

Pharmacoeconomic Spotlight on the Cost Effectiveness (CE) of Vascular Endothelial Growth Factor (VEGF) Inhibitor Therapy on Diabetic Macular Edema (DME)

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Abstract

Diabetic macular edema (DME) is the most persistent factor of vision impairment in people with diabetes. The aim of this review paper was to identify more cost effective therapy among bevacizumab and ranibizumab in term of monotherapy and/or combination therapy with laser. A short review of studies conducted over the past ten years included in our literature review were found using an electronic database search of PubMed and Science Direct of the English language medical literature applying the keywords of ‘cost effectiveness’, ‘biological drugs’ and ‘diabetic macular edema’ and combinations of these terms. The references cited in these articles were explored to identify additional reports. Recent data showed that cost effectiveness of biological therapies in the treatment of diabetic macular edema favors bevacizumab

monotherapy formerly, in comparison with ranibizumab monotherapy, followed by combination of bevacizumab with laser in comparison with combination of ranibizumab with laser and lastly combination of bevacizumab with laser in comparison with bevacizumab monotherapy. The cost effectiveness analysis in this study has favored vascular endothelial growth factor (VGEF) therapy using bevacizumab on diabetic macular edema over the use of ranibizumab. The researchers and analysts within this field should conduct comprehensive longitudinal studies to overcome lack of sufficient evidence based data.

Keywords

Cost effectiveness, diabetic macular edema, ranibizumab, bevacizumab, biological drugs.

1. Introduction

Diabetic macular edema (DME) is most common cause of vision impairment in people with diabetes. If DME is left untreated, it may lead to blindness. Almost 7 – 12 % of estimated 415 million people with diabetes show the sign of DME. From those having DME, about 1 – 3% suffered visual impairment because of DME. As the prevalence of diabetes is expected to increase by more than 50% globally from 2000 to 2030, with the number of diabetes cases estimated to reach 300 million worldwide by 2025, the complication involving DME is anticipated to be increased (Chen et al., 2010). Thus, the increasing prevalence of DME is likely to drive demand for effective but lower cost treatment that can alleviate burden of vision loss worldwide (Korobelnik, 2016). The treatments for this complication include bevacizumab, a full length humanized monoclonal anti-VEGF and ranibizumab which is a Fab fragment derived from bevacizumab and aflibercept. These drugs inhibit VEGF from binding to its receptors preventing increased vascular leakage that is considered to be related to retinal damage and progression of DME. However, most of the studies had only focused on cost

effectiveness of certain treatment of DME like ranibizumab and bevacizumab because they are the only established available therapy with sufficient data. For example, studies conducted by (Brown et al., 2015, Dewan et al., 2012, Haig et al., 2016, Mitchell et al., 2012) focused only on cost effectiveness of ranibizumab. This paper has reviewed and compared the data from the studies involving cost effectiveness of all the treatment available for DME. The aims of this review paper were to compare the cost effectiveness between monotherapy bevacizumab and monotherapy ranibizumab, combination of bevacizumab and laser with the combination of ranibizumab and laser, monotherapy bevacizumab and combination of bevacizumab and laser and finally, to identify more cost effective therapy among bevacizumab and ranibizumab. This review article is intended to inform all healthcare professionals especially the diabetologist and pharmacist for choosing the highest cost-effective drug that can produce optimum outcome and improve patients' quality of life.

2. Methodology

All the related articles and journals were searched and found through computerized systems including Science Direct and

MEDLINE (PubMed). These are electronic databases that contain comprehensive collection of scientific articles and journals in the fields of science from different countries over the years. Few keywords had been used to allocate those particular articles needed such as “*cost effectiveness*”, “*biological drugs*”, “*ranibizumab*”, “*bevacizumab*”, and “*diabetic macular edema (DME)*”. Cross references upon the obtained articles were done as well as complimentary method of the computerized search. This was conducted by searching manually all related articles through the list of references. The inclusion criteria for the articles were that all articles must be in English language. Abstracts that contain one or more of the key search terms were identified. Studies referred were published within the last 10 years from current year (2017). Studies that involved the use of biological drugs ranibizumab and bevacizumab in the treatment of DME, either mono or combined therapy and cost effective analysis studies comparing costs and outcomes of two or more interventions were included. On the other hand, studies not meeting the said criteria were excluded.

3. Results & Discussion

Bevacizumab is strikingly more cost effective than ranibizumab when comparing results from either one-year studies or multiple-year studies. This may be contributed due to the fact that bevacizumab supply in bulk has allowed repackaging in syringes for about \$ 60 each, and ranibizumab ready-made formulation in syringes costs \$ 1,170 each. The combination of bevacizumab and laser photocoagulation therapy (\$ 2,511/QALY) is more cost-effective as compared to the combination of ranibizumab with laser photocoagulation therapy (\$ 9,657/QALY). In comparing bevacizumab monotherapy (\$ 3,667/QALY) and combination therapy (\$ 2,511/QALY), the combination therapy is slightly more cost-effective. A detail description is given (Table 1).

3.1 Bevacizumab Monotherapy Versus Ranibizumab Monotherapy

As of today, multiple studies had been conducted for assessing the cost of monoclonal antibody therapy in treating diabetic macular edema (DME). The agent of choice is ranibizumab and bevacizumab, while aflibercept is a new agent which is rarely used. Despite the efficacy of each agent, it is important to determine the cost

effectiveness in order to ensure affordability. For ranibizumab therapy, the commonly used doses are 0.3 mg and 0.5 mg, whereas 0.3 mg dose is generally preferred due to better side effect tolerability. In cost effectiveness study on 0.3 mg of ranibizumab found two different results of cost per QALY gained based from two different trials which are \$23,119 and \$19,251 respectively (Smiddy, 2011). Another research found that the cost per QALY was \$21,703.61. The average cost per QALY gained was \$ 21,357 (Ross et al., 2016). Multiple years of treatment study, found that the cost per QALY gained was \$18,452 (Brown et al., 2015). Next, cost per QALY gained of \$ 56, 443 was found in study conducted for 14 years therapy duration (Korobelnik, 2016). A study conducted for 10 years period of therapy obtained a result of cost per QALY gained \$ 11,557. The average cost per QALY gained was \$ 28,817 (Ross et al., 2016).

On the other hand, for 0.5 mg ranibizumab, a study found that the cost per QALY gained of ranibizumab was \$ 3,074 (Régnier et al., 2015) while in another study the cost was \$ 5,809 for 3 years period of study. The average cost per QALY gained was \$ 4,441.50 (Haig et al., 2016). These values

were small as compared to 0.3 mg therapy due to its higher efficacy and less common application in DME therapy. Therefore, this review paper will focus more on 0.3 mg therapy results in order to compare the cost effectiveness of bevacizumab therapy.

Studies on bevacizumab therapy (1.25 mg) for diabetic macular edema found that the cost per QALY gained were \$ 2,013 and \$ 4,160 based from two different trials (Smiddy, 2011). Another study obtained a result of cost per QALY gained to be \$ 4,829 for 1-year of study and \$ 5,852 for 10 years period of study. In total, the average cost per QALY gained in 1-year study is \$ 3,667 (Korobelnik, 2016). Comparing the cost per QALY gained of 1-year study and also multiple years from societal perspective between ranibizumab therapy and bevacizumab therapy, it was found that bevacizumab is strikingly more cost effective as compared to ranibizumab. This can be explained by the fact that bevacizumab formulation can be repackaged by the hospital staffs in 1.25 mg syringes for ophthalmic use at \$ 60 only/syringe while ranibizumab 0.3 mg costs \$ 1,170/syringe. Ranibizumab is more expensive due to ready-made formulation available in syringes by the manufacturer. Therefore, no

cost reduction or repackaging could be performed.

3.2 Bevacizumab Combination Versus Ranibizumab Combination

The other treatment option available for diabetic macular edema (DME) is combination between pharmacological and non-pharmacological treatment. Among the available combination, biological drugs and laser therapy which are bevacizumab with laser therapy combination and ranibizumab with laser therapy. The laser therapy used in this combination is laser photocoagulation. Laser therapy is the first line for the treatment of DME (Bucsics et al., 2016), however, it comes with many complications that can lead to increase cost of productivity losses and the effectiveness is less compared to VEGF inhibitor therapy (Haig et al., 2016). In order to provide DME patients with more effective treatments, laser therapy is combined with bevacizumab or ranibizumab. Through these combinations, a modest additional benefit can be achieved at a low additional cost (Pershing et al., 2014). A study, 0.5 mg ranibizumab PRN combined with laser therapy was used. The study was conducted on patients with DME due to type 1 or type 2 diabetes mellitus for 36 months. The cost effectiveness obtained

from this study was \$ 6635/QALY gained (Haig et al., 2016). In another study conducted on patients who had clinically significant DME for one year, the treatment applied was a combination of 0.3 mg ranibizumab and laser therapy. As a result, the cost effectiveness obtained was \$ 16958/QALY gained. A study conducted on 57 years old patients with newly diagnosed DME that were treated with 0.3 mg ranibizumab combined with laser therapy and 1.25 mg bevacizumab combined with laser therapy for two years. The cost effectiveness of combination of 0.3 mg ranibizumab with laser therapy and combination of 1.25 mg bevacizumab with laser therapy were \$ 5379/QALY gained and \$ 2511/QALY gained, respectively. After comparing the cost effective data from these three studies, between combination of ranibizumab with laser therapy and combination of bevacizumab with laser therapy, it can be seen that combination therapy of bevacizumab is more cost-effective as compared to the other option. If all the data related to combination therapy of ranibizumab is viewed as average, which is \$ 9657/QALY gained; the combination of bevacizumab is still more cost effective. Thus, based on this data comparison, the combination of bevacizumab with laser

therapy is more cost-effective as compared to the combination of ranibizumab with laser therapy (Bucsics et al., 2016).

3.3 Bevacizumab Combination Versus Bevacizumab Monotherapy

From the above discussion, it can be perceived that bevacizumab therapy used as monotherapy or combination therapies are more cost-effective as compared to ranibizumab therapy. Thus, in this part, a comparison between bevacizumab monotherapy and combination of bevacizumab with laser therapy has been performed. When comparing between these two treatments of bevacizumab, there is a slight advantage of using the combination therapy where the cost per QALY gained was just \$ 2,511 while monotherapy was \$ 3,667. This can be explained by a substantial benefit that can be gained by utilizing the combination therapy with a relatively small additional cost. By using combination therapy, the effectiveness of the treatment is much higher than monotherapy and the incremental cost is only small. Thus, combination therapy of bevacizumab is more cost-effective than bevacizumab monotherapy.

4. Study Limitations

The limitations of this study include lack of discounting and inflation rate applications on the monetary values discussed between different studies, in addition to different currency used by one of the studies by (Korobelnik, 2016) which compared dollar and pound currencies. We have converted the pound currency to US dollars according to current 2017 conversion rates in order to allow direct comparisons between costs. In addition, lack of data and study of aflibercept in treating DME may affect the analysis of cost effectiveness of treatment options in this paper; therefore, we did not include aflibercept in our analysis. Parameters in measuring therapy outcomes and QALY may be different in between studies reviewed in this paper. For example, in a study conducted by (Chalk et al., 2014) stated that measures such as the EQ-5D does not capture aspects of sensory deprivation sufficiently and may not quantify the quality of life of DME patients living with visual impairment. Moreover, differences in study demographics and choice of comparator groups may affect the results of the studies used in this review, therefore generalization may not always be appropriate.

5. Conclusion and Recommendations

In conclusion, recent data showed that cost effectiveness of biological therapies in the treatment of diabetic macular edema favors bevacizumab monotherapy formerly, in comparison with ranibizumab monotherapy, followed by combination of bevacizumab with laser in comparison with combination of ranibizumab with laser and lastly combination of bevacizumab with laser in comparison with bevacizumab monotherapy. The cost effectiveness analysis in this study has favored vascular endothelial growth factor (VEGF) therapy using bevacizumab on diabetic macular edema over the use of ranibizumab. The cost effectiveness analysis in this study has favored VEGF inhibitor therapy using bevacizumab on DME over the use of ranibizumab. Healthcare professionals should consider endorsing the use of bevacizumab, either monotherapy or in combination with laser photocoagulation in an effort to produce optimum outcome that contribute to the improvement of patients' quality of life with minimal costs conferred to the patient. Further research regarding cost effectiveness of biologic therapies using VEGF inhibitors in treating DME need to be conducted with adjustment of the different inflation rate and monetary

value. Moreover, the researchers and analysts within this field should conduct comprehensive longitudinal studies to overcome lack of sufficient evidence based data. Standardization of outcome measures in DME study should be performed in consensus among leading research institutions in order to allow generalization of the data to other countries. Mass public education on the importance and impact of cost effectiveness studies of biologic treatments in DME should be conducted in order to encourage more involvement of volunteers in the trials or studies conducted by researchers.

Competing Interests

Authors have declared no competing interests.

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Table 1: Studies Investigating Cost Effectiveness of Vascular Endothelial Growth Factor Inhibitor Therapy on DME

Author/Year	Title	Method	Subject	Finding	Conclusion	Limitation
Smiddy, W. E. (2011)	Economic Considerations of Macular Edema Therapies	Results from published clinical trials (index studies) of laser, intravitreal corticosteroids, intravitreal anti-vascular endothelial growth factor (VEGF) agents, and vitrectomy trials were used to ascertain visual benefit and clinical protocols. Calculations followed from the costs of 1 year of treatment for each treatment modality and the visual benefits as ascertained.	Patient diagnosed with Diabetic Macular Edema Mean age: Ranibizumab i. DRCR trial - 63 years ii. READ trial - 62 years Bevacizumab i. PACORES trial – 60 years ii. BOLT trial – 65 years	Equivalent data on aflibercept were not available at the time of this study. Ranibizumab iii. DRCR trial - cost per QALY of \$23,119 iv. READ trial - cost per QALY of \$19,251 Bevacizumab iii. PACORES trial - cost per QALY of \$2013 iv. BOLT trial - cost per QALY of \$4160	Bevacizumab was the most cost-effective treatment and the ranibizumab was the least in treating DME when compared with other available therapy of DME.	Equivalent data on aflibercept were not available at the time of this study.
Régnier, S. A., et al 2015	Cost effectiveness of ranibizumab versus aflibercept in the treatment of visual	A Markov model previously reviewed by the National Institute for Health and Care Excellence was used to simulate the long-term	345 patients aged ≥ 18 years, with type 1 or 2 diabetes mellitus and visual impairment due	Lifetime cost for ranibizumab is lower than aflibercept. Total cost/ QALY for aflibercept is	From UK health professionals' perspective, the treatment of DME by using	Limited data for comparison of the effectiveness between the treatments of DME by using ranibizumab versus

	impairment due to diabetic macular edema: a UK healthcare perspective	<p>outcomes and costs of treating DME.</p> <p>The efficacy of ranibizumab and aflibercept derived from RESTORE study</p> <p>The comparison in the efficacies of ranibizumab and aflibercept is derived from network of meta-analysis.</p>	to DME.	<p>\$3994/QALY</p> <p>Total cost/QALY for ranibizumab (0.5mg PRN) and ranibizumab (0.5mg TandE) are \$3074/QALY and \$3521/QALY, respectively.</p>	ranibizumab is more cost effectiveness than that by aflibercept.	aflibercept.
Brown, G. C., et al 2016	The Cost effectiveness of Ranibizumab for the Treatment of Diabetic Macular Edema	<p>Performed an incremental cost-utility analysis using societal and third-party insurer cost perspectives.</p> <p>Costs and outcomes were discounted with net present value analysis at 3% per annum.</p> <p>Cost effectiveness was quantified with the cost-utility ratio (CUR) measured as</p>	<p>Used published data from the identical RISE and RIDE clinical trials.</p> <p>These were protocol-identical, double-masked studies comparing monthly, intravitreal sham injections with 0.3mg and 0.5mg ranibizumab</p>	<p>CUR of societal cost perspective is - \$30866/QALY.</p> <p>CUR of third-party insurer cost perspective using all direct medical costs \$4587/QALY.</p> <p>WHO criteria; intervention cost less than \$49 000/DALY in 2012 USD is very cost effective.</p> <p>The NIHCE in the United Kingdom</p>	Intravitreal ranibizumab therapy for the treatment of DME is considerably cost-effective conferring to WHO and NIHCE criteria in cost effectiveness.	The fact that RIDE and RISE outcomes were modeled from months 25 through 168 using a last observation carried forward model could bias toward treatment benefit.

			<p>injections in a 1:1:1 ratio for the treatment of DME.</p> <p>The sham cohort (n = 257) and the 0.3-mg ranibizumab treatment cohorts (n = 250).</p> <p>Visual data include the randomized 2-year results, with the 24-month visions carried forward using a last observation carried forward methodology for months 25 through 168 (14 years).</p>	<p>generally accepts interventions costing less than £20 000/QALY (approximately \$32 000/QALY in USD as of October 2012) as cost effective.</p>		
Ross, E. L., et al 2016	<p>Cost effectiveness of Aflibercept, Bevacizumab, and Ranibizumab</p>	<p>Post hoc analysis of efficacy and safety for 1 year and mathematical modelling for 10 years of cost</p>	<p>624 participants</p> <p>-Aflibercept: 209</p> <p>-Ranibizumab: 208</p>	<p>1. Comparing of aflibercept (2 mg) ranibizumab (0.3 mg) and bevacizumab (1.25 mg) and compare using COST/QALY</p>	<p>Bevacizumab is more cost-effective than ranibizumab due to the cost. The</p>	<p>The packaging affects the cost that contribute to higher cost of bevacizumab</p> <p>The baseline is only</p>

<p>for Diabetic Macular Edema Treatment</p> <p>Analysis from the Diabetic Retinopathy Clinical Research Network Comparative Effectiveness Trial</p>	<p>effectiveness result. Using Snellen equivalent method of vision as the baseline of either 20/32 till 20/40 as better vision 20/50 above as worse vision provided from Electronic-Early Treatment Diabetic Retinopathy Study letter score.</p>	<p>- Bevacizumab: 207</p> <p>Participants were divided into 2 subgroups of better vision and worse vision</p>	<p>2. All participants 1 year:</p> <ul style="list-style-type: none"> • Ranibizumab: US \$ 21,703.61 • Bevacizumab: US \$ 4,829.21 <p>10 years:</p> <ul style="list-style-type: none"> • Ranibizumab: US \$ 11,557.50 • Bevacizumab: US \$ 5,585.90 <p>3. Better baseline vision 1 year:</p> <ul style="list-style-type: none"> • Ranibizumab: US \$ 19,117.65 • Bevacizumab: US \$ 3,657.14 <p>10 years:</p> <ul style="list-style-type: none"> • Ranibizumab: US \$ 10,959.10 • Bevacizumab: US \$ 5,549.22 <p>4. Worse baseline vision 1 year:</p> <ul style="list-style-type: none"> • Ranibizumab: US \$ 4,607.96 • Bevacizumab: US \$ 6,075.33 <p>10 years:</p>	<p>cost of ranibizumab need to be reduced so that it could compete with bevacizumab on cost effectiveness</p>	<p>restricted to visual acuity</p>
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- Ranibizumab: US \$ 12,210.53
- Bevacizumab: US \$ 6,166.67

Ranibizumab cost must be decreased 69% - 80% (1 year) and 62% - 84% (10 years) to reach cost effectiveness \$100,000/QALY with bevacizumab.

<p>Korobelnik, J.-F 2016</p>	<p>Optimal Dose and Cost Effectiveness of Ranizumab Treatment of Diabetic Macular edema</p>	<p>Combined searches were made in BIOSIS PreviewsR, British Library Inside Conferences, EmbaseR, EmbaseR Alerts and MEDLINER, with no date restriction. Title and abstract terms searched for included MeSH terms for clinical studies in DMO, or diabetic retinopathy restricted to ranibizumab 0.5 mg or 0.3 mg.</p>	<p>From RDE and RISE studies, number of patient in analysis were 382 at Month 24, 382 at Month 36, 112 at Month 48 and 377 at Month 24, 377 at Month 36, 166 at Month 48 respectively The treatment involved were randomized 1:1:1 to monthly</p>	<p>By using data from the RIDE and RISE studies, it was found that cost effectiveness for ranibizumab 0.3mg to treat one eye was \$30173.33/QALY and cost effectiveness for two eyes was \$56443.24.</p>	<p>Using a 0.3mg ranibizumab is more cost effectiveness in one eye compared to treatment of two eyes.</p>	<p>This study uses different monetary unit in order to compare the cost effectiveness between 0.3mg and 0.5mg ranibizumab. The ranibizumab 0.5mg is not conclude in the finding because there is no data about QALY for ranibizumab 0.5mg.</p>
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			intravitreal injections:			
			1. RBZ 0.3 mg;			
			2. RBZ 0.5 mg;			
			3. Sham			
Haig, J., et al 2016	Cost effectiveness of Ranibizumab in the Treatment of Visual Impairment Due to Diabetic Macular Edema	Markov model was used. Main outputs were costs (in 2013 ca\$). Health outcomes (in quality-adjusted life-years [QALY]) and the incremental costeffectivenessRatio (ICER) was calculated.	Patient with DME due to DM type 1 or type 2. Mean age of the patients was 63.3 years	Cost effectiveness: <ul style="list-style-type: none"> • Ranibizumab monotherapy and combination therapy were cost-effective compared with laser monotherapy. • Ranibizumab monotherapy: USD\$5809 per QALY • Ranibizumab combination therapy: USD\$6635 per QALY 	Ranibizumab monotherapy and combination therapy resulted in increased quality-adjusted survival and time Without legal blindness, and lower costs from a societal perspective compared with laser monotherapy	A potential limitation of this study is the choice of comparator group.
Stein, J. D., et	Cost	Markov model with a	Hypothetical	The findings were	With	Long term outcome

<p>al 2014</p> <p>effectiveness of Various Interventions for Newly Diagnosed Diabetic Macular Edema</p>	<p>25-year time horizon. The interventions involved are focal laser plus intravitreal ranibizumab (L+R) and focal laser plus intravitreal bevacizumab (L+B).</p>	<p>cohort of 57-year-old patients with newly diagnosed CSDME.</p>	<p>extrapolated from DRCR trial.</p> <p>0.3mg Ranibizumab and laser:</p> <ul style="list-style-type: none"> • USD 5379/QALY gained <p>1.25mg Bevacizumab and laser:</p> <ul style="list-style-type: none"> • USD 2511/QALY gained. 	<p>bevacizumab and ranibizumab assumed to have equivalent effectiveness and similar safety profiles, bevacizumab therapy confers the greatest value among the different treatment options for CSDME.</p>	<p>data (more than 2 years) were limited as little is known about the longer-term natural history of CSDME among patients receiving these particular interventions .</p> <p>Generalizability was limited because DRCR.net trial included only patients whom physicians thought would benefit from laser treatment.</p>
<p>Pershing, S., et al 2014</p> <p>Cost effectiveness of Treatment of Diabetic Macular Edema</p>	<p>Decision-analytic Markov cohort model of the natural history and treatment of DME, integrating mortality, visual acuity, treatment costs, complications, and societal costs.</p>	<p>Patients with clinically significant DME. Type 1 or 2 diabetes and clinically significant DME. 50% were men, age was 63 years,</p>	<p>Results of Base-Case Analysis:</p> <p>Laser treatment plus ranibizumab achieved the greatest benefit, gaining 0.56 QALYs at a cost of \$6975 compared with laser treatment plus</p>	<p>Long-term outcome data for treated and untreated diseases are limited</p>	<p>The most effective treatment of DME is VEGF inhibitor injections with or without laser treatment. This therapy compares favorably with cost-effective interventions</p>

<p>The model compared the effect on health, longevity, and costs of the following management strategies:</p> <p>no treatment;</p> <p>monotherapy with a VEGF inhibitor (ranibizumab, 0.3 mg);</p> <p>monotherapy with triamcinolone, 4 mg;</p> <p>laser monotherapy;</p> <p>combination therapy with laser treatment plus a VEGF inhibitor;</p> <p>and combination therapy with laser treatment plus triamcinolone.</p> <p>We translated vision and complications into utility-based quality-of-life</p>	<p>and visual acuity of the better eye was 20/63.</p> <p>Patients had no previous cataract surgery and did not receive treatment of DME within 4 months. These characteristics were similar to those of the baseline populations of major clinical trials of DME</p>	<p>triamcinolone.</p> <p>One year's treatment: Monotherapy with a ranibizumab (Cost 106 213 QALY 6.16, Cost/QALY \$17,242) achieved similar outcomes to combination therapy with laser treatment plus ranibizumab (Cost 104 973, QALY 6.19, Cost/QALY \$16,958).</p> <p>Even after doubling the risk for endophthalmitis with bevacizumab, laser treatment plus ranibizumab cost more than \$3.5 million per QALY gained compared with laser treatment plus bevacizumab</p>	<p>for other conditions.</p>
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measures and analyzed these from a societal perspective, broadly considering all lifetime costs and benefits regardless of who benefited.

BOLT: Bevacizumab or Laser Therapy in the Management of Diabetic Macular Edema; DRCR: Diabetic Retinopathy Clinical Research

PACORES: Pan American Collaborative Retina Study; QALY: Quality-Adjusted Life Year; READ: Ranibizumab of Edema of the Macular in Diabetes

ICER: Incremental Cost-Effective Ratio; RISE and RIDE clinical trials: Ranibizumab Injection in Subjects with Clinically Significant Macular Edema with Center Involvement Secondary to Diabetes Mellitus Trials

DALY: disability-adjusted life year (similar to QALY); NIHCE: National Institute for Health and Care Excellence