Comparative Effectiveness Research of Aflibercept and Bevacizumab in Patients with Diabetic Macular Edema: A Bayesian Causal Inference Study Using Real-world Data to Update Evidence from the Randomized Controlled Trial

<Kyungseon Choi>[1, 2], <Sang Jun Park>[3], <Seng Chan You>[4], <Semin Jang>[1, 2], <Hae Sun Suh>[1, 2, 5]

[1] Department of Regulatory Science, Graduate School, Kyung Hee University, Seoul, Republic of Korea,

[2] Institute of Regulatory Innovation through Science, Kyung Hee University, Seoul, Republic of Korea,

[3] Department of Ophthalmology, Seoul National University College of Medicine, Seoul National University Bundang Hospital, Seongnam-si, Gyeonggi-do, Republic of Korea,

[4] Department of Biomedicine System Informatics, Yonsei University College of Medicine, Seoul, Republic of Korea,

[5] College of Pharmacy, Kyung Hee University, Seoul, Republic of Korea

Background

Diabetic retinopathy, a common complication of diabetes mellitus (DM), can lead to vision loss or blindness.[1] Diabetic macular edema (DME) is the most common cause of vision loss in diabetic retinopathy. To prevent vision loss, anti-vascular endothelial growth factors (VEGFs) are commonly used as effective management[2]; however, these drugs are expensive with a significant financial burden on patients.

Aflibercept, an anti-VEGF agent, is reimbursed in various countries, yet cheaper bevacizumab remains unapproved in South Korea and the UK. Recent systematic review and meta-analyses[3] compared their efficacy, with one randomized controlled trial[4] (RCT) and one real-world evidence[5] (RWE) study reported. While the RCT demonstrates aflibercept's superiority over bevacizumab in metrics like best corrected visual acuity (BCVA) and central subfield thickness (CST), RWE findings do not confirm significant BCVA differences in descriptive analysis.

However, previous RCT[4] lacked reporting on patient-centric outcomes like blindness or mortality, focusing instead on anatomical outcomes. Real-world clinical settings differ from RCT conditions due to varied patient characteristics, treatment criteria, and cost disparities, potentially impacting efficacy. Moreover, Bayesian statistics offer advantages over frequentist approaches in addressing biases and uncertainties and updating existing beliefs.

This study aims to evaluate aflibercept and bevacizumab effectiveness and efficacy in diabetic macular edema using frequentist and Bayesian statistics to inform clinical and regulatory decisions. Updating existing beliefs (the RCT evidence) with new real-world data (RWD), we seek to compare, synthesize and update evidence using Bayesian statistics, leveraging observational data networks for comprehensive analysis and continual updates. To compare aflibercept and bevacizumab in DME with long-term outcomes, the specific objectives are as follows: 1) To estimate the efficacy using RCT individual patient data (IPD). 2) To estimate the effectiveness using RWD. 3) To synthesize the combined efficacy and effectiveness using Bayesian statistics. 4) To update RCT evidence using RWD through Bayesian statistics.

Methods

In Objective 1, a frequentist-based post-hoc analysis of RCT IPD was conducted to compare the efficacy of bevacizumab versus aflibercept. Outcomes were defined as blindness-free survival (BFS), World Health Organization standard BFS (WHO-BFS), and overall survival (OS). We analyzed using the Cox proportional hazards model, with the hazard ratio as the estimated value. Secondary outcomes such as changes in BCVA and CST were analyzed using a linear mixed model (LMM). Covariates in both Cox and LMM models included age, sex, disease status, and drug factors.

In Objective 2, to compare the effectiveness of bevacizumab versus aflibercept, a retrospective cohort analysis was conducted using RWD from Bundang Seoul National University Hospital (SNUBH). SNUBH data was structured to OMOP-CDM and transformed into ophthalmology OMOP-CDM. The study population was defined as patients aged over 18 who received intraocular aflibercept or bevacizumab treatment between June 1, 2015, and December 31, 2019. To fully adopt the RCT inclusion criteria, eligible participants have had a diagnosis of diabetes mellitus or diabetic retinopathy prior to treatment and a CST of ≥300 μm. Exclusion criteria include a history of specific ocular diseases (e.g., retinal vascular occlusion, neovascular glaucoma) or prior pan-retinal photocoagulation. The treated eye was defined with selection criteria based on OCT measurements and anti-VEGF treatment criteria.

Propensity score was estimated using Bayesian additive regression tree (BART) and inverse probability weighting (IPTW) with standardized mortality ratio weighting (SMRW) was employed to correct for selection bias, considering covariates such as age, sex, disease status, measurements from eye examination and drug factors. The covariates over 0.20 standardized mean difference[6,7] were considered as unmatched covariates and we checked negative control. The outcomes and analysis methods were identical to those in Objective 1.

Objective 3 aims to synthesize evidence on the efficacy and effectiveness through a meta-analysis of the hazard ratios from Objectives 1 and 2. Due to heterogeneity between estimates, a Bayesian hierarchical model-based meta-analysis was used.

In Objective 4, Bayesian Cox proportional hazards models and Bayesian LMM were used to update evidence, with prior distributions from Objective 1. Non-informative prior analyses were conducted as sensitivity analyses.

Results

The study included 442 patients with DME from RCT IPD data set[8] and 504 patients with DME from RWD. After IPTW with BART and SMRW, most variables had SMDs below 0.2, but only renal disease exceeded 0.2 and was considered an unmatched covariate, and all negative controls were not significant (Table 1).

Table 1. Baseline characteristics of study population

	Randomized controlled trial data		Real-world data after IPTW			
	Aflibercept (N=224)	Bevacizumab (N=218)	Aflibercept (N=326.34)	Bevacizumab (N=471)	aSMD	V ratio
Before missing imputation						
Patients						
Age (yrs) - mean (SD)	59.46 (10.40)	61.38 (10.00)	58.74 (10.03)	60.52 (12.07)	0.15	1.43
Gender: female – N (%)	110 (49.1)	103 (47.2)	127.7 (39.1)	200 (42.5)	0.07	
Race: Asian – N (%)*	2 (0.9)	2 (0.9)				
Diabetes type – N (%)*						
Type 1	22 (9.8)	12 (5.5)	5.8 (1.8)	9 (1.9)	0.01	
Type 2	196 (87.5)	205 (94.0)	61.6 (18.9)	104 (22.1)	0.08	
Uncertain	6 (2.7)	1 (0.5)	258.9 (79.3)	358 (76.0)	0.08	
Hemoglobin A1c (%) – mean (SD)	8.06 (1.76)	8.00 (1.64)	7.83 (1.59)	7.76 (1.57)	0.05	0.96
Prior cardiovascular disease – N (%)	43 (19.2)	50 (22.9)	66.4 (20.4)	87 (18.5)	0.05	
Prior cerebrovascular disease – N (%)	13 (5.8)	19 (8.7)	20.6 (6.3)	42 (8.9)	0.09	
Prior hypertension – N (%)	177 (79.0)	182 (83.5)	92.0 (28.2)	160 (34.0)	0.12	
Prior cancer – N (%)	18 (8.0)	13 (6.0)	20.6 (6.3)	31 (6.6)	0.01	
Prior renal disease – N (%)	19 (8.5)	22 (10.1)	22.9 (7.0)	73 (15.5)	0.23	
Prior glaucoma/cataract – N (%)	60 (26.8)	45 (20.6)	88.5 (27.1)	150 (31.8)	0.1	
Prior PDR – N (%)						
NPDR	174 (77.7)	154 (70.6)	91.5 (28.0)	142 (30.1)	0.05	
PDR	28 (12.5)	33 (15.1)	143.4 (43.9)	227 (48.2)	0.09	

Uncertain	22 (9.8)	31 (14.2)	91.4 (28.0)	102 (21.7)	0.15	
Eye						
Eye: right – N (%)	120 (53.57)	97 (44.50)	128 (39.2)	219 (46.5)	0.15	
Prior focal/grid laser – N (%)	80 (35.7)	84 (38.5)	0 (0)	0 (0)	0	
Prior PRP – N (%)	32 (14.3)	40 (18.3)	0 (0)	0 (0)	0	
Prior anti-VEGF – N (%)	24 (10.7)	31 (14.2)	53.8 (16.5)	73 (15.5)	0.03	
BCVA – mean (SD)	0.42 (0.17)	0.42 (0.16)	0.45 (0.24)	0.49 (0.25)	0.12	1.07
CST – mean (SD)*	412.19 (136.99)	408.29 (129.42)	412.37 (124.73)	391.39 (142.49)	0.15	1.29
After missing imputation						
Hemoglobin A1c– mean (SD)	8.05 (1.76)	8.00 (1.64)	7.76 (1.53)	7.81 (1.59)		
BCVA – mean (SD)	0.42 (0.17)	0.42 (0.16)	0.49 (0.25)	0.51 (0.25)		

* CST was converted to Stratus.

aSMD, absolute standardized mean difference; BCVA, best corrected visual acuity; CST, central subfield thickness; IPTW, inverse probability weighting; NPDR, non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; PRP, pan-retinal photocoagulation; V ratio, variance ratio; VEGF, vascular endothelial growth factor.

In Objective 1, aflibercept showed significantly better efficacy than bevacizumab in all outcomes except OS (95% hazard ratio: BFS (0.325, 0.891), WHO-BFS (0.225, 0.840); coefficient: BCVA (0.070 ($p=0.001$)), CST (-53.61 ($p<0.001$)), however, in objective 2, no significant differences in effectiveness were observed between aflibercept and bevacizumab (Table 2).

Table 2. Results of objective 1 and 2: Evidence from randomized controlled trial and real-world evidence

		Cox proportional hazard model								
		BFS			WHO-BFS			OS		
		Adjusted HR	SE	P-value	Adjusted HR	SE	P-value	Adjusted HR	SE	P-value
Objective 1: Evidence from randomized controlled trial	Drug: aflibercept	0.5387	0.2573	0.0162	0.435	0.3362	0.0132	0.4718	0.4068	0.0648
	Age	1.0582	0.0149	0.3579	1.068	0.0186	0.0004	1.0880	0.0224	0.0002
	Gender: female	0.7985	0.2447	0.6339	0.707	0.3102	0.2643	0.7303	0.3811	0.4096
	CV disease	0.8631	0.3091	0.0700	0.861	0.38	0.6930	0.9642	0.4496	0.9354
	Cerebrovascular disease	1.9048	0.3557	0.1331	4.346	0.4158	0.0004	6.1751	0.4906	0.0002
	Renal disease	1.6870	0.3481	0.0352	2.088	0.4134	0.0749	2.5156	0.4478	0.0394
	Hypertension	3.5474	0.6013	0.4367	6.12	1.0246	0.0770	-*	-*	-*
	PDR: uncertain	1.4510	0.4787	0.6634	2.158	0.5725	0.1792	1.4680	0.4987	0.4414
	PDR	1.2206	0.4580	0.2682	0.913	0.6069	0.8815	1.0450	0.6333	0.9446
	Glaucoma/cataract	1.3594	0.2773	0.4392	1.057	0.3702	0.8812	0.4966	0.5043	0.1652
	Cancer	1.3442	0.3824	0.3579	1.386	0.4469	0.4647	0.3918	0.7749	0.2265
	HbA1c	1.1642	0.0676	0.0245	1.122	0.0899	0.2018			
	Focal/grid laser (eye)	1.2858	0.2618	0.3369	1.143	0.3223	0.6775			
	PRP (eye)	0.7685	0.4745	0.5789	0.842	0.5932	0.7716			
	Anti-VEGF (eye)	0.3511	0.4846	0.0308	0.172	0.7569	0.0201			
	BCVA (eye)	0.2111	0.8813	0.0776	8.834	1.1917	0.0675			
	CST in eye	1.0009	0.0010	0.3814	1.000	0.0016	0.7793			

		Linear mixed model					
		BCVA			CST		
		Coefficient	SE	P-value	Coefficient	SE	P-value
Objective 1: Evidence from randomized controlled trial	Intercept**	0.8043	0.1058	<0.0001	98.7606	40.4597	0.0147
	Drug: aflibercept	0.0700	0.0181	0.0001	-53.6119	6.9183	<0.0001
	Age	-0.0062	0.0010	<0.0001	1.1296	0.3829	0.0034
	Gender: female	-0.0418	0.0181	0.0217	-18.3239	6.9404	0.0086
	CV disease	0.0049	0.0227	0.8289	-2.8061	8.6933	0.747
	Cerebrovascular disease	-0.0382	0.0352	0.2783	10.6387	13.4540	0.4295
	Renal disease	0.0246	0.0319	0.4404	-32.2585	12.1770	0.0084
	Hypertension	-0.0459	0.0236	0.0523	-0.3493	9.0178	0.9691
	PDR: uncertain	0.0084	0.0406	0.8363	-16.0398	15.5746	0.3037
	PDR	-0.0013	0.0325	0.9677	-11.3801	12.4381	0.3607
	Glaucoma/cataract	-0.0482	0.0212	0.0234	-1.1430	8.1019	0.8879
	Cancer	0.0123	0.0362	0.7349	-19.6942	13.8621	0.1561
	HbA1c	-0.0129	0.0056	0.0221	1.8486	2.1588	0.3923
	Focal/grid laser (eye)	-0.0117	0.0201	0.5606	0.2884	7.6975	0.9701
	PRP (eye)	-0.0900	0.0376	0.017	31.8787	14.3924	0.0273
	Anti-VEGF (eye)	0.0021	0.0288	0.9412	6.5151	11.0469	0.5557
	BCVA (eye)	-0.1689	0.0625	0.0072	64.2779	23.9086	0.0075
	CST in eye	-0.0001	0.00008	0.1856	-0.6654	0.0300	<0.0001
	Measurement day**	0.0004	0.00002	<0.0001	-0.1012	0.0046	<0.0001
	Measurement day2**	-0.0000002	0.00000001	<0.0001	0.0000	0.0000	<0.0001

		Cox proportional hazard model								
		BFS			WHO-BFS			OS		
		Adjusted HR	Robust SE	P-value	Adjusted HR	Robust SE	P-value	Adjusted HR	Robust SE	P-value
Objective 2: Real-world evidence	Drug: aflibercept	1.7785	0.5867	0.3264	3.2928	1.0529	0.2577	1.6221	0.5306	0.3620
	Age	1.0383	0.0217	0.0831	1.0846	0.0393	0.0387	0.9925	0.0206	0.7158
	Gender: female	0.8343	0.3642	0.6189	1.0217	0.5595	0.9694	1.4362	0.7693	0.6380
	CV disease	1.0310	0.3912	0.9377	0.9781	0.4798	0.9632	2.2056	0.5879	0.1785
	Cerebrovascular disease	0.6199	0.6772	0.4802	0.6533	1.0235	0.6774	3.0436	1.0106	0.2707
	Renal disease	2.2293	0.3426	0.0193	6.2122	0.4575	<0.0001	14.2590	0.6190	<0.0001
	Hypertension	1.1137	0.4131	0.7943	0.7360	0.5616	0.5853	5.3360	0.7847	0.0329
	PDR	2.3699	0.5641	0.1261	1.0290	0.6988	0.9674	2.1546	0.9279	0.4081
	PDR: uncertain	1.2838	0.7781	0.7482	0.9173	1.0932	0.9370	1.8596	1.2523	0.6203
	Glaucoma/cataract	1.0974	0.5955	0.8760	1.0358	1.1271	0.9751	0.2427	1.1249	0.2082
	Cancer	0.4042	0.7693	0.2389	0.3263	0.9830	0.2546	-*	-*	-*
	HbA1c	0.9967	0.1510	0.9827	1.0967	0.1638	0.5730			
	Anti-VEGF (eye)	0.2194	0.6836	0.0265	0.1585	1.0853	0.0897			
	BCVA (eye)	0.1541	0.8524	0.0282	0.0528	1.3733	0.0322			
	CST (eye)	1.0026	0.0012	0.0261	1.0027	0.0018	0.1463			

		Linear mixed model					
		BCVA			CST		
		Coefficient	SE	P-value	Coefficient	SE	P-value
Objective 2: Real-world evidence	Intercept**	0.8344	0.1630	<0.0001	155.1996	35.5056	<0.0001
	Drug: aflibercept	0.0138	0.0990	0.8891	-15.9503	21.3384	0.4552
	Age	-0.0012	0.0016	0.4362	1.1825	0.3308	0.0004
	Gender: female	-0.0380	0.0341	0.2664	-12.7497	7.3792	0.0847
	CV disease	-0.0443	0.0457	0.3329	12.7777	10.4581	0.2225
	Cerebrovascular disease	0.0753	0.0602	0.2124	-6.9743	13.8470	0.6147
	Renal disease	-0.0533	0.0525	0.3107	-18.0569	11.4908	0.1168
	Hypertension	-0.0115	0.0406	0.7766	-8.6727	9.0238	0.3370
	PDR	-0.0859	0.0387	0.0274	3.7840	8.7143	0.6643
	PDR: uncertain	-0.0693	0.0476	0.1471	-16.4069	10.2481	0.1101
	Glaucoma/cataract	-0.0350	0.0366	0.3398	3.8823	8.3119	0.6407
	Cancer	-0.1062	0.0731	0.1481	-16.0157	15.3893	0.2986
	HbA1c	-0.0227	0.0110	0.0413	-1.3818	2.3530	0.5573
	Anti-VEGF (eye)	-0.0299	0.0473	0.5271	9.0527	9.7738	0.3548
	BCVA (eye)	-0.7089	0.0714	<0.0001	5.2975	16.0377	0.7413
	CST (eye)	-0.0003	0.0001	0.0036	-0.6651	0.0288	<0.0001
	Measurement day**	0.00007	0.00008	0.3504	-0.0878	0.0153	<0.0001
	Measurement day2**	-0.0000001	0.00000005	0.1891	0.00003	0.00001	0.0177

*Convergence issue

**Intercept and measurement day are only included in linear mixed model.

BCVA, best corrected visual acuity; BFS, blindness free survival; CST, central subfield thickness; CV, cardiovascular disease; HR, hazard ratio; NPDR, non-proliferative diabetic retinopathy; OS, overall survival; PDR, proliferative diabetic retinopathy; PRP, pan-retinal photocoagulation; SE, standard error; VEGF, vascular endothelial growth factor; WHO-BFS, world health organization-blindness free survival.

In Objective 3, in the evidence synthesis from efficacy and effectiveness, despite integrating RCT results, no significant differences were found between bevacizumab and aflibercept in BFS, WHO-BFS, OS, and BCVA (BFS (59%), WHO-BFS (57%), OS (60%), BCVA (65%)). However, there was a 98% probability that aflibercept would have lower CST than bevacizumab. Lastly, in Objective 4, Bayesian evidence update indicated a 10~65% probability that aflibercept would be superior in BFS, WHO-BFS, OS, and BCVA. However, there is a 100% probability that aflibercept would be superior to bevacizumab in CST (Table 3).

Table 3. Results of objective 3 and 4: Synthesized and updated evidence from randomized controlled trial and real-world data

			Estimate	SD	95% credible interval		Rhat
					Lower	Upper	
Objective 3: Evidence synthesis	Bayesian hierarchical model (reference: bevacizumab)	BFS: Population-level effects					
			-0.1137	1.0625	-2.2708	2.1891	1.00
		WHO-BFS: Population-level effects					
			-0.0643	1.2314	-2.3985	2.6417	1.00
		OS: Population-level effects					
			-0.1626	1.0687	-2.3427	2.0968	1.00
		BCVA: Population-level effects					
			0.0389	0.5964	-1.3539	1.3441	1.00
		CST: Population-level effects					
			-40.5601	16.3225	-69.5772	-4.5352	1.00
Objective 4: Evidence update	Bayesian Cox proportional hazard model (prior: randomized controlled trial)	BFS					
		Drug: aflibercept	0.0728	0.1771	-0.2773	0.4167	0.9999
		WHO-BFS					
		Drug: aflibercept	0.2935	0.2323	-0.1639	0.7466	0.9999
		OS					
		Drug: aflibercept	0.1316	0.3052	-0.4593	0.7345	1.0000
	Bayesian LMM (prior: randomized controlled trial)	BCVA					
		Drug: aflibercept	0.0678	0.0174	0.0335	0.1018	1.0003
		CST					
		Drug: aflibercept	-44.4075	6.0945	-56.2553	-32.408	1.0006
		BFS					

	Bayesian Cox proportional hazard model (non-informative prior)	Drug: aflibercept	0.7201	0.2668	0.2014	1.2484	1.0001
		WHO-BFS					
		Drug: aflibercept	1.5753	0.4394	0.7466	2.462	1.0001
		OS					
		Drug: aflibercept	1.3812	0.6808	0.1057	2.7691	1.0004
	Bayesian LMM (non-informative prior)	BCVA					
		Drug: aflibercept	0.0185	0.0551	-0.09	0.1255	1.0008
		CST					
		Drug: aflibercept	-12.7647	12.6235	-37.3831	12.119	1.0002

BCVA, best corrected visual acuity; BFS, blindness-free survival; CST, central subfield thickness; LMM, linear mixed model; OS, overall survival; SD, standard deviation; WHO, World Health Organization.

Conclusion

Aflibercept showed superior efficacy in certain measures compared to bevacizumab. However, in the RWD, the superiority was not significant. Using a Bayesian model with a 95% threshold, the synthesized and updated evidence indicated no significant difference between aflibercept and bevacizumab in BFS, WHO-BFS, and OS, though aflibercept remained superior in BCVA and CST.

This study's methodology leverages the OMOP-CDM and Bayesian statistics to continually update and synthesize evidence, overcoming traditional RCT limitations. The findings support that bevacizumab may be as effective as aflibercept, suggesting policy implications for cost-effective drug reimbursement decisions. Bayesian approach, integrating new data, would enhance regulatory science decision-making, particularly for high-cost drugs, by providing a comprehensive view of efficacy and effectiveness. Furthermore, utilizing HERMES[9], a cost analysis tool for the OMOP-CDM, could expand to the RWD economic evaluation with OMOP-CDM.

References

1. Jampol LM, Glassman AR, Sun J. Evaluation and Care of Patients with Diabetic Retinopathy. New England Journal of Medicine. 2020;382(17):1629-37.
2. Virgili G, Parravano M, Evans JR, Gordon I, Lucenteforte E. Anti-vascular endothelial growth factor for diabetic macular oedema: a network meta-analysis. Cochrane Database Syst Rev. 2018;10(10):Cd007419.
3. Santhakumaran S, Salimi A, Brunetti VC, Galic J. Efficacy and Safety of Aflibercept Therapy for Diabetic Macular Edema: A Systematic Review and Meta-Analysis. J Curr Ophthalmol. 2022;34(2):133-147. Published 2022 Jul 26. doi:10.4103/joco.joco_308_21
4. Diabetic Retinopathy Clinical Research Network. Aflibercept, Bevacizumab, or Ranibizumab for Diabetic Macular Edema. New England Journal of Medicine. 2015;372(13):1193-1203. doi:https://doi.org/10.1056/nejmoa1414264
5. Ciulla TA, Bracha P, Pollack J, Williams DF. Real-world Outcomes of Anti–Vascular Endothelial Growth Factor Therapy in Diabetic Macular Edema in the United States. Ophthalmology Retina. 2018;2(12):1179-1187. doi:https://doi.org/10.1016/j.oret.2018.06.004
6. Cohen J. Statistical Power Analysis for the Behavioral Sciences. 2nd ed. Routledge; 1988. doi:https://doi.org/10.4324/9780203771587
7. Andrade C. Mean Difference, Standardized Mean Difference (SMD), and Their Use in MetaAnalysis: As Simple as It Gets. J Clin Psychiatry. 2020;81(5):20f13681. Published 2020 Sep 22. doi:10.4088/JCP.20f13681
8. DRCR Retina Network - Public Site. public.jaeb.org. Accessed November 15, 2023. https://public.jaeb.org/drcrnet/stdy
9. Choi K, Park SJ, Han S, Kim S, Suh HS. HERMES: A health resources econometric analysis tool. OHDSI Symposium. 2023.