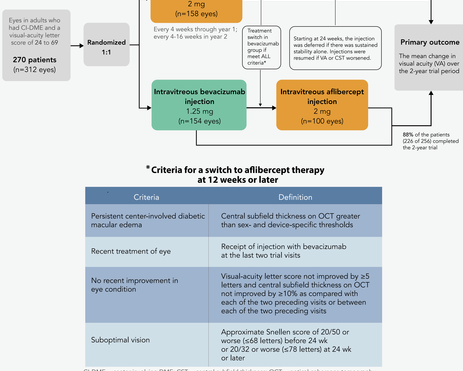
Aflibercept Monotherapy or Bevacizumab First for Diabetic Macular Edema

Jhaveri CD, Glassman AR, Ferris FL 3rd, et al. *N Engl J Med.* 2022;387:692-703.
doi:10.1056/NEJMoa2204225

Previous research showed both aflibercept and bevacizumab treatment were effective in improving visual acuity. As the cost of aflibercept is substantially higher than bevacizumab, many patients require step therapy, in which bevacizumab is used first, until unsatisfactory clinical response drives a switch to aflibercept. The purpose of this randomized clinical trial was to compare the effectiveness of two anti-vascular endothelial growth factor (VEGF) strategies for treating diabetic macular edema (DME): aflibercept monotherapy or bevacizumab first plus a switch to aflibercept therapy if the response was suboptimal.

Participants were randomized to receive either aflibercept-monotherapy or bevacizumab-first with a switch to aflibercept monotherapy if protocol-specified criteria were met.



***Criteria for a switch to aflibercept therapy at 12 weeks or later**

Criteria	Definition
Persistent center-involved diabetic macular edema	Central subfield thickness on OCT greater than sex- and device-specific thresholds
Recent treatment of eye	Receipt of injection with bevacizumab at the last two trial visits
No recent improvement in eye condition	Visual-acuity letter score not improved by ≥5 letters and central subfield thickness on OCT not improved by ≥10% as compared with each of the two preceding visits or between each of the two preceding visits
Suboptimal vision	Approximate Snellen score of 20/50 or worse (≤68 letters) before 24 wk or 20/32 or worse (≤78 letters) at 24 wk or later

CI-DME = center-involving DME; CST = central subfield thickness; OCT = optical coherence tomography.
* All four criteria had to be met for eyes to be switched from receiving bevacizumab first to receiving aflibercept therapy.

The baseline characteristics of the patients and eyes were similar in the two groups.

Baseline characteristics

Median VA letter score	20/63
Median CST	488 µm

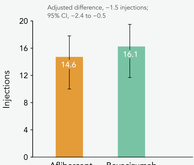
Baseline patient and study eye characteristics

	Aflibercept-monotherapy	Bevacizumab-first
Hemoglobin A1c [b], median (IQR), %	8.0 (7.2, 9.4)	8.0 (6.8, 9.4)
VA, Snellen equivalent, median	20/63	20/63
Lens status, phakic	128 (81%)	124 (81%)
Prior anti-VEGF for DME	25 (16%)	29 (19%)

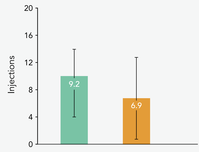
[b] Unavailable for 10 eyes in each group

Over the 2 years, 70% of the eyes in the bevacizumab-first group were switched to aflibercept therapy.

Mean injections in the two treatment groups



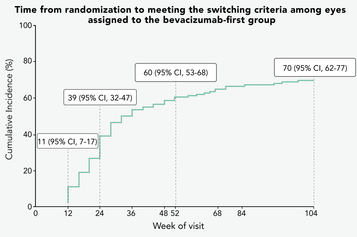
Mean injections by therapy in bevacizumab-first group



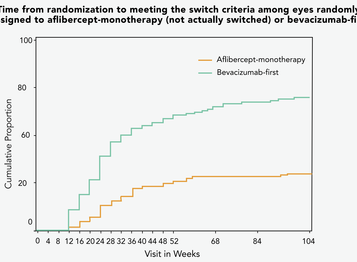
Treatment compliance by treatment group in eyes switched to aflibercept

Outcomes, N(%)	Bevacizumab-first Group (N=154 eyes)
Injections received before switch, mean (SD)	6.7 (3.2)
Injections received after switch, mean (SD)	9.5 (4.5)

Time from randomization to meeting the switching criteria among eyes assigned to the bevacizumab-first group



Time from randomization to meeting the switch criteria among eyes randomly assigned to aflibercept-monotherapy (not actually switched) or bevacizumab-first

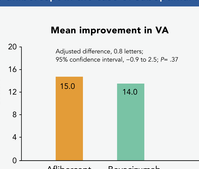


	Visit, time from randomization				
	Baseline	12 Weeks	24 Weeks	52 Weeks	104 Weeks
No. at risk					
Aflibercept-monotherapy	158	152	139	108	35
Bevacizumab-first	154	147	107	59	13
Cumulative Proportion (95% CI)					
Aflibercept-monotherapy		2.0% (1%, 6.0%)	13% (9%, 20%)	24% (20%, 34%)	30% (23%, 38%)
Bevacizumab-first		11% (7%, 17%)	39% (32%, 47%)	60% (53%, 68%)	70% (62%, 77%)

SD = standard deviation; CI = confidence interval.
Eyes that did not meet the switch criteria were censored at the last completed visit.

No significant difference was found in visual outcomes over the 2-year period between aflibercept-monotherapy and the treatment with bevacizumab first with a switch to aflibercept in the case of suboptimal response.

Mean improvement in VA



Subgroup analyses of primary outcome: change in VA from baseline over two years (area under the curve)

	Aflibercept-monotherapy Group		Bevacizumab-first Group		Adjusted Mean Difference (95% CI), letters[a]
	N	Mean(SD)	N	Mean(SD)	
OCT CST, stratus equivalent[b]					
≥400 µm	78	16.5 (7.8)	76	13.9 (9.6)	+2.4 (+0.2, +4.7)

[a] Treatment difference and 95% CI were obtained from a model including an interaction term for the baseline subgroup factor by treatment. Missing data were imputed by treatment group similarly to the primary analysis except that the subgroup factor was also included in the imputation model.
[b] Excluding eyes with unavailable baseline OCT CST

Conclusions

The authors found no evidence of a significant difference in visual outcomes over a 2-year period between aflibercept-monotherapy and treatment with bevacizumab-first with a switch to aflibercept in the case of suboptimal response.