IMPORTANCE Current draft guidelines set forth by the US Food and Drug Administration for compounded or repackaged medications would greatly limit the availability and use of bevacizumab by ophthalmologists across the country. Little evidence beyond highly publicized case reports exists for or against the need for additional regulation of compounded bevacizumab.

OBJECTIVE To determine whether the distribution of bevacizumab through compounding pharmacies increases the risk for endophthalmitis compared with the distribution of single-use vials of ranibizumab from the manufacturer.

DESIGN, SETTING, AND PARTICIPANTS A retrospective cohort study using medical claims data from ambulatory care centers across the United States that were submitted to a large, national US insurer. Cohorts were created using information on 530,382 intravitreal injections administered from January 1, 2005, through December 31, 2012. Any individual from this data set who received an intravitreal injection of bevacizumab or ranibizumab (n=383,810) and had at least 6 months of data before and 1 month after the injection was eligible. After exclusions (any previous diagnosis of endophthalmitis, multiple injected drugs given on the index day, or intraocular surgery within 15 days of the injection or between the injection and a diagnosis of endophthalmitis), our analysis involved 383,810 intravitreal injections given to 58,612 patients. Data collection and analysis occurred from February 16 through April 7, 2015.

MAIN OUTCOMES AND MEASURES The odds of developing endophthalmitis after an intravitreal injection of bevacizumab compared with ranibizumab.

RESULTS In total, 296,565 injections of bevacizumab were given to 51,116 patients and 87,245 injections of ranibizumab were given to 74,966 patients. We found 71 cases of endophthalmitis (49 in the bevacizumab cohort and 22 in the ranibizumab cohort) for an endophthalmitis rate of 0.017% (95% CI, 0.012%-0.021%; 1 case per 6061 injections) for bevacizumab and 0.025% (95% CI, 0.015%-0.036%; 1 case per 3968 injections) for ranibizumab. After controlling for age, race, sex, injection-related diagnosis, and year of injection, we found no significant association with development of endophthalmitis after a bevacizumab injection compared with ranibizumab (odds ratio, 0.66 [95% CI, 0.39-1.09]; P = .11).

CONCLUSIONS AND RELEVANCE The results of this study suggest bevacizumab as currently used across the United States does not increase the risk for endophthalmitis; therefore, additional regulations on the use of repackaged bevacizumab may be unnecessary.
Multiple clinical trials have demonstrated that intravitreal injections of anti–vascular endothelial growth factor agents are highly effective treatments for neovascular age-related macular degeneration, macular edema due to diabetes mellitus, or retinal vein occlusions. As such, injections of anti-vascular endothelial growth factor agents have become standard care for these conditions. Despite the rise in the use of injections, endophthalmitis continues to be the most important postinjection complication. Concern about this adverse event is central to the ongoing debate over the use of compounded or repackaged bevacizumab (Avastin; Genentech).

The lay press first brought this issue to the forefront of the public’s attention after widely reporting on several case series that were discovered within months of each other in 2011. Unfortunately, media sensationalism of this topic may have led to misplaced fear, with headlines such as “Avastin Injections Are Reported To Cause Blindness,” focusing on bevacizumab as the culprit and not the compounding process itself. The first (and to date only) peer-reviewed report to describe compounding-related endophthalmitis was published a few months after the lay press reports and described 12 cases of endophthalmitis in Florida, all linked to a single compounding pharmacy. This report appeared about a month after a letter to the editor of the New England Journal of Medicine that described the faulty practices witnessed at a compounding pharmacy in Tennessee thought to have led to another smaller contamination-related outbreak of endophthalmitis.

Concerns about compounding were further increased after several deaths from a large outbreak of fungal meningitis linked to contaminated compounded solutions of corticosteroids for intrathecal administration. In response to these concerns, Senate Bill S 95911 was introduced and would have allowed the US Food and Drug Administration (FDA) to ban all compounded medications, but the bill never received congressional approval. In February 2015, after placing additional regulations on compounding pharmacies, the FDA also released a draft guidance specifically allowing the use of compounded bevacizumab, but included language regarding “beyond use dates” that limited use to within 5 days of repackaging. This restrictive 5-day time frame does not allow for proper sterility testing (which typically takes 14 days) and would negate the ability of most ophthalmologists to use bevacizumab. In response, the American Academy of Ophthalmology13 and the American Society of Retina Specialists14 issued calls to action that delineated the specific concerns with the proposed new regulations and argued for heavy lobbying against the draft guidance.

Despite this ongoing policy debate, the evidence for or against an increased risk for endophthalmitis owing to repackaged bevacizumab is limited, and whether repackaging truly represents a public health hazard or policy makers are being influenced by highly publicized isolated incidents remains unclear. The purpose of this study was to compare the rates of endophthalmitis after intravitreal injections of bevacizumab and ranibizumab in a national cohort database containing data from January 1, 2005, through December 31, 2012.

Methods

Data Set
We used the Clinformatics Data Mart Database (OptumInsight) for this retrospective cohort study. This administrative medical claims database contains the deidentified billing claims of all covered individuals from a single large insurance company with beneficiaries in each of the 50 states. All outpatient medical claims (office visits, procedures, and medications given) and demographic data for each beneficiary during their enrollment are included. The subset of data available for this study included all patients in the database from January 1, 2005, through December 31, 2012. This study has been deemed exempt from review by the institutional review board of the University of Pennsylvania owing to the deidentified nature of the database.

Study Cohorts
All intravitreal injections (Current Procedural Terminology [CPT] code 67028) using bevacizumab and ranibizumab were identified within the data set and divided into cohorts based on the medicine injected. Each occurrence of an intravitreal injection was used as the index date and was considered a unique observation. For inclusion in the analysis, each index date required the individual who received the injection to have at least 6 consecutive months in the insurance plan before and at least 1 month after the injection. Any injection identified with a bilateral code (CPT 50) was considered to represent 2 injections. Table 1 gives a complete list of codes used during this study.

At any point when an individual was given a diagnosis code for endophthalmitis, all future injections were removed from the analysis. In addition, in an effort to isolate only cases of endophthalmitis related strictly to intravitreal injections, all index dates that occurred less than 15 days after an intraocular surgery or that had an intraocular surgery occur between the index date and the diagnosis of endophthalmitis were also excluded. Last, any intravitreal injections involving more than 1 drug were excluded.

Outcome Measures
The primary outcome measure for this study was the odds of developing endophthalmitis after an intravitreal injection of bevacizumab compared with ranibizumab. Cases
of endophthalmitis were defined by having a new endophthalmitis diagnosis code in conjunction with a code for an intravitreal tap and injection, a vitrectomy, or an intravitreal injection of antibiotics. Cases had to occur from 1 to 14 days after the index date. Cases that occurred on the same day as the index date were excluded owing to an inability to distinguish whether the intravitreal injection preceded the endophthalmitis-defining procedure. We also performed a sensitivity analysis in which the definition of endophthalmitis was expanded. For this analysis, in addition to the definition of endophthalmitis previously stated, we also included the cases that had a new diagnosis of endophthalmitis and an intravitreal injection on the same day (but were not required to have intravitreal antibiotics).

### Statistical Analysis

Data collection and analysis occurred from February 16 through April 7, 2015. We calculated odds ratios (ORs) by logistic regression for univariate and multivariate analyses. Covariates of interest were collected at the time of the index date and included basic demographic information of age, race, and sex. In addition, the injection-associated diagnosis was categorized as age-related macular degeneration, macular edema due to diabetes mellitus, retinal vein occlusions, or other. During the last 8 to 10 years, the rate of endophthalmitis after intravitreal injection is thought to have decreased. To account for any variation in the rates with time in the model, the year of the injection was included as a variable. We used STATA software (version 12; StataCorp) for all statistical analysis.

### Results

A total of 383,810 intravitreal injections of bevacizumab and ranibizumab were given to 58,612 patients during the 2005-2012 study period that met the inclusion criteria for the study (Figure). Of these, 296,565 injections (51,116 patients) used bevacizumab and 87,245 injections (7,496 patients) used ranibizumab. Table 2 provides cohort demographic characteristics. The bevacizumab cohort was younger and had fewer female patients ($P < .001$ for both comparisons). With regard to race, the bevacizumab group included a higher percentage of black and Hispanic patients compared with the ranibizumab cohort ($P < .001$). Although age-related macular degeneration was the most common injection-associated disease in both cohorts, the bevacizumab cohort included more injections related to diabetes mellitus, retinal vein occlusions, and other diagnoses ($P < .001$).

A total of 71 cases of endophthalmitis (49 in the bevacizumab cohort and 22 in the ranibizumab cohort) occurred in the observation period. The mean (SD) time to diagnosis was 4.75 (3.53) days after injection. The overall rate (95% CI) of endophthalmitis was 0.018% (0.014%-0.023%; 1 case per 5,411 injections), with individual rates of 0.017% (0.012%-0.021%; 1 case per 6,061 injections) for bevacizumab and 0.025% (0.015%-0.036%; 1 case per 3,968 injections) for ranibizumab. These rates correlated with a risk difference of 0.009% (95% CI, −0.020% to 0.0028%; $P = .11$) (Table 3). Sensitivity analysis...
with a less stringent definition of endophthalmitis increased the number of cases from 71 to 97 (69 in the bevacizumab cohort and 28 in the ranibizumab cohort) but did not appreciably alter the univariate (OR, 0.73 [95% CI, 0.47-1.12]; P = .15) or the multivariate (OR, 0.70 [95% CI, 0.45-1.10]; P = .13) analysis results for the association between bevacizumab and endophthalmitis.

Discussion

To the best of our knowledge, this study uses the largest single data source to evaluate the risk for endophthalmitis after bevacizumab injection compared with ranibizumab injection. This study analyzed 296 565 injections of bevacizumab and 87 245 injections of ranibizumab to find the rate (95% CI) of endophthalmitis to be 0.017% (0.012%-0.021%) after bevacizumab injection and 0.025% (0.015%-0.036%) after ranibizumab injection. Thus, bevacizumab as used across the United States was not associated with an increased risk for endophthalmitis compared with ranibizumab.

A central strength of this study is the manner in which the data were collected. As noted in many of the lay articles cited previously,5-8 numerous lawsuits have occurred owing to contaminated injections, which may have created a bias against the public reporting of outbreaks. The data used in this study circumvent this issue because billing claims are part of the health record and are offered to researchers only after extensive statistical deidentification. This process allows physicians to bill for endophthalmitis care without the concern of later public disclosure.
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A second advantage of this study was the use of a national cohort consisting of individuals from all 50 states. Given the sizable geographic distribution of the cohort, data from multiple compounding pharmacies likely are represented within this data set. In comparison, large single-center reports are likely to have all their bevacizumab come from a single pharmacy, which only verifies the safety of that specific distribution site.

Last, the data used for this study were derived from 2005 to the end of 2012. This time frame is significant because no additional regulation of compounding pharmacies had been passed before 2013, and yet no difference in endophthalmitis rates was seen, suggesting that additional regulation on bevacizumab may be unnecessary. Of course, this finding does not rule out the possibility of pharmacies evaluating their own practices and adjusting protocols as a reaction to the publicity of the outbreaks in late 2011, but again this reaction would only further underscore that bevacizumab is currently distributed in a safe manner.

As noted in the call to action by the American Society of Retina Specialists, the rate of endophthalmitis actually may be lower after bevacizumab than after ranibizumab intravitreal injections owing to the sterile protocols for loading bevacizumab syringes compared with the typical office setting used to load ranibizumab. Although the OR of 0.66 for endophthalmitis reported in this study suggested a protective effect for bevacizumab, this test result did not reach significance (P = .11). However, the endophthalmitis rates after bevacizumab (0.017%) and ranibizumab (0.025%) injections found in this study were remarkably similar to those reported in another very large single cohort of injections by Flynn and colleagues for bevacizumab and ranibizumab (0.013% and 0.020%, respectively). These results were also consistent with several smaller previous studies. The failure to find a significantly lower OR in this study may simply be owing to a lack of statistical power, and a larger study (a single cohort or a meta-analysis of available data) may in fact find a protective effect. This possibility needs to be given strong consideration because, if true, any FDA regulations aimed at reducing endophthalmitis by limiting repackaged bevacizumab may actually have the unintended consequence of increasing endophthalmitis rates by shifting use to less-safe office-loaded syringes.

Although the medical claims data used for this analysis provide several strengths, as noted above, some limitations need to be addressed. First, owing to the unidentified nature of claims data, we were unable to verify each case of endophthalmitis by reviewing a specific patient’s medical record. To reduce this potential limitation, separate analyses were run using stricter and more relaxed definitions of endophthalmitis in a sensitivity analysis. No difference was seen between the analyses.

An additional limitation was our inability to ascertain the positive or negative status of the culture in each endophthalmitis case. Although misclassification of endophthalmitis is a possibility in this study, we have no reason to believe that bias would favor less endophthalmitis with bevacizumab injection, particularly given previous reports showing higher incidence rates of sterile inflammation after bevacizumab compared with ranibizumab injections.

Next, owing to the deidentified nature of the data, we cannot determine which compounding pharmacies were used to supply the bevacizumab in this study. Also, the data used in this study come from a single medical claims database. Whether a similar study performed in a different medical claims database (eg, Medicare) would yield similar or different results remains unclear.

Last, no specific billing code exists for a single-use vial of bevacizumab to contrast with a compounded batch of bevacizumab. This limitation allows for the possibility that non-compounded bevacizumab was used in this study; however, given the reimbursement rates for bevacizumab injections (approximately $50-$80) and the relatively expensive cost of single-use bevacizumab (approximately $500), each physician choosing this option would lose money on every injection given, making the likelihood of this choice occurring in a significant portion of the 296,565 injections studied very low.

Conclusions

This study examines a national cohort likely representing numerous compounding pharmacies across the country and found that the manner in which bevacizumab was used from 2005 through 2012 did not alter the risk for endophthalmitis compared with ranibizumab. Although contamination of compounded medications is an issue that needs constant vigilance, this study supports the idea that tight adherence to current compounding protocols and practice standards can ensure the safe use of bevacizumab in ophthalmic practice without additional regulation.

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