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Visual Impairment and Blindness Avoided with Ranibizumab in Hispanic and Non-Hispanic Whites with Diabetic Macular Edema in the United States

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Objective: To estimate visual impairment (VI) and blindness avoided with intravitreal ranibizumab 0.3 mg treatment for central-involved diabetic macular edema (DME) among Hispanic and non-Hispanic white individuals in the United States.

Design: Population-based model simulating visual acuity (VA) outcomes over 2 years after diagnosis and treatment of DME.

Participants: Visual acuity changes with and without ranibizumab were based on data from the RISE, RIDE, and DRCR Network trials.

Methods: For the better-seeing eye, VA outcomes included VI, defined as worse than 20/40 in the better-seeing eye, and blindness, defined as VA of 20/200 or worse in the better-seeing eye. Incidence of 1 or both eyes with central-involved DME in 2010 were estimated based on the 2010 United States population, prevalence of diabetes mellitus, and 1-year central-involved DME incidence rate. Sixty-one percent of incident individuals had bilateral DME and 39% had unilateral DME, but DME could develop in the fellow eye.

Main Outcomes Measures: Cases of VI and blindness avoided with ranibizumab treatment.

Results: Among approximately 102 million Hispanic and non-Hispanic white individuals in the United States 45 years of age and older in 2010, an estimated 37 274 had central-involved DME and VI eligible for ranibizumab treatment. Compared with no ranibizumab treatment, the model predicted that ranibizumab 0.3 mg every 4 weeks would reduce the number of individuals with VI from 11 438 (95% simulation interval [SI], 7249–16 077) to 6304 (95% SI, 3921–8981), a 45% (95% SI, 36%–53%) reduction at 2 years. Ranibizumab would reduce the number of incident eyes with VA worse than 20/40 from 16 910 (95% SI, 10 729–23 577) to 9361 (95% SI, 5839–13 245), a 45% (95% SI, 38%–51%) reduction. Ranibizumab was estimated to reduce the number of individuals with legal blindness by 75% (95% SI, 58%–88%) and the number of incident eyes with VA of 20/200 or worse by 76% (95% SI, 63%–87%).

Conclusions: This model suggests that ranibizumab 0.3 mg every 4 weeks substantially reduces prevalence of VI and legal blindness 2 years after initiating treatment among Hispanic and non-Hispanic white individuals in the United States with central-involved DME that has caused vision loss. *Ophthalmology 2015;122:982-989 © 2015 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).*

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Diabetic retinopathy and diabetic macular edema (DME) are the leading causes of vision loss in working-age adults in the United States.[1] In persons with diabetes mellitus, severe vision loss usually is associated with proliferative diabetic retinopathy, whereas the leading cause of moderate vision loss, a loss of 15 letters or more (doubling of the visual angle), is macular edema.[2] Macular edema is characterized by swelling of the macula, the central part of the retina that mediates high-resolution vision.[3] In the Early Treatment Diabetic Retinopathy Study, the risk of moderate vision loss from clinically significant macular edema assigned to no treatment unless and until high-risk proliferative diabetic retinopathy developed was 33% after 3 years of follow-up.[2] Until recently, laser photocoagulation, as applied in the Early Treatment Diabetic Retinopathy Study, was the standard of care for treatment of clinically significant macular edema because it reduced the risk of 15-letter or more loss (approximately 3 lines or more of visual acuity [VA] on an Early Treatment Diabetic Retinopathy Study chart) by 50%.[2] However, 15% of treated patients were estimated to lose vision,[2] and in recent trials evaluating focal/grid laser treatment among patients with some vision

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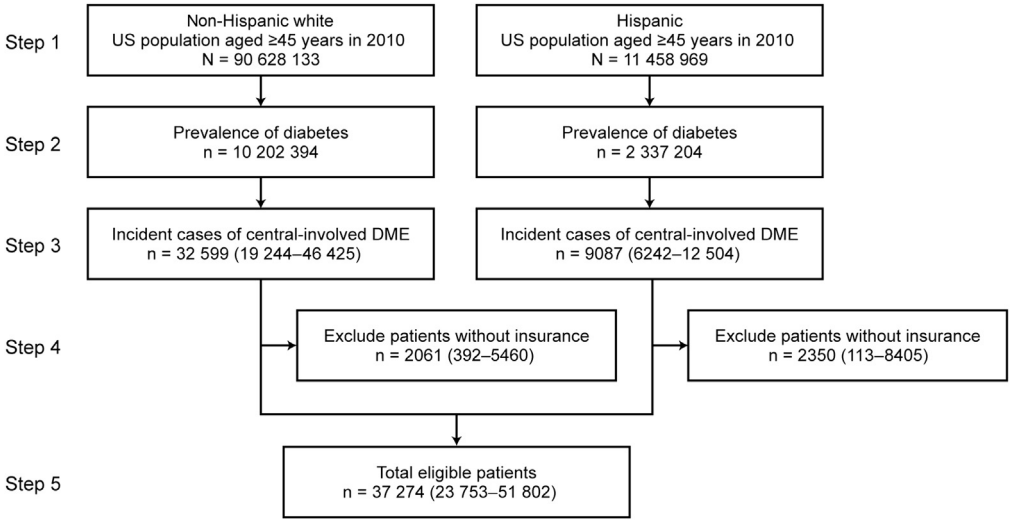

Figure 1. Flowchart showing the estimated total number of persons 45 years of age and older with central-involved diabetic macular edema (DME) causing vision of 20/32 or worse approximate Snellen equivalent who would be considered for ranibizumab treatment in the United States in 2010.

loss associated with DME, vision improvement was estimated to occur in only approximately 30% of patients.[4] More recent study results show that intravitreal injections of anti-vascular endothelial growth factor (VEGF) agents have been shown to have a greater chance of avoiding vision loss and improving vision.[4–6]

Given the impact of ranibizumab (Lucentis; Genentech, Inc., South San Francisco, CA) on VA in patients with DME, we undertook this study to estimate the number of non-Hispanic white and Hispanic persons with DME in the United States who may be able to avoid vision loss and blindness with the use of ranibizumab treatment.

Methods

A population-based effectiveness model was developed to simulate changes in VA with versus without treatment with ranibizumab 0.3 mg administered every 4 weeks in patients with central-involved DME and VA of 20/32 or worse approximate Snellen equivalent (defined as best-corrected VA [BCVA] letter score of ≤78). Eyes with central-involved DME but with vision better than 20/32 approximate Snellen equivalent were assumed not to be candidates for ranibizumab treatment at this time. Specifications for model parameters are listed in Table 1.

Estimate of Patients with Central-Involved Diabetic Macular Edema for Whom Ranibizumab Treatment Would Be Considered

The steps carried out to estimate the total number of patients with central-involved DME in the United States for whom ranibizumab treatment would be considered at this time are summarized in Figure 1. First, only non-Hispanic white and Hispanic individuals were considered in the model because the incidence of DME was available for these groups, but not for other racial or ethnic groups. Using data from the 2010 United States Census Bureau, individuals 45 years of age and older were stratified into 10-year age groups.[7] In step 2, the prevalence of self-reported diabetes was obtained from National Health and Nutrition Examination Survey 2005 through 2008 data.[8] Next (step 3), the 1-year incidence of central-involved DME for non-Hispanic white individuals was derived from the Wisconsin Epidemiologic Study of Diabetic Retinopathy,[9] and that for Hispanics was derived from the Los Angeles Latino Eye Study (LALES).[10] Cases of DME that did not involve the center of the macula or VA better than 20/32 approximate Snellen equivalent in the incident eye were excluded. The proportion of incident eyes with central-involved DME that had VA 20/32 or worse approximate Snellen equivalent (BCVA letter score ≤78) was estimated using data from LALES. Because we did not have access to the Wisconsin Epidemiologic Study of Diabetic Retinopathy data, the same proportion of incident eyes with central-involved DME with VA 20/32 or worse approximate Snellen equivalent from LALES was applied for non-Hispanic white individuals. Next (step 4), individuals without health insurance were excluded by assuming that they were unlikely to have access to ranibizumab. The percentage of the uninsured United States population by age and race or ethnic groups was derived from a population survey conducted by the United States Census Bureau in 2010.[11] Finally (step 5), the total number of persons eligible for treatment was derived by summing across all age and race or ethnic groups. This final number then was used to simulate treatment with and without ranibizumab 0.3 mg. These methods were repeated for treatment with ranibizumab 0.5 every 4 weeks.

Estimated Rates of Visual Impairment and Blindness

The 2-year rates of visual impairment (VI) and blindness for both the better-seeing eye and the incident eye were estimated using a person-level simulation. Visual impairment was defined as BCVA letter score of 68 or fewer in the better-seeing eye, that is, an approximate Snellen equivalent worse than 20/40.[12] Legal blindness was defined as a BCVA letter score of 38 or fewer in the better-seeing eye, that is, an approximate Snellen equivalent 20/200 or worse.[12]

The model was conducted as a 2-dimensional Monte Carlo simulation to account for various sources of patient-level variability and parameter uncertainty using TreeAge Pro 2009 software (TreeAge Software, Inc., Williamstown, MA). To achieve stable rates, 300 averages of 280 simulated patients (based on the sample size of relevant patients in A Study of Ranibizumab Injection in Subjects with Clinically Significant Macular Edema

[ME] with Center Involvement Secondary to Diabetes Mellitus [RISE; clinicaltrials.gov identification, NCT00473330], A Study of Ranibizumab Injection in Subjects with Clinically Significant Macular Edema [ME] with Center Involvement Secondary to Diabetes Mellitus [RIDE; clinicaltrials.gov identification, NCT00473382], and the Diabetic Retinopathy Clinical Research [DRCR] Network [clinicaltrials.gov identification, NCT00445003]) were sampled.[4,6] For each simulated person, the VA of the incident DME eye at baseline was sampled from the VA distribution of participants in the DRCR Network.[4] Sixty-one percent of these individuals had bilateral central-involved DME; therefore, the fellow eye VA also was sampled from the VA distribution of participants in the DRCR Network.[4] Approximately 39% of individuals were assumed not to have central-involved DME in their fellow eye at the start of the model, but could develop the condition over the 2-year period of the model. For the fellow eye without central-involved DME, the VA was sampled from the VA distribution of the fellow eye of individuals in the DRCR Network who did not have DME in the fellow eye. In the incident eye, the letter score change over 2 years was conditioned on the individual's baseline VA. For persons with baseline BCVA letter score of 73 or fewer (20/32 or worse), the 2-year letter score change was based on RISE and RIDE data. However, for baseline BCVA letter score of 78 to 74 (approximate Snellen equivalent of 20/32), the 2-year letter score change was based on data from the DRCR Network because the RISE and RIDE clinical trials did not include a sufficient number of participants in this VA range. Moreover, because the DRCR Network protocol did not include ranibizumab 0.3 mg every 4 weeks dosing, we applied data from the ranibizumab 0.5 mg as-needed arms and assumed that the efficacy was comparable with ranibizumab 0.3 mg every 4 weeks. The sampling distribution was on the actual patient-level data rather than a fitted distribution based on assumption. For the fellow eye, the letter score change over 2 years was conditioned on both the patient's DME status of the fellow eye and baseline VA. The risk of death was applied using United States age-specific mortality rates.[13] The mortality rate of people with diabetes was calculated by adjusting the overall mortality rate by a relative rate of mortality among patients with diabetes compared with people without diabetes.[14] The simulation also accounted for the patient's risk of treatment discontinuation every 4 weeks. While not receiving treatment, no further changes in BCVA were assumed; therefore, BCVA remained constant from the time of discontinuation to month 24.

Estimated Cases of Visual Impairment and Blindness

The predicted cases of patients with central-involved DME who had VI or worsened to blindness at month 24 were derived by applying the rates of these outcomes to the size of the treatment-eligible population. Calculations were performed for each age stratum, then summed across. This population-level simulation was carried out in @Risk software version 6.0 (Palisade Corporation, Ithaca, NY) using 10 000 iterations, accounting for parameter uncertainty, to estimate the confidence in the results expressed as a 95% simulation interval (SI). The difference in outcomes between the scenario without ranibizumab and the scenario with ranibizumab 0.3 mg was calculated to determine the cases of VI or legal blindness that were avoided. The percent reduction was calculated as the percent change in the cases with the outcome at 2 years with ranibizumab treatment.

Sensitivity analyses were carried out on the following parameters: (1) proportion of incident eyes with central-involved DME that had VA of 20/32 or worse and (2) proportion of patients with incident central-involved DME with VA of 20/32 or worse who also had DME in the fellow eye with VA of 20/32 or worse at baseline.

Results

Among approximately 102 million non-Hispanic white and Hispanic individuals 45 years of age or older in the United States in 2010, an estimated total of 37 274 (95% SI, 23 753–51 802) patients with a diagnosis of central-involved DME with VA of 20/32 or worse Snellen equivalent were eligible for ranibizumab treatment. For these 37 274 eligible individuals, VI in the better-seeing eye was predicted in 11 438 (95% SI, 7249–16 077) who did not receive ranibizumab treatment over 2 years (Fig 2). Over the same period, ranibizumab 0.3 mg every 4 weeks reduced VI to 6304 (95% SI, 3921–8981) individuals, resulting in 5134 (95% SI, 3014–7659) for whom VI was avoided, or a 45% (95% SI, 36%–53%) reduction in VI.

Without ranibizumab treatment, 16 910 (95% SI, 10 729–23 577) incident eyes with a BCVA worse than 20/40 were predicted over 2 years (Fig 3). Over the same period, ranibizumab 0.3 mg every 4 weeks reduced the number of incident eyes with a BCVA worse than 20/40 to 9361 (95% SI, 5839–13 245), resulting in 7549 (95% SI, 4551–10 859) eyes avoiding an approximate Snellen equivalent VA worse than 20/40, or a 45% (95% SI, 38%–51%) reduction in VA worse than 20/40.

Legal blindness, defined as BCVA of 20/200 or worse in the better-seeing eye, was predicted in 1686 (95% SI, 987–2479) individuals not receiving ranibizumab treatment over 2 years (Fig 4). Over the same period, treatment with ranibizumab 0.3 mg every 4 weeks reduced legal blindness to 411 (95% SI, 180–725) individuals, resulting in 1275 (95% SI, 663–2025) persons for whom legal blindness was avoided, or a 75% (95% SI, 58%–88%) reduction in legal blindness.

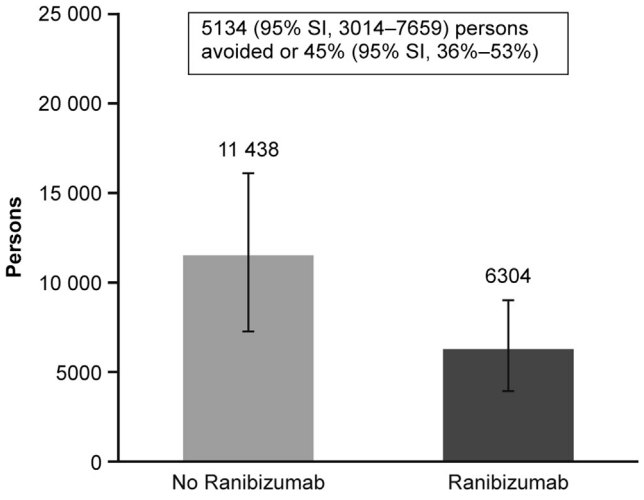

Figure 2. Bar graph showing the number of individuals with central-involved diabetic macular edema and visual acuity of 20/32 or worse approximate Snellen equivalent at baseline who had visual impairment in the better-seeing eye after 2 years (n = 37 274 treated patients). Visual impairment was defined as best-corrected visual acuity worse than 20/40 approximate Snellen equivalent in the better-seeing eye. SI = simulation interval.

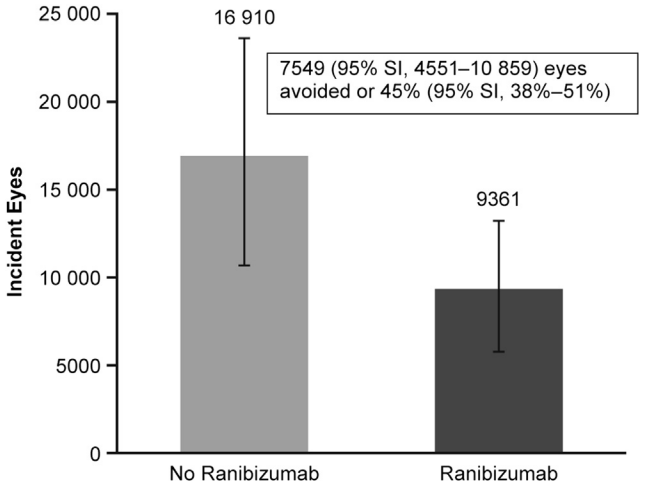

Figure 3. Bar graph showing the number of incident eyes with central-involved diabetic macular edema and visual acuity of 20/32 or worse approximate Snellen equivalent at baseline that had visual impairment after 2 years (n = 37 274 treated patients). Visual impairment was defined as best-corrected visual acuity worse than 20/40 approximate Snellen equivalent in the incident eye with central-involved DME. SI = simulation interval.

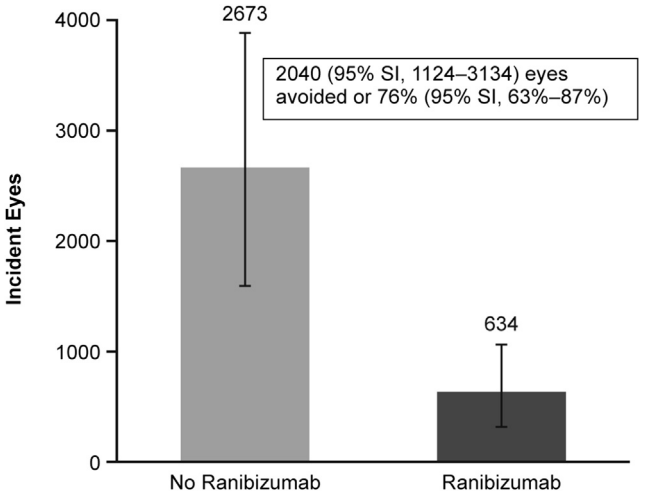

Figure 5. Bar graph showing the number of incident eyes with central-involved diabetic macular edema and visual acuity of 20/32 or worse approximate Snellen equivalent at baseline that had visual acuity of 20/200 or worse after 2 years (n = 37 274 treated patients). SI = simulation interval.

Without ranibizumab treatment, 2673 (95% SI, 1597−3878) incident eyes with a BCVA of 20/200 or worse were predicted over 2 years (Fig 5). Over the same period, treatment with ranibizumab 0.3 mg every 4 weeks reduced the number of incident eyes with a BCVA of 20/200 or worse to 634 (95% SI, 313−1059), resulting in 2040 (95% SI, 1124−3134) eyes in which VA of 20/200 or worse was avoided, or a 76% (95% SI, 63%−87%) reduction in VA 20/200 or worse.

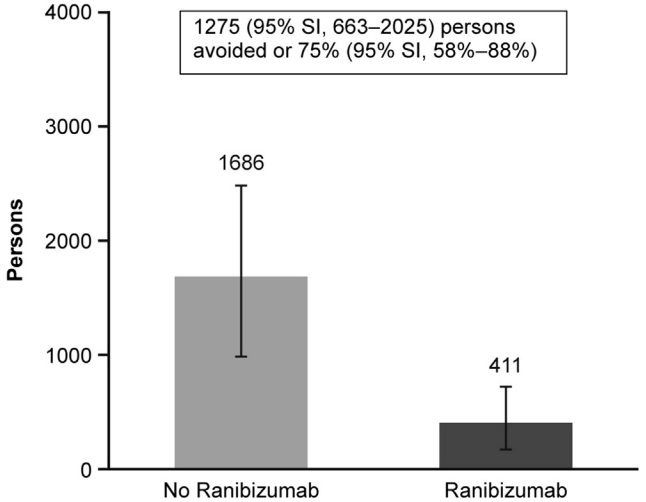

Figure 4. Bar graph showing the number of persons with central-involved diabetic macular edema and visual acuity of 20/32 or worse approximate Snellen equivalent at baseline who had legal blindness after 2 years (n = 37 274 treated patients). Legal blindness was defined as best-corrected visual acuity of 20/200 or worse in the better-seeing eye. SI = simulation interval.

Sensitivity Analyses

The proportion (24.4%) of incident eyes with central-involved DME that had a BCVA letter score of 78 or fewer (approximate Snellen equivalent worse than 20/32) was based on only 41 incident cases of clinically significant macular edema available in LALES.[8] The sensitivity of the results was tested by varying the base value by ±10% points. The resulting size of the treatment-eligible population ranged between 21 991 (95% SI, 14 014−30 563) and 52 557 (95% SI, 33 492−73 041), corresponding to low (14.4%) and high (34.4%) values of the sensitivity range. Table 2 shows the impact of this change on VI in the better-seeing eye after 2 years. In addition, the results of varying the parameter controlling for the proportion of fellow eyes that also had DME with BCVA letter score of 78 or fewer (approximate Snellen equivalent of 20/32 or worse) at baseline are provided in Table 2. Results for ranibizumab 0.5 mg every 4 weeks are available in Table 3 (available at www.aaojournal.org).

Discussion

In this study, we developed a population-based model that suggests that ranibizumab administered to patients with DME in a manner similar to that described in the RIDE and RISE studies would reduce the number of cases of VI by 45% (a reduction of 5134 individuals) and the number of cases of legal blindness by 75% (a reduction of 1275 individuals). These estimates are based on the approximately 37 274 Hispanic and non-Hispanic white adults with DME in the United States in whom ranibizumab treatment would be indicated and potentially used. Similarly, when considering the number of eyes, regardless of the vision in the fellow eye, VA worse than 20/40 would be avoided in 45% of eyes (7549 eyes) and VA of 20/200 or worse would be avoided in 76% of eyes (2040 eyes).

Table 1. Specifications for Model Parameter Inputs

Model Parameter	Value (Uncertainty or Variability)	Source and Notes
Population size in 2010		
Non-Hispanic white		2010 United States Census data[7]
45–54 yrs	31 141 170	
55–64 yrs	27 277 532	
65–74 yrs	16 940 823	
≥75 yrs	15 268 608	
Total	90 628 133	
Hispanic		2010 United States Census[7]
45–54 yrs	5 463 528	
55–64 yrs	3 213 817	
65–74 yrs	1 648 718	
≥75 yrs	1 132 906	
Total	11 458 969	
Prevalence of diabetes, % (SE)		
Non-Hispanic white		NHANES 2005–2008[8]
45–54 yrs	6.4 (0.9)	
55–64 yrs	10.8 (1.3)	
65–74 yrs	18.1 (1.8)	
≥75 yrs	14.4 (1.4)	
Hispanic		NHANES 2005–2008[8]
45–54 yrs	14.4 (2.6)	
55–64 yrs	24.6 (3.1)	
65–74 yrs	29.3 (5.0)	
≥75 yrs	25.1 (4.8)	
Annual incidence of central-involved DME, mean (SE)		
Non-Hispanic white	0.01308 (0.00271)	WESDR[9]
Hispanic	0.01587 (0.00245)	LALES[10]
Proportion of incident eyes with central-involved DME with VA of 20/32 or worse (BCVA letter score ≤78), %	24.4	LALES[10]
Annual incidence of central-involved DME with VA of 20/32 or worse (BCVA letter score ≤78), mean (SE)		
Non-Hispanic white	0.00319 (0.00066)	Derived based on information from WESDR[9] and LALES[10]
Hispanic	0.00387 (0.00060)	Derived based on information from WESDR[9] and LALES[10]
United States population without health insurance, % (SE)		
Non-Hispanic white		United States Census Bureau CPS[11]
45–54 yrs	13.5 (10.0)	
55–64 yrs	11.0 (9.7)	
65–74 yrs	1.3 (4.5)	
≥75 yrs	0.6 (3.2)	
Hispanics		United States Census Bureau CPS[11]
45–54 yrs	37.0 (40.9)	
55–64 yrs	31.4 (50.1)	
65–74 yrs	10.1 (44.2)	
≥75 yrs	6.4 (46.0)	
Mortality rate		
United States age-specific mortality rate		United States Life Tables[13]
Relative rate of mortality (diabetes vs. nondiabetes)	2.31	Gregg 2007[14] (this factor was applied to overall mortality rate to derive diabetes-specific mortality rate)
Patients with incident central-involved DME with VA 20/32 or worse who also had DME in fellow eye with VA 20/32 or worse at BL, %	60.6	Based on proportion of fellow eyes in RIDE and RISE[6] with DME and VA of 20/32 or worse (BCVA letter score ≤78)
Probability of developing central-involved DME in fellow eye (monthly)	0.0038 (SE = 0.0013)	18.3% over 4 yrs, LALES[10] probability for Hispanic also was used for white population
Probability of ranibizumab discontinuation (monthly)	0.0068	RIDE and RISE[6]
BCVA at BL, mean letter score (SD)		
Incident/treated DME eye	63.1 (11.1)	DRCR Network[4]
Fellow eye without central-involved DME	71.7 (17.4)	DRCR Network[4] (used data from individuals without DME in fellow eye)
Fellow eye had central-involved DME at BL or developed central-involved DME	63.1 (11.1)	DRCR Network[4]

Table 1. (Continued.)

Model Parameter	Value (Uncertainty or Variability)	Source and Notes
BCVA change after 24 months mean letter score (SD)*		
Incident eye with ranibizumab 0.3 mg	11.7 (11.2)	RIDE and RISE[6] for BL BCVA letter score ≤73; DRCR Network for BL BCVA letter score 74–78 (note: only data for ranibizumab 0.5 mg available; assumed efficacy similar to ranibizumab 0.3 mg)
Incident eye without ranibizumab	2.0 (14.2)	RIDE and RISE[6] for BL BCVA letter score ≤73; DRCR Network for BL BCVA letter score 74–78
Fellow eye without central-involved DME	0.5 (16.2)	RIDE and RISE[6] for BL BCVA letter score ≤73; DRCR Network for BL BCVA letter score 74–78
Fellow eye with either central-involved DME at BL or developed central-involved DME within 2 yrs, mean letter score (SD)		
Ranibizumab 0.3 mg	11.7 (11.2)	Assumed to have similar efficacy of ranibizumab-treated study eye in RIDE, RISE,[6] and DRCR Network. Actual BCVA change depended on when central-involved DME developed in the fellow eye and number of months to end of model. Changes in BCVA are assessed on a monthly basis.
No ranibizumab	2.0 (14.2)	
BCVA letter score change per month if discontinued from ranibizumab, mean	0.0	Assumed no further change in BCVA on discontinuation of ranibizumab.

BCVA = best-corrected visual acuity; BL = baseline; CPS = Current Population Survey; DME = diabetic macular edema; DRCR = Diabetic Retinopathy Clinical Research; LALES = Los Angeles Latino Eye Study; NHANES = National Health and Nutrition Examination Survey; RIDE = A Study of Ranibizumab Injection in Subjects with Clinically Significant Macular Edema (ME) with Center Involvement Secondary to Diabetes Mellitus; RISE = A Study of Ranibizumab Injection in Subjects with Clinically Significant Macular Edema (ME) with Center Involvement Secondary to Diabetes Mellitus; SD = standard deviation; SE = standard error; VA = visual acuity; WESDR = Wisconsin Epidemiologic Study of Diabetic Retinopathy.
*BCVA change after 24 months is conditioned on patient's VA at BL.

This model shows that with anti-VEGF treatment for central-involved DME, the greatest impact is a reduction in the number of persons with VI; however, preventing persons with blindness may be modest because deterioration of VA to this threshold is less likely to occur in DME. In terms of relative reduction, a greater percent reduction in individuals with legal blindness was predicted compared with the percent reduction in those with VI. A similar modeling approach conducted for anti-VEGF treatment in individuals with age-related macular degeneration (AMD) showed substantial reduction in both the cases of VI and of blindness.[15] Unlike in DME, individuals with AMD can experience a rapid loss in VA without anti-VEGF therapy. These models suggest that in the United States, with

Table 2. Sensitivity Analyses on the Number of Persons with Central-Involved Diabetic Macular Edema Who Had Visual Impairment in the Better-Seeing Eye at 2 Years

Treatment	Base Parameter Value (%)	Visual Impairment in Better-Seeing Eye (95% Simulation Interval)	Base Value −10% (%)	Visual Impairment in Better-Seeing Eye (95% Simulation Interval)	Base Value +10% (%)	Visual Impairment in Better-Seeing Eye (95% Simulation Interval)
Proportion of incident eyes with central-involved DME that had VA 20/32 or worse (≤78 letter score)						
No ranibizumab	24.4	11 438 (7249–16 077)	14.4	6749 (4277–9485)	34.4	16 128 (10 221–22 669)
Ranibizumab		6304 (3921–8981)		3719 (2314–5299)		8889 (5529–12 663)
Proportion of patients with incident central-involved DME with VA 20/32 or worse (≤78 letter score) who also had DME in fellow eye with VA 20/32 or worse (≤78 letter score) at baseline						
No ranibizumab	60.6	11 438 (7249–16 077)	50.6	10 036 (6548–13 896)	70.6	12 764 (8072–17 934)
Ranibizumab		6304 (3921–8981)		5497 (3520–7714)		7052 (4411–10 026)

DME = diabetic macular edema; VA = visual acuity.

monthly ranibizumab treatment, AMD and DME may eventually no longer be the leading causes of blindness and VI in working-age (DME) and older (AMD) Americans.

There were several limitations in this study. Our model considered only incident cases of central-involved DME for 1 year (2010). Because incident cases from the second year were not included, these results are conservative. Moreover, other race or ethnic groups and prevalence cases of DME were not included, which would substantially increase the number of cases of VI and blindness avoided. The actual VA of incident eye at the time of DME diagnosis in the United States population is unknown. We applied the baseline VA distribution from the DRCR Network. For individuals with baseline BCVA of 20/32 to 20/40 approximate Snellen equivalent, the VA change over 2 years, if treated with ranibizumab 0.3 mg every 4 weeks, was assumed to be similar to ranibizumab 0.5 mg as-needed as used by the DRCR Network.[4] Although persons with an incident eye with BCVA of 20/32 to 20/40 are less likely to experience marked gains in VA, the model is likely to underestimate the gain based on ranibizumab as-needed dosing instead of dosing every 4 weeks. Furthermore, this model did not evaluate outcomes for ranibizumab administered less often than monthly for 2 years, in which re-treatment and follow-up intervals were based on changes in VA or OCT or both since the most recent injection. However, in 2 other trials evaluating ranibizumab compared with laser photocoagulation for central-involved DME causing VI in which re-treatment and follow-up intervals were based on changes in VA or OCT since the most recent injection, VA outcomes were similar to those in RIDE and RISE.[4,5] This is especially evident when looking at subgroups with baseline VA averaging approximately 20/80, similar to the baseline VA in RIDE and RISE. These similar outcomes suggest that the projected benefits of ranibizumab treatment identified in our model likely would be similar if alternative as-needed follow-up and re-treatment regimens were followed, as was carried out in other studies that also have shown that the VA benefits are maintained as the median number of treatments decreases to 3 to 4 in the second year, 1 to 2 in the third year,[16] 0 to 1 in the fourth year, and 0 in the fifth year after initiating anti-VEGF therapy.[17]

Finally, although we do not yet know how well this DME model translates to clinical practice, the impact of anti-VEGF therapy has been explored for AMD in a small retrospective cohort study from Johns Hopkins University in patients with incident neovascular AMD.[18] Two cohorts were identified: one from 2002, before the availability of anti-VEGF therapy, and the other from 2008, after anti-VEGF therapy became available. Substantial reductions in the 2-year prevalences of blindness and VI after neovascular AMD were observed in the cohort of patients treated in 2008 (where 98% were treated with anti-VEGF therapy) compared with the cohort of patients treated in 2002 who did not receive anti-VEGF therapy. Although there are many limitations with retrospective cohort data, this study suggests that these models may translate to clinical practice.

In conclusion, using a simulation model of the United States population of persons 45 years of age and older, ranibizumab 0.3 mg every 4 weeks likely reduces legal blindness at a rate of somewhere between 58% and 88% and reduces VI at a rate between 36% and 53% at 2 years after initiating treatment in non-Hispanic white and Hispanic individuals with central-involved DME causing some vision loss. These projected benefits of ranibizumab treatment are particularly important given the potential for preventing poor visual outcomes in eligible persons, including a substantial number of working-age adults in the United States.

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Abbreviations and Acronyms:
AMD = age-related macular degeneration; **BCVA** = best-corrected visual acuity; **DRCR** = Diabetic Retinopathy Clinical Research; **DME** = diabetic macular edema; **LALES** = Los Angeles Latino Eye Study; **RIDE** = A Study of Ranibizumab Injection in Subjects with Clinically Significant Macular Edema (ME) with Center Involvement Secondary to Diabetes Mellitus; **RISE** = A Study of Ranibizumab Injection in Subjects with Clinically Significant Macular Edema (ME) with Center Involvement Secondary to Diabetes Mellitus; **SI** = simulation interval; **VA** = visual acuity; **VEGF** = vascular endothelial growth factor; **VI** = visual impairment.

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