combined aflibercept groups versus 8 of 133 eyes (6.0%) in the control group (adjusted difference, 52.3%; $P < 0.001$). At 52 weeks, 88 of 135 eyes (65.2%) in the aflibercept 2q16 group (adjusted difference, 50.1%) and 107 of 134 eyes (79.9%) in the aflibercept 2q8/pro re nata group (adjusted difference, 64.8%;) compared with 20 of 133 eyes (15.0%) in the control group ($P < 0.001$ for both comparisons) showed a two-step or greater improvement in DRSS level. Fewer eyes treated with aflibercept compared with sham developed vision-threatening complications and CI-DME through week 100 ("22 of 135 eyes [16.3%] in the 2q16 group [adjusted difference, -34.2%;] and 25 of 134 eyes [18.7%] in the 2q8/ pro re nata group [adjusted difference, -31.7%;] compared with 67 of 133 eyes [50.4%] in the control group; $P < 0.001$ for both comparisons").[388] A post hoc analysis of the PANORAMA trial found that aflibercept seemed to reduce the risks of NPDR worsening, using increased areas of fluorescein leakage and retinal nonperfusion as biomarkers.[389]

The DRCR Protocol W similarly compared the efficacy of aflibercept 2 mg to sham in preventing potentially vision-threatening complications in eyes with moderate to severe NPDR. Patients were randomized to receive aflibercept 2 mg or sham at baseline for 1, 2, and 4 months and then every 4 months through 2 years. After year 2 and up to year 4, treatment was deferred if the eye had mild NPDR or better. Aflibercept was allowed in both groups if CI-DME with vision loss (≥ 10 letters at 1 visit or 5 to 9 letters at 2 consecutive visits) or high-risk PDR had developed. At 2 years, aflibercept-treated eyes had lower rates of CI-DME with vision loss or PDR (16.3%) compared with sham (43.5%); (HR = 0.32; $P < 0.001$). The probability of developing PDR was 13.5% in the aflibercept group versus 33.2% in the sham group, and probability of developing CI-DME with vision loss was 4.1% in the aflibercept group versus 14.8% in the sham group at 2 years. There was no difference in visual acuity; mean (SD) change in visual acuity from baseline to 2 years was -0.9 (5.8) letters with aflibercept and -2.0 (6.1) letters with sham (adjusted mean difference, 0.5 letters; $P = 0.47$).[129]

At 4 years after the pro re nata dosing was instituted, the 4-year cumulative probability of developing PDR or CI-DME with vision loss was 33.9% for aflibercept-treated eyes versus 56.9% for sham (adjusted HR = 0.40; $P < 0.001$). Mean (SD) change in visual acuity from baseline was -2.7 (6.5) letters for aflibercept-treated eyes and -2.4 (5.8) letters for sham (adjusted mean difference, -0.5 letters; $P = 0.52$).[390]

Other Treatments

Vitrectomy surgery typically is reserved for cases with persistent disease activity despite medical management with anti-VEGF or PRP, or if disease is unamenable to medical management alone. Typical indications for vitrectomy include:

- Nonclearing vitreous hemorrhage
- Tractional retinal detachment involving or threatening the macula
- Combined rhegmatogenous and tractional retinal detachment
- Dense premacular subhyaloid hemorrhage

The DRVS demonstrated improved outcomes if vitrectomy for vitreous hemorrhage is done within 1 to 6 months of onset compared with later vitrectomy at 1 year.[391, 392] Vitreous hemorrhage should be followed with serial ultrasounds to evaluate for possible retinal tear, tractional retinal detachment that threatens the macula, or rhegmatogenous retinal detachment. Recent advances, including endolaser and small-gauge instruments have improved outcomes and decreased adverse events.[393] One meta-analysis suggested that preoperative anti-VEGF treatment reduces the duration of surgery, the number of retinal breaks, and the amount of intra-operative bleeding.[394] *(I+, Moderate quality, Strong recommendation)* A Cochrane systematic review suggested that preoperative or intra-operative bevacizumab may reduce the incidence of post-operative vitreous hemorrhage.[395, 396] *(I+, Moderate quality, Strong recommendation)*

Anti-VEGF or vitrectomy are reasonable initial treatments for eyes with persistent vitreous hemorrhage alone. As summarized above, the DRCR study showed anti-VEGF