Has the Time Come to Re-evaluate the Treatment Paradigm for Diabetic Retinopathy?

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DISCLOSURES

- **Financial disclosures**
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  - IS: Employee/Stockholder: Genentech, Inc.

- **Study disclosures**
  - This study includes research conducted on human subjects
  - Institutional Review Board approval was obtained prior to study initiation
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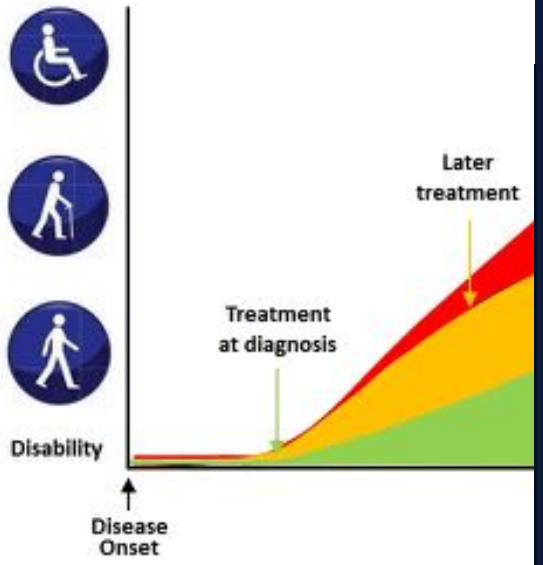
Key Takeaways

- The index study examined whether the current evidence supports a paradigm shift towards earlier intervention in patients with diabetic retinopathy (DR)
- Analyses of real-world data have associated proliferative diabetic retinopathy (PDR) with the development of sustained blindness in clinical practice
- Meanwhile, landmark trials showed that patients with moderately severe or severe NPDR were vulnerable to DR progression without treatment, and more likely to achieve DR improvement with anti-VEGF therapy
- Given the trend towards greater mean vision gains with greater DR improvement in RIDE/RISE, these data suggest that the time has come to consider earlier intervention to delay progression towards PDR

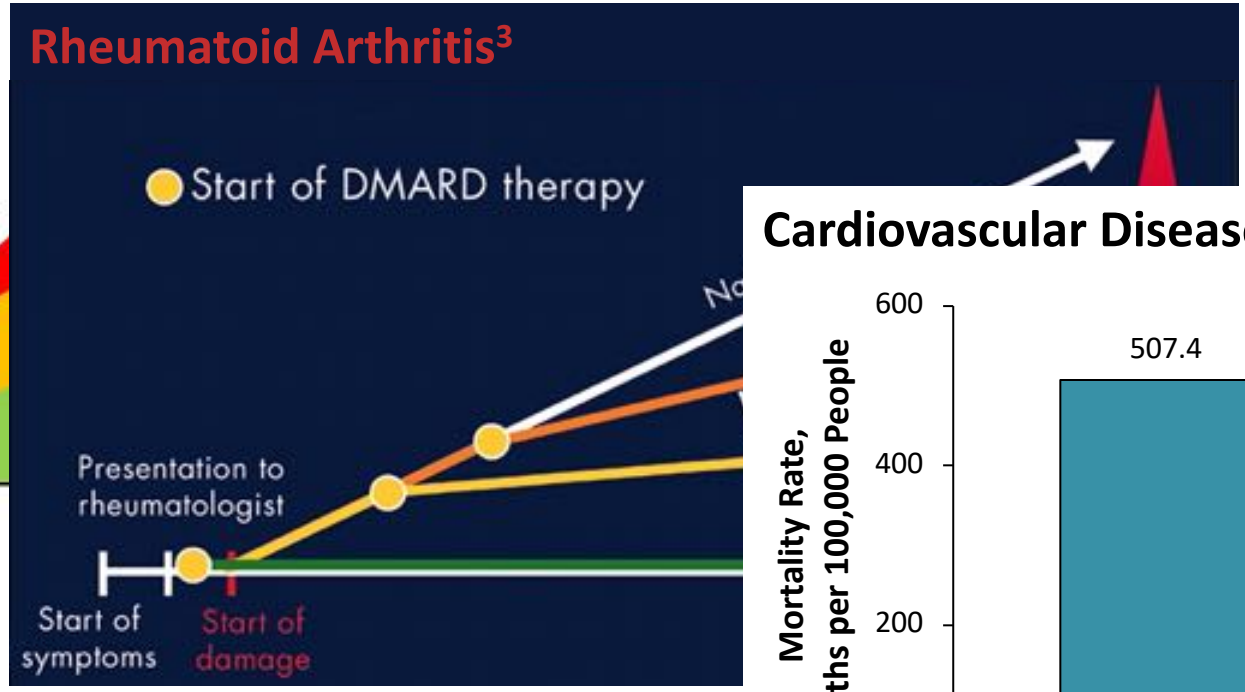
DR, diabetic retinopathy; NPDR, nonproliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; VEGF, vascular endothelial growth factor.

Early Intervention Is Associated With Delayed Disease Progression and Improved Patient Outcomes Across the Medical Field

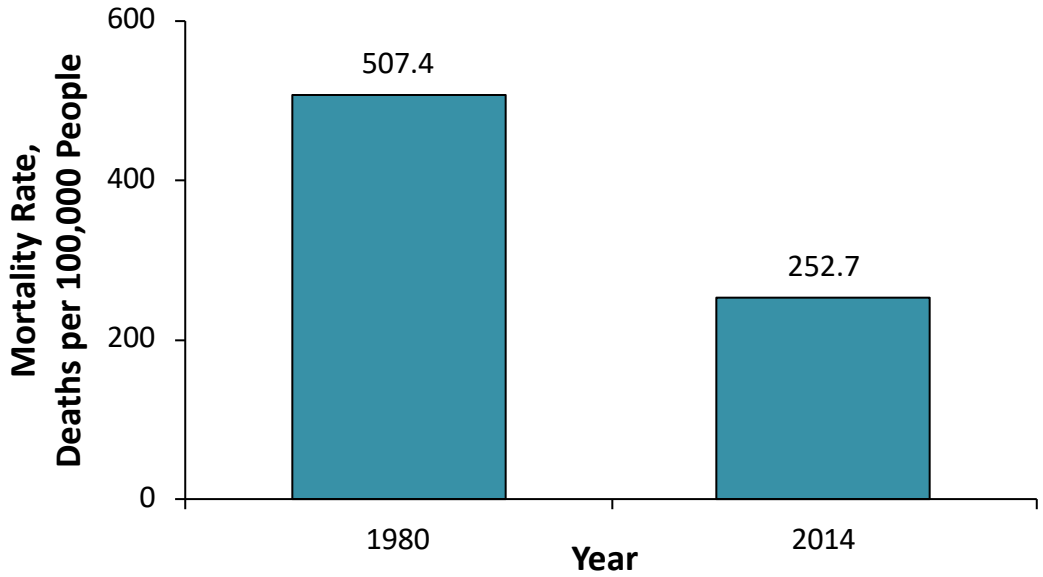
Multiple Sclerosis[1,2]



Rheumatoid Arthritis[3]



Cardiovascular Disease[4]

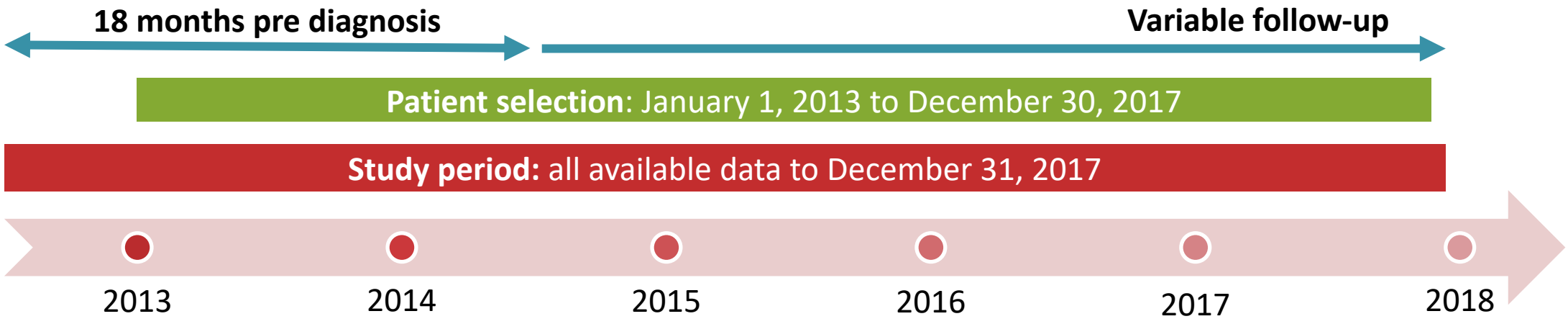


1. Figure reproduced with permission from: Giovannoni G. Barts MS Blog. DMTs slow the onset of progression in relapsing MS. June 7, 2012. http://multiple-sclerosis-research.blogspot.com/2012/06/research-dmt-slow-onset-of-progression.html. Accessed January 9, 2020. 2. Bergamaschi R et al. *Mult Scler*. 2016;22(13):1732-1740. 3. Figure reproduced with permission from: Breedveld FC, Kalden JR. *Ann Rheum Dis*. 2004;63(6):627-633. 4. Roth GA et al. *JAMA*. 2017;317(19):1976-1992.
DMARD, disease-modifying antirheumatic drug.

Do clinical trial and real-world evidence support a paradigm shift towards earlier intervention in patients with DR?

Progression to Sustained Blindness in Current Clinical Practice: An IRIS® Registry (Intelligent Research in Sight) Analysis

- **Aim:** To characterize the development of sustained blindness in patients with DR
- **Method:** Retrospective analysis of the AAO IRIS Registry
  - First comprehensive clinical data registry for US-based eye care providers
  - Developed to drive quality improvement in ophthalmic care



Nguyen QD et al. Presented at: American Diabetes Association 79th Scientific Sessions; June 7-11, 2019; San Francisco, CA (manuscript in development).
AAO, American Academy of Ophthalmology; DR, diabetic retinopathy.

IRIS Registry Analysis

AAO IRIS Registry
1/1/2013–12/31/2017
N = 821,360

Include eyes in patients ≥ 18 years of age with:

- **Newly diagnosed DR**
  - ≥ 18 months with no documented DR followed by ≥ 2 confirmed diagnoses of DR in study eye
- **Good vision**
  - ≥ 2 VA readings of ≤ 20/40 before or up to 3 months post index date, including 1 VA reading of ≤ 20/40 ≤ 3 months from index

Exclude eyes with:

- Diagnosis of DR before index date
- Any history of retinal conditions (wet or dry AMD, GA, RVO, mCNV, DME, RD, VH, NVG)
- Any history of retinal treatment (PRP, focal laser, anti-VEGF, intravitreal steroids, vitrectomy, RDR)

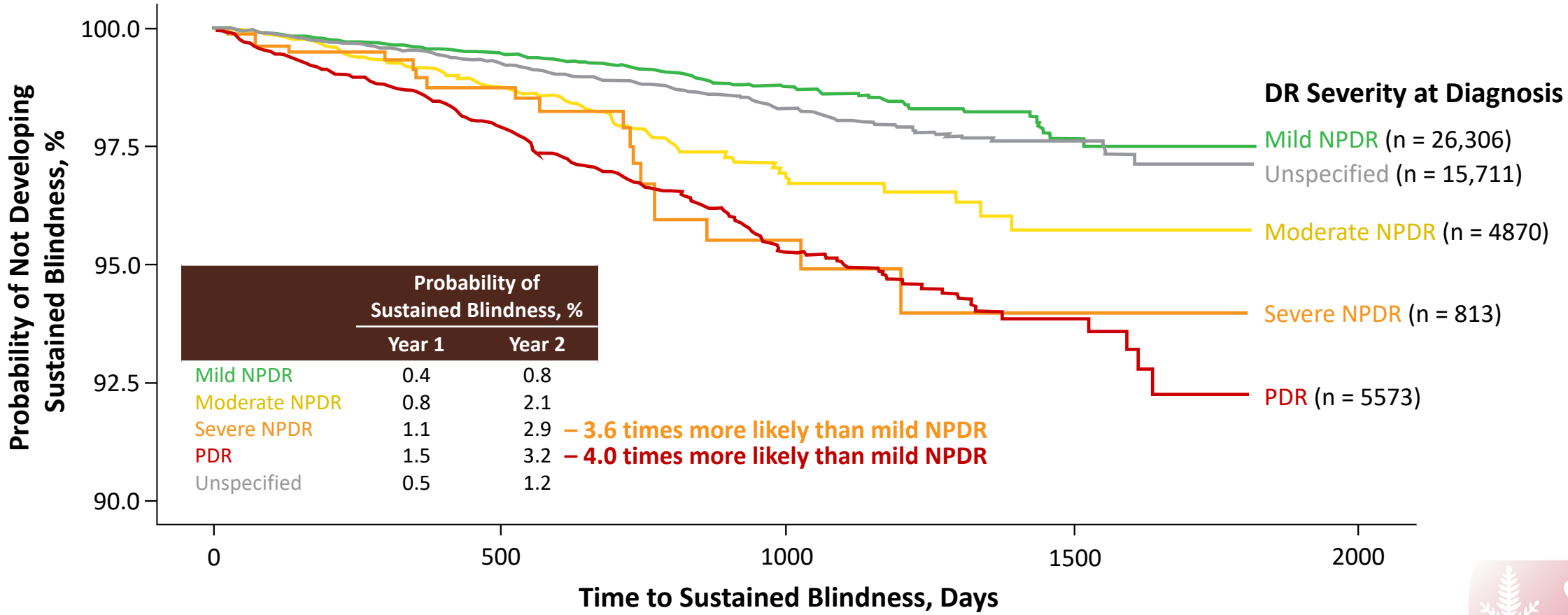
N = 53,535

Event of interest: development of sustained blindness during follow-up

- ≥ 2 VA readings of 20/200 or worse ≥ 3 months apart
- No improvement beyond 20/100 after first 20/200 reading
- Time of event of sustained blindness = date of first VA reading of 20/200 or worse

Nguyen QD et al. Presented at: American Diabetes Association 79th Scientific Sessions; June 7-11, 2019; San Francisco, CA (manuscript in development). AAO, American Academy of Ophthalmology; AMD, age-related macular degeneration; DME, diabetic macular edema; DR, diabetic retinopathy; GA, geographic atrophy; mCNV, myopic choroidal neovascularization; NVG, neovascular glaucoma; PRP, panretinal photocoagulation; RD, retinal detachment; RDR, retinal detachment repair; RVO, retinal vein occlusion; VA, visual acuity; VEGF, vascular endothelial growth factor; VH, vitreous hemorrhage.

IRIS Registry: Higher Probability of Developing Sustained Blindness in Patients Diagnosed With Severe NPDR or PDR

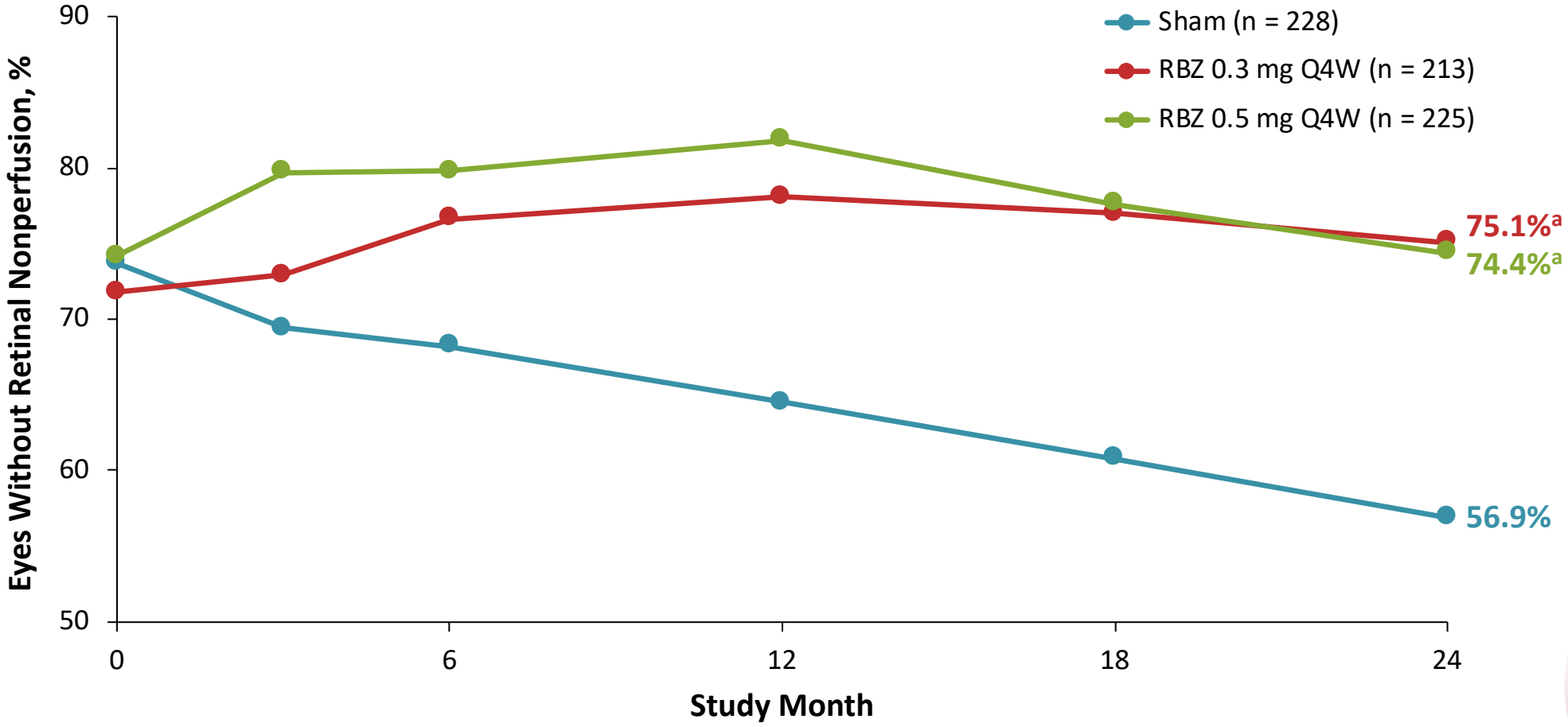


Log-rank $P < 0.0001$.

Nguyen QD et al. Presented at: American Diabetes Association 79th Scientific Sessions; June 7-11, 2019; San Francisco, CA (manuscript in development).

DR, diabetic retinopathy; NPDR, nonproliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy.

RIDE/RISE: Anti-VEGF Therapy Slowed Progression of Retinal Nonperfusion Over 24 Months

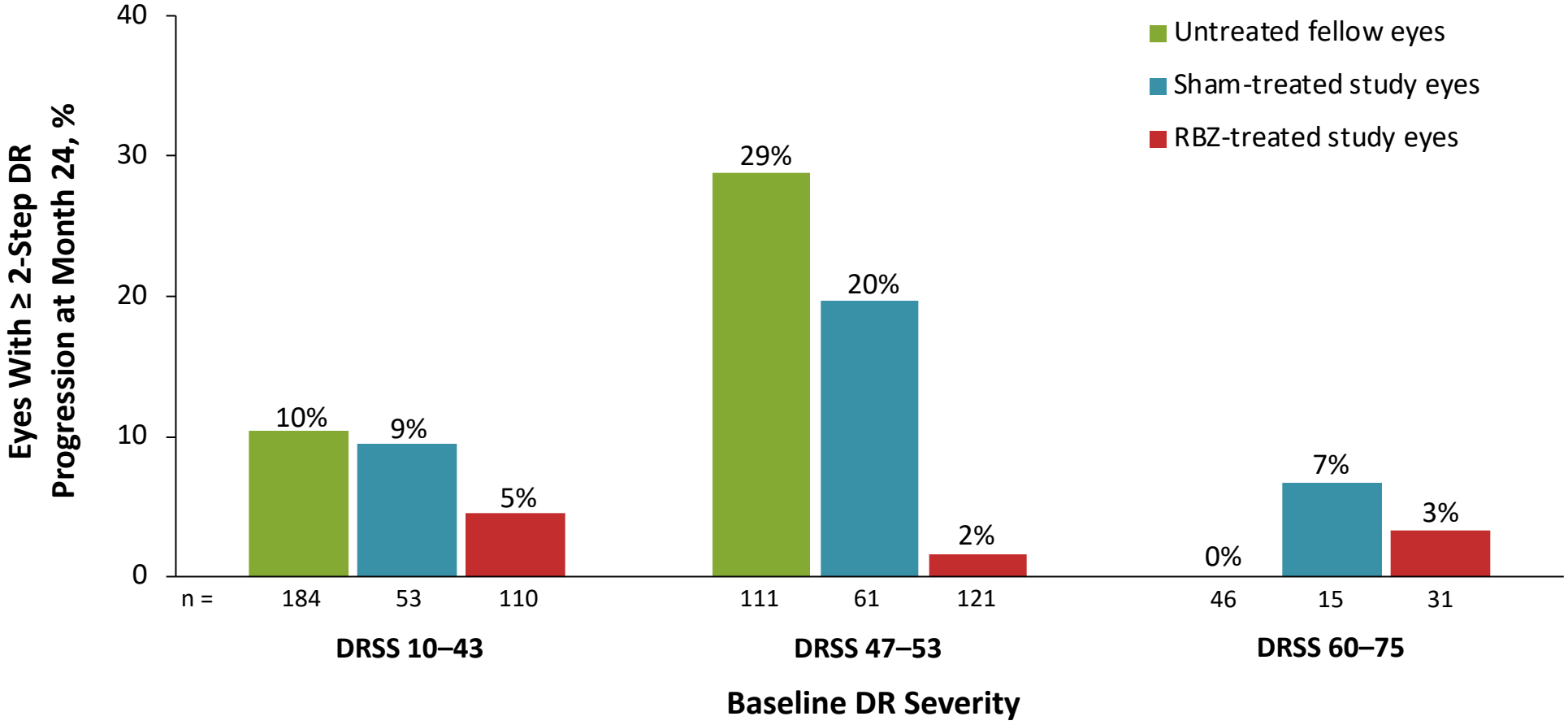


[a] $P < 0.001$ versus sham.

Campochiaro PA et al. *Ophthalmology*. 2014;121(9):1783-1789.

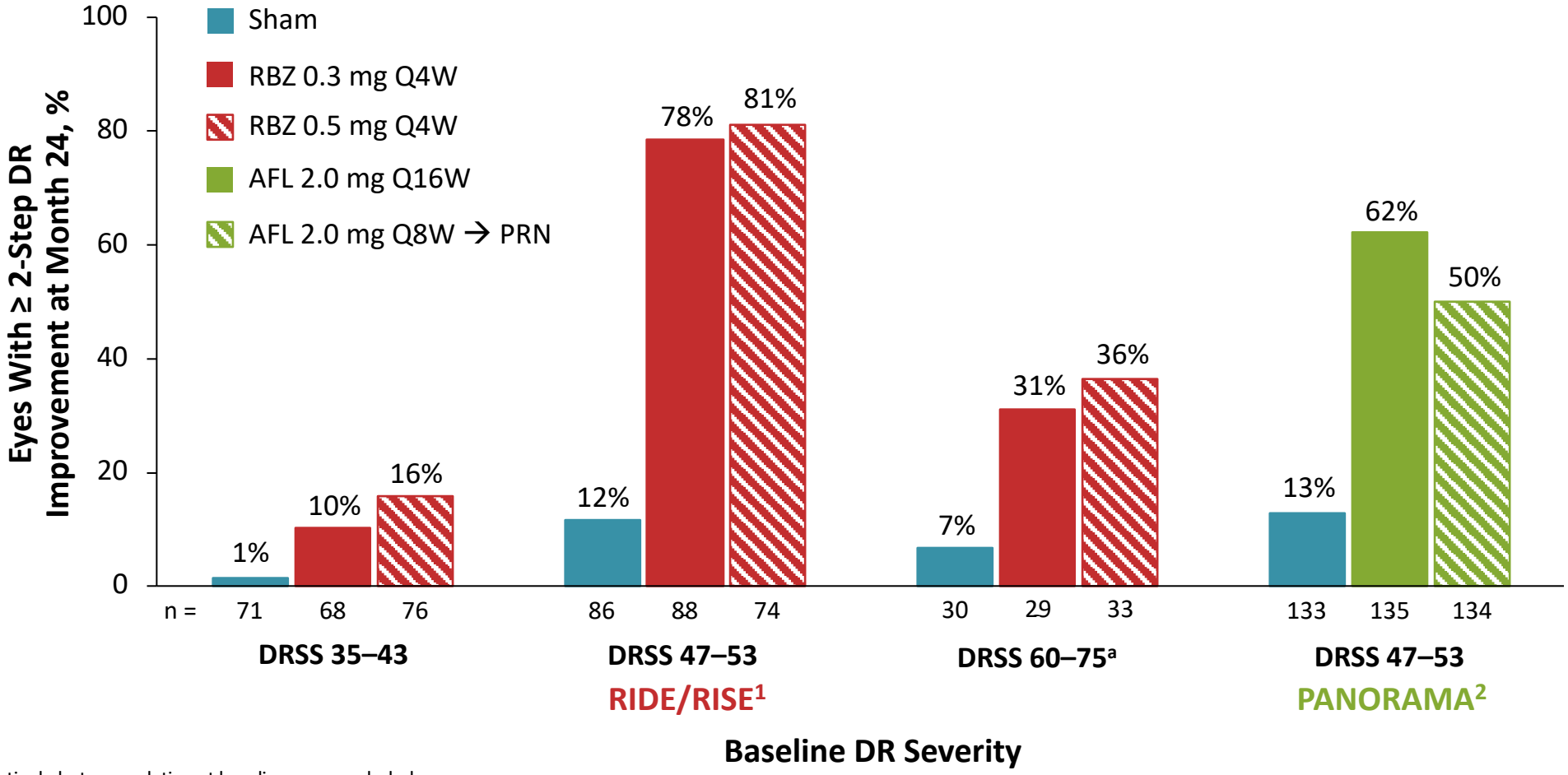
Q4W, every 4 weeks; RBZ, ranibizumab; VEGF, vascular endothelial growth factor.

RIDE/RISE: Rates of DR Progression Were Greatest in Untreated Fellow Eyes With Moderately Severe or Severe NPDR (DRSS 47–53)



Analyses excluded eyes with prior panretinal photocoagulation at baseline; RBZ 0.3 mg and 0.5 mg treatment arms combined.
Bakri SJ et al. Presented at: 37th Annual Meeting of the American Society of Retina Specialists; July 26-30, 2019; Chicago, IL (manuscript in development).
DR, diabetic retinopathy; DRSS, Diabetic Retinopathy Severity Scale; NPDR, nonproliferative diabetic retinopathy; RBZ, ranibizumab.

RIDE/RISE and PANORAMA: High Rates of DR Improvement With Anti-VEGF Therapy in Eyes With Moderately Severe or Severe NPDR

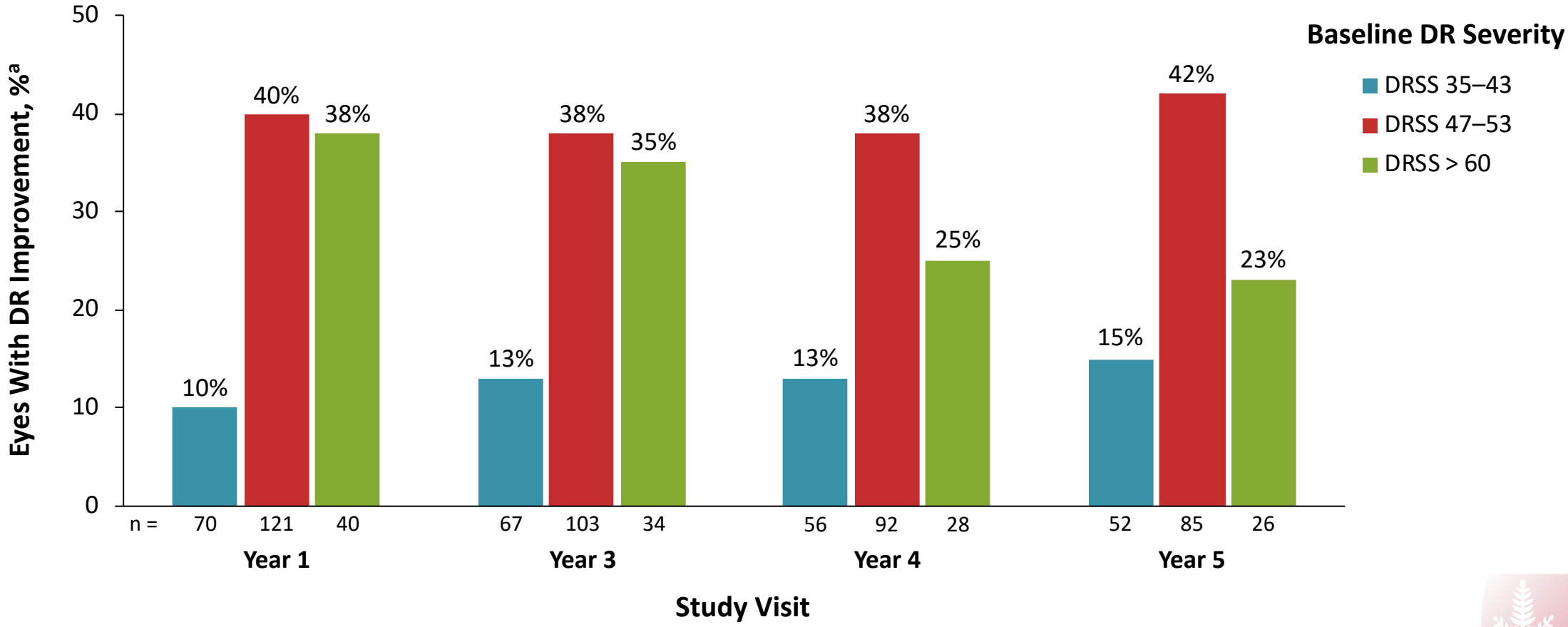


[a] Eyes with prior panretinal photocoagulation at baseline were excluded.

1. Wykoff CC et al. *Ophthalmol Retina*. 2018;2(10):997-1009. 2. Wykoff CC et al. Presented at: Angiogenesis, Exudation, and Degeneration 2020; February 8, 2020; Miami, FL.

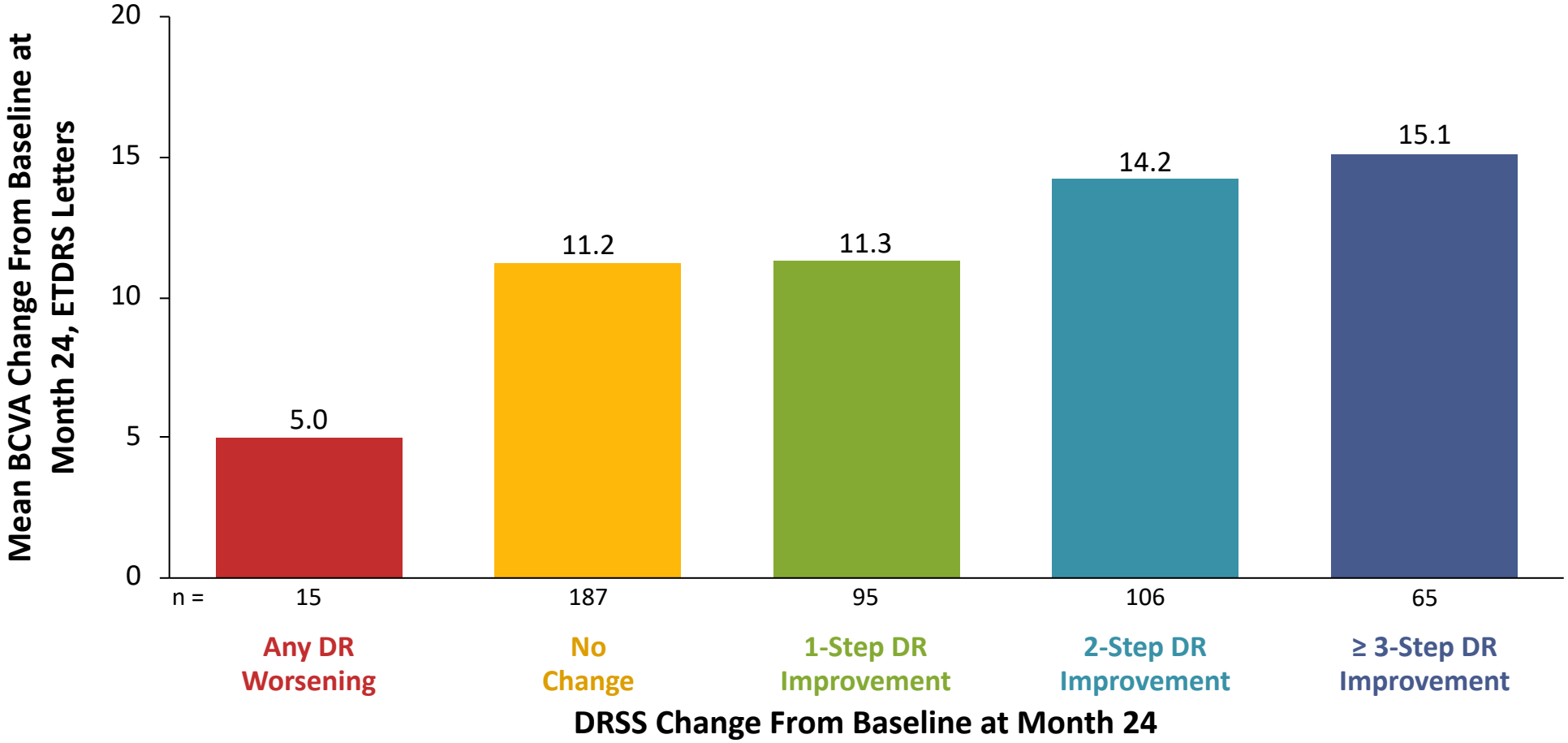
AFL, aflibercept; DR, diabetic retinopathy; DRSS, Diabetic Retinopathy Severity Scale; NPDR, nonproliferative diabetic retinopathy; PRN, pro re nata (as-needed); Q4W, every 4 weeks; Q8W, every 8 weeks; Q16W, every 16 weeks; RBZ, ranibizumab; VEGF, vascular endothelial growth factor.

Protocol I: Rates of DR Improvement With RBZ Were Numerically Greater in Eyes With Moderately Severe or Severe NPDR Over 5 Years



[a] In eyes with NPDR (DRSS 35–43 or 47–53) at baseline, DR improvement was defined as an ≥ 2-step DRSS improvement versus baseline. In eyes with active proliferative DR (PDR; DRSS > 60) at baseline, DR improvement was defined as an ≥ 2-step DRSS improvement versus baseline, or regression to no PDR (DRSS ≤ 53 if no prior panretinal photocoagulation [PRP]; DRSS level 60 if PRP was present at study entry).
Bressler SB et al. *Retina*. 2018;38(10):1896-1904.
DR, diabetic retinopathy; DRSS, Diabetic Retinopathy Severity Scale; NPDR, nonproliferative diabetic retinopathy; RBZ, ranibizumab.

RIDE/RISE: Trend Toward Greater Mean Vision Gains With Greater DR Improvement Among RBZ-Treated Eyes



Analyses included study eyes randomized to monthly RBZ 0.3 mg and 0.5 mg at RIDE/RISE baseline (n = 468).
Ehrlich JS et al. Presented at: 2014 Annual Meeting of the Association for Research in Vision and Ophthalmology; May 4-8, 2014; Orlando, FL.
BCVA, best-corrected visual acuity; DR, diabetic retinopathy; DRSS, Diabetic Retinopathy Severity Scale; ETDRS, Early Treatment Diabetic Retinopathy Study; RBZ, ranibizumab.

CONCLUSIONS

- IRIS Registry analyses have associated PDR with the development of sustained blindness in current clinical practice
- Landmark trials found that patients with **moderately severe** or **severe** NPDR (DRSS 47–53) are vulnerable to DR progression without treatment, and are more likely to achieve DR improvement with anti-VEGF therapy
- Further analyses revealed a trend toward greater mean vision gains, with greater DR improvement among anti-VEGF–treated eyes in RIDE/RISE
- These data raise the question of whether the time has come to re-evaluate therapeutic goals in DR management, including early intervention to delay progression towards PDR

DR, diabetic retinopathy; DRSS, Diabetic Retinopathy Severity Scale; NPDR, nonproliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; VEGF, vascular endothelial growth factor.