15.73 (14.48-17.06)
≥80	16.39 (14.97-17.91)	11.07 (9.46-12.91)	9.37 (8.53-1.29)	29.16 (26.34-32.15)
Males				
40-49	NA	NA	NA	1.56 (1.27-1.90)
50-54	0.34 (0.23-0.50)	0.23 (0.16-0.33)	0.15 (0.11-0.21)	2.65 (2.28-3.08)
55-59	0.41 (0.34-0.50)	0.28 (0.23-0.34)	0.22 (0.19-0.26)	3.77 (3.33-4.26)
60-64	0.63 (0.53-0.75)	0.42 (0.36-0.50)	0.37 (0.32-0.43)	5.32 (4.79-5.92)
65-69	1.08 (0.91-1.29)	0.73 (0.61-0.87)	0.66 (0.56-0.76)	7.48 (6.74-8.28)
70-74	1.98 (1.69-2.32)	1.33 (1.14-1.56)	1.19 (1.04-1.37)	10.40 (9.29-11.63)
75-79	3.97 (3.18-4.24)	2.49 (2.15-2.88)	2.16 (1.91-2.46)	14.30 (12.55-16.25)
≥80	11.90 (9.78-14.41)	8.29 (6.76-1.12)	6.60 (5.52-7.89)	25.62 (21.69-29.98)
Black Participants				
Females				
40-49	0.50 (0.40-0.63)	0.50 (0.40-0.63)	NA	3.01 (2.41-3.76)
50-54	0.68 (0.57-0.80)	0.49 (0.41-0.59)	0.19 (0.15-0.22)	4.03 (3.41-4.75)
55-59	0.82 (0.71-0.96)	0.60 (0.52-0.70)	0.22 (0.19-0.26)	4.88 (4.26-5.59)
60-64	1.00 (0.86-1.15)	0.73 (0.63-0.84)	0.27 (0.23-0.31)	5.91 (5.25-6.63)
65-69	1.21 (1.04-1.42)	0.89 (0.76-1.03)	0.32 (0.28-0.38)	7.13 (6.35-7.99)
70-74	1.47 (1.23-1.76)	1.08 (0.90-1.28)	0.39 (0.33-0.48)	8.58 (7.53-9.75)
75-79	1.79 (1.45-2.21)	1.31 (1.06-1.61)	0.48 (0.39-0.60)	10.29 (8.81-11.98)
≥80	2.44 (1.85-3.20)	1.78 (1.35-2.33)	0.66 (0.50-0.86)	13.66 (11.14-16.64)
Males				
40-49	0.31 (0.16-0.60)	0.31 (0.16-0.60)	NA	3.90 (2.79-5.43)
50-54	0.42 (0.25-0.70)	0.25 (0.15-0.41)	0.17 (0.10-0.29)	4.71 (3.67-6.03)
55-59	0.52 (0.33-0.80)	0.30 (0.20-0.47)	0.22 (0.14-0.33)	5.34 (4.35-6.53)
60-64	0.63 (0.42-0.95)	0.37 (0.25-0.56)	0.26 (0.17-0.39)	6.04 (5.06-7.19)
65-69	0.77 (0.50-1.18)	0.45 (0.29-0.70)	0.32 (0.20-0.48)	6.82 (5.73-8.11)
70-74	0.93 (0.57-1.53)	0.55 (0.33-0.91)	0.38 (0.23-0.63)	7.71 (6.32-9.37)
75-79	1.14 (0.63-2.05)	0.67 (0.37-1.21)	0.47 (0.26-0.84)	8.69 (6.84-10.97)
≥80	1.56 (0.72-3.35)	0.92 (0.42-1.98)	0.67 (0.29-1.38)	10.50 (7.63-14.29

Abbreviations: CI, confidence interval; GA, geographic atrophy; NA, not applicable; NV, neovascular.
*At least 1 druse 125 µm or larger in diameter must be present in either or both eyes.

Appendix 2: Norwegian population

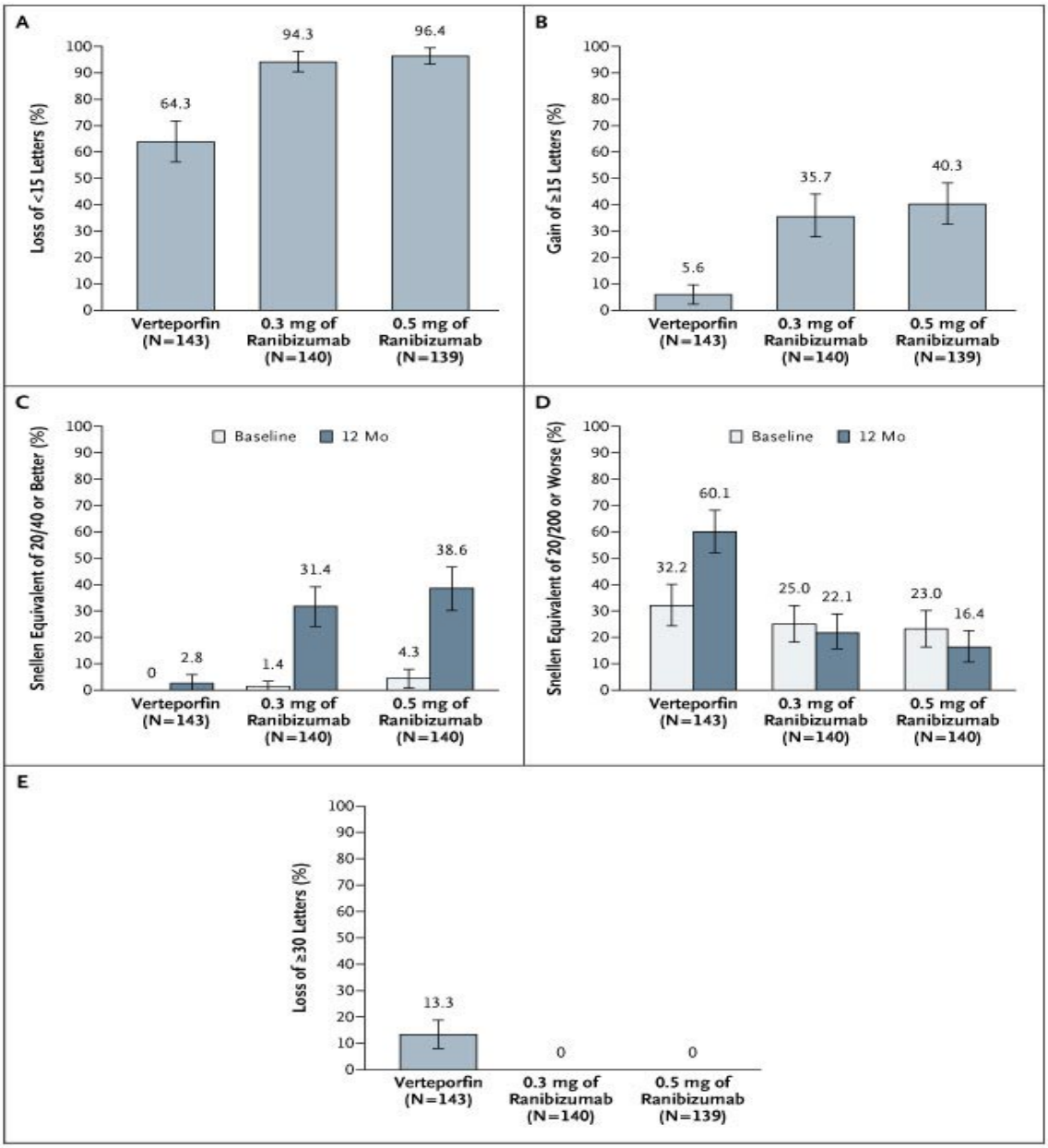
The table shows data from Statistics Norway of the Norwegian population above 40 years old in 2006.

Middelfolkemengde, etter alder, tid og statistikkvariabel					
	2006				
	Personer				
40-49 år	658523				
50-59 år	602786				
60-69 år	429558				
70-79 år	287947				
80-89 år	185691,5				
90 år og over	31327,5				

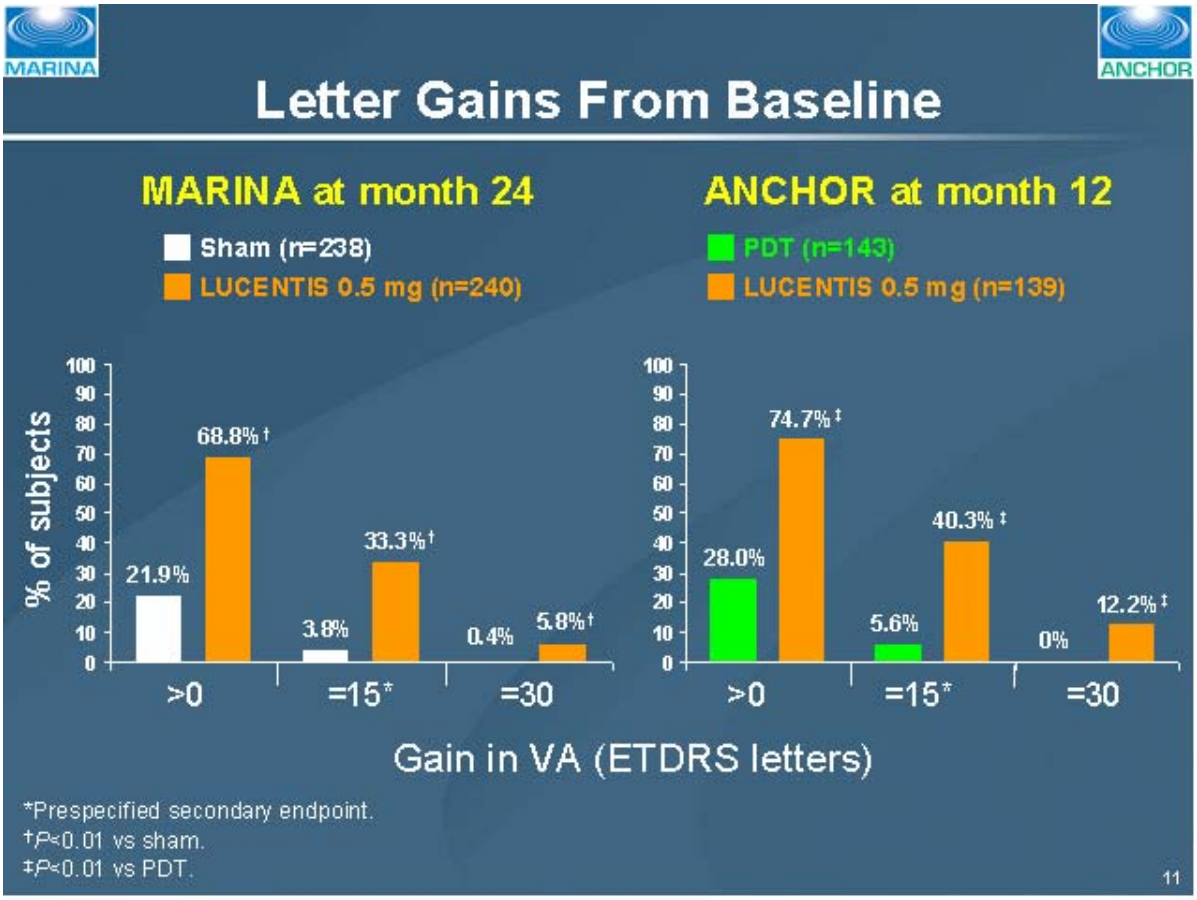
Appendix 3: Primary outcomes of ANCHOR and TAP

The tables show the primary outcomes of ANCHOR and TAP, which represents the proportion of patients losing fewer than 3 lines / 15 letters of visual acuity. The table from ANCHOR is supplied with subgroup analysis.

PRIMARY OUTCOMES FROM ANCHOR:



ANCHOR SUBGROUP ANALYSIS:



PRIMARY OUTCOMES TAP REPORT NO. 8:

Change in visual acuity[a]	Number (%) of patients	
	Month 24 (*n* =76)	Month 60 (*n* =77)
≥6-line increase	2 (3)	3 (4)
≥3-line to <6-line increase	8 (11)	6 (8)
≥1-line to <3-line increase	7 (9)	7 (9)
No change	18 (24)	12 (16)
≥1-line to <3-line decrease	15 (20)	22 (29)
≥3-line to <6-line decrease	16 (21)	20 (26)
≥6-line decrease	10 (13)	7 (9)
Mean lines (letters) lost	1.5 (7.4)	1.6 (8.0)

Appendix 4: Probabilities used in the Treeage model

Name of model parameter	Description	Base case value	Lower bound	Upper bound	Source
p2040Ran05	Probability of having VA ? 20/40 after one year of treatment with 0,5mg Lucentis	0.403	0.321	0.485	ANCHOR (22)
p2080Ran05	Probability of having 20/40> VA ? 20/80 after one year of treatment with 0,5mg Lucentis	0.344	0.265	0.423	ANCHOR (22)
p20160Ran05	Probability of having 20/80> VA ? 20/160 after one year of treatment with 0,5mg Lucentis	0.213	0.145	0.281	ANCHOR (22)
p2040Ran03	Probability of having VA ? 20/40 after one year of treatment with 0,3mg Lucentis	0.357	0.278	0.436	ANCHOR (22), student opinion
p2080Ran03	Probability of having 20/40> VA ? 20/80 after one year of treatment with 0,3mg Lucentis	0.362	0.282	0.442	ANCHOR (22), student opinion
p20160Ran03	Probability of having 20/80> VA ? 20/160 after one year of treatment with 0,5mg Lucentis	0.224	0.155	0.293	ANCHOR (22), student opinion
p2040PDT	Probability of having VA ? 20/40 after one year of treatment PDT	0.098	0.042	0.154	ANCHOR (22), TAP (14;16;24), student opinion
p2080PDT	Probability of having 20/40> VA ? 20/80 after one year of treatment with PDT	0.218	0.141	0.295	ANCHOR (22), TAP (14;16;24), student opinion
p20160PDT	Probability of having 20/80> VA ? 20/160 after one year of treatment with PDT	0.341	0.252	0.430	ANCHOR (22), TAP (14;16;24), student opinion
p1_1	Probability of staying in state 1 from year 1 to year 2	0.98	0.957	1,000	Expert opinion, student opinion
p1_2	Probability of going from state 1 to state 2 in year 2	0.01	0,000	0.026	Expert opinion, student opinion
p1_3	Probability of going from state 1 to state 3 in year 2	0.005	0,000	0.017	Expert opinion, student opinion
p2_2	Probability of staying in state 2 from year 1 to year 2	0.94	0.901	0.979	Expert opinion, student opinion
p2_3	Probability of going from state 2 to state 3 in year 2	0.04	0.008	0.072	Expert opinion, student opinion
p3_3	Probability of staying in state 3 from year1 to year 2	0.90	0.85	0.95	Expert opinion, student opinion

Appendix 5: Time trade-off utility values associated with visual acuity levels.

Visual Acuity in Better-Seeing Eye	Utility value
20/20 (with 20/20–20/25 in the other eye)	.97
20/20 (with ≤20/40 in the other eye	.92
20/25	.87
20/30	.84
20/40	.80
20/50	.77
20/70	.74
20/100	.67
20/200	.66
20/300	.63
20/400	.54
Counting fingers	.52
Hand motions	.35
Light perception	.35
No light perception	.26

Appendix 6: One-way sensitivity analysis on all model parameters

The sensitivity analysis shows the ICER of treatment with 0.3 mg ranibizumab compared to PDT treatment, when the lower and upper bounds on each model parameter are considered. The results on the ICER of treatment with 0.5 mg ranibizumab were excluded in the table because all these results were far above the cost-effectiveness threshold of NOK 425,000. Hence, the model parameters regarding only the treatment with 0.5 mg of ranibizumab are also excluded.

Name of parameter	Description	Low	High
cHome	Costs of home care	806,674	672,316
cOTCpdt	Other treatment costs, PDT	770,624	708,365
cOTCran	Other treatment costs, ranibizumab	648,589	830,401
cPDT	Drug cost verteporfin	807,219	671,771
cPhysVis	Cost of physician visit	729,373	749,616
cRan03	Drug cost 0.3 mg ranibizumab	486,091	992,898
cRehab	Costs of rehabilitation	767,148	711,842
cVAids_20160	Costs of vision aids for health state 3	741,434	737,555
cVAids_20160worse	Costs of vision aids for health state 4	751,504	727,486
cVAids_2080	Costs of vision aids for health state 2	738,384	740,606
fPhysVisPDTfirst	Frequency of physician visits first year with PDT	824,401	588,551
fPhysVisPDTsecond	Frequency of physician visits second year with PDT	839,278	612,499
fPhysVisRan	Frequency of physician visits with ranibizumab	Dominator	1,227,432
p1_1	Probability of staying in healthstate 1 from year 1 to year 2	754,008	736,999
p1_2	Probability of going from healthstate 1 to healthstate 2 in year 2	744,651	736,927
p1_3	Probability of going from healthstate 1 to healthstate 3 in year 2	741,624	737,369
p20160PDT	Probability of being in healthstate 3 after 1 year of treatment with PDT	528,299	1,000,753
p20160Ran03	Probability of being in healthstate 3 after 1 year of treatment with 0.5 mg ranibizumab	946,824	594704
p2040PDT	Probability of being in healthstate 1 after 1 year of treatment with PDT	533,757	1,036,325
p2040Ran03	Probability of being in healthstate 1 after 1 year of treatment with 0.3 mg ranibizumab	1,214,189	537,125
p2080PDT	Probability of being in healthstate 2 after 1 year of treatment with PDT	511,736	1,054,634
p2080Ran03	Probability of being in healthstate 2 after 1 year of treatment with 0.3 mg ranibizumab	1,082,202	613,906
p2_2	Probability of staying in healthstate 2 from year 1 to year 2	750,71	733,794
p2_3	Probability of going from healthstate 2 to healthstate 3 in year 2	747,087	734,771
p3_3	Probability of staying in healthstate 3 from year 1 to year 2	729,918	749,14
q20160	Utility value of being in health state 3	710,717	770,701
q20160worse	Utility value of being in health state 4	589,768	991,113
q2040	Utility value of being in health state 1	880,916	533,818
q2080	Utility value of being in health state 2	795,692	690,712

10. References

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