The Dissertation Committee for Shan Jiang Certifies that this is the approved version of the following dissertation:

Safety, Effectiveness, and Cost among Texas Medicaid Patients with Diabetic Macular Edema (DME) or Age-Related Macular Degeneration (AMD)

Committee:

Jamie C. Barner, Supervisor

Karen L. Rascati

James P. Wilson

Kristin M. Richards

Esmond D. Nwokeji

Adam H. Turpcu

Safety, Effectiveness, and Cost among Texas Medicaid Patients with Diabetic Macular Edema (DME) or Age-Related Macular Degeneration (AMD)

By

Shan Jiang, B.S.; B.Eco.; M.S.

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Dedication

To my parents, Xiaoguang Jiang and Jian Wang, for making sacrifices in their life to make this dream come true.

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Safety, Effectiveness, and Cost among Texas Medicaid Patients with Diabetic Macular Edema (DME) or Age-Related Macular Degeneration (AMD)

Shan Jiang, PhD

The University of Texas at Austin, 2014

Supervisor: Jamie C. Barner

Although bevacizumab is one of the most commonly used treatments for DME and AMD, there are concerns regarding safety and effectiveness due to its off-label use. The study objectives were to determine if: 1) the risk of cardiovascular/ hemorrhagic events (safety) and visual impairment (effectiveness) differed by bevacizumab use (i.e., use vs. non-use and number of treatments) among DME and AMD patients; and 2) direct medical costs differed between DME and DME control patients.

A retrospective cohort analysis was conducted with Texas Medicaid medical and prescription data (9/1/07-12/31/12) for patients: 18- 63 years, continuously enrolled 1-year pre- and post-index, and diagnosed with DME or AMD. The index date was the first date of diagnosis. The dependent variables were: 1) cardiovascular/hemorrhagic risk; 2) visual impairment; 3) direct medical costs. The independent variables were bevacizumab use and number of bevacizumab treatments. Covariates were disease state, Charlson

Comorbidity Index (CCI) score, total medication use, number of laser treatments, and demographics. Propensity scoring technique was used to match: 1) bevacizumab users and non-users; and 2) DME and DME control cohorts. Descriptive analyses, logistic regression, Cox-regression, and generalized linear models were employed.

A final cohort of 3,647 DME, 297 AMD, and 57,897 DME control patients were included. The majority (DME and AMD) was between 45-63 years of age (86.6%), Hispanic (54.0%), and female (65.1%). The mean total number of unique medications and mean CCI were 2.7 ± 3.4 and 6.0 ± 3.3, respectively. Total direct medical costs/person (Mean (±SD)) incurred by DME, DME control, and AMD subjects in the post-index period were $6,704(±9,338), $5,495(±10,153), and $4,935(±12,702), respectively. No differences in cardiovascular/ hemorrhagic risk were found between bevacizumab users and non-users. The claims data lacks the detail to determine the effectiveness of bevacizumab. DME control patients had lower overall direct medical costs than DME patients ($p<0.0001$).

In conclusion, although bevacizumab is a less expensive off-label alternative of ranibizumab, the choice between bevacizumab and ranibizumab should be made through careful consideration. However, as the use of anti-VEGF agent increases, further research should be conducted to determine if any changes in cardiovascular adverse events occur.

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Chapter 1: INTRODUCTION

Note: See Appendix A for a table of abbreviations.

Diabetic macular edema (DME)* is a form of diabetic retinopathy (DR) caused by continued leakage from retinal blood vessels and it is the leading cause of blindness among working-age adults in most developed countries.[1] DME is a complication of diabetes mellitus with high glycosylated hemoglobin (A1C) as one main risk factor.[2,3] DME prevalence ranges from 2.7% to 11.1% among adults who have diabetes†in the US.[4-7] Each year, DME is diagnosed in 0.73% to 2.1% of patients with diabetes.[8-10]

Age-related macular degeneration (AMD) is a medical condition involving damage to the central retina. It is the leading cause of blindness in elderly individuals, especially among Caucasians. AMD has both dry and wet forms, with the wet form considered as advanced AMD. The overall prevalence of neovascular AMD (i.e., wet form) in the United States in 2000 was 1.5% or 1.75 million people; however, this is expected to increase to 2.95 million in 2020.[11,12] Among patients older than 43, the 1-year incidence of early and advanced AMD is 0.95% and 0.21%, respectively.[13]

DME and AMD result in increased medical costs and lost productivity due to vision loss, which could be burdensome to patients, employers, and payers. One study compared the costs between DR patients with a control group of non-DR patients with

* Note: A list of abbreviations is provided on p.97.

† When using the word 'diabetes', it refers to both type 1 and type 2 diabetes.

diabetes. The authors found that DR patients had significantly ($p<0.0001$) higher costs than the control group ($18,218 and $11,898, respectively) and this difference was larger among DME vs. non-DME subgroups ($28,606 and $16,363, respectively).[14] Another study using Medicare data found that DME is a significant ($p<0.0001$) independent predictor of medical costs and that it leads to 31% higher 1-year costs and 29% higher 3-year costs when compared to non-DME patients with diabetes.[15] The annual direct cost of AMD has been estimated at US $575-733 million per year.[16] One study found that Medicare payments for AMD have increased from $3,567 per person in 1994 to $5,991 per person in 2006. The authors also reported that the overall cost will increase as the elderly population increases, leading to higher numbers of diagnosis in the future.[17]

Although ranibizumab (Lucentis®; Genentech) was approved by the FDA to treat AMD in 2006 and DME in 2012, bevacizumab (Avastin®; Genentech) has been used as an off-label treatment option for both AMD and DME. However, efficacy and safety of bevacizumab have not been fully understood. Study comparisons of efficacy between bevacizumab and ranibizumab suggest no difference in first year and second year visual acuity (VA) outcomes. Regarding safety, bevacizumab seems to have higher adverse event rates compared to ranibizumab, but the results are inconclusive.[18-20] With bevacizumab, the risk of gastrointestinal perforations, surgery, wound healing complications, and hemorrhage is elevated, which is noted in the black-box warning. One review summarized that more thromboembolic events and nonocular hemorrhaging were detected in patients treated for AMD.[21]

Post-marketing surveillance is important in detecting safety signals after approval. However, due to the off-label nature of bevacizumab, there is no pharmacovigilance program to collect this information. Most of the previous studies were conducted within clinical trial settings, which do not typically reflect actual practice or patient medication taking behaviors. Thus, it is important to assess safety and effectiveness of bevacizumab through observational studies. This study will use Texas Medicaid data to examine the safety, effectiveness, and cost of medications used to treat AMD and DME in a nonelderly underserved population.

Chapter 2: LITERATURE REVIEW

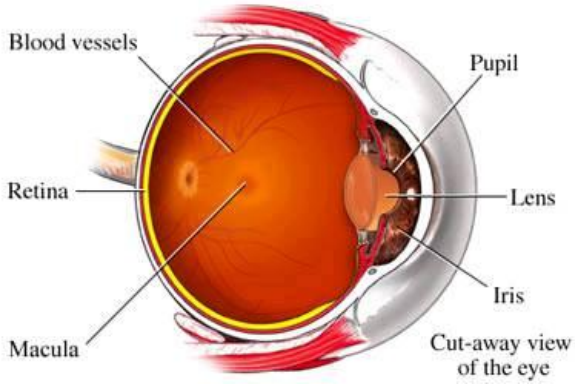
2.1 CHAPTER OVERVIEW

This chapter provides an overview of DME and AMD disease definition, epidemiology, disease progression, as well as risk factors. DME and AMD as disease states will be described separately, followed by cost, treatment, and treatment-associated problems (including treatment safety, effectiveness, and treatment status), where DME and AMD will be discussed together. In addition, the rationale for this study and the objectives will be provided at the end of this chapter. Prior to describing each disease state in detail, a brief explanation of the similarities and differences between DME and AMD are as follows:

1) Both are macular conditions that cause vision loss and a significant financial burden.
2) DME involves leakage of fluids into the center of the macula, whereas AMD occurs when cells in the macula break down (dry form) or abnormal blood vessels grow under the macula (wet form), causing leakage (Figure 2.1).
3) DME progresses from diabetic retinopathy (DR), which is a complication of diabetes, whereas AMD usually occurs in individuals 50 years old and over, but it is not necessarily associated with diabetes.

4) Both of the conditions can be treated with laser photocoagulation, photodynamic therapy, and anti-vascular endothelial growth factor (VEGF) injections. Note: these will be discussed in more detail in section 2.5.3.

Figure 2.1 Diagram of the eye



The diagram of the eye showing macula and blood vessels

Source: http://www.retinabatonrouge.com/images/Eye%20Anatomy.jpg

2.2 DIABETIC MACULAR EDEMA

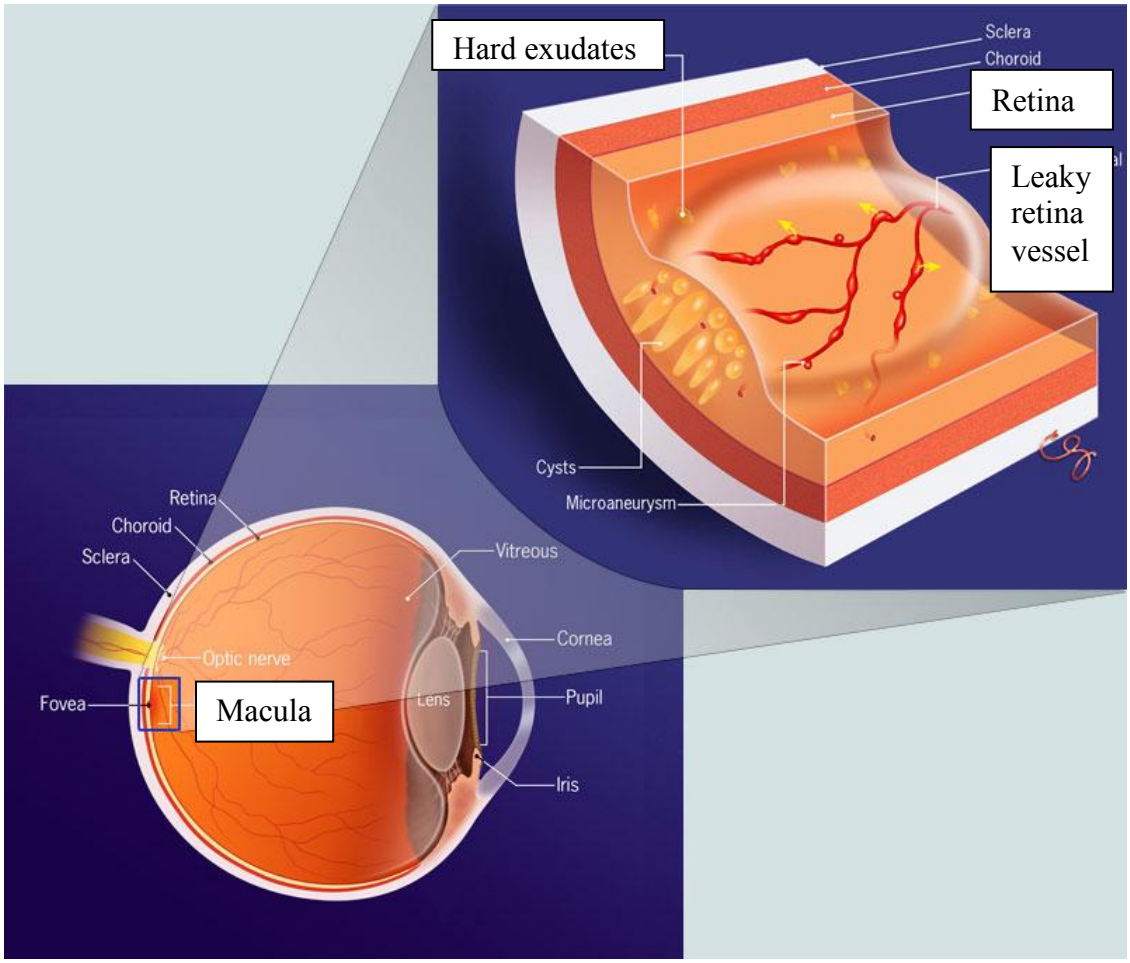
2.2.1 Definition of diabetic macular edema

Diabetic macular edema (DME), diabetes retinopathy (DR), and clinically significant macular edema (CSME) are all terms used when describing macular edema. DME is a common complication of DR caused by continued leakage from retinal blood

vessels and it is the leading cause of blindness in most developed countries among working-age adults (ages 20 to 44).[1] The leakage from retinal blood vessels causes accumulation of excess extracellular fluid in the macula, disruption of the blood-retina barrier, and abnormal permeability, which are associated with increased levels of vascular endothelial growth factor (VEGF).[22] Figure 2.2 shows the diagram of eye when DME is present. DME can develop at any stage of DR. DME is a type of DR, and DR is one of the most common complications in patients with diabetes and one of the most debilitating disorders of microvasculature of the retina.[23]

Another condition associated with DME is CSME. CSME is the threshold level at which laser photocoagulation, a procedure that is used to treat DME, is warranted. CSME refers to the clinical diagnosis of any one of the following criteria: 1) retinal thickening within 500 μm of the macular center; 2) hard exudates within 500 μm of the macular center with adjacent retinal thickening; or 3) one or more disc diameters of retinal thickening, part of which is within one disc diameter of the center of retina.[24] For the purposes of this study, the focus will be DME. However, because of scant literature, Chapter 1 will include studies on DR and CSME because DME patients are sometimes grouped together with them.

Figure 2.2 Diagram of diabetic macular edema



The diagram shows leaky retinal vessel, swelling macula, thickening retina and hard exudates.

Source: http://treatmydme.com/images/What-is-DME-image-large.jpg

2.2.2 Epidemiology of diabetic macular edema

In this section, prevalence and incidence of DME, as well as vision loss due to DR and DME will be reported. Because DME is developed from DR, some brief statistics of DME are reported as a subset of DR and vision threatening diabetic retinopathy (VTDR) (which includes severe DR, proliferative DR, and CSME). DME prevalence has been reported in several studies and it ranges from 2.7% to 11.1% among adults with diabetes in the US (Table 2.1). According to the Wisconsin Epidemiological Study of Diabetic Retinopathy (WESDR) 1980-1982, DME prevalence among younger onset diabetes patients (≤ 30 years old) and older onset diabetes patients (> 30 years) was 11.1% and 8.4%, respectively.[4] The Eye Diseases Prevalence Research Group estimated the prevalence of VTDR among diabetes (8.2%) and the general population (0.75%) in 1999.[5] During 2002-2004, Wong et al. estimated the prevalence of DME to be 9% among patients with diabetes. African Americans (11.1%) and Hispanics (10.7%) have a significantly higher (p=0.007) prevalence of DME than whites (2.7%) and Asians (8.9%).[6] A more recent study by Zhang et al. in 2010 showed that prevalence of VTDR and CSME was 4.4% and 2.7%, respectively, among adults with diabetes in the US.[7] Population differences, such as age, race, and the diagnosis of diabetes, help to explain these prevalence ranges.

Studies have reported on the 1-year incidence of DME, ranging from 0.73% to 2.1% among patients with diabetes (Table 2.2). Leske et al. estimated the 9-year incidence of CSME to be 8.7% (0.97%/year) among patients with diabetes based on the

Barbados Incidence Study of Eye Diseases I (1992-1997) and II (1997-2003).[8] The WESDR study published in 1989 reported the 4-year incidence of DME to be 8.2% (2.05%/year) in the younger group (≤ 30 years) among patients with diabetes. The incidences were 8.4% (insulin user: 2.1%/year) and 2.9% (non-insulin user: 0.73%/year) in the older group (>30 years).[9] A later WESDR study published in 1995 estimated the 10-year incidence of DME to range from 10% and 14% (1.0% -1.4%/year), respectively, in Americans with diabetes.[10]

DR and DME are major causes of vision loss in patients with diabetes. The prevalence of vision loss among patients due to DR was 3.7% between 1999 to 2002 and 5.3% between 2005 to 2008.[25] DR accounts for 12,000 to 24,000 new cases of blindness every year.[14] The 14-year incidences of visual impairment and blindness due to DR were 12.7% and 2.4%, respectively among patients with type 1 diabetes.[10] Vision loss can occur rapidly, with more than half of DME patients losing two or more lines of visual acuity within 2 years.[26]

Table 2.1 Prevalence of diabetic macular edema

Study/Author	Year	Population	DME%[a]	CSME%	VTDR%
WESDR[4]	1980-1982	Diabetes, Wisconsin ≤ 30 yrs old (onset)	11.10%	5.90%	N/A
		Diabetes, Wisconsin > 30 yrs old (onset)	8.40%	7.50%	N/A
Eye Diseases Prevalence Research Group[5]	1999	Diabetes	N/A	N/A	8.20%
		General population	N/A	N/A	0.75%
	2020	General population	N/A	N/A	1.02%
Wong et al.[6]	2002-2004	Diabetes, all races	9%	5.6%	N/A
		African Americans	11.1%	7.5%	
		Hispanics	10.7%	6.9%	
		White	2.7%	2.0%	
		Asian	8.9%	3.0%	
Zhang et al.[7]	2005-2008	Diabetes, ≥ 40 yrs old, all races	N/A	2.7%	4.4%;
		Non-Hispanic Black			9.3%
		Non-Hispanic White			2.7%
		General population, ≥ 40 yrs old	N/A	0.4%	0.6%

CSME=clinically significant macular edema; VTDR=vision threatening diabetic retinopathy; WESDR= Wisconsin Epidemiological Study of Diabetic Retinopathy

Table 2.2 Incidence of diabetic macular edema

Study/Author	Year	Population	1-year incidence
Leske et al. [8]	1992-2003	Diabetes	0.97%
WESDR [9]	1989	Diabetes (≤ 30 years)	2.1%
		Diabetes (>30 years), insulin user	2.1%
		Diabetes(>30 years), non-insulin user	0.73%
WESDR [10]	1995	Diabetes	1.0% -1.4%

WESDR=Wisconsin Epidemiological Study of Diabetic Retinopathy

2.2.3 Disease progression and risk factors of diabetic macular edema

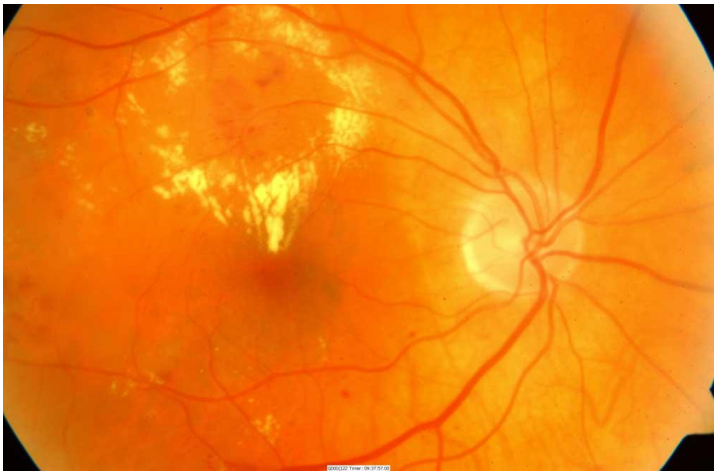
As stated above, DME is a common complication of DR. DR is a progressive disease with the following stages: 1) no apparent DR, 2) nonproliferative DR, and 3) proliferative DR. DME can occur at any stage of DR, but it is more common in the late stage (i.e., stage 3). Approximately half of DR patients develop DME. Vision loss occurs when fluid leaks into the center of the macula, which causes the macula to swell, leading to blurred vision (Figures 2.2, 2.3).[27] If DME is present, it can be categorized into three levels: mild, moderate, and severe. The severity depends on the degree of retinal thickening and whether the hard exudates (fluid that filters from the circulatory system into lesions) were present near the center of the macula (Figure 2.4).[1] The longer the patient has diabetes, the greater the chance of developing DME.[2] In addition, higher

glycosylated hemoglobin levels (i.e., A1C), severe retinopathy, and hypertension are associated with higher 10-year incidence of macular edema.[10]

Figure 2.3 Normal vision and vision loss caused by diabetic macular edema

Source: http://drugdiscoveryopinion.com/images/retinopathy.jpg

Figure 2.4 Exudates in diabetic macular edema



The bright yellow spots are the exudates.

Source: http://www.virginiaretina.org/pix/macular_edema_exudates.jpg

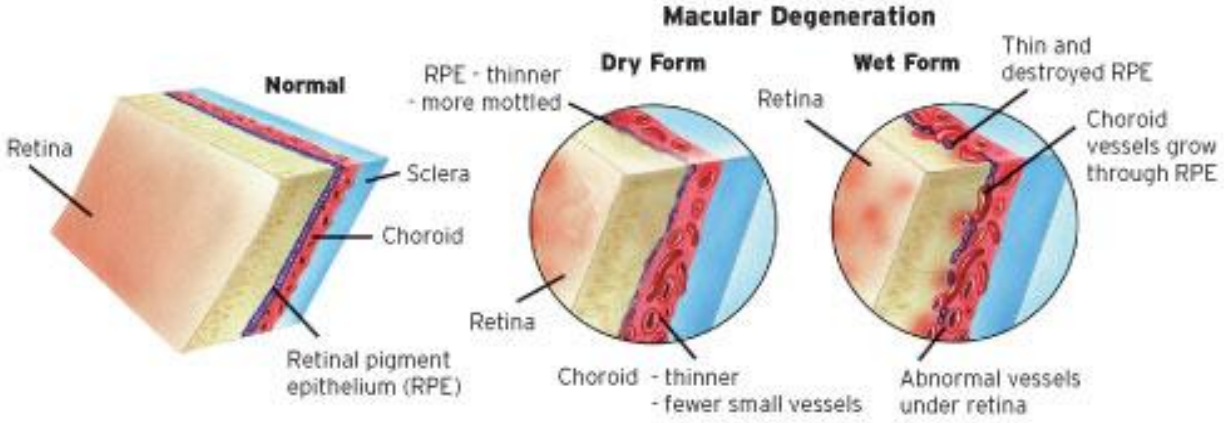
2.3 AGE-RELATED MACULAR DEGENERATION

2.3.1 Definition of age-related macular edema

Age-related macular degeneration (AMD) is a medical condition which occurs when the macula is gradually damaged.[28] The macula is the most sensitive part of retina (Figure 2.1 for a diagram of the eye) and it helps to provide sharp and detailed central vision. Once the macula is damaged, patients have difficulty recognizing faces, driving, and reading, as well as with up close vision. AMD is the leading cause of vision loss among older adults. It has two forms; dry and wet. The dry from and the wet form are also called non-neovascular AMD and neovascular AMD, respectively. The dry form is

caused by the breakdown of the light-sensitive cells in the macula. The wet form is caused by the leakage of blood and fluid from new blood vessels under the macula (Figure 2.5). Figure 2.6 shows a diagram of the eye where deposits of broken down light-sensitive cells can be seen in the dry form and blood leakage can be seen in the wet form.

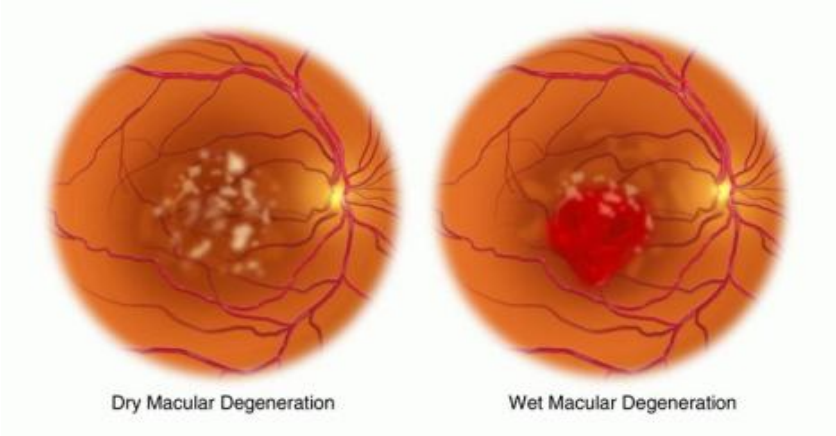
Figure 2.5 Diagram of dry and wet macular degeneration



The graph shows the growing of blood vessels through Retinal Pigment Epithelium (RPE).

Source:http://www.familyhealthonline.ca/fho/growingolder/_images/GO_macular_dia2.jpg

Figure 2.6 Diagram of eye for dry and wet forms of macular degeneration



Dry form: the yellow spots are the deposits of the light sensitive cells

Wet form: the red spots are the leaking blood vessels

Source:http://media.summitmedicalgroup.com/media/db/relayhealthimages/macdeg_2.jpg

2.3.2 Epidemiology of age-related macular edema

AMD mainly affects the older population. It does not necessarily lead to blindness, but vision loss will occur if the disease progresses into advanced AMD. According to the Age-Related Eye Disease Study (AREDS) group, the 1.3 million patients with AMD will develop advanced AMD within 5 years if untreated. This number is expected to double by 2020.[29] This section will report and summarize the prevalence and incidence of AMD.

AMD prevalence differs by age group. The prevalence is 1% in people aged 65-74 years and 5% in those aged 75-84 years. This number increases to 13% in those 85 years and older.[30] Prevalence of early and late AMD among Caucasians older than 40 years was estimated to be 6.8% and 1.5%, respectively.[31] The overall prevalence of neovascular AMD (i.e., wet form) in the US in 2000 was 1.5% or 1.75 million people; however, this is expected to increase to 2.95 million in 2020.[11,12] Thus, depending on the timeframe (i.e., early vs. late), age group, and type (i.e., wet vs. dry), AMD prevalence can range from 1% to 13%. The 15-year cumulative incidence for early and advanced AMD was 14.3% (0.95%/year) and 3.1% (0.21%/year) among patients older than 43 years based on data collected between 1993 to 2005.[13]

2.3.3 Disease progression and risk factors of age-related macular edema

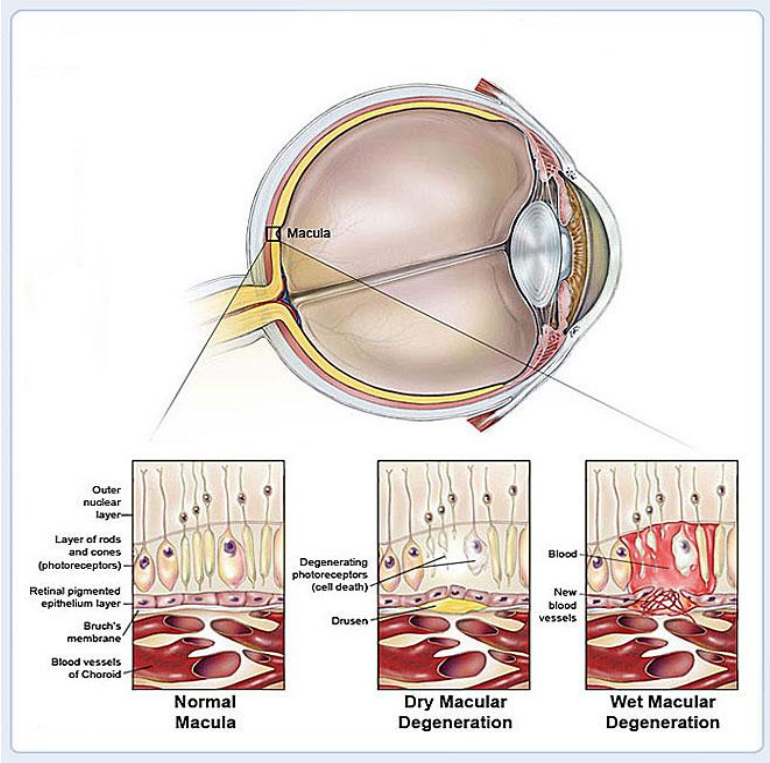
Dry AMD develops before wet AMD and it has three stages; early AMD, intermediate AMD, and advanced dry AMD. The stages are defined by the size and number of drusen, which are the yellow deposits under the retina (Figures 2.6, 2.7). Large areas of drusen lead to disease progression, which indirectly causes vision loss. Patients in early AMD may not have any symptoms or vision loss, but as it progresses into intermediate AMD, some patients will see a blurry spot in their central vision (Figure 2.8). The blurred area increases with advanced dry AMD and it blocks large areas of

straight-ahead vision. Wet AMD is derived from the dry form and can occur at any time during the three stages of dry AMD.[32]

Increasing age is a major risk factor for AMD. In addition, smoking and race are the other important risk factors. Caucasians are more likely to develop AMD than other races. Ocular risk factors include darker iris pigmentation, previous cataract surgery, and hyperopic refraction. Systemic factors, such as obesity, sunlight exposure, and cardiovascular diseases are also risk factors. In addition, evidence exists regarding genetics in the development of AMD. Thus, those with a family history of AMD may be at higher risk.[28]

Vision loss usually occurs in advanced AMD, which includes both advanced dry AMD and wet AMD (Figure 2.7). In general, up to 5% of patients with early AMD will progress to advanced AMD during a 5-year period, and about 15% of patients will progress into the late stage over 15 years. Patients typically lose one to three lines of visual acuity (outcome measure of vision using an eye chart) after 3 months without treatment.[33] In addition, people with advanced AMD in one eye are at higher risk of developing advanced AMD in the other eye. Once vision loss occurs, it is hard to reverse, but treatment can slow or even stop the progression of the disease. In addition to vision loss, patients with AMD have a higher risk of hearing loss.[34] Finally, there is an association between Alzheimer's disease and AMD, but the relationship may be explained because they share a common pathogenic mechanism.[35]

Figure 2.7 Diagram of age-related macular degeneration progression



The dry form shows the degenerating of photoreceptors and the growth of drusen. The wet form shows the growth of the new blood vessels and the leakage of blood.

Source: http://nursingcomments.com/wp-content/uploads/2010/03/separate-mac.jpg

Figure 2.8 Normal vision and vision loss caused by age-related macular degeneration

Source:http://www.doctorsvisioncenter.com/wp-content/uploads/age-related-macular-degeneration1.jpg

2.4 Cost

DME and AMD is often very costly to manage. In addition to healthcare costs, vision loss can have a significant impact on productivity and patient quality of life. As a result, it is important to examine both direct and indirect costs of DME and AMD. The following paragraphs will describe the overall burden, direct costs and indirect costs of DME and AMD.

The burden of vision loss and blindness is tremendous in the US. According to the 2000 census, an estimated 937,000 people were blind and 2.4 million had low vision. AMD is the leading cause of blindness among Caucasians and DR is the leading cause of blindness among working age adults.[11,14] In 1990, the federal government spent $4.1 billion on blindness and the working-age adult group comprised 97% of the total cost.[36] However, in 2004, the overall financial burden of major visual disorders among adults older than 40 years was estimated to be $35.4 billion, much higher than the $4.1 billion in 1990. The $35 billion was composed of $16 billion in direct medical costs, $11 billion in direct non-medical costs, and $8 billion in productivity losses. The burden caused by DR (including DME) and AMD was $493 million and $575 million, respectively. The cost was higher among DME patients between 40 to 64 years old ($298 million) than patients 65 and older ($195 million). The lower cost in the older groups is partly due to the lower number of estimated cases in the older group.[16] The Medicare payment for AMD in 2008 was $724 million, which was an increase from $575 million in 2004.[17] It is likely that new therapies on the market were partially responsible for increases in costs.

2.4.1 Direct cost

Direct cost of DME

The direct annual cost of DME ranges from $11,290 to $28,606 per patient depending on the year and population. Using data from 31 large self-insured companies in the US, Lee et al. compared direct medical costs between employees who were aged

18-64 years with DME and those with diabetes only. Patients with DME had significantly higher annual average costs for hospitalizations ($7,886 vs. $3,551; p < 0.0001), emergency department visits ($247 vs. $139; $p < 0.0001$) and outpatient visits ($10,557 vs. $5,353; $p < 0.0001$).[14] Shea et al. evaluated Medicare beneficiaries' direct medical costs related to DME from 2000 to 2004. Inpatient costs comprised almost half of the total direct costs. The cost prior to diagnosis of DME was 27% lower than the incident year.[15] Medicare payments during the first year of diagnosis increased by $1,630 from the time period between 1991 and 1995, and increased by $1,176 from 1996 to 2000. DR was the most costly eye disease to manage among others (e.g., AMD, cataract, and glaucoma).[37]

Direct cost of AMD

The annual direct cost of AMD ranges from $2,371 to $5,991 per patient in the US. From 1995 to 1999, Coleman et al. assessed Medicare costs for dry AMD and wet AMD. Patients with wet AMD had significantly higher (p<0.001) mean payments ($2,371) over the previous 5 years when compared to the dry AMD group ($1,569) and the control group ($1,428).[38] In a later study, Day et al. evaluated Medicare payments for patients with newly diagnosed AMD and found that the Part B payments had increased significantly from $3,567 in 1994 to $5,991 in 2006 (p<0.01, 73% was due to the increase in eye care expenditures). The payments more than doubled from $1,504 in 1994 to $3,264 in 2006 (p<0.001) due to the increase in the use of anti-vascular endothelial

growth factor (VEGF) injections. Expenditures in the Day et al. study were higher than the Coleman et al. study because Day et al. adjusted to 2008 dollars and included only newly diagnosed AMD patients and Coleman et al. did not exclude previously treated patients.[17] As anti-VEGF therapy became more popular in treating AMD, a study estimated the cost of anti-VEGF injections based on the 2008 Medicare Part B claims among AMD patients. The annual payments by Medicare were $20 million for bevacizumab and $537 million for ranibizumab, when 64.4% of the patients received bevacizumab and 35.6% received ranibizumab.[39]

2.4.2 Indirect cost

Indirect cost is an important part of the overall cost for DME and AMD. Indirect costs are usually composed of lost productivity for the patient, unpaid caregiver (e.g., family, friend), and the loss of productivity due to premature mortality. As mentioned earlier, the productivity loss of visual disorders among adults older than 40 years was estimated to be $8 billion, with $6.3 billion in decreased workforce participation and $1.73 billion in decreased wages.[16] Cruess et al. estimated productivity loss, aides/home modifications, and the value of lost well-being to be $4.4 billion, $305 million, and $11.7 billion among patients with vision loss in Canada in 2007. The indirect cost per patient was $19,370.[40]

Lee et al. reported that indirect costs account for a substantial cost difference in employees with and without DR (cost difference=$1,174, $p < 0.0001$). The indirect costs of DME and non-DME patients were $5,091 and $1,819, respectively (significance not

reported).[14] Indirect costs for AMD have not been well studied because AMD patients are usually beyond working age, so their lost productivity is difficult to estimate. Indirect costs are usually incurred by caregivers of AMD patients. Schmier et al. estimated that the annual caregiver cost of AMD patients ranged from $225 to $47,086 depending on the severity of vision loss and using an average caregiver pay at $15.65/hour. The cost increased when visual acuity worsened.[41] A study estimated the annual indirect cost of AMD to be £449 per patient in UK ($711US).[42] To date, no studies exist estimating the indirect cost of AMD in the US. Brown et al. examined the annual loss in gross domestic product (GDP) due to AMD and found that it totaled to $1.24 billion due to wage reduction and $1.63 billion due to unemployment in the US. [43] In general, vision loss resulting from DMD/AMD could lead to potential burden to patients and their families. Further studies are needed to estimate the indirect costs of DME/AMD and the benefit gained from prevented vision loss.

Summary

Overall, vision loss and blindness caused by DME and AMD result in a significant burden to society, payers, and patients. The current literature has mostly evaluated direct costs from Medicare or private insurance data. DME seems to have higher costs compared to AMD perhaps due to additional costs related to treating diabetes. Comparing the cost between patients with DME and those with diabetes and no DME and evaluating the cost of DME and AMD in different populations may provide useful information for health care professionals and payers.

2.5 CLINICAL GUIDELINES AND TREATMENT

2.5.1 Diagnosis

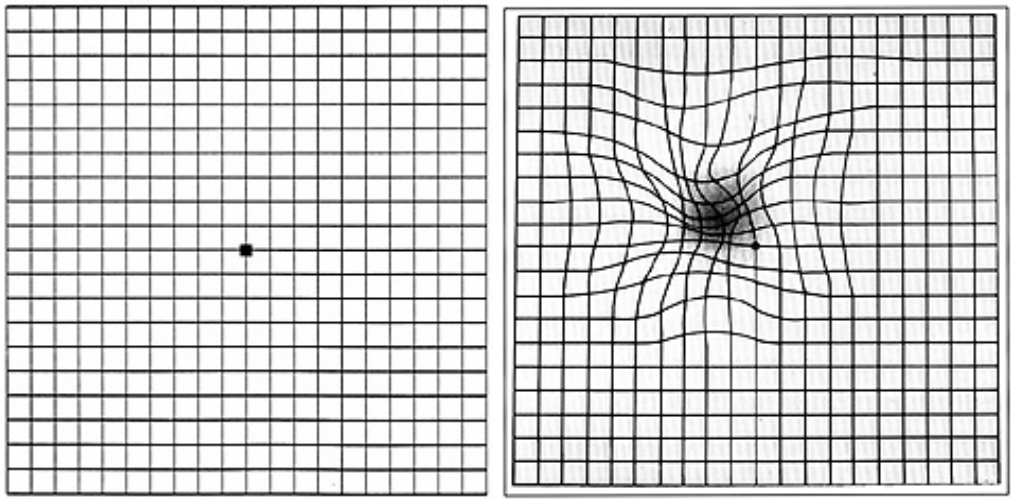
When diagnosing DME and AMD, the following are conducted: 1) eye examinations (visual acuity tests and slit-lamp biomicroscopy); 2) diagnostic testing using optical coherence tomography (OCT), fluorescein angiography (FA), and fundus autofluorescence (FAF) imaging; and 3) medical, family, and smoking history. In this section, eye examination and diagnostic tests will be explained. Terms used in these examinations and tests are also used in research and cost calculations.

Eye exams

Slit-lamp biomicroscopic examination is an important procedure used in diagnosing DME and AMD. The anterior eye structures as well as the retina can be accessed through the slit-lamp fundus stereo biomicroscopy. This was the standard clinical procedure for determining the need for focal laser photocoagulation exams. The American Academy of Ophthalmology (AAO) guidelines recommend using slit-lamp biomicroscopy to detect choroidal neovascularization (CNV).[44] However, slit-lamp biomicroscopic is a less objective and sensitive in detecting DME compared to OCT, which is currently more widely used.[45] OCT will be discussed in detail in the diagnostic tests section.

The most obvious symptom of DME/AMD is vision loss, including decreased visual acuity and blurry or distorted near vision, especially for patients with AMD. However, vision loss cannot be the only method used to detect AMD. This is because individuals could have AMD, but they may not show any sign of decreased vision, especially in the early stage. An Amsler grid exam is often used to detect vision loss. (Figure 2.9)

Figure 2.9 Amsler grid exam



What an Amsler grid normally looks like	What an Amsler grid looks like to patients with AMD

Source: http://www.nei.nih.gov/health/maculardegen/amsler_grid.gif

Diagnostic tests

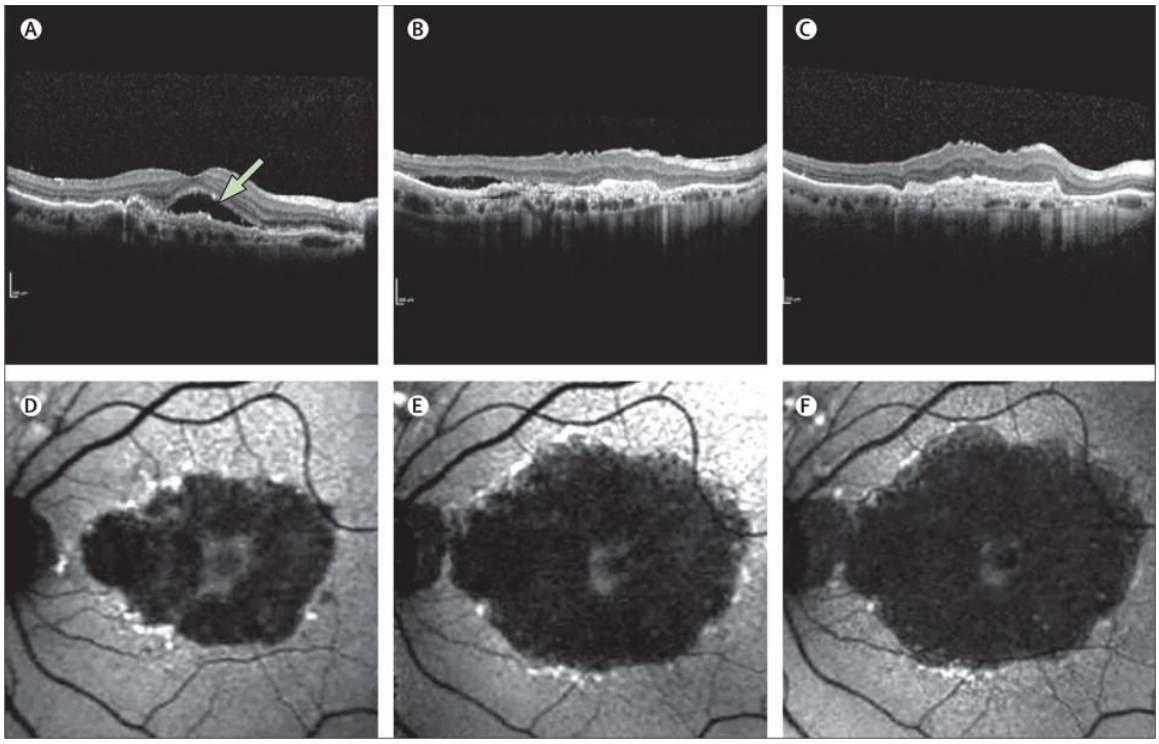
As a review, DME is signaled by macula thickening and fluid leakage. AMD, on the other hand, is characterized by geographic atrophy (dry form) and subretinal fluid or hemorrhage (wet form). Geographic atrophy and drusen are early signs of AMD. As AMD progresses, drusen will grow and then get absorbed, followed by the growth of new blood vessels and the leakage of blood through the retinal pigment epithelium (RPE).

Two procedures, OCT and FA, are commonly used when diagnosing and making retreatment decisions. [56,57] OCT assesses the anatomical features of the retina and FA assesses the physiological aspects of disease progression.[46] It has been recommended to use OCT to determine the presence of subretinal fluid and the degree of retinal thickening and to use FA to detect the existence of CNV.[44] OCT shows a cross-sectional outline of the neovascular choroidal neovascularisation complex (Figure 2.10).[47] The images from OCT help clinicians monitor and evaluate the neovascular membranes for any thickening and leakage.[48-50] Retinal thickness larger than 300 μm can be detected by experienced examiners. It is a very sensitive technique for quantifying macular thickness in patients with DME as well as AMD. [48-51] FA, on the other hand, is used to detect leaking microaneurysms in DME. It is also used to detect drusen growth as well as leakage of blood through RPE in AMD. To be more specific, FA is able to detect drusen, RPE atrophy, choroidal neovascular membranes, serious pigment epithelial detachments, and

subretinal fibrosis or scars (staining defects). A yellow dye (fluorescein) is injected intravenously and photographs are taken to assess the chorodial and retinal blood flow.

FAF imaging is a diagnostic test with growing popularity. It is used to map the occurrence of fluorophores in the retina. It is increasingly used to detect geographic atrophy (dry form AMD), which is characterized by areas of decreased autofluorescence signaling and increasing dark areas of geographic atrophy (Figure 2.10).[52]

Figure 2.10 Imaging from OCT (A-C) and FAF imaging (D-F)



OCT=optical coherence tomography; FAF=fundus autofluorescence
A- C: The OCT images showing the change in subretinal fluid during the course of anti-VEGF treatment. (A: untreated; B: treatment in progress; C: treated)
D- F: FAF images showing the enlargement of geographic atrophy (dark areas) with the reduced autofluorescence signal in the progression of AMD.
Source: http://ars.els-cdn.com/content/image/1-s2.0-S0140673612602827-gr3.jpg

Another method used in the diagnosis of AMD is indocyanine green angiography (ICGA). This test procedure uses a different intravenous dye from fluorescein angiography, which improves identification and characterization of neovascular variants of AMD. It is recommended in diagnosing wet AMD.[53]

History

Besides the eye examination and diagnosis tests, diabetes history (including date of disease onset, use of medication, and A1C level) and other chronic problems such as hypertension and dyslipidemia should be considered when diagnosing DME. Family, medical, and smoking history should all be taken into account in diagnosing both DME and AMD.

2.5.2 Clinical guidelines

In practice, clinical guidelines' recommendations are helpful in making healthcare decisions in diagnosis, treatment, and follow-up. Clinical guidelines are developed based on the highest quality evidence available. Several clinical guidelines have been developed over the years to offer guidance in the management of AMD and DME. Commonly used guidelines developed in the US are the Preferred Practice Pattern for Age-Related Macular Degeneration and Preferred Practice Pattern for Diabetic Retinopathy developed by AAO.[44,54] Other commonly used guidelines are Ranibizumab and Pegaptanib for the Treatment of Age-related Macular Degeneration and Ranibizumab for Treating Diabetic Macular Oedema, both of which were developed by the National Institute for Health and Clinical Excellence (NICE).[55,56] The Royal College of Ophthalmologists (ROC) offered further guidelines in the use of ranibizumab in AMD in commencing, continuing, and discontinuing treatment as an addition for the NICE guidelines.[57] Mitchell has developed clinical guidelines for using ranibizumab in treating AMD based on the existing clinical

trials.[58] In this section, the clinical guidelines for AMD will be discussed, followed by DME, with emphasis on the use of anti-VEGF therapy. Recommendations from clinical guidelines can be categorized into three parts: diagnosis, treatment, and follow-up examinations.

Clinical guidelines for AMD

Ranibizumab

Treatment and follow-up recommendations from AAO, NICE, and Mitchell guidelines for ranibizumab are summarized in Table 2.3.[44,55,58] The main recommendations can be summed up with the following: 1) ranibizumab should be administered when subfoveal CNV is present or the best corrected visual acuity (BCVA) is between 6/12 to 6/96 with a lesion ≤ 12 disc areas; and 2) monthly injections should be initiated for 3 consecutive months with monthly follow-up and retreatment if needed. Subsequent follow-up regarding retreatment depends on: 1) ophthalmologist judgment; and 2) patient reported symptoms and results from eye examinations/OCT. Treatment should cease when the disease is not active or if the patient is not responding (deterioration in vision or anatomical damages).

Bevacizumab

Although not approved by the FDA for treating AMD, bevacizumab has been widely used off-label by clinicians around the world. Treatment and follow-up recommendations from guidelines for bevacizumab are summarized in Table 2.4.[44,59] The

AAO has recommended similar treatment and follow-up for bevacizumab as with ranibizumab, which is monthly treatment for 3 months with monthly follow-up. The guideline has recommended that the ophthalmologist should inform the patient of off-label bevacizumab use.[46] Bashshur et al. offered guidelines for retreatment with bevacizumab. Retreatment decisions should occur when patients have: 1) recurrence of subretinal fluid detected by OCT; 2) an increase in central retinal thickness (CRT) by 100μm; 3) a new hemorrhage; 4) a decrease of 5 letters in visual acuity; or 5) an increase in leakage detected by FA or OCT. Follow up examinations should be conducted monthly until the desirable outcomes are achieved.[44,59] Evidence from clinical trials such as CATT and IVAN has demonstrated the efficacy of bevacizumab and provided support for monthly use of bevacizumab.[60,61] Relevant clinical trials will be described in detail in the treatment section.

Most of the cases of subfoveal CNV could be treated with anti-VEGF therapies, but anti-VEGF therapies are not recommended in specific cases. AAO guidelines recommend observation for early AMD and vitamin/mineral supplements for intermediate AMD. In addition, FA or fundus photos tests are not required in these stages. Laser photocoagulation is recommended for extrafoveal CNV (CNV is found between 200 μm and 2500 μm from the geometric center of the foveal avascular zone). Photodynamic therapy (PDT) with verteporfin was recommended for subfoveal CNV in some special cases when the classic component (in contrast to the occult component) is >50% of the lesion.[44]

Table 2.3 Clinical guideline recommendations for treatment of AMD with ranibizumab

	AAO[44]	NICE[55]	Mitchell[58]
Criteria for use	Subfoveal CNV present	BCVA between 6/12 to 6/96; no permanent structural damage of central fovea; lesion size ≤ 12 disc areas in greatest linear dimension; evidence of disease progression:1) blood vessel growth detected by FA; 2) or VA decrease	Subfoveal lesions; Active disease (abnormal retinal thickness detected by OCT, intraretinal or subretinal hemorrhage, increased CNV size detected by FA)
Discontinuation	N/A	Persistent deterioration in VA and detected anatomical changes that indicate non-response to therapy	Structural foveal damage; Confounding severe ocular disease
Treatment regimen	Once a month; Quarterly treatment following monthly injections for 4 months when monthly treatment is not feasible	Initiate with monthly treatment for three month then as needed	Commence treatment immediately after diagnosis; Initiate with at least 3 monthly treatments; monthly treatment recommended after the initial treatment
Follow up	Return for exams 4 weeks after treatment; Inform patients to report adverse events	OCT guided retreatment	Return for exams 4 weeks after treatment; The exam includes VA assessment, slit-lamp fundus and OCT; FA is recommended for patients with vision loss

AMD=age related macular edema; AAO=American Academy of Ophthalmology guidelines; NICE=National Institute for Health and Clinical Excellence guidelines; CNV=chorodial neovascularization; BCVA=best corrected visual acuity; FA=fluorescein angiography; VA=visual acuity; OCT=optical coherence tomography

Table 2.4 Clinical guideline recommendations for treatment of AMD with bevacizumab

	AAO[44]	Bashshur [59]
Criteria for use	Subfoveal CNV present; Inform patients of off-label use.	N/A
Treatment regimen	Administered by intravitreal injection once a month; Quarterly treatment following monthly injections for 4 months when monthly treatment is not feasible.	Provide retreatment when:1) recurrence of subretinal fluid detected on OCT; 2) an increase in CRT by 100μm; 3) a new hemorrhage; 4) a decrease of 5 letters; 5) or an increased leakage detected by FA or OCT
Follow up	Return for exams 4 weeks after treatment. Inform patients to report adverse events.	Monthly until the desirable outcomes are achieved.

AMD=age related macular edema; AAO=American Academy of Ophthalmology guidelines; CNV=chorodial neovascularization; FA=fluorescein angiography; OCT=optical coherence tomography; CRT=central retinal thickness

Clinical guidelines for DME

The relevant guidelines for DME are the Preferred Practice Pattern for Diabetic Retinopathy developed by AAO and the Ranibizumab for Treating Diabetic Macular Oedema developed by NICE.[54,56] Because the progression of DME is highly related to duration of diabetes and A1C level, the AAO guidelines recommend an eye examination schedule for patients with diabetes. For patients with type 1 diabetes, the first eye examination should be scheduled at 3-5 years after diagnosis. The first eye examination for type 2 diabetes patients should be at the same time of diagnosis. A yearly follow-up eye examination is recommended for all the patients with diabetes. The guidelines emphasize the important role of an experienced opthalmologist in: 1) examining the eye; 2) emphasizing blood glucose and blood pressure control; and 3) informing patients about the importance of early diagnosis and treatment.[54]

The AAO guidelines emphasize the following for diagnosis of DR: 1) conduct eye examinations (VA, slit-lamp biomicroscopy, intraocular pressure, peripheral retina, and vitreous exams); 2) use ancillary tests (OCT, FA, and color fundus photography) to make clinical determination; 3) consider medical history, eye examination results, and diagnostic tests when making decisions.[54]

The traditional treatment for CSME has been laser surgery. Focal laser photocoagulation has been recommended with a 2-4 month follow-up examination for CSME. Anti-VEGF therapy has been recommended as an adjunctive treatment to laser

surgery with a monthly follow-up. However, the use of ranibizumab (anti-VEGF treatment) in DME was approved by the FDA in August 2012. A longer time period may be needed for the guidelines to include anti-VEGF therapy as an independent treatment.[54] In the latest version (February 2013) of NICE's guidelines, the use of ranibizumab is recommended as a treatment option for patients with DME with CRT $\geq$ 400 μm.[56] However, the NICE guidelines do not mention the use of the bevacizumab in treating DME.

2.5.3 Treatment

Visual acuity

Prior to describing the various treatment options for DME/AMD, a description of the main vision outcomes will be discussed. Visual acuity is the main outcome measure in DME and AMD clinical trials. VA has also been used to diagnosis DME/AMD, determine retreatment, and measure patient improvement. The LogMAR chart is usually used to measure VA. The chart includes 5 letters per line. Thus, a three line improvement equals a 15-letter improvement, which has been used as an outcome measure in clinical trials. The score is based on the total number of letters read (formula: LogMAR VA=0.1 + LogMAR value of the best line read - 0.02 X (number of letters read)) and the sizes of the letters progress geometrically. As a result, it allows for a greater accuracy compared

to other eye charts. Figure 2.11 provides the LogMAR chart and a conversion scale to other eye charts.

Figure 2.11 LogMAR chart and conversion scale

Source:

http://en.wikipedia.org/wiki/File:LogMAR_chart.jpg

Visual acuity scales			
20 feet (Snellen)	**6 meters (Snellen)**	**Decimal**	**LogMAR**
20/200	6/60	0.10	**1.00**
20/160	6/48	0.125	**0.90**
20/125	6/38	0.16	**0.80**
20/100	6/30	0.20	**0.70**
20/80	6/24	0.25	**0.60**
20/63	6/19	0.32	**0.50**
20/50	6/15	0.40	**0.40**
20/40	6/12	0.50	**0.30**
20/32	6/9.5	0.63	**0.20**
20/25	6/7.5	0.80	**0.10**
20/20	6/6	1.00	**0.00**
20/16	6/4.8	1.25	**-0.10**
20/12.5	6/3.8	1.60	**-0.20**
20/10	6/3	2.00	**-0.30**

Laser photocoagulation

Laser photocoagulation surgery is a procedure in which a laser is used to cauterize ocular blood vessels in an attempt to mitigate damage and remove undesired growth. It is usually performed on an outpatient basis to treat various eye conditions. Laser photocoagulation was the standard treatment for both AMD and DME before anti-VEGF injections become available, and it is still the standard treatment for DME. The wide use of laser photocoagulation in treating DME began in 1985 when the Early Treatment Diabetic Retinopathy Study (ETDRS) showed that laser photo-coagulation can substantially reduce the risk of visual loss among patients with CSME.[24] This result was confirmed by Lee et al. who evaluated long term outcomes of the procedure.[62] The use of laser photocoagulation in treating AMD also began in the 1980s. Several studies have evaluated and confirmed the effect of laser treatment of neovascular AMD.[63,64] Although laser photocoagulation can prevent further vision loss, it has shown little effect in improving vision. It also often causes minor visual field loss in the areas where the laser is used.

Photodynamic therapy

PDT is another type of laser treatment used on selected areas of the retina. Verteporfin (a photosensitizing agent) is injected in the arm and it travels to abnormal vessels in the eye. When the laser is used, verteporfin is activated and it destroys the

neovascular that caused vision damage.[65] The Treatment of Age-related Macular Degeneration with Photodynamic Therapy study described 2-year PDT outcomes. Loss of more than three lines of vision was prevented in two-thirds (67%) of the PDT-treated group,[66] demonstrating that PDT use alone has limitations. A combination of PDT and anti-VEGF therapy, which has been used more frequently recently, will be discussed in detail in the real world studies section.

Anti-VEGF injection therapy

Anti-VEGF is a family of secreted polypeptides (proteins) that plays an important role in normal vascular genesis and angiogenesis. It contains seven members, including VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E, VEGF-F, and a placental growth factor. VEGF-A has always been considered the most important mediator of angiogenesis and vascular leakage in wet AMD and DME.[67] The important isoforms of VEGF-A are 121, 165, 189, and 206, which were named by the number of amino acids formed during alternative splicing processes. VEGF's intraocular neovascularization function is associated with the progression of DME and AMD.[68] An AMD patient's neovascular membrane contains VEGF isoforms VEGF165 and VEGF121, and VEGF blockade can prevent the formation of clinically significant choroidal neovascularization (CNV).[69] The effect of VEGF blockade is supported by animal models.[70,71] Krzystolik et al. found that the incidence of CNV was significantly lower ($p<0.001$) in eyes treated with anti-VEGF

verses the control group in a monkey model.[70] Eyetech Study Group showed an inhibition of 80% of retinal neovascularization when treated with anti-VEGF in a mouse model (p= 0.0001).[71] Three anti-VEGF therapies have been approved by the FDA to treat AMD, with bevacizumab being used off-label (Table 2.5). One anti-VEGF therapy has been approved in the treatment of DME, with three used off-label (Table 2.6).

Table 2.5 Anti-VEGF therapies to treat age-related macular degeneration

Anti-VEGF therapy	Approved status	Dosing frequency	Cost per administration (US $)	Clinical trials	Major outcome
Ranibizumab	FDA Approved (June 2006)	0.5mg/4 weeks	$1950	MARINA,[72] ANCHOR,[73] PIER[74], SAILOR[58]	25% - 41% gained ≥ 15 letters
Bevacizumab	Phase III trials Used as off-label	1.25mg/4 weeks	$42	CATT[60]	Efficacy equivalent to ranibizumab
Pegaptanib	FDA Approved (December 2004)	0.3mg/6 weeks	$507	VISION[75]	70% lost ≤ 15 letters
Aflibercept	FDA Approved (November 2011)	2mg/3 monthly injections, then bimonthly	$1850	VIEW1,2[76]	Equivalent to monthly ranibizumab

Table 2.6 Anti-VEGF therapies to treat diabetic macular edema

Anti-VEGF therapy	Approved status	Dosing frequency	Cost per administration (US $)	Clinical trials	Major outcome
Ranibizumab	FDA Approved (August 2012)	0.3mg/4 weeks	1950	RISE,RIDE[77]	RISE:44.8% gained ≥ 15 letters RIDE: 33.6% gained ≥ 15 letters
Bevacizumab	Phase II trials Used as off-label	1.25mg/4 weeks	507	DRCR[78]	37% showed central subfield thickness reduction of 11%
Pegaptanib	Phase II trials Used as off-label	0.3mg/6 weeks	42	MDRS[79]	18% gained ≥ 15 letters
Aflibercept	Phase II trials Used as off-label	2mg/ 3 monthly injections then bimonthly	1850	DA VINCI[80]	23.8% - 45.5% gained ≥ 15 letters

Clinical trials: Efficacy and safety of anti-VEGF therapies

Pegaptanb

Pegaptanib (Macugen®; Eyetech Pharmaceuticals) was the first approved anti-VEGF to treat AMD. It is an aptamer (a single strand of nucleic acid) that targets VEGF165.[81] The effect of pegaptanib was compared with sham injection (control), and no difference ($p=0.12$) was found regarding the proportion of patients who gained ≥ 15 letters.[79] However, in the VISION study, a higher percentage of patients who received pegaptanib 0.3 mg injections lost ≤ 15 letters compared to control (70% vs 55%, $p<0.001$).[75] Although pegaptanib was not directly compared to traditional therapies in this study, its efficacy is similar to laser coagulation and PDT because the patterns of vision decline are similar. A possible explanation for this is pegaptanib selectively binds to only VEGF165, and not to any of the other available isoforms.[65] As a result, pegaptanib may not have a competitive advantage over other therapies used to treat AMD and DME. Clinical trials among patients with DME are ongoing and clinical guidelines do not recommend its use. Thus, it will not be included in treatment comparisons in this study.

Aflibercept

Aflibercept (Eylea®, Eyetech®) is an anti-VEGF treatment that was approved (November, 2011) by the FDA to treat AMD. It is a fusion protein that binds all VEGF isoforms. The VEGF binding is claimed to be tighter than any of the other therapies

available.[65] VIEW1 and VIEW2 are phase III clinical trials that compared aflibercept with ranibizumab on efficacy and safety. The results have shown that aflibercept has similar efficacy as ranibizumab. In VIEW1 and VIEW2, aflibercept and ranibizumab had similar protective effects on vision (VIEW1: 95.1% vs 94.4%; VIEW2: 95.6% vs 94.4%). The proportion of patients who gained ≥ 15 letters were also similar between aflibercept and ranibizumab (VIEW1: 37.5% vs 30.9%; VIEW2: 29.4% vs 34.0%). The number of adverse events did not differ between ranibizumab and afibercept. Both of the treatments were well tolerated and no evidence of dose-response adverse events was found.[76]

Aflibercept may be a potential anti-VEGF treatment for DME. Ongoing clinical trials are comparing its efficacy with traditional therapy. The phase II clinical trial, DA VINCI, showed that after aflibercept treatment, the proportion of patients who gained ≥ 15 letters was much higher in the aflibercept group compared to control group (i.e., laser treatment group) (42.2% vs 14.0%, $p<0.005$). The visual acuity gain was also higher than the control group ($p<0.001$).[80] However, further studies should be conducted to provide evidence on the efficacy of aflibercept in treating DME. Because it was just recently approved for AMD in 2011 and it is in phase II trial for DME, it will not be included in this study.

Ranibizumab

Ranibizumab (Lucentis®; Genentech) is a high-affinity humanized binding fragment that neutralizes all isoforms of VEGF-A. Therefore, it has an obvious advantage compared to pegaptanib, which only binds to VEGF165.[82] It was designed to completely

neutralize VEGF-A in the microenvironment of central neovascular lesions even when the ratio of inhibitor to VEGF is low in order to minimize the frequency and number of injections needed.[82] The high affinity leads to high selectivity and longer biological activity in the eye. Pharmacokinetics results have shown that ranibizumab remained biologically active for 1 month after a single injection. The serum levels of the drug were 1,000 to 2,000 fold lower than the ocular levels so the systemic adverse events are expected to be low.[83]

Ranibizumab was approved by the FDA for the treatment of wet AMD in June 2006. Its effect on improving visual acuity has been supported by clinical trials. The injection not only prevented further vision loss, it also improved vision acuity. Summarizing the clinical trials findings, 25% - 41% of patients treated with ranibizumab gained ≥ 15 visual acuity letters. [72,74,84] Several studies have compared ranibizumab with sham injection (control). The MARINA study (phase III clinical trial) found that 24.8% to 33.8% of patients in the treatment group improved ≥ 15 letters, compared to 5% in the sham-injection group ($p<0.001$).[72] In another phase III clinical trial (PIER), compared to sham injections, higher percentages (78.3% to 82.0%) of ranibizumab treated patients lost <15 letters during the 2 year trial ($p<0.0002$).[74] Several studies have examined ranibizumab safety. Results from SAILOR have revealed a death incidence of 0.7% to 1.5% and a stroke rate of 0.6% to 1.2%.[58] The long term (3-year) safety of ranibizumab was evaluated by the SECURE study, retinal hemorrhage (12.8%), cataract (11.5%), hypertension (9.0%), and nasopharyngitis (9.0%) were the most frequent adverse events.[84] However, no new safety issues were identified.

Combination therapy (PDT with anti-VEGF) has its advantages in treating AMD. To compare combination therapy with traditional treatment (PDT), several clinical trials have been conducted.[73,85] The FOCUS study compared visual acuity outcomes of ranibizumab+PDT versus PDT alone. Among ranibizumab+PDT treated patients, the visual acuity was 12.4 letters higher than patients treated with only PDT ($p<0.05$).[85] The 2-year results from the ANCHOR study showed the majority (89.9% to 90%) of ranibizumab+PDT treated patients lost < 15 letters and more than one-third (34% to 41%) of patients gained ≥ 15 letters ($p<0.0001$).[73] Another study from the ANCHOR research group has used the National Eye Institution Visual Function Questionnaire-25 (NEI VFQ-25) to compare patient reported outcomes between ranibizumab and PDT. Patients using ranibizumab had a higher improvement in NEI VFQ-25 scores than patients treated with PDT (8.1 vs 2.2, $p<0.001$).[86]

Ranibizumab was approved to treat DME in August 2012. RISE and RIDE are phase III clinical trials for ranibizumab conducted on patients with DME. The visual acuity improvement (proportion of patients who gained ≥ 15 letters) of ranibizumab (0.3mg) was significantly higher than sham injection (RISE: 44.8% vs 18.1%, $p<0.0001$; RIDE: 33.6% vs 12.3%, $p<0.0001$, respectively). Although 0.3mg is the only approved dose, ranibizumab (0.5mg) also showed better improvement compared to control in the clinical trials (RISE: 39.2% vs 18.1%, $p<0.001$; RIDE: 45.7% vs 33.6%, $p<0.0001$).[77] Because ranibizumab was recently approved (2012) to treat AMD and because of preliminary data review has revealed small sample sizes, it will not be included in this study.

Bevacizumab

Bevacizumab (Avastin®; Genentech) is also a humanized variant of anti-VEGF antibody, which binds all VEGF isoforms. The antibody targets VEGF and suppresses the tumor growth by prohibiting the formation of abnormal blood vessels.[87] VEGF binding also reduces neovascularization in the eye, which makes bevacizumab an ideal candidate for the treatment of AMD and DME. However, the VEGF affinity of bevacizumab is 5 to 20 fold lower than ranibizumab.[82] Bevacizumab was initially developed as an anti-cancer agent and FDA approved to treat in metastatic colorectal cancer, metastatic breast cancer, and non-small cell pulmonary cancer. Bevacizumab has been used off-label for treating AMD and DME.[88] It is more widely used than ranibizumab in practice because of its lower cost compared to ranibizumab (approximate annual cost: $504 vs. $23,400, respectively).

Outcomes of ranibizumab and bevacizumab have been compared in several other clinical trials with mixed results.[60,61,89,90] Overall, the efficacy of bevacizumab and ranibizumab does not seem to differ. The CATT study compared efficacy and safety between bevacizumab and ranibizumab and the results suggested no significance difference in visual acuity outcomes during the first and second years (difference in letters gained: 1.4, p=0.21).[60] Similar to the results from the CATT study, Biswas et al. did not detect any difference in visual acuity between bevacizumab and ranibizumab (letters gained: 3.96 vs 3.56, p=0.563).[90] According to the IVAN study, the ranibizumab

group gained 1.99 more letters than the bevacizumab group, but the result was non-significant.

Bevacizumab has a much longer half-life than ranibizumab (20 days vs 0.5 days), which could lead to more ocular and systemic adverse events.[44] Bevacizumab had a higher adverse event rate in the CATT study. Safety results on death rate, myocardial infarction, and stroke showed no difference between ranibizumab and bevacizumab, but the proportion of serious adverse events was generally higher for bevacizumab.[60] However, other studies did not show any difference. [60,61,89,90] Further research is needed to specify the relationship between adverse events and the VEGF blockade effect of bevacizumab. More studies are needed to provide further evidence for the efficacy and safety of bevacizumab in treating AMD.

Regarding bevacizumab in treating DME, the evidence is even more limited. Bevacizumab is superior to traditional therapy (e.g. laser coagulation) in treating DME according to the phase II clinical trial DRCR. The DRCR study compared efficacy between bevacizumab and laser coagulation. They found that after being treated with bevacizumab (1.25mg), patients had a greater reduction in central subfield thickness (CST) at 3 weeks compared with laser treatment (-35μm vs. +21μm p=0.009). Bevacizumab treated patients also experienced a 1-line improvement in visual acuity (letters gained: -2 vs +5, p=0.01).[78]

Summary

Among the above four anti-VEGF injections, bevacizumab is the most commonly used treatment due to its low cost and satisfactory efficacy. However, there are safety concerns of bevacizumab because it has a longer half-life and its risk in gastrointestinal perforations, surgery and wound healing complications, and hemorrhage has been noted in black-box warning when it is used in oncology treatment. In addition, there is no post-marketing safety monitoring due to the off-label use in DME and AMD. As a result, the safety and effectiveness of bevacizumab in treating DME and AMD remains unclear.

2.6 PROBLEMS ASSOCIATED WITH TREATMENT AND OBSERVATIONAL STUDIES

Efficacy and safety of anti-VEGF treatments used in clinical trials were reviewed in the last section. However, there is a gap between the outcomes in clinical settings and real world settings. This section will review the problems associated with treatment and summarizes existing observational studies.

2.6.1 Treatment effectiveness and safety

Effectiveness

Visual acuity improvement, visual impairment and blindness avoided are the common outcomes measurements of effectiveness for anti-VEGF therapies. Two studies

have supported the effectiveness of anti-VEGF therapies as well as combination therapies in the real world settings. Gupta et al. found both loading dose group and as needed group of ranibizumab treatment achieved satisfactory outcomes in improving visual acuity (proportion of patients who gain ≥ 15 letters: 29.8% vs 12.9%, $p<0.01$) among patients with AMD.[91] The combination of PDT and anti-VEGF therapies has been commonly used. The two types of therapies have distinctive mechanisms but may result in the complementary effects even when the number of treatments is reduced. The effect of combination therapy was supported by Kaiser et al. in a retrospective database study. At 1-year follow-up, as many as 36% of patients gained ≥ three lines (15 letters).[92] A study by Bressler et al. showed that monthly ranibizumab treatment for 2 years would reduce legal blindness as well as visual impairment by 72% and 37%, respectively. [93]

Safety

Safety of anti-VEGF treatment can be categorized into ocular safety and systemic safety. The main ocular complications reported for the anti-VEGF therapies are risk of endophthalmitis (inflammation of the internal coats of the eye), retinal tear or detachment, uveitis (uvea inflammation), and vitreous hemorrhage. The main systemic safety problems are related to cardiovascular effects (i.e., hypertensive emergencies, hypertension, arterial thrombembolic events), nonocular hemorrhaging, and gastrointestinal perforations (as the result of hemorrhaging). [21,94]

Ranibizumab and bevacizuamb are both VEGF inhibitors. One of the main functions of VEGF inhibitors is promoting vascular homeostasis, and the inhibiting of it would cause coagulation cascade and the activation of platelets, which will increase the risk to arterial thromboembolic events (ATEs).[94,95] The systemic adverse events were first detected from the use of bevacizumab among patients with cancer. Although there is blood-ocular barrier prohibiting the transmission of the medication into systemic circulation, the barrier is always damaged among patients with neovascular disease.[96] As a result, the systemic safety of anti-VEGF injections should be of concern. Because AMD patients are generally older and DME patients usually have had diabetes for a relatively long time, AMD and DME patients are already at risk for cardiovascular events. Thus evaluating safety of anti-VEGF therapy is of particular importance.[97,98] However, the safety concern of ranibizumab and bevacizumab should be examined differently. Unlike bevacizumab, a full-length recombinant antibody, ranibizumab is an antibody fragment that has a much shorter systemic elimination half-life (2 hours vs 20 days).[94] As a result, the systemic safety concern is higher for bevacizumab. In addition, concern has been raised, especially for bevacizumab in treating DME. Because of its off-label use, there is a lack of safety information from clinical trials and observational studies.

Safety of anti-VEGF treatment has been evaluated in several observational studies. Ocular complications of anti-VEGF injections are relatively low, but still higher than adverse event rates of patients without anti-VEGF. A review combined the results of both RCTs and non-RCTs regarding ocular complications among ranibizumab patients and showed the rates of vitreous hemorrhage, retinal tear, endophthalmitis, retinal

detachment, uveitis, and traumatic lens damage were 8.0%, 2.1%, 1.9%, 1.5%, 1.3%, and 0.4%, respectively, among patients treated with anti-VEGF.[12,46,69,70,89] Day et al. calculated the rate of ocular complications per injection. The rates of endophthalmitis, uveitis, and vitreous hemorrhage per injection are 0.09%, 0.11%, and 0.23%, respectively, during the 2-year follow-up.[99] However, the intravitreal injection technique, not the medication itself, is more likely to be responsible for the ocular adverse events.

As for systemic adverse events, a higher risk of thromboembolic events and nonocular hemorrhaging were detected in anti-VEGF treated patients.[21] This trend is supported by several clinical studies which reported an increased risk of adverse events in the treatment group.[72-74] In general, according to both real world studies and clinical trials, the adverse events rates are higher in anti-VEGF treated patients. Thus, treatment decisions regarding anti-VEGF injections should be made with caution.[73,99] Adverse event rates were higher among bevacizumab users than ranibizumab users.[100,101] A chart review has shown that bevacizumab users have almost a 10 times higher chance of developing ATEs compared to ranibizumab users (12.4% vs 1.4%, $p<0.0001$).[100] Curtis et al. showed that ranibizumab has a lower hazard of mortality (0.85, $p<0.01$) compared to bevacizumab using Medicare data.[101] The higher rate of cardiovascular adverse events among bevacizumab users is also supported by the CATT study 2-year results, which showed a higher risk of systemic adverse events for bevacizumab users.[60]

As for DME, ranibizumab has demonstrated its safety in clinical trials, but little is known regarding safety of bevacizumab due to the lack of clinical trials and head to head comparisons.[102] Observational effectiveness and safety studies are even more limited.

Summary

As mentioned earlier, ranibizumab and bevacizuamb are both VEGF inhibitors. One of the main functions of VEGF inhibitors is to promote vascular homeostasis, and the inhibiting of it would cause coagulation cascade and the activation of platelets, which will increase the risk to arterial ATEs and hemorrhage.[21,94,95] The existing literature has indicated the potential cardiovascular and hemorrhagic risk of bevacizumab may be higher than ranibizumab.[100,101] In addition, due to the off-label nature of bevacizumab, safety information cannot be detected through pharmacovigilance surveillance. As a result, retrospective claims data may be a valuable source for collecting safety information of bevacizumab, especially for DME.

2.6.2 Treatment status

Treatment status of AMD

How anti-VEGF therapies were used in the practice remained unknown until the Curtis et al. study. To evaluate the recent growth in the use of anti-VEGF therapies in treating AMD, Curtis et al. examined the use of laser photocoagulation, photodynamic therapy, and anti-vascular endothelial growth factor (VEGF) injections (e.g., pegaptanib, ranibizumab, and bevacizumab) among Medicare beneficiaries 1 year after diagnosis. While anti-VEGF injection use increased significantly ($p<0.001$) from 2006 (60.3%) to 2008 (72.7%), PDT and laser treatment use decreased (12.8% to 5.3% and 5.5% to 3.2%, respectively) over the same time period.[103] Although bevacizumab was used off-label to treat AMD, it was more commonly used than ranibizumab in treating newly diagnosed AMD patients (54.0% vs 26.1% in 2008). In 2008, a higher percentage of patients switched from ranibizumab to bevacizumab (13.6%) than from bevacizumab to ranibizumab (7.9%). Over 2 years (2006 to 2008), bevacizumab use increased by 39.9%, while use of ranibizumab remained the same. However, use of first FDA approved anti-VEGF therapy, pegaptanib, decreased dramatically by 93.8%.[103] However, this is the only study found comparing the use of anti-VEGF injections with other treatment therapies. Further information is needed regarding the selection of treatment in real practice.

Treatment status of DME

However, in treating DME, laser is still the most frequently used therapy. Petrella et al. used the Southwestern Ontario database to evaluate treatment characteristics of patients with visual impairments due to DME. Only 15%-18.2% of the patients received anti-VEGF monotherapy while 53.4%-69.4% of the patients received laser monotherapy. The proportion of patients with laser-anti-VEGF combination therapy (7.8%-12.9%) was lower than the laser monotherapy.[104] To our knowledge, little research based on US data has been conducted to evaluate the characteristics of anti-VEGF therapy, especially for treating DME.

2.7. DIABETES MANAGEMENT AND EARLY DIAGNOSIS

2.7.1 Management of diabetes and DME

As mentioned earlier, the duration of diabetes and high A1C levels are two major risk factors of DME. Prevention and DME clinical course depends heavily on the management of diabetes. The level of blood glucose (A1C) is positively related to the degree of visual impairment. In a retrospective Canadian study, patients with visual impairment had a higher A1C level (7.6±2.2 vs 6.3±0.3, p value not reported).[104] Keeping blood glucose levels under control will reduce the risks of developing retinopathy, as well as slow the progression of the disease.[105,106]

Care for patients with DME usually starts with a general practitioner who makes a diabetes diagnosis. Only a small proportion of patients with diabetes have been referred by their primary care physicians to ophthalmologists.[107] As a result, patients were not treated early enough or did not have an opportunity to be treated at all, even though there are available and effective treatments. After patients have been referred to an ophthalmologist, it is important that the ophthalmologist provides counseling regarding the importance of maintaining A1C levels. In addition, vision rehabilitation and social services should be recommended to patients with serious vision loss. Overall, it is very important for both primary care providers and ophthalmologists to understand the importance of diabetes management in DME disease progression. Optimal outcomes can only be achieved by cooperation among health care providers and patients.

2.7.2 The importance of early diagnosis and treatment

Early detection of the DME depends on educating patients and healthcare providers. Although diabetes cannot be prevented with healthy diet and exercise in some cases, DME progression could be avoided or moderated with prevention and screening.

Patients with diabetes should be encouraged to have annual eye exams. AAO guidelines recommend that people with type 2 diabetes receive a dilated eye examination at the time of diagnosis followed by annual exam.[54] So far, the status of eye exams among patients with diabetes is far from satisfactory. Based on several studies, 38% to

66% of the patients with diabetes reported that they did not receive an eye exam in the previous year.[108-110] The Los Angeles Latino Eye Study found that 64% of the patients with type 2 diabetes did not have a dilated eye exam in the previous year of study and 36% never had an exam.[108] Schoenfeld et al. found that two-thirds of the patients did not have any eye exams in the past 12 months.[109] According to the National Committee for Quality Assurance's Health Plan Employers Data Information Set System, the proportion of patients who did not receive annual eye examination among patients with diabetes was 45%, 38%, and 49% for participants in commercial health plans, Medicare, and Medicaid, respectively. [110]

Early diagnosis of DME is also challenged by the diagnosis of diabetes. The onset time of type 2 diabetes is hard to determine. As a result, proper patient education and eye exam could be delayed by the diagnosis of diabetes. Immediate referral to the ophthalmologic at the time of diagnosis is especially important. Early diagnosis of AMD is very important too. Vision loss will occur in the first month of diagnose if untreated[74,111] The size of subfoveal CNV will grow at the speed of 10 μm per day without any proper treatment.[112] The vision loss of control group in the PIER clinical trial seemed to be the worst during the first month.[74] The rapid decline in vision when untreated was also detected by a retrospective multicenter study in Spain.[111]

2.8. STUDY RATIONALE AND OBJECTIVES AND HYPOTHESES

Vision loss and blindness can greatly reduce patients' quality of life. DME and AMD can burden patients both economically and mentally. Although bevacizumab is one

of the most commonly used treatments for DME and AMD, there are concerns regarding safety and effectiveness due to its off-label use. The literature regarding safety and effectiveness of using bevacizumab in DME is even more limited than AMD and no study has compared the use of this drug between DME and AMD patients. DME and AMD patients have different characteristics and should be treated differently. It is important to compare the safety and effectiveness of bevacizumab between DME and AMD patients and provide insight regarding use of bevacizumab in treating DME and AMD.

As a result, this study will compare the safety and effectiveness of bevacizumab users and nonusers among DME and AMD patients in order to provide more information regarding the use of bevacizumab. The direct medical costs will be compared between DME and DME control patients (patients with diabetes but no DME) to estimate incremental DME costs.

To our knowledge, no study has been conducted using Texas Medicaid data to: 1) compare direct medical costs between DME and non-DME patients with diabetes among the nonelderly (<65 years old) and 2) assess costs associated with AMD in a relatively younger population (40-65 years old). In addition, little is known regarding the safety and effectiveness of anti-VEGF therapies in real world settings, especially for bevacizumab. This study will be the first one to use Texas Medicaid data to examine the cost of AMD and DME and the safety and effectiveness of bevacizumab. The study objectives are:

1) To determine if demographic and clinical characteristics differ among DME and AMD patients.

- $H_{1a:}$ There is no significant difference in age among DME and AMD patients.
- $H_{1b:}$ There is no significant difference in gender among DME and AMD patients.
- $H_{1c:}$ There is no significant difference in race among DME and AMD patients.
- $H_{1d:}$ There is no significant difference in Charlson Comorbidity Index among DME and AMD patients.
- $H_{1e:}$ There is no significant difference in total number of medications used among DME and AMD patients.
- $H_{1f:}$ There is no significant difference in number of laser treatments used among DME and AMD patients.
- $H_{1g:}$ There is no significant difference in number of bevacizumab treatments used among DME and AMD patients.

2) To determine if the *risk of cardiovascular/hemorrhagic events* differs by bevacizumab use among DME and AMD patients, while controlling for covariates.

- $H_{2a:}$ There is no significant difference in *risk of cardiovascular/hemorrhagic events* between bevacizumab users and nonusers among DME and AMD patients, while controlling for covariates.
- $H_{2b:}$ There is no significant difference in *risk of cardiovascular/hemorrhagic events* by the number of bevacizumab treatments among DME and AMD patients, while controlling for covariates.
- $H_{2c:}$ There is no significant difference in *time to first cardiovascular/hemorrhagic* between bevacizumab users and non-users among DME and AMD patients, while controlling for covariates.

3) To determine if the *risk of visual impairment* differs by the bevacizumab use among AMD and DME, while controlling for covariates.

- $H_{3a:}$ There is no significant difference in *risk of visual impairment* between bevacizumab users and nonusers among AMD and DME patients, while controlling for covariates.
- $H_{3b:}$ There is no significant difference in *risk of visual impairment* by the number of bevacizumab treatments among AMD and DME patients, while controlling for covariates.

4) To determine if *direct medical costs* differ between DME and DME control patients, while controlling for covariates.

- H_4: There is no significant difference in direct medical costs between DME and DME control patients, while controlling for covariates.

5) To describe direct medical costs of patients with AMD.

Chapter 3 METHODS

The study methodology will be provided in detail in this chapter. The following topics will be discussed in order: study design and data source (inclusion criteria, study design, data collection); study variables (dependent and independent variables); and statistical analytical methods (statistical tests, sample size calculations).

3. 1 INSTITUTIONAL REVIEW BOARD APPROVAL

This study was reviewed by the Institutional Review Board (IRB) of The University of Texas at Austin (IRB protocol number: 2013-02-0014) on 02/18/2013. The IRB review and oversight was waived because the study was not considered to involve human subjects. De-identified secondary data was used.

3.2 STUDY DESIGN AND DATA SOURCE

3.2.1 Inclusion/exclusion criteria

Texas Medicaid recipients who met the following eligibility criteria were included:

1) 18-63 years of age at the index date;

2) Continuously enrolled 1 year pre- and post-index; also continuously enrolled 1 year pre- and post- treatment for subjects in objectives 2 and 3.

3) For the DME control cohort and DME cohort: have a diagnosis of diabetes during the 12 months pre-index period (International Classification of Disease, Ninth Revision, Clinical Modification [ICD-9-CM] code 250.xx);

4) For the DME cohort: have a diagnosis of diabetic macular edema (ICD-9-CM 362.07), cystoids macular edema (ICD-9-CM 362.53), or retinal edema (ICD-9-CM 362.83) during the selection period (09/01/08-12/31/11);

5) For the AMD cohort: have a diagnosis of exudative senile macular degeneration (ICD-9-CM 362.52), serous detachment of retinal pigment epithelium (ICD-9-CM 362.42), or hemorrhagic detachment of retinal pigment epithelium (ICD-9-CM 362.43) during the selection period.

For the DME and AMD cohorts, patients with a pre-index diagnosis of DME or AMD will be excluded. Patients diagnosed with both DME and AMD will also be excluded. Patients will be excluded from the DME control cohort if they have a diagnosis for any retinal disorder (ICD-9-CM 362.xx). Because bevacizumab is also used to treat metastatic colorectal cancer, non-small cell lung cancer, metastatic renal cell carcinoma, and glioblastoma with progressive disease, patients with those diagnoses at any point during the pre- and post-index periods will be excluded. Because ranibizumab has only recently been approved to treat DME in 2012, patients treated with ranibizumab will be excluded from the study. Peptanib and aflibercept users will be excluded because they comprised only on a very small number of patients who used the medication during the study period. Table 3.1 summarizes the relevant ICD-9-CM codes used to form the cohorts.

Table 3.1 Relevant ICD-9-CM codes for the study cohorts

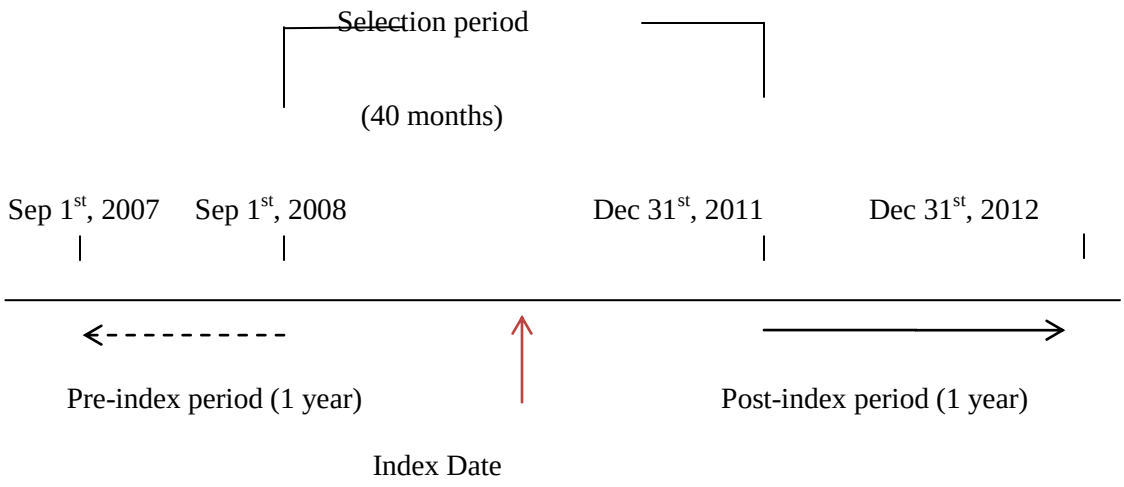
Disease State	ICD-9-CM
DME	Diabetic macular edema (362.07) Cystoids macular edema (362.53) Retinal edema (362.83)
DME control	Diabetes (250.xx)
AMD	Exudative senile macular degeneration (362.52) Serous detachment of retinal pigment epithelium (362.42) Hemorrhagic detachment of retinal pigment epithelium (362.43)

3.2.2 Study design

This is a retrospective secondary database analysis utilizing nonelderly Texas Medicaid recipients. The study has three cohorts: DME cohort, DME control cohort, and AMD cohort. The subjects in the DME cohort must have a DME diagnosis and diabetes during the selection period (Sep 1st 2008-Dec 31st 2011). The index date is the date of the earliest claim with a diagnosis of DME during the selection period. In the control cohort, subjects have been diagnosed with diabetes but have no evidence of retinal disorder throughout the pre- and post-index periods. The index date for the control cohort was chosen randomly during the selection period. In the AMD cohort, the index date is the date of the earliest claim with a diagnosis of AMD in the selection period (Figure 3.1).

For objectives 2 and 3, a treatment date and a 1-year pre- and post- treatment period were used. Treatment date is the date of the first bevacizumab injection during the post-index period.

Figure 3.1 Data extraction and patient selection period



3.2.3 Data source

Medicaid is a health program that offers healthcare benefits to low-income individuals. The federal government has established general guidelines for the program, but each state has its own requirements. It is administrated by each state with supervision from the Centers for Medicare and Medicaid Services (CMS). State Medicaid programs are mandated to provide basic healthcare services to those who are qualified to enroll and there is no restriction to the number of people that can be enrolled.[113]

The Texas Medicaid program covered 4.5 million Texas residents in 2009, representing 13% of the adult population (age 19-64) and 13% of the disabled population (people under age 65 who are reported as eligible due to a disability.) Texas Medicaid provides both acute care and long term care to enrollees, which includes physician services, lab and X-ray tests, inpatient/outpatient services, and home health and personal care. [114]

3.2.4 Data collection

Data from Texas Medicaid were extracted from September 1, 2007 to December 31, 2012. Data from September 1, 2008 to December 31, 2011 was used to identify the patients (selection period). Prescription claims over a 2-year period were analyzed (1 year pre-index and 1 year post-index) (Figure 3.1). Data for patients receiving Supplemental Security Income (SSI) was also collected for DME, DME control, and AMD patients during the same time period.

3.3 STUDY VARIABLES

3.3.1 Dependent variables

The study dependent variables are: 1) cardiovascular/hemorrhagic risk; 2) visual impairment; and 3) direct medical costs. Each of the variables is described in detail below. Table 3.2 lists the dependent variables and their operational definitions.

Table 3.2 Dependent variables

Dependent Variables	Operational definition
Cardiovascular/ hemorrhagic risk (Obj. 2)	Diagnosed with any of the following diseases during the post-treatment period (incident cases): *Cardiovascular* • Hypertension • Proteinuria • Heart failure • Arterio thrombotic event: ▪ Myocardial infarction ▪ Cerebrovascular accident • Venous thrombotic event *Hemorrhagic* • Subarachnoid hemorrhage • Intracerebral hemorrhage • Other hemorrhage: ▪ Duodenal ulcer hemorrhage ▪ Gastric ulcer hemorrhage ▪ Gastrointestinal hemorrhage ▪ Rectal hemorrhage • Gastrointestinal fistula • Gastrointestinal perforation
Visual impairment (Obj. 3)	Patients who were blind, had vision impairment, visual disturbances, or low vision, or receiving SSI due to blindness
Direct medical cost (Obj. 4&5)	Direct medical cost in DME, DME control, and AMD cohorts during 1-year1-year post-index period, adjusted to 2013 US dollars 1) Medical services cost: hospital inpatient stay, emergency department visits, outpatient visits and other services 2) Prescription medication cost

AMD=age-related macular degeneration; DME=diabetic macular edema; PDT=photodynamic therapy; SSI=Supplemental Security Income; VEGF=vascular endothelial growth factor

Cardiovascular/hemorrhagic risk

As mentioned earlier, bevacizuamb is an anti-VEGF inhibitor. Its use causes a coagulation cascade and the activation of platelets, which increases the risk of arterial thromboembolic events (ATEs) and hemorrhage.[21,94,95] The risk of cardiovascular and hemorrhagic events will be examined together in this section because they both are induced by VEGF receptor inhibition.

Patient claims associated with cardiovascular/hemorrhagic events were identified using the ICD-9-CM codes listed in Table 3.3 which were derived from clinical trials, observational studies and literature reviews.[18,21,100,101] Only incident cardiovascular post-index events were included (i.e., had no pre-treatment events). Cardiovascular/hemorrhagic events were coded dichotomously (yes/no) in the post-treatment period. Diagnoses were derived from inpatient and outpatient data.

Table 3.3 ICD-9-CM codes for cardiovascular and hemorrhagic events

Cardiovascular/hemorrhagic events		ICD-9-CM
Cardiovascular		
Hypertension		401 – 405
Heart failure		428.xx
Proteinuria		791.0x, 593.6
Arterio-thrombotic event:	Myocardial infarction	410.xx
	Cerebrovascular accident	432-434, 436.xx
Venous thrombotic event		415.xx, 451.xx, 453.xx
Hemorraghic		
Subarachnoid hemorrhage		430.xx, 852.0, 852.1, 852.2, 852.3
Intracerebral hemorrhage		431.xx
Other Hemorrhage	Duodenal ulcer hemorrhage	532.xx
	Gastric ulcer hemorrhage	531.xx
	Gastrointestinal hemorrhage	578.xx
	Rectal hemorrhage	569.3
Gastrointestinal fistula		569.81, 537.4
Gastrointestinal perforation		530.4, 531.1, 531.2, 531.5, 531.6, 532.1, 532.2, 532.5, 532.6, 533.1, 533.2, 533.5, 533.6, 534.1, 534.2, 534.5, 534.6, 557.x, 562.x, 540.x, 569.83

Visual impairment

Only incident visual impairment post-index events were included (i.e., had no pre-index or pre-treatment events). Two methods were utilized. First, diagnoses were examined in the post-index period and patients having ICD-9-CM codes of 368.xx (visual disturbances) or 369.xx (blindness and low vision) were identified. Second, the SSI data were also linked with patient records to identify patients' disability status. The category of Assistance Code is a five-category code indicating the reason for receiving SSI, with code 4 indicating blindness (Table 3.4).

Table 3.4 ICD-9-CM codes and SSI status for patients with visual impairment

Visual impairment	Code
Blindness, low vision	ICD-9-CM: 368-369
Receiving SSI due to blindness	Category of Assistance Code: 4

SSI=Supplemental Security Income

Direct medical cost

Direct medical costs refer to the medical service costs and prescription medication costs during the post-index period. They were summed for DME, DME control, and AMD cohort. Medical services costs include hospital inpatient stay, emergency department visits, outpatient visits and other services. Prescription costs include all the costs of prescription prescribed in the 1- year post-index period.

In addition to the direct medical cost, we also calculated the disease related cost of DME and AMD. Disease-related costs include the cost related to diabetes and DME/AMD. To be counted as diabetes-related inpatient cost, the claim must have had a header or admission diagnosis of 250.xx. A header diagnosis of 250.xx was used to identify diabetes related outpatient cost. Diabetes-related prescription medication costs refer to the cost of the anti-diabetic medications. The following AHFS codes were used to identify anti-diabetic medications: metformin (682004), sulfonylureas (682020), thiazolidindiones (682028), insulin (682008), miscellaneous, antidiabetic agents (682092). The costs related to DME/AMD refer to imaging, treatment, and ophthalmologist visits related to the treatment of DME/AMD during the post-index period. Other medical services costs include hospital inpatient stay, emergency department visits, outpatient visits and other DME/AMD services. Please see Table 3.5 for the relevant Current Procedural Terminology [CPT] codes for diagnosis and treatment procedures. The ophthalmologist visits codes are usually composed of two parts. The evaluation and management (E/M) service codes (99201-99215) and examination codes (92002-92014). New patients typically have E/M codes ranging from 99201 to 99205 and eye examination codes are either 92002 or 92004. Established patient E/M codes range from 99211 to 99215 and eye examination codes are 92012 and 92014. To be included in the DME/AMD-related cost, the medical claim must have had a diagnosis of DME/AMD as well as a CPT/HCPCS code indicating ophthalmologist visit or treatments.

Table 3.5 Current Procedural Terminology [CPT] codes for treatment procedures

Procedure	CPT Code
Flourescein angiography (FA)	92235
Optical coherence tomography (OCT)	92135 (02/10/2006 - 12/31/2010); 92134 (01/01/2011 - present)
Fundus autofluorescence photography (FAF)	92250
Laser photocoagulation	67220, 0017T
Photodynamic therapy (PDT)	67221, 67225
Intravitreous (anti-VEGF) injections	67028
Ophthalmologist visit	99201 - 99215; 92002 – 92014

VEGF=vascular endothelial growth factor

3.3.2 Independent variables

The main independent variables were bevacizumab use (yes/no) and number of bevacizumab treatments. Several covariates, such as disease state (DME, DME control, AMD), demographics (age, gender, and race), Charlson Comorbidity Index (CCI) score, total medication use, and laser or photodynamic treatments were also included in the study. Table 3.6 lists the independent variables and their operational definitions.

Table 3.6 Independent variables

Independent variables		
Bevacizumab use		0=Nonuser 1=User
Number of treatments		The total number of bevacizumab treatments in the post-treatment period
Covariates		
Disease state		Disease state at index date 0=DME control (diagnosed with diabetes, no retinal disorder) 1=DME (diagnosed with DME) 2=AMD (diagnosed with AMD)
Demographics	Age	Age at index date
	Gender	0=Male 1=Female
	Race	1=White 2=Black 3=Hispanic 4=Asian 5=American Indian 6=Unknown
Carlson Comorbidity Index Score		The sum of weights related to each comorbidity condition at index, used as a matching criteria
Total medications used		Total number of unique medications taken at index date
Number of laser therapies		Total number of laser therapies during the 1-year post-index period

Bevacizumab use and number of bevacizumab treatments

This study only examined the use of bevacizumab because ranibizumab was recently approved to treat DME in 2012 and peptanib and aflibercept were used only on a very small number of patients during the study period. For patients in the DME and AMD cohort, bevacizumab users were identified and the number of bevacizumab treatments was calculated. A dichotomous variable (bevacizumab user vs. nonuser) and a continuous variable (number of bevacizumab treatments) were used to describe the use of bevacizumab. The Healthcare Common Procedure Coding System (HCPCS) is a classification system developed to reimburse inpatient and outpatient services. The HCPCS codes were used to identify the type of anit-VEGF injection. For example, if bevacizumab injection was used in the ophthalmologist office for treating AMD, a code of J9035 together with an intravitreous injection procedure code 67028 would be coupled together in the database (See Table 3.7).

Table 3.7 HCPCS[a] codes for the anti-VEGF injections

	J code	Effective date	Dose	Payment amount	Code name	Other relevant codes
Bevacizumab	J3490	06/30/2006 – 12/31/2009	0.25 mg	$1-$100	Unclassified drugs	Intravitreous injection procedure 67028; Injection of bevacizumab Q2024 (6/30/2006 - 12/31/2009), C9257 (1/1/2010- present)
	J3590	06/30/2006 – 12/31/2009	0.25 mg	$1-$100	Unclassified biologics	
	J9035	06/30/2006 – present	10 mg	-	Cancer	
Ranibizumab	J3490	06/30/2006 - 12/31/2007	0.1 mg	$1500-$2000	Unclassified drugs	Intravitreous injection procedure 67028
	J3590	06/30/2006 - 12/31/2007	0.1 mg	$1500-$2000	Unclassified biologics	
	J2778	01/01/2008- present	0.1 mg	-	Ranibizumab	
Pegaptanib	J2503	01/01/2006- present	0.3mg	-	Pegaptanib	Intravitreous injection procedure 67028; Injection of pegaptanib S0198 (07/01/2005 - present)
Aflibercept	J3490	11/18/2011 - 12/31/2012	0.1 mg	$1500-$2000	Unclassified drugs	Intravitreous injection procedure 67028; Injection of aflibercept Q2046 (11/18/2011 - present)
	J3590	11/18/2011 - 12/31/2012	0.1 mg	$1500-$2000	Unclassified biologics	
	J0178	01/01/2013- 12/31/2012	1 mg	-	Aflibercept	

[a] Healthcare Common Procedure Coding System

Disease state

Patient disease states were identified using the ICD-9-CM codes in Table 3.1. DME control patients had a diagnosis of diabetes during the selection and pre-index periods. Patients with any retinal disorder were excluded. DME patients were diagnosed with DME during the selection period and had a diagnosis of diabetes on or 1-year prior to the index date. AMD patients were diagnosed with AMD during the selection period. As mentioned previously, patients diagnosed with both DME and AMD were excluded.

Charlson Comorbidity Index score

Comorbidity is an important covariate in our study. The comorbidity scores are usually used in claims database studies to measure disease severity. This can be conducted by measuring the degree of comorbid conditions (CCI score or the number of prescription medications (Chronic Disease Score (CDS)). Because this study uses medical claims with diagnosis data, the CCI was used to measure disease severity. The CCI was developed as a method for classifying comorbid conditions which are related to the mortality risk.[115] Common comorbid conditions, such as myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, liver disease, diabetes, renal disease, malignancy, and acquired immunodeficiency syndrome (AIDS), were assigned with weight and included in the calculation. Several adaptations have been made to the original CCI. Deyo et al. adapted a clinical comorbidity index based on ICD-9-CM and procedure codes.[116] It has

been commonly used in administrative database studies.[17,116] The index score ranges from 0-37, where 0 represents no comorbidity and 37 represents highest degree of comorbidity. Table 3.8 shows the CCI with the Deyo adaption, which was used in our study. Table 3.8 shows a list of disease states and their corresponding weights in calculating the CCI. ICD-9-CM and procedure codes were used to identify the disease states in the Medicaid database. The CCI is based on the disease states for each subject and the corresponding weights. For example, a person with chronic pulmonary disease (weight=1) and metastatic solid tumor (weight=6) would have a CCI of 7.

Table 3.8 Charlson Commorbidity Index with Deyo adaptations.[115,116]

Comorbid Conditions	Weights	Deyo adaptations
Myocardial infarction	1	410-410.9, 412*
Congestive heart failure	1	428-428.9
Peripheral vascular disease	1	441-441.9*, 443.9*, 785.4*, V43.4*, procedure 38.48
Cerebrovascular disease	1	430- 438*
Dementia	1	290.0-290.9*
Chronic pulmonary disease	1	490-496*, 500-505*, 506.4*
Rheumatologic disease	1	710.0-710.1*, 710.4*, 714.0-714.2*, 714.81*, 725*
Ulcer disease	1	531-534.9, 531.4-531.7, 532.4-532.7, 533.4-533.7, 534.4-534.7,
Mild liver disease	1	571.2*, 571.4-571.49*, 571.5*, 571.6*
Diabetes	1	250.-250.3*, 250.7*
Diabetes with chronic complications	2	250.4-250.6*
Hemiplegia or paraplegia	2	342-342.9*, 344.1*
Moderate or severe renal disease	2	582- 582.9*, 583-583.7*, 585*, 586*, 588-588.9*
Any tumor	2	140-172.9, 174-195.8, 200-208.9
Leukemia	2	
Lymphoma	2	
Moderate or severe liver disease	3	572.2-572.8*, 456.0-456.21*
Metastatic solid tumor	6	196-199.1
AIDS	6	042-044.9

* The codes with an asterisk were included in the calculation if listed during or prior to index admission; Other codes are included in the calculation only if recorded prior to the index admission.

Participant demographic and clinical characteristics

Patient characteristics (age, gender, and race) were extracted from the data and coded as shown in Table 3.6. The total number of medications refers to the total number of unique medications taken at index date. Patients treated with laser therapy were identified and the total number of laser treatments was counted during the post-treatment period.

3.4 STATISTICAL ANALYSIS

Statistical Analysis System (SAS) version 9.2 was used for data analysis. All analyses were two tailed and the significance level was set at $p<0.05$. Frequency tests and histograms were used to examine distributions and detect outliers. Propensity scoring technique (caliper matching approach) was used to match 1) bevacizumab users and non-users; 2) DME and DME control cohorts. Descriptive statistics, chi-square, t-test and Wilcoxon tests were used to address Objectives 1 and 5. Logistic and Cox regression analyses were used to address Objectives 2 and 3. Cost comparisons (Objective 4) were conducted using generalized linear models with gamma distributions. The following table shows the statistical tests used for each objective and hypothesis included in this study (Table 3.9).

Table 3.9 Study objectives/hypotheses and the according statistical analysis tests

Objectives/ hypotheses	Dependent variables	Measurement level	Independent variables	Measurement level	Statistical analysis
Objective 1: To determine if demographic and clinical characteristics differ among DME and AMD patients.					
H_{1a}: There is no significant difference in *age* among DME and AMD patients.	Age	Continuous	Disease state (DME/AMD)	Nominal	Descriptive statistics and t-test
H_{1b}: There is no significant difference in *gender* among DME and AMD patients.	Gender	Nominal			Descriptive statistics and chi-square test
H_{1c}: There is no significant difference in *race* among DME and AMD patients.	Race	Nominal			Descriptive statistics and chi-square test
H_{1d}: There is no significant difference in *Charlson Comorbidity Index* among DME and AMD patients.	Charlson Comorbidity Index	Continuous			Descriptive statistics and t-test
H_{1e}: There is no significant difference in *total number of medications* used among DME and AMD patients.	Total number of medications	Continuous			Descriptive statistics and t-test
H_{1f}: There is no significant difference in *number of laser treatments* used among DME and AMD patients.	Total number of laser treatments	Continuous			Descriptive statistics and Wilcoxon
H_{1g}: There is no significant difference in *number of bevacizumab treatments* used among DME and AMD patients.	Total number of bevacizumab treatments	Continuous			Descriptive statistics and t-test

Table 3.9 Study objectives/hypotheses and the according statistical analysis tests, cont

Objective 2: To determine if the *risk of cardiovascular/ hemorrhagic events* differs by bevacizumab use among AMD and DME patients, while controlling for covariates.					
H_{2a}: There is no significant difference in *risk of cardiovascular/hemorrhagic events* between bevacizumab users and nonusers among AMD and DME patients, while controlling for covariates.	Cardiovascular/hemorrhagic event	Dichotomous (Y/N)	Bevacizumab use	Dichotomous (Y/N)	Logistic regression
H_{2b}: There is no significant difference in *risk of cardiovascular/hemorrhagic events* by the number of bevacizumab treatments among AMD and DME patients, while controlling for covariates.	Cardiovascular/hemorrhagic event	Dichotomous (Y/N)	Number of Bevacizumab treatments	Continuous	Logistic regression
H_{2c}: There is no significant difference in *time to first cardiovascular/hemorrhagic events* between bevacizumab users and non-users treatments among AMD and DME patients, while controlling for covariates.	Time to cardiovascular/hemorrhagic events	Continuous	Bevacizumab use	Dichotomous (Y/N)	Cox regression

Table 3.9 Study objectives/hypotheses and the according statistical analysis tests, cont

Objective 3: To determine if the *risk of visual impairment* differs by bevacizumab use among AMD and DME patients, while controlling for covariates.					
$H_{3a:}$ There is no significant difference in *risk of visual impairment* between bevacizumab users and nonusers among AMD and DME patients, while controlling for covariates.	Visual impairment	Dichotomous (Y/N)	Bevacizumab use	Dichotomous (Y/N)	Logistic regression
$H_{3a:}$ There is no significant difference in *risk of visual impairment* by the number of bevacizumab treatments among AMD and DME patients, while controlling for covariates.	Visual impairment	Dichotomous (Y/N)	Number of Bevacizumab treatments	Continuous	Logistic regression
Objective 4: To determine whether direct medical costs differ between DME and DME control groups, while controlling for covariates.					
H_4: There is no significant difference in direct medical costs between DME and DME control groups, while controlling for covariates.	Total direct medical cost	Continuous	Disease state DME/DME control	Nominal (Dichotomous)	Generalized linear model with gamma distribution
Objective 5: To describe direct medical costs of patients with AMD.					
	Total direct medical cost	Continuous	N/A	N/A	Descriptive statistics

3.4.1 Statistical analysis assumptions and sample size calculations

In this section, the statistical analysis will be described in more detail, including characteristics, use, and assumptions. The required sample size was calculated for each analysis method and Table 3.10 shows the parameter estimates used to determine sample size. All sample size estimations were based on power=0.80, and α=0.05. Effect sizes varied depending on the tests being conducted. The function forms and link functions of the regression methods are summarized in Table 3.11.

Descriptive statistics

For objective 1, descriptive statistics and ANOVA were used to compare age, Charlson Comorbidity Index, and the total number of medications used among DME, DME control and AMD cohort. To compare gender and race differences among the three cohorts, descriptive statistics and chi-square tests were used. For objectives 4 and 5, descriptive statistics were used to describe the costs of the DME and AMD cohorts.

Logistic regression

Logistic regression was used to address part of objectives 2 and 3. The dependent variable for logistic regression is dichotomous and a logit link function was used to connect the predictors and the response variable. There are no assumptions regarding normality, homoscedasticity, and linearity for logistic regression. However, the

observations should be independent of each other. The sample size need for logistic regression was determined to be 794. (Table 3.10)

Cox proportional regression

Cox proportional regression, a type of survival analyses, was used to address part of objectives 2 and 3. It is a type of survival analysis. The event rate, which was cardiovascular or visual impairment event in this study, was modeled as a log-linear function of predictors. The predictors in this study were treatment status and the covariates. The regression coefficient represents the effect of the treatment status on the time to event. No assumptions are made about the form of baseline hazard because the model is non-parametric. However, two important issues should be addressed before applying the model results. The first issue is non-informative censoring, which requires the reason of censoring not related to the occurring of the event. Another important issue is proportional hazards, which means the hazard functions for any two individuals are proportional at any point in time. For example, if one patient's possibility to have a cardiovascular event is twice of another patient in the beginning, this patient's possibility to have a cardiovascular event is twice of another patient in any later time.

The sample size needed for Cox proportional regression was calculated by PASS 12 software. The sample size was calculated based on a range of cardiovascular/hemorrhagic event and visual impairment rates reported in the literature (range: 0.05-0.3).[19,93] The largest sample size needed was 399. (Table 3.10)

Generalized linear models with gamma distribution

Generalized linear models (GzLM) with gamma distribution were used to address objective 4. For this model, the response variable is positive and right skewed. It has been frequently used to evaluate costs and expenditure data. Generalized linear models with a gamma distribution should meet the same assumptions as the general linear models. A link function reversing or taking the log of the response variable can be used to make the predictor response variable connect in a linear way. The sample size needed for this type of model was 688. (Table 3.10)

Overall, based on all statistical analyses and sample size estimations, the largest sample size needed in this study was 794.

Table 3.10 Sample size estimation [a]

Statistical Analysis Tests	Logistic Regression[b]	Generalized Linear Models with Gamma distribution[c]	Cox-proportional regression[d]
Required sample size	794	688	399

[a] Required sample sizes were calculated using α=0.05, power=0.8
[b] Assuming a Poisson distribution, R^2=0.3, odds ratio of 1.5, and Pr(Y=1|X=1) H_O=0.05
[c] The required sample size will not be higher than the required sample size of multiple regression; thus the multiple regression sample size was used
[d] R^2=0.3, log hazard ratio of 1.5, Pr(Y=1|X=1) H_O=0.05, SD of X=0.5

Table 3.11 Summaries of characteristics of regressions

	Function form	Link Function[a]	Responsive variable	Typical use
Logistic regression	$Y=\ln\left(\frac{\mu}{1-\mu}\right)=\beta X$	$\frac{e^{\beta X}}{1+e^{\beta X}}=\mu$	Binary	Yes/no response
GzLM gamma distribution	$Y=-\mu^{-1}=\beta X$	$-(\beta X)^{-1}=\mu$	Right skewed	Cost/ expenditure
Cox proportional regression[c]	$Y=\lambda(t\|x)=\lambda_o(t)e^{\beta X}$	N/A	Proportional	Time to event analysis

[a] Link function connects the linear predictors to the natural mean of response variable (μ)
[b] X is a vector of predictors ($\beta X=\beta_0+\beta_1X_1+\beta_2X_2+_{\ldots}+\beta_nX_n$)
[c] Cox proportional regression is not a general linear model
$\lambda_o(t)$ is a function of time and it is the nonparametric part of the model

Chapter 4 RESULTS

4.1 CHAPTER OVERVIEW

This chapter provides the study results in the order of objectives. First, the patient selection process and baseline characteristics of the final cohort are presented. Then the statistical analysis and interpretations for each study objective are presented in detail.

4.2 SELECTION PROCESS AND BASELINE CHARACTERISTICS

The initial sample (N=267,909) was composed of all patients with ICD-9 codes 362.xx (retinal disorder) or 250.xx (diabetes) between 09/01/2007 to 12/31/2012. Table 4.1 lists the criteria of patient selection for DME/AMD. A final DME/AMD cohort of 3,944 patients, including 3,647 DME patient and 297 AMD patients were included in this study. DME control patients were selected if they met the following criteria: diagnosed with diabetes (ICD-9=250.xx); no retinal disorder (ICD-9=362.xx); 18-63 years of age; and continuously enrolled. A total of 57,897 patients were included in the DME control group.

Table 4.1: DME and AMD Patient Attrition in the Texas Medicaid Database

Criteria	Subjects Excluded		Subjects Remaining	
	N	%	N	%
Initial Sample N = 267,909				100.0
Diagnosis of 4 types of cancer treated by bevacizumab[a]	2	0.0008	267,907	99.9
Patients with no diagnosis of either DME or AMD	253,734	94.7	14,173	5.3
Diagnosis of both DME and AMD	599	4.2	13,574	96.8
No diagnosis of DME or AMD between Sep 1, 2008 and Dec 31, 2011	5,626	41.4	7,948	58.6
Diagnosis of DME or AMD in the pre-index period (365 days prior to the index date)	1,108	13.9	6,840	86.1
Treated with bevacizumab in pre-index period (365 days prior to the index date)	89	1.3	6,751	98.7
Age <18 or >63 on the index date	555	8.2	6,196	91.8
Not continuously enrolled 365 days before and after the index date	2,252	36.3	3,944	63.7
Final sample			**3,944**	**1.5**

DME= diabetic macular edema; AMD= age-related macular degeneration

[a] Patients diagnosed with metastatic colorectal cancer, non-small cell lung cancer, metastatic renal cell carcinoma, or glioblastoma with progressive disease were excluded.

Baseline characteristics of DME/AMD patients are presented in Table 4.2. The baseline characteristics of DME control patients will be presented in Objective 4. The majority of patients was between 45-63 years of age (86.6%), Hispanic (54.0%), and female (65.1%). The mean total number of unique medications and CCI were 2.7 ± 3.4 and 6.0 ± 3.3, respectively. Less than half (45.5%) of the patients had a CCI greater than six. Less than half (45.1%) of the patients were treated with laser during the post index period and only 7.4% had more than three therapies. A total of 13.5% patients were treated with bevacizumab, and only 2.3% used more than three injections during the 1-year post-index period.

Table 4.2: Baseline Summary Statistics for Final Sample of DME and AMD Patients

Demographic & Clinical Characteristics	**N**	**%**
Age groups		
18-34	146	3.7
35-44	385	9.8
45-54	1,115	28.3
55-63	2,298	58.3
Total	**3,944**	**100.0**
Mean (SD)	**54.2(8.3)**	
Race/ethnicity		
Caucasians	984	25.0
African Americans	695	17.6
Hispanics	2,130	54.0
Others	135	3.4
Total	**3,944**	**100.0**
Gender		
Males	1,376	34.9
Females	2,568	65.1
Total	**3,944**	**100.0**
Total number of unique medications		
0	1,569	39.8
1	437	11.1
2	286	7.3
3	365	9.3
≥4	1,287	32.6
Total	**3,944**	**100.0**
Mean (SD)	**2.7(3.4)**	
Charlson Comorbidity Index score		
0-3	1,237	31.4
4-6	914	23.2
≥7	1,793	45.5
Total	**3,944**	**100.0**
Mean (SD)	**6.0(3.3)**	
Number of laser therapies		
0	2,166	54.9
1-3	1,485	37.7
≥4	293	7.4
Total	**3,944**	**100.0**
Mean (SD)	**1.0(1.4)**	
Median [Min, Max]	**0[0,9]**	
Number of bevacizumab treatments		
0	3,414	86.5
1-3	410	11.2
≥4	84	2.3
Total	**3,944**	**100.0**
Mean (SD)	**0.30(1.0)**	
Median [Min, Max]	**0[0,15]**	

DME= diabetic macular edema; AMD= age-related macular degeneration

4.3 STUDY OBJECTIVES

4.3.1 Objective 1: Demographic and clinical characteristics among DME and AMD patients

Objective 1 was to determine if demographic and clinical characteristics differ among DME and AMD patients. Baseline characteristics and comparison are shown in Table 4.3.

Table 4.3: Comparison of Demographic and Clinical Characteristics between DME and AMD Patients (Unmatched Sample)

Characteristics	DME (N=3647)	AMD (N=297)	p-value
Demographic			
Age, Mean(±SD)[a]	54.2(8.1)	54.3(9.6)	0.83
Females (%)[b]	64.7	70.0	0.06
Race/ethnicity (%)[b]			
Hispanics	50.2	51.2	<0.0001*
Caucasians	24.2	34.0	
African Americans	18.4	8.4	
Others	3.2	6.4	
Clinical			
Total number of unique medications, Mean(±SD)[a]	2.8(3.4)	2.4(2.7)	0.07
Charlson Comorbidity Index, Mean(±SD) [a]	6.2(3.2)	3.1(3.5)	0.02*
Laser surgery (%)[b]	26.6	2.4	<0.0001*
Total number of laser therapies, Mean(±SD) [c]	1.1(1.5)	0.1(0.5)	<0.0001*
Bevacizumab injection (%)[b]	13.1	18.2	0.0132*
Total number of bevacizumab injections, Mean(±SD) [c]	0.3(0.9)	0.6(1.7)	0.0095*

DME= diabetic macular edema; AMD= age-related macular degeneration
[a] T-test
[b] Chi-square
[c] Wilcoxon
*Significant at $p < 0.05$

Demographic characteristics

There was a significant difference in race/ethnicity between DME and AMD patients. DME patients had a significantly ($p<0.0001$) higher proportion of African Americans compared to AMD patients (18.4% vs. 8.4%, respectively). Caucasians were significantly ($p<0.0001$) more prevalent among AMD than DME patients (34.0% vs. 24.2%, respectively). There were no significant differences in age ($p=0.83$) or gender ($p=0.06$) between DME and AMD patients.

Clinical characteristics

AMD patients had significantly ($p=0.02$) lower Charlson Comorbidity Index scores than DME patients (3.1±3.5 vs. 6.3±3.2, respectively). The proportion of patients receiving laser therapies was also significantly ($p<0.0001$) lower (2.4% vs. 26.6%, respectively) for AMD patients, whereas the proportion of patients receiving bevacizumab treatments was significantly ($p=0.0095$) higher (18.2% vs. 13.1%, respectively).

H_{1a}: *There is no significant difference in **age** among DME and AMD patients.* **(Not Rejected)**

H_{1b}: *There is no significant difference in **gender** among DME and AMD patients.* **(Not Rejected)**

H_{1c}: *There is no significant difference in **race** among DME and AMD patients.* **(Rejected)**

H_{1d}: *There is no significant difference in **Charlson Comorbidity Index** among DME and AMD patients.* **(Rejected)**

H_{1e}: *There is no significant difference in total number of* ***unique medication used*** *among DME and AMD patients.* **(Not Rejected)**

H_{1f}: *There is no significant difference in* ***number of laser treatments*** *among DME and AMD patients.* **(Rejected)**

H_{1g}: *There is no significant difference in* ***number of bevacizumab treatments*** *among DME and AMD patients.* **(Rejected)**

4.3.2 Objective 2: Risk of cardiovascular/ hemorrhagic events among DME and AMD patients

4.3.2.1 Objective 2 overview

Objective 2 was to determine if the *risk of cardiovascular/ hemorrhagic events* differs by bevacizumab use among AMD and DME patients, while controlling for covariates. The number of incidence of cardiovascular/hemorrhagic events was summed to avoid unstable analysis when running logistic regression. Due to the small sample of incident cases on some conditions, the adverse events were categorized into three subgroups: 1) cardiovascular events (heart failure, proteinuria, myocardial infarction (MI), cerebrovascular accident, and venous thrombotic events); 2) hypertension; and 3) hemorrhagic events (bleeding). Incident cardiovascular and hypertension during the 1-year post-treatment were identified. Any bleeding event during the 1-year post-treatment period was included because no evidence indicates new bleeding events were related to previous events.[101] Thus bleeding events may have been incident or prevalent. The result for each event is listed in Table 4.4. Logistic regression and Cox regression were used to address objective 2. The matching process for each subgroup is discussed in detail in the section 4.3.2.2.

Table 4.4: Number and Incidence of Adverse Events among Bevacizumab Users and Non-users (Matched Sample)

	Treated			Not Treated			Total		
Adverse Events	**Incident cases**	**N**	**%**	**Incident cases**	**N**	**%**	**Incident cases**	**N**	**%**
Cardiovascular	**24**	**290**	**8.2**	**27**	**290**	**9.3**	**51**	**580**	**8.8**
Heart Failure	15	290	5.2	15	290	5.2	30	580	5.2
Proteinuria	2	290	0.7	5	290	1.7	7	580	1.2
Myocardial infarction	1	290	0.3	1	290	0.3	2	580	0.3
Cerebrovascular accident	4	290	1.4	3	290	1	7	580	1.2
Venous thrombotic event	2	290	0.7	3	290	1	5	580	0.9
Hypertension	**17**	**68**	**25.0**	**19**	**68**	**27.9**	**36**	**136**	**26.5**
Bleeding	**7**	**365**	**1.9**	**4**	**365**	**1.1**	**11**	**730**	**1.5**

4.3.2.2 Propensity score matching

Propensity score matching (caliper method, caliper set at 0.01) was used for all the three subgroups (cardiovascular, hypertension, and bleeding). The procedure includes identifying potential covariates, generating propensity scores, conducting propensity matching, and testing the differences between matched pairs. For each subgroup other than bleeding, non-incident adverse events cases were excluded from the sample before matching. Bleeding was not considered a chronic condition. We allowed the post-treatment non-incident events to be included. The statistics are presented in detail in each subgroup's result.

Cardiovascular subgroup

For the cardiovascular subgroup, a total of 2,280 out of 3,944 patients (57.8%) were excluded. A total of 365 patients were excluded because of pre-treatment/index cardiovascular events. The remaining 1,915 patients were excluded because they: 1) were not continuously enrolled in the 1-year post-treatment period; or 2) were not treated in any way (i.e., no anti-VEGF or laser). Patients who did not receive treatment were excluded because their disease severity may have been lower. Table 4.5 shows the comparison of demographic and clinical characteristics between unmatched bevacizumab user and non-user groups. A total of 1664 (n=3,944-2,280=1,664) cardiovascular subgroup patients were eligible for the propensity score matching step. Variables including total number of unique medications, CCI, and total number of laser therapies were chosen to calculate the propensity score. Those variables were chosen because those baseline characteristics were potentially different between the patients and controls.

Table 4.5: Demographic and Clinical Characteristics of Bevacizumab Users and Non Users and Incident Cardiovascular Events (Unmatched Sample)

	User (N=391)	**Non User (N=1273)**	**p-value**
Age, Mean(±SD)[a]	54.5(8.5)	54.2(8.0)	0.4528
Females (%)[b]	58.1	64.4	0.0228*
Race/ethnicity (%)[b]			
Hispanics	61.1	58.9	0.4262
Caucasians	22.8	22.3	
African Americans	12.3	15.6	
Others	3.8	3.2	
Total number of unique medications, Mean(±SD)[a]	1.7(2.9)	2.6(3.0)	<0.0001*
Charlson Comorbidity Index, Mean(±SD) [a]	6.2(3.3)	6.1(3.1)	0.5043
Total number of laser therapies, Mean(±SD)[a]	1.4(1.6)	2.0(1.4)	<0.0001*

[a] T-test
[b] Chi-square

A total of 580 patients were matched in the cardiovascular subgroup with 1,084 (65.1%) lost in the matching process. After matching there were no significant differences between the bevacizumab users and non-users regarding demographic and clinical characteristics (Table 4.6). The 580 patients served as the final sample for the logistic and Cox regression analyses for the cardiovascular subgroup.

Table 4.6: Demographic and Clinical Characteristics of Bevacizumab Users and Non-Users and Incident Cardiovascular Events (Matched Sample)

	User (N=290)	**Non User (N=290)**	**p-value**
Age, Mean(±SD)[a]	54.4(8.7)	54.6(7.6)	0.7745
Females (%)[b]	60.3	66.2	0.1431
Race/ethnicity (%)[b]			
Hispanics	62.1	63.1	0.6838
Caucasians	21.4	17.9	
African Americans	13.1	14.5	
Others	3.5	4.5	
Total number of unique medications, Mean(±SD)[a]	1.5(2.5)	1.5(2.5)	0.9199
Charlson Comorbidity Index, Mean(±SD)[a]	6.4(3.2)	6.3(3.2)	0.7050
Total number of laser therapies, Mean(±SD)[a]	1.9(1.6)	1.9(1.6)	0.9586

[a] T-test
[b] Chi-square

Hypertension subgroup

For the hypertension subgroup, a total of 3,570 patients (90.5%) were excluded. A total of 1,665 were excluded because of pre-treatment/index hypertension events. The remaining 1,915 were excluded because they: 1) were not continuously enrolled in the 1-year post-treatment period; or 2) were not treated in any way (i.e., no anti-VEGF or laser). Table 4.7 showed the comparison of demographic and clinical characteristics for the unmatched bevacizumab user and non-user groups. A total of 374 (n=3,944-3,570=374) patients were eligible for propensity score matching. The same variables as the cardiovascular subgroup were used to calculate the propensity score, including total number of unique medications, CCI score, and total number of laser therapies.

Table 4.7: Demographic and Clinical Characteristics of Bevacizumab Users and Non Users and Incident Hypertension (Unmatched Sample)

	User (N=92)	**Non User**	**p-value**
Age, Mean(±SD)[a]	53.4(9.9)	53.1(9.2)	0.7553
Females (%)[b]	58.7%	56.7%	0.7417
Race/ethnicity (%)[b]			
Hispanics	55.4%	53.9%	0.9677
Caucasians	26.1%	28.4%	
African Americans	13.0%	13.1%	
Others	5.4%	4.6%	
Total number of unique medications, Mean(±SD)[a]	1.8(1.2)	2.3(1.9)	0.1554
Charlson Comorbidity Index Mean(±SD)[a]	4.4(3.5)	5.5(3.1)	0.0036*
Total number of laser therapies [a] Mean(±SD)[a]	1.8(1.2)	2.3(1.9)	<0.0001*

[a] T-test
[b] Chi-square
*Significant at $p < 0.05$

A total of 136 patients were matched in the hypertension subgroup with 238 (63.6%) excluded in the matching process. After matching there were no significant differences between the bevacizumab users and non-users (Table 4.8). The 136 patients served as the final sample for logistic regression and Cox regression analyses for the hypertension subgroup.

Table 4.8: Demographic and Clinical Characteristics of Bevacizumab Users and Non-Users and Incident Hypertension (Matched Sample)

	Treated (N=68)	**Not treated (N=68)**	**p-value**
Age, Mean(±SD)[a]	53.7(10.8)	53.4(9.0)	0.5249
Females (%)[b]	60.3	58.8	0.8613
Race/ethnicity (%)[b]			
Hispanics	58.8	60.3	0.5038
Caucasians	25.0	5.9	
African Americans	11.8	25.0	
Others	4.4	8.8	
Total number of unique medications, Mean(±SD)[a]	2.0(3.2)	2.5(2.7)	0.3697
Charlson Comorbidity Index Mean(±SD)[a]	4.7(3.4)	5.0(3.4)	0.5249
Total number of laser therapies[a] Mean(±SD)[a]	1.6(1.6)	1.6(1.6)	1.0000

[a] T-test
[b] Chi-square

Bleeding subgroup

For the bleeding subgroup, a total of 1,915 patients (48.6%) were excluded 1) were not continuously enrolled in the 1-year post-treatment period; or 2) were not treated in any way (i.e., no anti-VEGF or laser). Table 4.9 shows the comparison of demographic and clinical characteristics for the unmatched bevacizumab users and non-users groups. A total of 2,029 (n=3,944-1,915=2,029) patients were eligible for the propensity score matching. Total number of unique medication, CCI, and total number of laser therapies were chosen as the covariates to calculate the propensity score.

Table 4.9: Demographic and Clinical Characteristics of Bevacizumab Users and Non-Users and Incident Bleeding (Unmatched Sample)

	User (N=494)	**Non User (N=1,535)**	**p-value**
Age, Mean(±SD)[a]	54.5(8.3)	54.3(7.9)	0.5862
Females (%)[b]	57.5%	64.3%	0.0065
Race/ethnicity (%)[b]			
Hispanics	61.1%	57.9%	0.2958
Caucasians	22.7%	22.7%	
African Americans	12.8%	16.2%	
Others	3.4%	3.1%	
Total number of unique medications, Mean(±SD)[a]	1.7(3.0)	2.7(3.2)	<0.0001*
Charlson Comorbidity Index Mean(±SD)[a]	6.7(3.3)	6.4(3.1)	0.1925
Total number of laser therapies[a] Mean(±SD)[a]	1.4(1.7)	2.0(1.4)	<0.0001*

[a] T-test
[b] Chi-square
*Significant at $p < 0.05$

A total of 730 patients were matched in the bleeding subgroup with 1,299 (64.0%) lost in the matching process. After matching there were no significant differences between the bevacizumab users and non-users (Table 4.10). The 730 patients served as the final sample for the logistic regression analyses for the bleeding subgroup.

Table 4.10: Demographic and Clinical Characteristics of Bevacizumab Users and Non-Users and Incident Bleeding (Matched Sample)

	User (N=365)	**Non User (N=365)**	**p-value**
Age, Mean(±SD)[a]	54.5(8.4)	53.4(7.8)	0.7571
Females (%)[b]	61.0	64.1	0.4001
Race/ethnicity (%)[b]			
Hispanics	62.2	61.9	0.7480
Caucasians	21.4	19.2	
African Americans	12.9	15.3	
Others	3.6	3.6	
Total number of unique medications, Mean(±SD)[c]	1.5(2.5)	1.5(2.5)	0.9376
Charlson Comorbidity Index Mean(±SD)[a]	6.8(3.2)	6.6(3.2)	0.2444
Total number of laser therapies[b] Mean(±SD)[a]	1.9(1.8)	1.9(1.7)	0.9644

[a] T-test
[b] Chi-square
[c] Wilcoxon

4.3.2.3 Cardiovascular/ hemorrhagic risk (Logistic regression models)

After each subgroup was matched using propensity scoring, logistic regression was conducted to assess the risk of cardiovascular, hypertension, and bleeding events. All the events are incident events except for bleeding. The odds ratio, 95% confident interval, Wald chi-square statistics, and p-values are reported for each independent variable and covariate. Model fit statistics are included in the table footnote.

The risk of cardiovascular events

Logistic regression showed that the likelihood of incident cardiovascular events among bevacizumab users was not significantly different from non-users (Table 4.11). Regarding covariates, non-whites were 54% less likely to have a cardiovascular event compared to whites (OR=0.460, 95%CI= [0.227, 0.932], p=0.0311). For every one point increase in CCI score, patients were 28% more likely to have a cardiovascular event (OR=1.280, 95%CI= [1.149,1.427], p<0.0001).

Table 4.11: Logistic Regression Analysis Comparing the Likelihood of Incident Cardiovascular Events among Bevacizumab Users and Non-Users (N=580)

	Odds Ratio	95% CI		Wald X^2	p-value
User Type					
Bevacizumab users†	1.241	0.671	2.296	0.4726	0.4918
Covariates					
DME patients†	2.119	0.251	17.863	0.4769	0.4898
Age	1.024	0.981	1.069	1.1441	0.2848
Male†	0.814	0.428	1.546	0.3959	0.5292
Non-whites†	0.460	0.227	0.932	4.6473	0.0311*
Total number of unique medications	0.941	0.821	1.078	0.7645	0.3819
Charlson Comorbidity Index	1.280	1.149	1.427	20.0416	<0.0001*
Total number of laser therapies	0.936	0.769	1.140	0.4333	0.5104

DME= diabetic macular edema; AMD= age-related macular degeneration
†Reference categories: Non-users, AMD patients, females, whites
Model Fit Statistics: Likelihood ratio = 29.6440, df = 8, p = 0.0008
*Significant at $p < 0.05$

A second logistic regression found that there is no significant difference in incident cardiovascular risk and number of bevazumab injections during the 1-year post-treatment period (Table 4.12). Non-whites were 55.8% less likely to have a cardiovascular event compare to whites (OR=0.442, 95%CI= [0.218, 0.895], p=0.0234). For every one point increase in CCI scores, patients were 27.4% more likely to have a cardiovascular event (OR=1.274, 95%CI= [1.147, 1.416], p<0.0001).

Table 4.12: Logistic Regression Analysis Comparing the Likelihood of Incident Cardiovascular by Number of Bevacizumab Injections (N=580)

	Odds Ratio	95% CI		Wald X^2	p-value
User Type					
Number of bevacizumab injections	0.925	0.756	1.132	0.5748	0.4484
Covariates					
DME patients†	2.234	0.267	18.662	0.5504	0.4481
Age	1.028	0.984	1.074	1.5556	0.2123
Male†	0.754	0.398	1.426	0.7552	0.3848
Non-whites†	0.442	0.218	0.895	5.1392	0.0234*
Total number of unique medications	0.936	0.817	1.074	0.8867	0.3464
Charlson Comorbidity Index	1.274	1.147	1.416	20.4869	<0.0001*
Total number of laser therapies	0.950	0.781	1.155	0.2681	0.5888

DME= diabetic macular edema; AMD= age-related macular degeneration

†Reference categories: AMD patients, females, whites

Model Fit Statistics: Likelihood ratio =31.3730, df = 8, p = 0.0001

*Significant at $p < 0.05$

The risk of hypertension events

Logistic regression showed that the likelihood of incident hypertensive events among bevacizumab users was not significantly different from non-users (Table 4.13). For every one point increase in CCI scores, patients were 32.9% more likely to have a hypertensive event (OR=1.329, 95%CI= [1.145, 1.543], p=0.0002).

Table 4.13: Logistic Regression Analysis Comparing the Likelihood of Incident Hypertension among Bevacizumab Users and Non-Users (N=136)

	Odds Ratio	95% CI		Wald X^2	p-value
User Type					
Bevacizumab users†	0.968	0.386	2.430	0.0048	0.9449
Covariates					
DME patients†	0.787	0.163	3.806	0.0886	0.7660
Age	1.040	0.988	1.095	2.2864	0.1305
Male†	1.352	0.527	3.472	0.3937	0.5303
Non-whites†	0.842	0.291	2.438	0.1002	0.7516
Total number of unique medications	1.119	0.967	1.295	2.2647	0.1323
Charlson Comorbidity Index	1.329	1.145	1.543	13.9424	0.0002*
Total number of laser therapies	0.966	0.725	1.287	0.0568	0.8117

DME= diabetic macular edema; AMD= age-related macular degeneration

†Reference categories: Non-users, AMD patients, females, whites

Model Fit Statistics: Likelihood ratio = 21.5483, df = 8, p = 0.0058

*Significant at $p < 0.05$

A second logistic regression found no significant difference in incident hypertension risk and number of bevazumab injections during the 1-year post-treatment period (Table 4.14). For every one point increase in CCI scores, patients were 32.8% more likely to have a hypertensive event (OR=1.328, 95%CI= [1.144, 1.542], p=0.0002).

Table 4.14: Logistic Regression Analysis Comparing the Likelihood of Incident Hypertension by Number of Bevacizumab Injections (N=136)

	Odds Ratio	95% CI		Wald X^2	p-value
User Type†					
Number of bevacizumab injections	0.960	0.700	1.317	0.0636	0.8009
Covariates					
DME patients †	0.738	0.157	3.477	0.1471	0.7013
Age	1.039	0.988	1.094	2.1983	0.1382
Male†	1.367	0.534	3.498	0.4252	0.5144
Non-whites†	0.856	0.298	2.463	0.0830	0.7733
Total number of unique medications	1.116	0.965	1.290	2.1838	0.1395
Charlson Comorbidity Index	1.328	1.144	1.542	13.8983	0.0002*
Total number of laser therapies	0.973	0.727	1.303	0.0337	0.8544

DME= diabetic macular edema; AMD= age-related macular degeneration

†Reference categories: AMD patients, females, whites

Model Fit Statistics: Likelihood ratio = 21.6083, df = 8, p = 0.0057

*Significant at $p < 0.05$

The risk of bleeding events

Logistic regression showed that the likelihood of post-treatment bleeding events among bevacizumab users was not significantly different from non-users (Table 4.15). No other covariates were significantly related to bleeding. Different from the previous two subgroups, the bleeding events were not necessarily incident event. Because bleeding was not considered chronic conditions, new events were not necessarily related to the past event.

Table 4.15: Logistic Regression Analysis Comparing the Likelihood of Bleeding among Bevacizumab Users and Non-Users (N=730)

	Odds Ratio	95% CI		Wald X^2	p-value
User Type					
Bevacizumab users†	0.583	0.192	1.768	0.9091	0.3403
Covariates					
Age	1.012	0.943	1.085	0.1044	0.7466
Male†	1.573	0.541	4.577	0.6912	0.4058
Non-whites†	0.579	0.176	1.906	0.8092	0.3684
Total number of unique medications	0.853	0.624	1.166	0.9965	0.3182
Charlson Comorbidity Index	1.077	0.906	1.280	0.7022	0.4021
Total number of laser therapies	0.936	0.668	1.311	0.1485	0.6999

DME= diabetic macular edema; AMD= age-related macular degeneration

†Reference categories: Non-users, females, whites

Note: Treatment group (DME and AMD) was deleted due to small cell sizes

Model Fit Statistics: Likelihood ratio = 3.6302, df = 7, p = 0.8213

*Significant at $p < 0.05$

A second logistic regression found no significant difference in post-treatment bleeding risk and number of bevazumab injections (Table 4.16). No other covariates were significantly related to bleeding.

Table 4.16: Logistic Regression Analysis Comparing the Likelihood of Bleeding by Number of Bevacizumab Injections (N = 730)

	Odds Ratio	95% CI		Wald X^2	p-value
User Type					
Number of bevacizumab injections	1.068	0.759	1.503	0.1415	0.7068
Covariates					
Age	0.997	0.927	1.073	0.0047	0.9455
Male†	1.964	0.589	6.554	1.2053	0.2723
Non-whites†	0.640	0.164	2.499	0.4113	0.5213
Total number of unique medications	0.908	0.671	1.229	0.3903	0.5321
Charlson Comorbidity Index	1.080	0.890	1.310	0.6106	0.4346
Total number of laser therapies	0.902	0.615	1.323	0.2772	0.5986

DME= diabetic macular edema; AMD= age-related macular degeneration
†Reference categories: Females, whites
Note: Treatment group (DME and AMD) was deleted due to small cell sizes
Model Fit Statistics: Likelihood ratio = 3.0936, df =7, p = 0.8762
*Significant at $p < 0.05$

4.3.2.4 Time to cardiovascular event (Cox proportional hazards regression model)

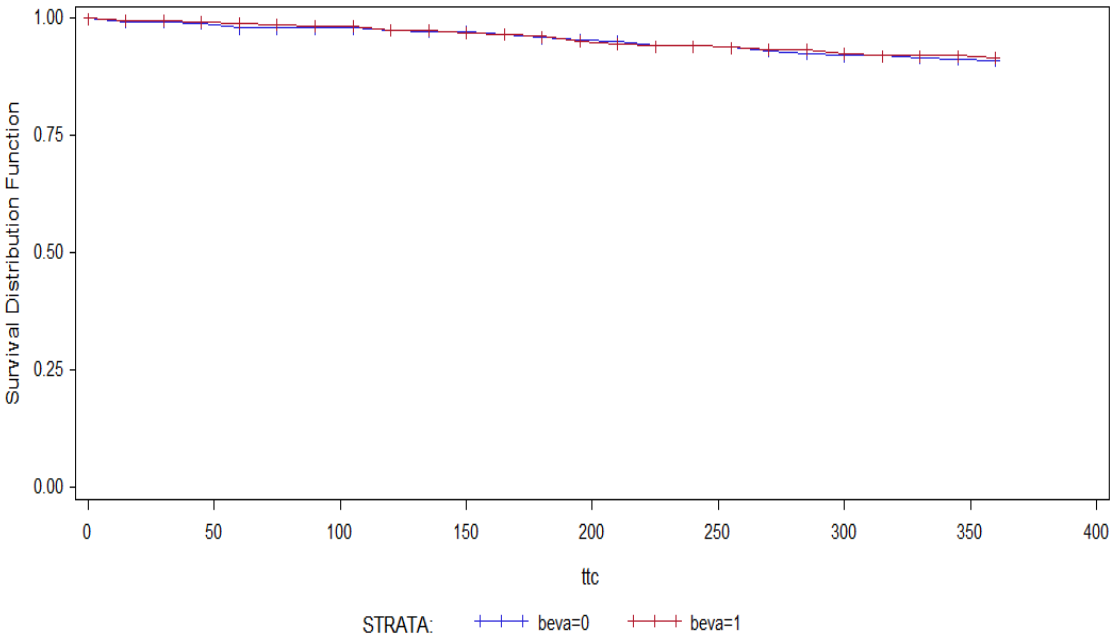
Cox proportional hazards regression model was used for each subgroup to determine the time to first post-treatment (users) or post-index (non-users) cardiovascular and hypertension events. Because bleeding cases were not incident, Cox regression was not performed in this subgroup. If patients did not experience a cardiovascular or hemorrhagic event during the 1-year post-index period, then 365 days from the index date was used as the censor date. All the patients were eligible during the 1-year post-treatment (users) or post-index period (non-users). Kaplan Meier curves comparing time to adverse events were generated for each subgroup. The hazard ratio, 95% confident interval, Wald chi-square statistics, and p-values are reported for each independent variable and covariate. Model fit statistics are included in the table footnote. Before

utilizing Cox proportional hazard regression model, testing was conducted to ensure the proportional of hazards assumptions were met by examining at the interaction between survival time (in natural logarithm form) and each study covariate.

Time to cardiovascular events

A Kaplan Meier graph was generated and is shown in Figure 4.1. From the graph, the two curves overlap in similar patterns. The statistical analysis will be presented in the next section with the Cox regression results.

Figure 4.1: Time to cardiovascular events



Ttc= time to cardiovascular events; beva= bevacizumab use (nonusers=0; users=1)

Before Cox regression models were run, the proportionality assumption was tested. Results of the proportionality assumption test are shown in Table 4.17. The proportionality assumption was met for all the covariates and interaction terms.

Table 4.17: Test for Proportionality of Hazards for Covariates (Cardiovascular)

Covariates	**Hazard Ratio**	**95% CI**		**Wald Chi-Square**	**p-Value**
DME patients†	0.000	0.000	0.000	0.3572	0.5501
Age	0.865	0.730	1.025	2.7930	0.0947
Male†	2.793	0.070	111.109	0.2988	0.5846
Non-whites†	3.374	0.105	108.481	0.4715	0.4923
Total number of unique medications	0.831	0.358	1.927	0.1867	0.6657
Charlson Comorbidity Index	1.379	0.787	2.416	1.2590	0.2618
Total number of laser therapies	1.151	0.421	3.144	0.0751	0.7840
Interaction‡: DME patients	6.766	0.010	4799.122	0.3259	0.5681
Interaction: Age	1.035	0.999	1.073	3.6577	0.0558
Interaction: Male	0.867	0.420	1.788	0.1500	0.6985
Interaction: Non-whites	0.889	0.444	1.780	0.1095	0.7407
Interaction: Total number of unique medications	1.025	0.870	1.208	0.0876	0.7673
Interaction: Charlson Comorbidity Index	0.979	0.877	1.094	0.1350	0.7133
Interaction: Total number of laser therapies	0.964	0.789	1.177	0.1298	0.7186

DME= diabetic macular edema; AMD= age-related macular degeneration
†Reference categories: AMD patients, females, whites
‡Interaction with the natural logarithm of survival time has been tested for each variable.
Model Fit Statistics: Likelihood ratio = 32.6928, df = 14, p < 0.0032

Cox regression results are presented in Table 4.18. There was no significant difference in risk of cardiovascular events between bevacizumab users and non-users. Regarding covariates, non-whites had 2.0 times higher cardiovascular risk compared to whites (HR=2.047, 95%CI=[1.083, 3.868], p=0.0273). For every one point increase in CCI scores, patients were 24.7% more likely to have a cardiovascular event (HR=1.247, 95%CI=[1.136, 1.370], p<0.0001).

Table 4.18: Cox Proportional Hazards Regression Model Comparing Survival Time to Incident Cardiovascular Events among Bevacizumab Users and Non-Users (N=580)

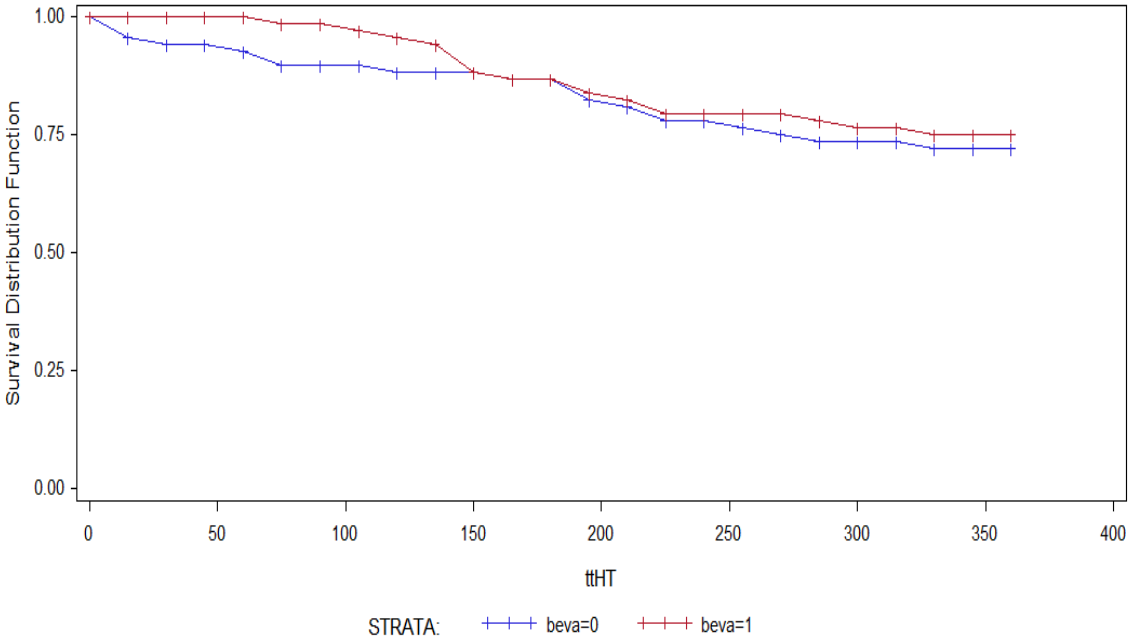
	Hazard Ratio	**95% CI**		**Wald Chi-Square**	**p-Value**
User Type					
Bevacizumab users†	0.847	0.480	0.3288	1.495	0.5663
Covariates					
DME patients†	0.464	0.060	0.5385	3.608	0.4631
Age	1.024	0.984	1.3464	1.066	0.2459
Male†	1.287	0.711	0.6922	2.330	0.4054
Non-whites†	2.047	1.083	4.8690	3.868	0.0273*
Total number of unique medications	0.934	0.821	1.0844	1.062	0.2977
Charlson Comorbidity Index	1.247	1.136	21.3584	1.370	<0.0001*
Total number of laser therapies	0.946	0.789	0.3642	1.134	0.5462

DME= diabetic macular edema; AMD= age-related macular degeneration
†Reference categories: Non-users, AMD patients, females, whites
Model Fit Statistics: Likelihood ratio = 30.6716, df = 8, p < 0.002
*Significant at p < 0.05

Time to hypertension events

A Kaplan Meier curve was generated and is presented in Figure 4.2. The statistical analysis will be presented in the next section with the Cox regression results.

Figure 4.2: Time to hypertension events



TtHT= time to incident hypertension events; beva= bevacizumab use (nonusers=0; users=1)

Results of the proportionality assumption test are shown in Table 4.19. The proportionality assumption was met for all the covariates and interaction terms.

Table 4.19: Test for Proportionality of Hazards for Covariates (Hypertension)

Covariates	**Hazard Ratio**	**95% CI**		**Wald Chi-Square**	**p-value**
DME patients†	0.020	0.000	1210.010	0.4864	0.4855
Age	1.235	0.900	1.689	1.7044	0.1919
Male†	11.015	0.260	467.462	1.5741	0.2096
Non-whites†	25.012	0.325	1923.361	2.1114	0.1462
Total number of unique medications	0.694	0.418	1.155	1.9727	0.1602
Charlson Comorbidity Index	2.704	1.215	6.016	5.9397	0.0148*
Total number of laser therapies	0.767	0.198	2.964	0.1482	0.7002
Interaction‡: DME patients	2.243	0.263	19.160	0.5448	0.4604
Interaction: Age	0.965	0.907	1.027	1.2387	0.2657
Interaction: Male	0.604	0.284	1.288	1.7006	0.1992
Interaction: Non-whites	0.545	0.229	1.301	1.8683	0.1717
Interaction: Total number of unique medications	1.097	0.989	1.217	3.0660	0.0799
Interaction: Charlson Comorbidity Index	0.862	0.735	1.010	3.3626	0.0667
Interaction: Total number of laser therapies	1.049	0.802	1.372	0.1210	0.7279

†Reference categories: AMD patients, females, whites
‡Interaction with the natural logarithm of survival time has been tested for each variable.
Model Fit Statistics: Likelihood ratio = 35.3817, df = 16, p < 0.035;
*Significant at $p < 0.05$

Cox regression results are presented in Table 4.20. No difference was found in risk between bevacizumab users and non-users. Patients with a one point increase in CCI scores were 29.3% more likely to develop post-treatment/index have a hypertension adverse event (HR=1.293, 95%CI=[1.152, 1.450], p<0.0001).

Table 4.20: Cox Proportional Hazards Regression Model Comparing Survival Time to Incident Hypertension among Bevacizumab Users and Non-Users (N=136)

Covariates	Hazard Ratio	95% CI		Wald Chi-Square	p-value
User Type					
Bevacizumab users†	0.855	0.413	1.770	0.1791	0.6722
Covariates					
DME patients†	1.164	0.344	3.943	0.0595	0.8072
Age	1.037	0.989	1.088	2.3051	0.1290
Male†	0.914	0.436	1.914	0.0574	0.8107
Non-whites†	1.284	0.533	3.097	0.3104	0.5774
Total number of unique medications	1.094	0.991	1.208	3.1378	0.0765
Charlson Comorbidity Index	1.293	1.152	1.450	19.1225	<0.0001*
Total number of laser therapies	0.964	0.768	1.208	0.1031	0.7482

†Reference categories: Nonusers, AMD patients, females, whites
Model Fit Statistics: Likelihood ratio = 24.8932, df = 8, p =0.016
*Significant at $p < 0.05$

H2a**: There is no significant difference in **risk of cardiovascular/hemorrhagic** events between **bevacizumab users** and nonusers among DME and AMD patients, while controlling for covariates. **(Not rejected)

H2b**: There is no significant difference in **risk of cardiovascular/hemorrhagic** events by the **number of bevacizumab treatments** among DME and AMD patients, while controlling for covariates. **(Not rejected)

H2c**: There is no significant difference in **time to first cardiovascular/hemorrhagic** event between **bevacizumab users** and nonusers among DME and AMD patients, while controlling for covariates. **(Not rejected)

4.3.3 Objective 3: Risk of visual impairment among DME and AMD patients

4.3.3.1 Objective 3 overview

Objective 3 was to determine if the *risk of visual impairment* differs by bevacizumab use among AMD and DME patients, while controlling for covariates. Visual impairment was originally defined as having an incident post-treatment visual impairment. However, after matching, the number of incident cases was too small (N=9) to conduct this type of analysis. Thus, for this objective, we used non-incident (i.e., prevalent) cases for analyses. Since time to event requires incident cases, this analysis was not conducted. Logistic regression was used and the matching process for each subgroup is discussed in 4.3.3.2.

4.3.3.2 Propensity score matching

Propensity score matching (caliper method, caliper set at 0.01) was used in this objective to match bevacizumab users with non-users. A total of 1,915 patients (48.6%) were excluded because they: 1) were not continuously enrolled in the 1-year post-treatment period; or 2) were not treated in any way (i.e., no anti-VEGF or laser). Table 4.21 compared demographic and clinical characteristics for the unmatched bevacizumab users and non-users. A total of 2,029 (n=3,944-1,915=2,029) patients were eligible for propensity score matching. Total number of unique medication, CCI, and total number of laser therapies were chosen as the covariates to calculate the propensity score. Those variables were chosen because they represented the main differences between the groups.

Table 4.2: Demographic and Clinical Characteristics of Bevacizumab Users and Non Users and Visual Impairment (Unmatched Sample)

	Users (N=494)	**Non Users (N=1535)**	**p-value**
Age, Mean(±SD)[a]	54.5(8.3)	54.3(7.9)	0.5862
Females (%)[b]	57.5%	64.3%	0.0065
Race/ethnicity (%)[b]			
Hispanics	61.1%	57.9%	0.2958
Caucasians	22.7%	22.7%	
African Americans	12.8%	16.2%	
Others	3.4%	3.1%	
Total number of unique medications, Mean(±SD)[a]	1.7(3.0)	2.7(3.2)	<0.0001*
Charlson Comorbidity Index Mean(±SD)[a]	6.7(3.3)	6.4(3.1)	0.1925
Total number of laser therapies[a] Mean(±SD)[a]	1.4(1.7)	2.0(1.4)	<0.0001*

DME= diabetic macular edema; AMD= age-related macular degeneration

[a] T-test

[b] Chi-square

*Significant at $p < 0.05$

A total of 730 patients were matched with 1,299 (64.0%) lost in the matching process. After matching there were no significant differences between the bevacizumab users and non-users (Table 4.22). The 730 patients served as the final sample for the logistic regression.

Table 4.22: Demographic and Clinical Characteristics of Bevacizumab Users and Non-Users and Visual Impairment (Matched Sample)

	Users (N=365)	Non Users (N=365)	p-value
Age, Mean(±SD)[a]	54.5(8.4)	53.4(7.8)	0.7571
Females (%)[b]	61.0	64.1	0.4001
Race/ethnicity (%)[b]			
Hispanics	62.2	61.9	0.7480
Caucasians	21.4	19.2	
African Americans	12.9	15.3	
Others	3.6	3.6	
Total number of unique medications, Mean(±SD)[c]	1.5(2.5)	1.5(2.5)	0.9376
Charlson Comorbidity Index Mean(±SD)[a]	6.8(3.2)	6.6(3.2)	0.2444
Total number of laser therapes[a] Mean(±SD)[a]	1.9(1.8)	1.9(1.7)	0.9644

DME= diabetic macular edema; AMD= age-related macular degeneration

[a] T-test

[b] Chi-square

[c] Wilcoxon

4.3.3.3 Visual impairment risk (Logistic regression models)

After each subgroup was matched using propensity scoring, logistic regression was conducted to accesses the risk of visual impairment. The odds ratio, 95% confident interval, Wald chi-square statistics, and p-values were reported for each independent variable and covariate. Model fit statistics are included in the table footnote.

The risk of visual impairment

Logistic regression found that the likelihood of post-treatment visual impairment among bevacizumab users were not significantly different from non-users (Table 4.23). Age was the only covariate associated with the risk of visual impairment. For every 1-

year increase in age, patients were 3.6% more likely to have visual impairment (OR=1.036, 95%CI=[1.003,1.070], p=0.0337).

Table 4.23: Logistic Regression Analysis Comparing the Likelihood of Visual Impairment among Bevacizumab Users and Non-Users (N=730)

	Odds Ratio	**95% CI**		**Wald X^2**	**p-value**
User Type					
Bevacizumab users†	0.841	0.454	1.560	0.3004	0.5836
Covariates					
Age	1.036	1.003	1.070	4.5114	0.0337*
Male†	0.926	0.488	1.759	0.0550	0.8146
Non-whites†	1.304	0.583	2.918	0.4180	0.5179
Total number of unique medications	0.907	0.818	1.006	3.4227	0.0643
Charlson Comorbidity Index	1.062	0.963	1.173	1.4472	0.2290
Total number of laser therapies	0.958	0.800	1.147	0.2200	0.6390

DME= diabetic macular edema; AMD= age-related macular degeneration
†Reference categories: Non-users, females, whites
Note: Treatment group (DME and AMD) was deleted due to small cell sizes
Model Fit Statistics: Likelihood ratio = 10.0998, df = 7, p = 0.1830
*Significant at $p < 0.05$

A second logistic regression found that there was no significant difference in visual impairment risk by number of bevazumab injections (Table 4.24). Age was the only covariate associated with the risk of visual impairment. For every 1-year increase in age, patients were 3.5% more likely to have visual impairment (OR=1.035, 95%CI=[1.002,1.070], p=0.0359)

Table 4.24: Logistic Regression Analysis Comparing the Likelihood of Visual Impairment by Number of Bevacizumab Injections (N=730)

	Odds Ratio	95% CI		Wald X^2	p-value
User Type					
Number of bevacizumab injections	1.044	0.863	1.263	0.1948	0.6589
Covariates					
Age	1.035	1.002	1.070	4.4033	0.0359*
Male†	0.930	0.490	1.766	0.0491	0.8246
Non-whites†	1.310	0.586	2.930	0.4318	0.5111
Total number of unique medications	0.907	0.818	1.006	3.4392	0.0637
Charlson Comorbidity Index	1.065	0.965	1.176	1.5502	0.2123
Total number of laser therapies	0.955	0.797	1.144	0.2515	0.6161

DME= diabetic macular edema; AMD= age-related macular degeneration
†Reference categories: Females, whites
Note: Treatment group (DME and AMD) was deleted due to small cell sizes
Model Fit Statistics: Likelihood ratio = 10.0045, df =7, p = 0.1883
*Significant at $p < 0.05$

H3a**: There is no significant difference in **risk of visual impairment** between **bevacizumab users** and nonusers among AMD and DME patients, while controlling for covariates. (**Not Rejected)

H3b**: There is no significant difference in the **risk of visual impairment** by the **number of bevacizumab treatments** among AMD and DME patients, while controlling for covariates. **(Not Rejected)

4.3.4 Objective 4: Direct medical costs

4.3.4.1 Objective 4 overview

Objective 4 was to determine whether direct medical costs differ between DME and DME control groups, while controlling for covariates. Direct cost was defined as medical and medication cost combined during the 1-year post-index period in Texas Medicaid program. For each patient, inpatient, outpatient, prescription, and overall cost were calculated and summarized. In addition, disease-related cost, which was composed of diabetes-related inpatient and outpatient cost, DME-related outpatient cost, and anti-diabetic medication cost were calculated. Diabetes-related costs were included only when diabetes was the header diagnosis. DME costs were included when the visit was determined to be DME-related. In order to qualify, the claim must contain a diagnosis code of DME as well as CPT/HCPCS codes indicating ophthalmology visit or treatment related to DME. For objective 4, a generalized estimating equation (GEE) of generalized linear model (GLM) was used to compare overall, inpatient, outpatient, and prescription costs between DME and DME control groups. DME and DME control patients were matched and process will be discussed in detail in 4.25.

4.3.4.2 Propensity score matching

Table 4.3.4.1 compared demographic and clinical characteristics for unmatched DME and DME control groups. A total of 61,537 patients were eligible for propensity score matching. At first, patients were matched based on age, total number of unique medications, and CCI score because we thought those variables present the main differences between the two groups. After the first matching attempt, the differences of

age and race group were still significant. Then race group was added and matching was conducted again. However, race was still not matched between DME and DME control groups. Therefore, the first matching method was used to obtain better matched results on age, number of unique medications, and CCI. Table 4.25 compared demographic and clinical characteristics for DME and DME control groups. A total of 61,543 patients were eligible for propensity score matching.

Table 4.25: Demographic and Clinical Characteristics of DME and DME Control Patients (Unmatched Sample)

	DME (N=3,647)	**DME control (N=57,896)**	**p-value**
Age, Mean(±SD)[a]	54.2(8.1)	50.5(10.4)	<0.0001*
Females (%)[b]	64.7	65.3	0.4411
Race/ethnicity (%)[b]			
Hispanics	54.2	31.3	<0.0001*
Caucasians	24.2	34.4	
African Americans	18.4	24.4	
Others	3.2	4.3	
Total number of unique medications, Mean(±SD)[a]	2.8(3.4)	3.2(3.5)	<0.0001*
Charlson Comorbidity Index, Mean(±SD) [a]	6.2(3.2)	3.0(2.6)	<0.0001*

DME= diabetic macular edema

[a] T-test

[b] Chi-square

*Significant at $p < 0.05$

A total of 7,266 patients were matched with 88.2% lost in the matching process. After matching there were no significant differences between the DME and DME control groups regarding gender, total number of unique medications, and CCI (Table 4.26). However, DME patients were younger and they had a higher proportion of Hispanics compared to the DME control group. The 7,266 patients served as the final sample for cost calculations and regression analyses.

Table 4.26: Demographic and Clinical Characteristics of DME and DME Control Patients (Matched Sample)

	DME (N=3,633)	DME control (N=3,633)	p-value
Age, Mean(±SD)[a]	54.2(8.2)	55.2(7.1)	<0.0001*
Females (%)[b]	64.7	64.1	0.6069
Race/ethnicity (%)[b]			
Hispanics	54.2	32.7	<0.0001*
Caucasians	24.2	35.3	
African Americans	18.4	28.5	
Others	3.2	3.4	
Total number of unique medications, Mean(±SD)[a]	2.8(3.4)	2.7(3.4)	0.2642
Charlson Comorbidity Index, Mean(±SD)[a]	6.2(3.1)	6.1(3.2)	0.1567

DME= diabetic macular edema

[a] T-test

[b] Chi-square

*Significant at $p < 0.05$

4.3.4.3 Disease-related cost and overall direct medical cost

DME, DME control, and AMD costs/patient are shown in Table 4.27. All costs were adjusted to 2013 US dollars and the CPI percent change for medical care service and commodities was used (www.bls.gov). Although the cost of AMD is not included in Objective 4, it is included in the table for comparison purposes. AMD cost will be discussed in the section presenting Objective 5 results. Disease-related costs/person for DME and DME control patients were $3,247±6,923 and $1,183±7,815. Total direct medical costs/person (Mean±SD) incurred by the study DME, DME control, and AMD subjects in the post-index period were $6,704±9,338 and $5,495±10,153, $4,935±12,702, respectively.

Table 4.27: Disease-related Costs/Person and Overall Costs/Person for Study Cohorts

Cost ($)	**DME (N=3633)**	**DME control (N=3633)**	**AMD (N=297)**
Disease-related costs	**Mean(±SD) Median**	**Mean(±SD) Median**	**Not Applicable**
Diabetes-related inpatient cost	1,052 (6,407) 0	806 (7,506) 0	
Diabetes-related inpatient cost for non-zero cost patients	13,959 (18,744) 7,715 (n=269)	14,545 (28,447) 7,131 (n=200)	
Diabetes-related outpatient cost	593 (1,021) 286	396 (1,157) 152	
DME-related outpatient cost	504 (823) 208	0 0	
Anti-diabetic medication cost	1,098 (1,930) 10	681 (1,462) 0	
Total	**3,247 (6,923) 1,278**	**1,183 (7,815) 328**	
Overall cost	**Mean(±SD) Median**	**Mean(±SD) Median**	**Mean(±SD) Median**
Inpatient cost	1,095 (6,447) 0	817 (7,513) 0	845 (11,568) 0
Inpatient cost for non-zero cost patients	14,210 (19,200) 7,758 (n=285)	14,638 (28,718) 7,081 (n=204)	35,076 (66,505) 8,922 (n=8)
Outpatient cost	2,343 (3,614) 1,104	1,274 (3,409) 329	1,093 (2,141) 412
Medication cost	3,266 (5,154) 821	3,404 (5,523) 624	2,897 (5,070) 708
Total	**6,704 (9,338) 3,725**	**5,495 (10,153) 2,033**	**4,935 (12,702) 1660**

DME= diabetic macular edema; AMD= age-related macular degeneration

4.3.4.4 Cost comparisons (GLM-GEE Model)

Because of non-normality the generalized linear model (GzLM) with generalized estimating equation (GEE) was used to compare the direct medical cost between DME and DME control patients. The dependent variables in the four GzLM-GEE models were overall, inpatient, outpatient, and medication cost.

Table 4.28 shows the detailed results of the first GzLM-GEE model. DME control patients had lower overall costs than DME patients ($p<0.0001$). Older ($p<0.0001$) and male ($p=0.0386$) patients are associated with lower overall costs. Patients with more prescriptions ($p<0.0001$) and more comorbidities ($p<0.0001$) at index date had higher costs.

Table 4.28: Generalized Linear Regression Analysis Comparing Overall Cost of DME Patients and DME Control Patients (N=7,266)

	Estimate	**95% CI**		**Wald Chi-Square**	**p-value**
DME control patients†	-0.1948	-0.2528	-0.1369	43.40	<0.0001*
Covariates					
Age	-0.0206	-0.0244	-0.0167	109.00	<0.0001*
Male†	-0.0637	-0.1240	-0.0033	4.28	0.0386*
Non-Whites†	-0.0404	-0.1037	0.0229	1.57	0.2109
Total number of unique medications	0.1796	0.1700	0.1892	1344.60	<0.0001*
Charlson Comorbidity Index	0.0682	0.0592	0.0771	221.62	<0.0001*

DME= diabetic macular edema
†Reference categories: DME patients, females, whites
*Significant at $p < 0.05$

Table 4.29 shows detailed results of second GzLM-GEE model. There were no significant (p=0.0720) differences in inpatient costs between DME and DME control patients . Older (p<0.0001), female (p<0.0001), non-white (p=0.0314) patients, and those with more prescriptions (p<0.0001) were associated with lower inpatient cost. Patients with more comorbidities (p<0.0001) at index had higher costs.

Table 4.29: Generalized Linear Regression Analysis Comparing Inpatient Cost of DME Patients and DME Control Patients (N=7,266)

	Estimate	**95% CI**		**Wald Chi-Square**	**p-value**
DME control patients†	-0.1167	-0.2439	0.0104	17.36	0.0720
Covariates					
Age	-0.0410	-0.0494	-0.0325	99.11	<0.0001*
Male†	0.2903	0.1580	0.4226	34.80	<0.0001*
Non-Whites†	-0.1516	-0.2897	-0.0135	44.85	0.0314*
Total number of unique medications	-0.1081	-0.1256	-0.0905	106.53	<0.0001*
Charlson Comorbidity Index	0.3373	0.3166	0.3580	1044.83	<0.0001*

DME= diabetic macular edema
†Reference categories: DME patients, females, Whites
*Significant at $p < 0.05$

Table 4.30 shows detailed results of the third GzLM-GEE model. DME control patients had lower outpatient cost than DME patients (p<0.0001). Male (p<0.0001) patients were associated with lower outpatient cost. Non-white (p=0.0003) patients, those with more prescription (p<0.0001) and more comorbidities (p<0.0001) at index had higher costs.

Table 4.30: Generalized Linear Regression Analysis Comparing Outpatient Cost of DME Patients and DME Control Patients (N=7,266)

	Estimate	95% CI		Wald Chi-Square	p-value
DME control patients†	-0.5761	-0.6388	-0.5134	324.26	<0.0001*
Covariates					
Age	-0.0036	-0.0077	0.0005	3.00	0.0834
Male†	-0.1288	-0.1940	-0.0636	14.98	<0.0001*
Non-Whites†	0.1251	0.0570	0.1932	12.95	0.0003*
Total number of unique medications	0.0842	0.0745	0.0939	288.56	<0.0001*
Charlson Comorbidity Index	0.0613	0.0514	0.0712	146.49	<0.0001*

DME= diabetic macular edema
†Reference categories: DME patients, females.
*Significant at $p < 0.05$

Table 4.31 shows detailed results of the fourth GzLM-GEE model. DME control patients had higher total medication cost than DME patients (p<0.0001). Older (p<0.0001) and male (p=0.0095) patients, and those with higher CCI (p<0.0001) scores at

index had lower medication cost. Patients with more prescriptions (p<0.0001) at index had higher costs.

Table 4.31: Generalized Linear Regression Analysis Comparing Total Medication Cost of DME Patients and DME Control Patients (N=7,266)

	Estimate	95% CI		Wald Chi-Square	p-value
DME control patients†	0.1779	0.0941	0.2617	17.33	<0.0001*
Covariates					
Age	-0.0193	-0.0248	-0.0138	47.22	<0.0001*
Male†	-0.1151	-0.2022	-0.0281	6.72	0.0095*
Non-Whites†	0.0362	-0.0555	0.1278	0.60	0.4393
Total number of unique medications	0.3891	0.3714	0.4068	1854.94	<0.0001*
Charlson Comorbidity Index	-0.0442	-0.0572	-0.0312	44.44	<0.0001*

DME= diabetic macular edema
†Reference categories: DME patients, females, whites
*Significant at p < 0.05

H4: *There is no significant difference in* ***direct medical costs*** *between* ***DME and DME control patients****, while controlling for covariates.* ***(Rejected)***

4.3.5 Objective 5: direct medical costs of AMD

4.3.5.1 Objective 5 overview

Objective 5 was to determine the direct medical cost of AMD. Direct cost was defined as medical and medication cost combined during the 1-year post-index period. For each patient, inpatient, outpatient, prescription, and overall costs were calculated.

4.3.5.2 Overall direct medical cost

See Table 4.27 for the detailed cost for DME, DME control, and AMD patients.

4.4 SUMMARY OF HYPOTHESES TESTING

The results of all hypotheses testing in this study are summarized in Table 4.32.

Table 4.32 Results of Hypotheses Testing

Objectives/ Hypotheses	Statistical Analysis	Result
Objective 1: To determine if demographic and clinical characteristics differ among DME and AMD patients.		
$H_{1a:}$ There is no significant difference in *age* among DME and AMD patients.	Descriptive statistics and ANOVA	**Not Rejected**
$H_{1b:}$ There is no significant difference in *gender* among DME and AMD patients.	Descriptive statistics and chi-square test	**Not Rejected**
$H_{1c:}$ There is no significant difference in *race* among DME and AMD patients.	Descriptive statistics and chi-square test	**Rejected**
$H_{1d:}$ There is no significant difference in *Charlson Comorbidity Index* among DME and AMD patients.	Descriptive statistics and t-test	**Rejected**
$H_{1e:}$ There is no significant difference in *total number of medications* used among DME and AMD patients.	Descriptive statistics and t-test	**Not Rejected**
$H_{1f:}$ There is no significant difference in *number of laser treatments* used among DME and AMD patients.	Descriptive statistics and Wilcoxon	**Rejected**
$H_{1g:}$ There is no significant difference in *number of bevacizumab treatments* used among DME and AMD patients.	Descriptive statistics and t-test	**Rejected**
Objective 2: To determine if the *risk of cardiovascular/ hemorrhagic events* differs by the number of bevacizumab treatments among AMD and DME patients, while controlling for covariates.		
$H_{2b:}$ There is no significant difference in *risk of cardiovascular/hemorrhagic events* between bevacizumab users and nonusers among AMD and DME patients, while controlling for covariates.	Logistic regression	**Not Rejected**
$H_{2b:}$ There is no significant difference in *risk of cardiovascular/hemorrhagic events* by the number of bevacizumab treatments among AMD and DME patients, while controlling for covariates.	Logistic regression	**Not Rejected**

Table 4.32 Results of Hypotheses Testing, cont

$H_{2c:}$ There is no significant difference in *time to first cardiovascular/hemorrhagic events* by the number of bevacizumab treatments among AMD and DME patients, while controlling for covariates.	Cox regression	**Not Rejected**
Objective 3: To determine if the *risk of visual impairment* differs by the number of bevacizumab treatments among AMD and DME patients, while controlling for covariates.		
$H_{3a:}$ There is no significant difference in *risk of visual impairment* between bevacizumab users and nonusers among AMD and DME patients, while controlling for covariates.	Logistic regression	**Not Rejected**
$H_{3b:}$ There is no significant difference in *risk of visual impairment* by the number of bevacizumab treatments among AMD and DME patients, while controlling for covariates.	Logistic regression	**Not Rejected**
Objective 4: To determine whether direct medical costs differ between DME and DME control groups, while controlling for covariates.		
H_4: There is no significant difference in direct medical costs between DME and DME control groups, while controlling for covariates.	GzLM model estimated with gamma distribution	**Rejected**
Objective 5: To describe direct medical costs of patients with AMD.		

AMD=Age related macular degeneration; DME=Diabetic macular edema; Generalized linear models (GzLM).

Chapter 5 DISCUSSION and CONCLUSIONS

5.1 CHAPTER OVERVIEW

This chapter provides a detailed discussion of the study's results. First, the purpose of this study is reviewed. Next, the objectives are discussed, including a section on the study's strengths and limitations. Lastly, conclusions and future research opportunities are discussed.

5.2 REVIEW OF STUDY PURPOSE

The aims of this study were to compare safety, effectiveness, and cost associated with DME and AMD patients. Medicaid data from Sep 2007 to Dec 2012 were used. Previous database studies mainly focused on AMD patients and limited information exists regarding DME patients treated with bevacizumab and the resulting safety, effectiveness, and cost outcomes. Thus, the discussion below will be limited with regard to comparisons with other studies in the literature.

5.3 STUDY OBJECTIVES

Five objectives and thirteen hypotheses were addressed in this study. In this section, study results are discussed, and implications, recommendations, as well as future research suggestions are provided along with each objective.

5.3.1 Objective 1

Discussion

The goal of Objective 1 was to determine if demographic and clinical characteristics differ among Texas Medicaid DME and AMD patients. Regarding demographics, our study showed no differences in age between AMD and DME patients, whereas other studies have found that AMD patients are older.[30] This discrepancy is likely due to the differences in inclusion criteria and the patient population. We used a Medicaid population and truncated our upper age limit at 63 (to exclude dual eligible patients), which resulted in a relatively younger population (i.e., nonelderly with an average age of 53 years), while most other studies used Medicare populations where the lower age limit was 65. Although AMD is more prevalent in the elderly population, it is not surprising that we did not find a significant difference in age given our study's inclusion criteria of nonelderly patients. Regarding race, a higher proportion of AMD patients were Caucasian (34.0% vs. 24.2%), which was consistent with Lim et al., who reported that Caucasians were more likely to develop AMD than any other race.[28]

Clinical characteristic findings revealed that a higher proportion of AMD patients were bevacizumab users (18.2% vs. 13.1%), and a lower proportion were on laser therapy (2.4% vs. 26.6%) when compared to DME patients. These findings are in accordance with the American Association of Ophthalmology guidelines, which recommend anti-VEGF therapy (including bevacizumab) as first line therapy for AMD and laser photocoagulation as first line therapy for DME.[44,54] In addition, our findings are consistent with two observational studies.[15,103] However, these two studies had higher treatment prevalence, which was probably due to their older study populations (i.e., Medicare patients). AMD patients' mean CCI scores were lower (3.1±3.5 vs. 6.2±3.2) than DME patients. One possible reason is that DME patients had additional points added

to their CCI scores due to having diabetes (1 point), as well as having diabetes with chronic complications (2 points); whereas AMD patients typically do not have diabetes.

Summary, implications, recommendations

In summary, Objective 1 revealed differences in patient and clinical characteristics between DME and AMD patients. Although some of our findings may differ from other observational studies because of study populations (i.e., Medicaid vs. Medicare), these results provide a profile of the characteristics of nonelderly DME and AMD patients. Medicaid may want to examine the patient characteristics and consider implementing measures to: increase awareness of DME and AMD, prevent progression of each disease state, and initiate treatment earlier, if warranted, in the nonelderly population. Diabetes management program emphasizing ophthalmology examines and treatment could be implemented focusing on underserved African American and Hispanic population.

5.3.2 Objective 2

Discussion

Objective 2 was to determine if the risk of cardiovascular/hemorrhagic events differed by bevacizumab use among AMD and DME patients. Our study showed no difference in the risk of cardiovascular, hypertension, and bleeding events between bevacizumab users and non-users. Although the literature is scant, several comparisons can be drawn between our study, clinical trials, and an observational study of Medicare patients (see Table 5.1). Although our study examined a broader scope of adverse events

compared to other studies in the literature, for a subset of outcomes (i.e, myocardial infarction, cerebrovascular accidents, and bleeding) our results of no increased risk are consistent with the findings from an observational study of Medicare patients with AMD who were treated with bevacizumab.[101] In contrast, the CATT clinical trials revealed an increase of 50% (from 2% to 3%) in adverse events after bevacizumab treatment.[18] However, due to small sample sizes, clinical trials are not powered to detect differences in rare adverse events. Furthermore, patients enrolled in clinical trials are subject to selection bias, and they typically have fewer comorbidities; both of which could result in a population that is less severe than the general public.

Although a chart review and Curtis' study showed a higher percentage of adverse events among bevacizumab users than ranibizumab users,[100,101] our study does not have a large enough sample to compare the safety of bevacizumab and ranibizumab.

Table 5.1 also shows that similar to other studies, our study showed that myocardial infarction, cerebrovascular accidents, venous thrombotic events, and bleeding were low. However, our study events were similar or higher than the CATT clinical trials, [18] but lower than an observational study that used Medicare AMD patients.[101] This may explain by age differences across the three populations: our study of nonelderly; the CATT clinical trials of possibly less severe patients; and the Medicare (i.e., elderly) observational study of AMD patients. Thus it would be expected that the Medicare population would be older and thus have a higher likelihood of more adverse events.

Table 5.1: Comparison of Cardiovascular/ Hemorrhagic Adverse Event Rates with Bevacizumab users

	Current study Medicaid (N[a])	**CATT[18] Clinical Trials[b] (N=300)**	**Curtis et al.[101] Medicare (N=38,718)**
Adverse events	**N (%)**	**N (%)**	**N (%)**
Cardiovascular	**24 (8.2)** (N=290)	-	-
Heart Failure	15 (5.2)	-	-
Proteinuria	2 (0.7)	-	-
Myocardial infarction	1 (0.3)	1 (0.3)	378 (1.2)
Cerebrovascular accident	4 (1.4)	2 (0.7)	659 (2.1)
Venous thrombotic event	2 (0.7)	1 (0.3)	-
Hypertension	**17 (25)** (N=68)	-	-
Bleeding	**7 (1.9)** (N=365)	-	**1719 (5.5)**

[a] Sample size differs across conditions
[b] Age range:≥50; Age (Mean±SD): 79.2±7.4.

Our study also found no relationship between number of bevacizumab treatments (accumulated dose) and risk of cardiovascular/hemorraghic events. There were also no differences in time to event analysis between bevacizumab users and non-users. Although Duan et al. showed the positive relationship between AMD and MI, our study did not detect a higher risk for AMD patients. This may be explained by the differences in age (elderly vs. nonelderly) as discussed previously. In addition, our study sample only included patient between 18 to 63 years of year where the average age of AMD patient is usually around 80.

In addition, our actual sample size was smaller than the estimated sample size (Table 3.10) for the logistic regression analyses examining risk of cardiovascular and hypertension patients. A large number of patients were excluded because of pre-index cardiovascular events (i.e., non-incident cases). Post-hoc power analyses were conducted and the power calculations for cardiovascular and hypertension groups were 0.28 and

0.06, respectively. However, when examining the p-values for each of the analyses (0.45, 0.95), they were rather large, which may indicate that even with a large sample size, we may not have been able to detect any differences.

Summary, implications, recommendations

Our study showed no difference in the risk of cardiovascular and bleeding events between DME and AMD bevacizumab users and nonusers. Claims database studies examining bevacizumab safety are important because of its off-label use in treating AMD and DME. For medications that are used on-label, adverse drug events are reported and collected through pharmacovigilance efforts. However, there are no systematic efforts to collect these data when medications are used off-label. Our study adds to the literature by examining adverse events in a nonelderly AMD and DME population.

DME patients in Texas Medicaid are undertreated for bevacizumab. Based on our analysis, 13.5% of Texas Medicaid recipients diagnosed with AMD or DME were treated with bevacizumab. Only 84 patients (2.3%) has at least three injections during the 1-year post-index period, which is undertreated compared to the clinical trials (at least 6 injections per year). As a result, the result might be different when majority of patient had more than 3 injections per year. Future studies could further investigate this issue, and as the use of ranibizumab increases, comparisons can be made among the anti-VEGF agents. Although no increased cardiovascular risks were observed with bevacizumab use, Medicaid should consider closely monitoring its use for adverse events.

5.3.3 Objective 3

Discussion

Objective 3 was to determine if visual impairment differed between bevacizumab users and non-users. Our results revealed no significant difference between bevacizumab users and non-users. Comparisons with other studies in the literature are difficult to make because most other studies were clinical trials or they focused on ranibizumab.[72-74,77] However, one phase II clinical trial revealed better visual acuity improvement among bevacizumab users compared to non-users.[78]

One very likely reason that we found no difference in visual impairment was because of limitations of the Medicaid claims database. Although we initially proposed to use ICD-9 codes and SSI designation, the database lacked the needed level of detail to validly operationalize visual impairment. The majority (94.0%) of patients was already receiving SSI for blindness in the pre-treatment period and this continued throughout the study period. So receipt of SSI was not a valid proxy for changes in visual acuity since it appeared that once patients started receiving the income, it continued throughout the study period, regardless of changes in vision status. Regarding ICD-9 codes, documentation was scant or did not include the level of detail needed to determine changes in the degree of visual impairment.

Summary, implications, recommendations

To our knowledge, this is the first study using claims data to compare the effectiveness of bevacizumab and other treatments among DME and AMD younger adult patients (≤65 years old). However, our findings regarding visual acuity may not be valid due to the limitations of the study database. Medicaid may want to request more complete documentation of visual acuity outcomes for reimbursement. Future research could focus on more comprehensive databases (e.g., electronic health records) that document more

valid and reliable visual impairment outcomes so that effectiveness can be measured more accurately.

5.3.4 Objective 4

Discussion

Objective 4 was to determine whether direct medical costs differed between DME and DME control groups. To our knowledge, only one other study calculated costs of DME patients.[15] Compared to DME control patients, DME patients had significantly higher overall direct medical cost, which is consistent with Shea et al.'s findings. Total direct medical cost in our study was $6704, which was lower than the $9462 findings from the Shea et al. study (see Table 5.2). The differences in cost between these two studies may be due to differences in study populations and study timeframes. Shea et al. derived costs from Medicare data, with patients who are generally older (65+ years old) and have more comorbidities which may lead to more service utilization, as well as more costly services utilization (e.g., hospitalizations, emergency department visits). This was shown in the Shea et al. study where inpatient costs were higher than outpatient costs. Medicaid patients' outpatient costs in our study were almost three times higher when compared to Medicare patients in the Shea et al. study. A potential reason for this difference is that Medicaid patients are younger and may be at early stages of diabetes and DME. In the earlier stages, disease management is more focused on DME prevention and/or progression, which could involve more frequent screening and early treatment. The majority of these activities occur during office visits, which are outpatient costs. In contrast, with a Medicare population, the disease may have progressed and the focus may

be more reactive versus preventive and patients may need more inpatient visits to resolve issues.

Another possible explanation for the discrepancies in direct medical cost is the different study timeframes, which represent inflation and changes in use of treatments (laser vs. anti-VEGF). Shea et al.'s study included costs from 2000 to 2004 whereas our costs were calculated from 2008 to 2012 and then adjusted to 2013 dollars. Also the use of anti-VEGF agents was not very prevalent until after 2006. Since it is an expensive treatment that is administered in ophthalmology office, it may explain differences in outpatient costs.

Table 5.2: DME Costs in Both Medicaid and Medicare Populations

Cost ($)	**Our study: Medicaid (N=3,633)**	**Shea et al. Medicare[15] (N=13,115)**
Overall cost/patient	**Mean(SD)**	**Mean(SD)**
Inpatient cost	1,095 (6,447)	4,871 (11,355)
Outpatient cost	2,343 (3,614)	893 (1,449)
Medication cost	3,266 (5,154)	3,698 (3,172)
Total	**6,704 (9,338)**	**9,462(NR)[a]**

DME= diabetic macular edema; NR=Not reported

[a] Total cost is the sum of the cost of inpatient, outpatient, and medication costs; However, the study reported a total cost of $11,290(15,565) because it also include costs of nursing facilities, home health, durable medical equipment, and hospice, which were not delineated separately in the study.

In addition, we found that DME patients had significantly higher outpatient cost but lower medication costs than DME control patients. One explanation could be how treatment is categorized for DME and DME control. Treatment (laser or anti-VEGF injection) for DME patients is usually conducted in an ophthalmologist's office which is included in outpatient costs rather than medication costs. Whereas, in the DME control group, treatment is primarily with oral antidiabetic agents, which would be included in medication costs.

Summary, implications, recommendations

To our knowledge, this is the first study using Medicaid data to calculate cost related to DME and AMD. Compared to Shea's study, our study has the following strengths. First, we used propensity score to match DME patients to patients who have diabetes but no DME. Although age and race were still different after matching, the two groups are much more similar compared to the baseline. Secondly, we examined the cost of treatment-naïve patients, which may be more comparable because it reflects costs when treatment is initiated. Thirdly, our cost analysis reflected the change in treatment

patterns for DME since 2006, which was when anti-VEGF treatment increased in use. We also examined the characteristics associated with higher costs. Younger patients with higher number of prescriptions and comorbidities were associated with higher direct medical costs. One possible explanation is that patients who developed DME at a younger age may potentially have higher A1C levels compared to their control counterparts (i.e., diabetes but no DME). Patients with more advanced diabetes have more hospitalizations and prescriptions, which lead to higher cost. Because there are more safety concerns for patients with more comorbidities, ranibizumab may be considered over bevacizumab because ranibizumab is believed to be the safer anti-VEGF choice, although it is more costly.

Findings from this objective have several implications. First, newly diagnosed and treated DME is associated with substantial direct medical costs. Payers and patients should be focused on DME prevention to decrease disease burden. Second, compared to Shea's study, it appears that outpatient costs have increased in recent years, while overall and inpatient costs have decreased during the same time period.[15] It is possible that in the recent years, along with the increase of awareness of DME, the disease was detected earlier and treatment were given earlier. This implies that more intensive outpatient prevention and early treatment could result in avoidance of future inpatient services. Medicaid may want to consider early screening and treatment among young Medicaid patients who are in the early stages of DME. Even more important is to focus on diabetes management and A1C control to prevent progression to DME. Patient with high A1C level should be monitored especially. Medicaid MTM program could enroll diabetes patients and pharmacists could provide service to help them manage their A1C level. Regular eye exams should be scheduled for patients with diabetes and any visual changes should be addressed early to prevent any further vision loss.

5.3.5 Objective 5

Discussion

Objective 5 was to determine the direct medical cost of AMD. The average overall direct medical cost for AMD in our study is $4,935 per person year. Compared to Day et al.'s study costs ($5,991), our mean cost was approximately one thousand dollars lower.[17] As we mentioned earlier, anti-VEGF is the first line treatment and ranibizumab or bevacizumab is recommended by in the AAO guideline.[44] However, ranibizumab is not widely used among Medicaid patients because of its cost. Approximately 50 patients were treated with ranibizumab during our study period, which is why they were excluded from analysis. However, in the Day et al. study, which was a Medicare population, a higher proportion of patients used ranibizumab, which likely explains the cost difference between their study and ours. In Day's study, among the overall cost of $5,991, 27% ($1,609) comprised expenditures for anti-VEGF. In contrast to Medicare, AMD patients in our Medicaid study were prescribed bevacizumab (a less expensive off-label anti-VEGF option). As a result, Medicaid patients in our study had lower costs associated with AMD than Medicare patients in the Day study. This finding is supported by Smiddy et al.'s study where an 80% cost reduction was associated with switching from ranibizumab to bevacizumab.[117]

Summary, implications, recommendations

Although anti-VEGF therapies have significant clinical benefits for AMD, the choice among anti-VEGF therapies (bevacizumab vs. ranibizumab) must be integrated with the consideration of the economic burden. Although our study was not powered to compare the two therapies, this may be a focus of future studies.

5.4 STRENGTHS AND LIMITATIONS

Strengths of our study include the use of claims data to examine the safety, effectiveness, and cost of bevacizumab treatment. Although clinical trials have the strongest internal validity design, they are typically not powered to identify rare adverse events. In addition, due to its artificial nature, clinical trials do not reflect costs in the 'real world.' In our study, patients were selected and matched based on meaningful criteria to reduce bias. First, comparisons were made based on incident events (with the exception of bleeding events) so that the possibility of recurrent cardiovascular events could be ruled out, which helps to establish a stronger association between the treatment and risk. Second, continual enrollment was assured in not only the pre/post-index period, but also the pre/post-treatment period. This is important because the differences between diagnosis and treatment would cause variations in the length of follow-up periods between bevacizumab users and non-users. Giving users and non-users an equal length of post-treatment time was needed for objectives 2 and 3, where post-treatment safety and effectiveness were compared. Third, propensity scores were used to match patients with controls based on relevant demographic and clinical characteristics. Furthermore, we controlled the factors that might be associated with the outcome by including them in the regression equation. Another advantage of this study design is that adverse events were compared among DME and AMD patients. To our knowledge, none of the previous studies that assessed cardiovascular and bleeding events used as broad of a scope as our study. In previous studies, myocardial infarction, stroke, and bleeding were the only conditions studied. A third strength is the inclusion of DME/AMD as a covariate. We examined whether AMD patients had higher cardiovascular and bleeding risk compared to DME patients. A final strength is the detailed cost estimations. In order to understand

the cost distribution, we separated the cost comparison into overall, inpatient, outpatient, and medication costs. Disease-related costs were also reported.

To our knowledge, this is the first study to systematically examine the risk of bevacizumab treatment for DME and AMD patients. Although no elevated risks were found in cardiovascular, hypertension, and bleeding among bevacizumab users, the results must be interpreted with caution and the following factors should be considered. Although bevacizumab users were matched with non-users with propensity scores, it is possible that there were unmeasured/unknown factors that make bevacizumab users different from non-users. ICD-9 codes cannot be used to determine the reason for cardiovascular/ hemorrhagic events. We only know that an event has occurred, but not why. Thus, causality cannot be established. In addition, bevacizumab is under used in Texas Medicaid, there might be more safety concerns when the use of the injection increase. As mentioned previously, visual impairment/acuity outcomes could not be assessed validly using the Texas Medicaid claims database.

Claims data lacks the information to calculate direct non-medical and indirect costs. Patients with visual impairment and blindness depend on caregivers or family members to conduct activities of daily living. The overall burden cannot be estimated without these costs. Another limitation is associated with Texas Medicaid, where ranibizumab use was limited. Although our study focused on the safety and effectiveness of bevacizumab, it would be interesting to compare bevacizumab with ranibizumab. The Texas Medicaid population provided unique insight into the Latino population with DME and AMD. In addition, generalizability of the study may be limited as results cannot be generalized to other populations or other state Medicaid programs. Without incident cases, the relationship between treatment and visual acuity improvement cannot be established. Finally, bevacizumab therapies were not randomly assigned to patients, so

patients may have been subject to selection bias. Patients with more comorbidity may have been channeled to non-anti-VEGF therapies to avoid potential cardiovascular or bleeding events.

5.5 CONCLUSIONS

In conclusion, we did not find an increased risk in cardiovascular and bleeding events associated with DME and AMD patients who receive bevacizumab in Texas Medicaid compared to those who did not. DME patients had higher direct medical cost compared to patients who had diabetes and no DME.

When determining treatment for AMD and DME patients, several factors should be considered. Anti-VEGF (ranibizumab and bevacizumab) is the first line therapy for AMD. Although clinical trials raised safety concerns regarding bevacizumab when compared to ranibizumab, this study did not identify any signs of increased risk of systemic adverse events. We should keep in mind that bevacizumab is a less expensive off-label alternative of ranibizumab and the choice between bevacizumab and ranibizumab should be made through careful consideration. As for DME patients, a trend of increasing use of anti-VEGF was detected but laser is still the main therapy. We did not find any increased risk in cardiovascular or bleeding associated with the use of bevacizumab. However, as the use of anti-VEGF agents increases, further research should be conducted to determine if any changes in cardiovascular adverse events occur.

Appendix A

Abbreviations

Acquired immunodeficiency syndrome (AIDS)
Age-Related Eye Disease Study (AREDS)
Age-related macular degeneration (AMD)
American Academy of Ophthalmology (AAO)
Arterial thromboembolic events (ATEs)
Best corrected visual acuity (BCVA)
centers for Medicare and Medicaid Services (CMS)
Central retinal thickness (CRT)
Charlson Comorbidity Index (CCI)
Choroidal neovascularization (CNV)
Chronic Disease Score (CDS)
Clinically significant macular edema (CSME)
Current Procedural Terminology (CPT)
Diabetic Macular Edema (DME)
Diabetic retinopathy (DR)
Early Treatment Diabetic Retinopathy Study (ETDRS)
Evaluation and management (E/M)
Fluorescein angiography (FA)
Fundus autofluorescence (FAF)
Generalized linear models (GzLM)
Glycosylated hemoglobin (A1C)
Gastrointestinal (GI)
Gross domestic product (GDP)
Indocyanine green angiography (ICGA)
Institutional Review Boards (IRB)
International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM)
National Institute for Health and Clinical Excellence (NICE)
Optical coherence tomography (OCT)
Photodynamic therapy (PDT)
Royal College of Ophthalmologists (ROC)
Statistical Analysis System (SAS)
Supplemental Security Income (SSI)
Healthcare Common Procedure Coding System (HCPCS)
Vascular endothelial growth factor (VEGF)
Vision threatening diabetic retinopathy (VTDR)
Visual acuity (VA)
Wisconsin Epidemiological Study of Diabetic Retinopathy (WESDR)

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Vita

Shan Jiang was born in Beijing, China on November 1st, 1986. In 2010, she graduated from Peking University with a Bachelor and a Master degree in Pharmaceutical science, with a double major in Economics. In the same year, she entered the College of Pharmacy at The University of Texas at Austin.

Permanent address (or email): sjiang@utexas.edu

This dissertation was typed by Shan Jiang.