Progression to Proliferative Diabetic Retinopathy in Nonproliferative Diabetic Retinopathy Eyes without Diabetic Macular Edema in the United States

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Disclosures

- Ehsan Rahimy is a consultant to Regeneron Pharmaceuticals, Inc.
- Rahul N. Khurana is a consultant to Alkahest, Allergan plc, Clearside Biomedical, Genentech, Inc., Regeneron Pharmaceuticals, Inc., and has received research funding from Allergan plc, Clearside Biomedical, Roche, and Santen Pharmaceutical Co., Ltd.
- Nick Boucher is a salaried employee of Vestrum Health
- Steven Sherman, Hadi Moini, and Kimberly Reed are employees of and hold shares in Regeneron Pharmaceuticals, Inc.
- Andrew A. Moshfeghi has served as a consultant to Allegro, Allergan plc, Alimera, Regeneron Pharmaceuticals, Inc., Genentech, Inc., Clearside, Bausch, EyePoint, and Novartis and as a speaker for Allergan plc. He has also received research support from Regeneron Pharmaceuticals, Inc. and Genentech and holds equity interest in Pr3vent, OptiSTENT, and Visunex
- De-identified electronic medical records of patients were used for this analysis. On this basis, IRB approval was not obtained
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Background and Purpose

- In patients with DR, the rate of progression from NPDR without DME to PDR, and the baseline characteristics that predict progression may inform optimal treatment strategies
- This retrospective analysis evaluated DR progression from NPDR to PDR in routine clinical practice in the US in the following eyes:
  - Anti-VEGF-naïve eyes: Eyes that did not receive anti-VEGF before converting to PDR
  - Treated eyes: Eyes that received anti-VEGF and/or laser before converting to PDR

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

Study Design

- Retrospective analysis of electronic medical records from 251 retina specialists in the US (Vestrum Health; Naperville, Illinois)

Anti-VEGF-Naïve Eyes

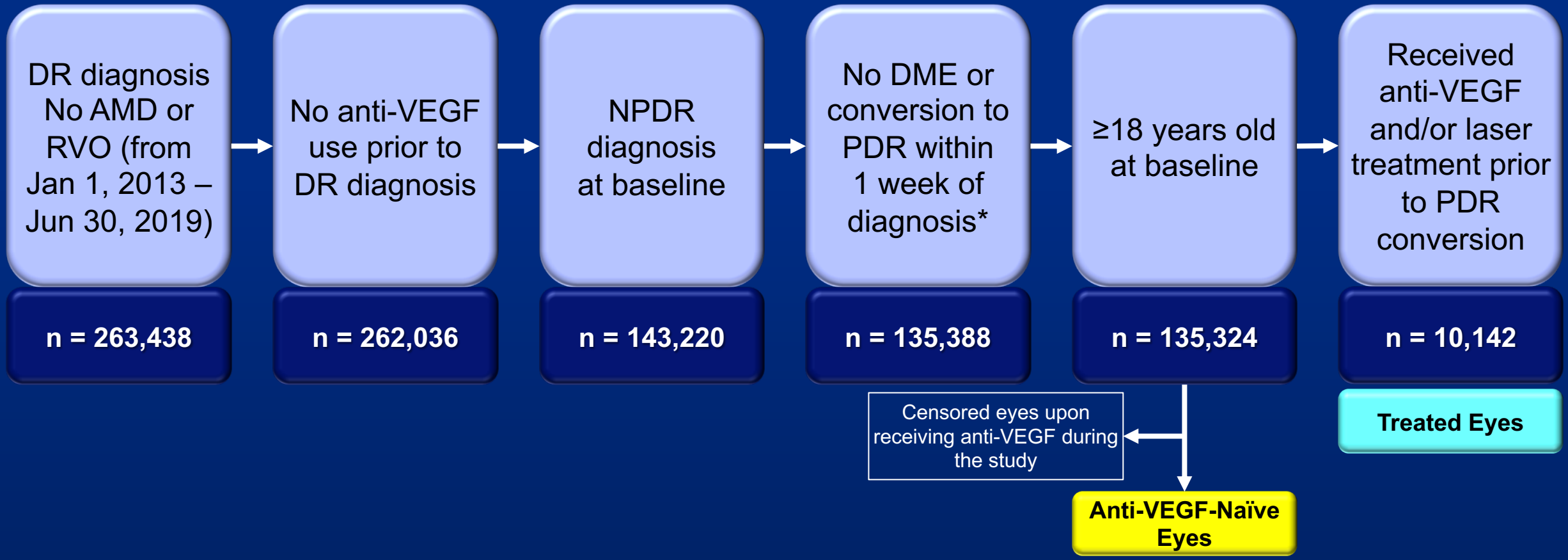
- **Inclusion Criteria**
  - Data collected between January 1, 2013 – June 30, 2019
  - Anti-VEGF treatment naïve DR patients with NPDR at index
  - No conversion to PDR or DME within a week of the index DR diagnosis
  - At least 18 years of age at index DR diagnosis
- **Exclusion Criteria**
  - AMD or RVO during the study period
- **Censoring Criterion**
  - Eyes were censored upon receiving anti-VEGF treatment prior to converting to PDR

Treated Eyes

- "Treatment with anti-VEGF and/or laser before converting to PDR" was an inclusion criterion
- All other inclusion and exclusion criteria were the same
- No censoring

AMD, age-related macular degeneration; RVO, retinal vein occlusion.

Patient (Eye) Selection



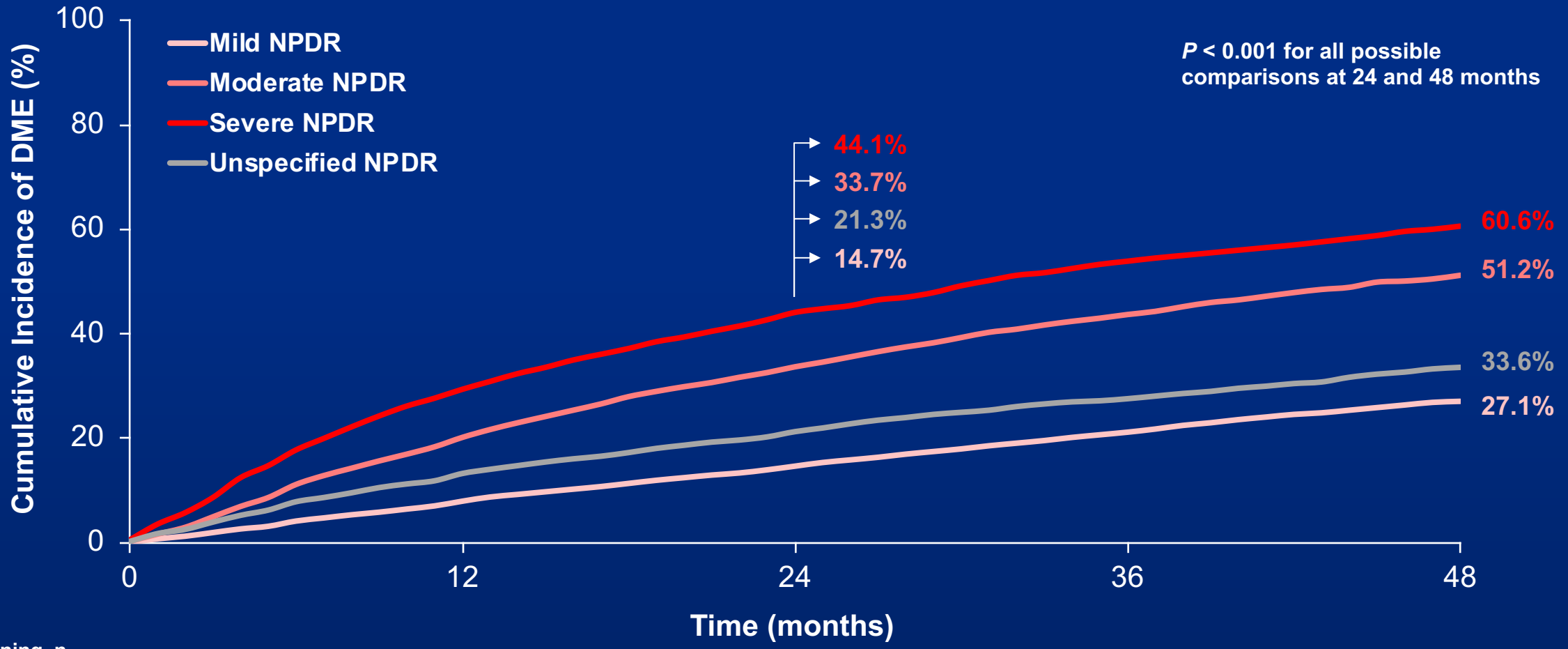
*Patients with diagnosis codes for PDR or DME within a week of their NPDR diagnosis were excluded in addition to those with evidence of vitreous hemorrhage/retinal detachment and/or retinal edema during the same period.

Baseline Characteristics of Anti-VEGF-Naïve NPDR Eyes

	Mild	Moderate	Severe	Unspecified	Total
N	70,050	39,116	10,692	15,466	135,324
Severity, % of total	52	29	8	11	100
Mean age, years (SD)	64 (12.7)	63 (12.4)	59 (12.8)	65 (12.4)	64 (12.7)
Female, %	49	49	45	48	49
Diabetes type					
Type 1, %	20	25	27	26	23
Type 2, %	62	57	55	60	60
Unspecified, %	18	17	18	14	17
Hypertension, %	66	64	60	69	66
Cataracts, %	37	36	37	25	35
Mean VA, letters (SD)[a]	73 (13.2)	72 (13.8)	72 (14.2)	72 (14.0)	73 (13.6)
Mean IOP, mmHg (SD)[b]	16 (3.8)	16 (3.9)	16 (4.0)	16 (3.7)	16 (3.8)

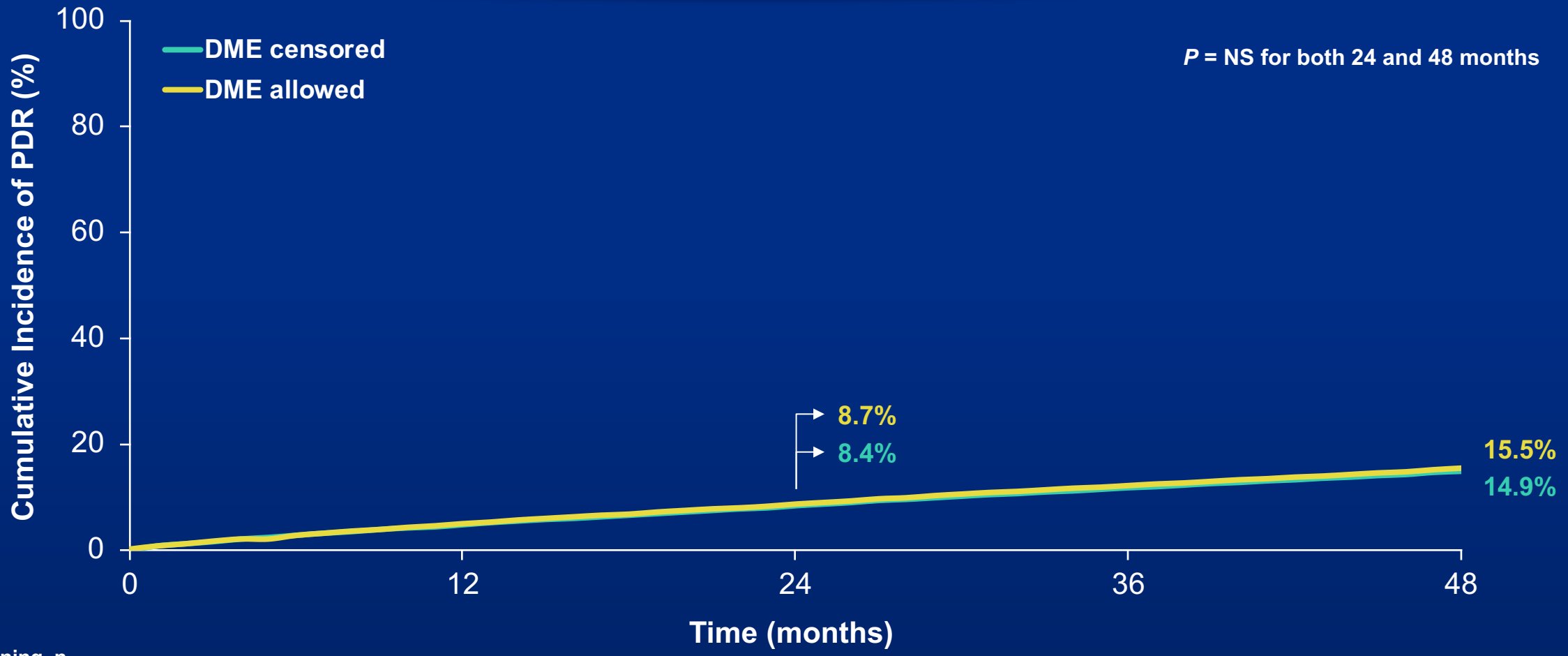
[a]n = 56,627 for mild; n = 30,883 for moderate; n = 8,253 for severe; n = 12,014 for unspecified; and n = 107,777 for total. [b]n = 68,730 for mild; n = 38,193 for moderate; n = 10,468 for severe; n = 14,917 for unspecified; and n = 132,308 for total. IOP, intraocular pressure; VA, visual acuity; SD, standard deviation.

Cumulative Incidence of DME Development by Baseline NPDR Severity in Anti-VEGF-Naïve Eyes



Eyes remaining, n					
Mild	70,050	24,715	14,003	8,011	4,138
Moderate	39,116	13,971	7,562	4,082	2,191
Severe	10,692	3,196	1,585	753	377
Unspecified	15,466	7,221	5,608	4,094	2,700

Cumulative Incidence of Conversion from NPDR to PDR in Anti-VEGF-Naïve Eyes By Allowing or Censoring DME

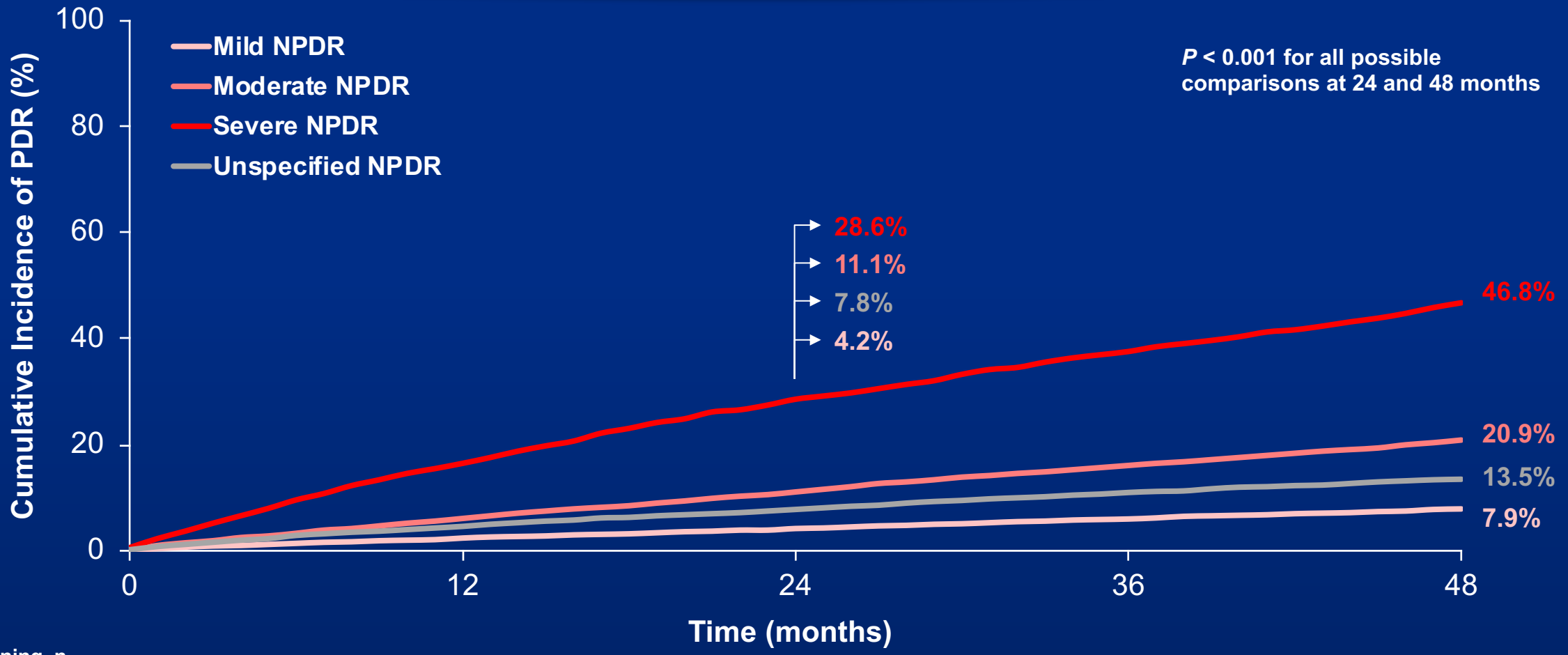


Eyes remaining, n

DME censored	135,324	48,112	27,267	15,812	8,619
DME allowed	135,324	52,181	31,682	19,471	11,200

NS, not significant.

Cumulative Incidence of Conversion from NPDR to PDR in Anti-VEGF-Naïve Eyes
By Baseline NPDR Severity



Eyes remaining, n

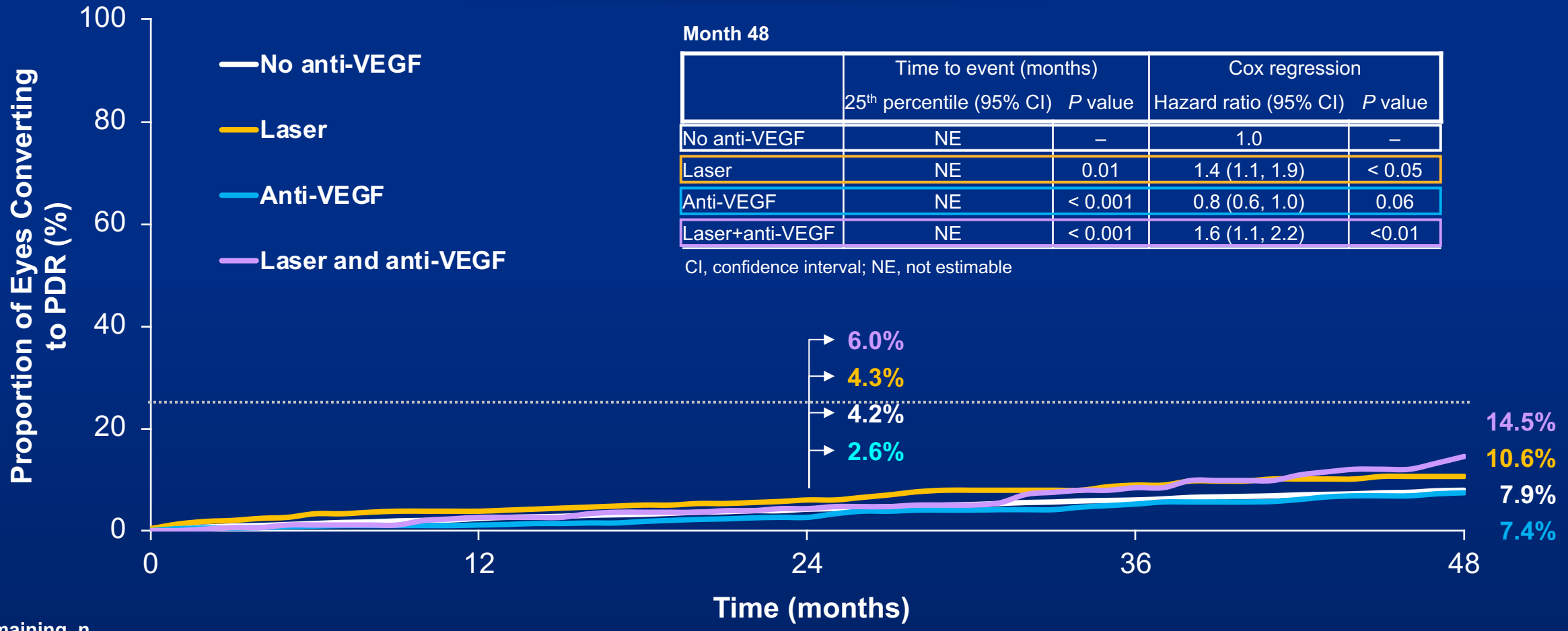
Mild	70,050	25,433	14,923	8,833	4,732
Moderate	39,116	15,265	8,967	5,218	2,998
Severe	10,692	3,410	1,721	848	412
Unspecified	15,466	8,074	6,072	4,573	3,059

Demographics and Baseline Characteristics of Treated Eyes

	Mild	Moderate	Severe	Unspecified	Total
N	2,788	3,911	1,768	1,595	10,142
Severity, % of total	27	39	17	16	100
Mean age, years (SD)	65 (11.6)	63 (10.8)	60 (11.3)	65 (10.6)	63 (11.2)
Female, %	51	49	46	46	49
Diabetes type					
Type 1, %	23	24	26	26	24
Type 2, %	65	64	61	62	64
Unspecified, %	11	12	12	13	12
DME in follow-up, %	80	88	78	88	84
Hypertension, %	69	65	62	67	66
Cataracts, %	34	33	34	26	32
Mean VA[a], letters	68	70	69	69	69
Mean IOP[b], mm Hg	16.0	16.0	15.8	15.7	15.9

[a]n = 2,272 for mild; n = 3,166 for moderate; n = 1,388 for severe; n = 1,221 for unspecified; and n = 8,047 for total. [b]n = 2,723 for mild; n = 3,870 for moderate; n = 1,723 for severe; n = 1,525 for unspecified; and n = 9,841 for total.

Cumulative Incidence of Conversion to PDR By Baseline NPDR Severity and Treatment: Mild NPDR



Month 48

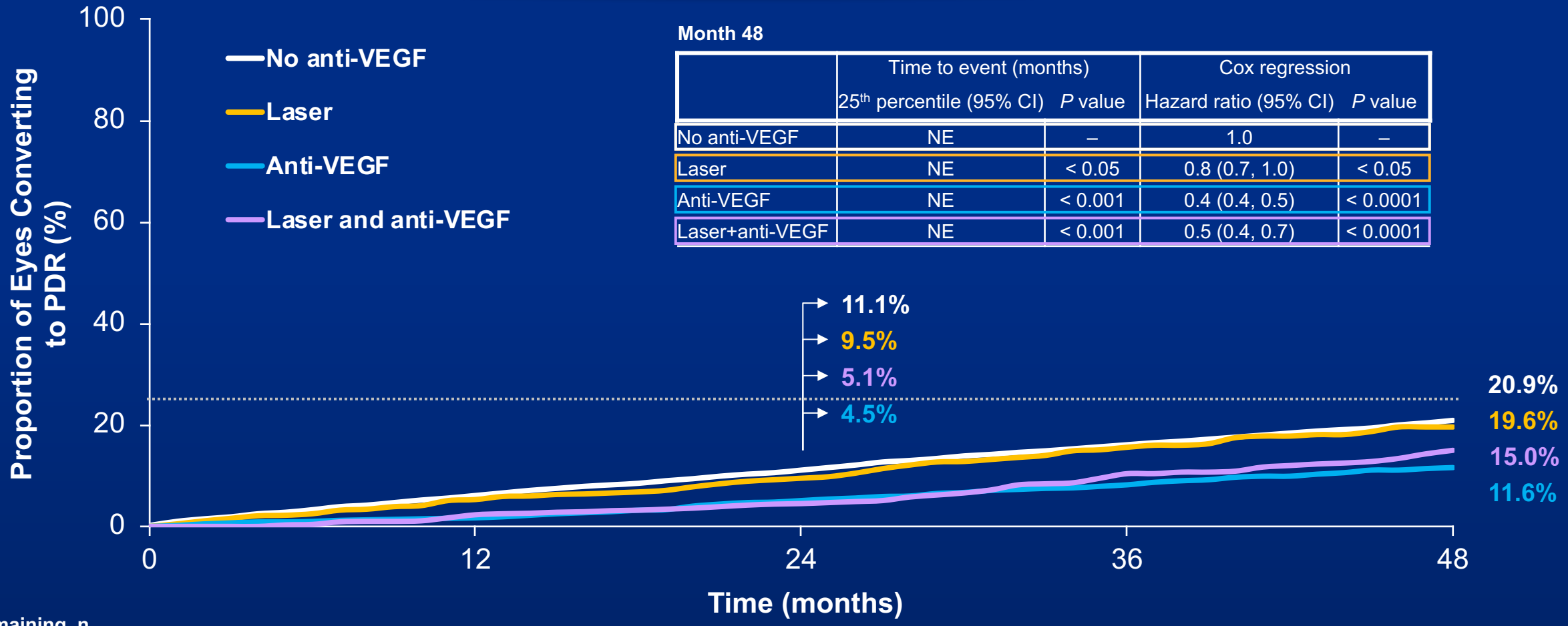
	Time to event (months)		Cox regression	
	25th percentile (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
No anti-VEGF	NE	–	1.0	–
Laser	NE	0.01	1.4 (1.1, 1.9)	< 0.05
Anti-VEGF	NE	< 0.001	0.8 (0.6, 1.0)	0.06
Laser+anti-VEGF	NE	< 0.001	1.6 (1.1, 2.2)	<0.01

CI, confidence interval; NE, not estimable

Eyes remaining, n

No anti-VEGF	70,050	25,433	14,923	8,833	4,732
Laser	683	490	377	258	170
Anti-VEGF	1,741	1,433	1,097	720	418
Laser+anti-VEGF	364	316	277	203	134

Cumulative Incidence of Conversion to PDR By Baseline NPDR Severity and Treatment: Moderate NPDR



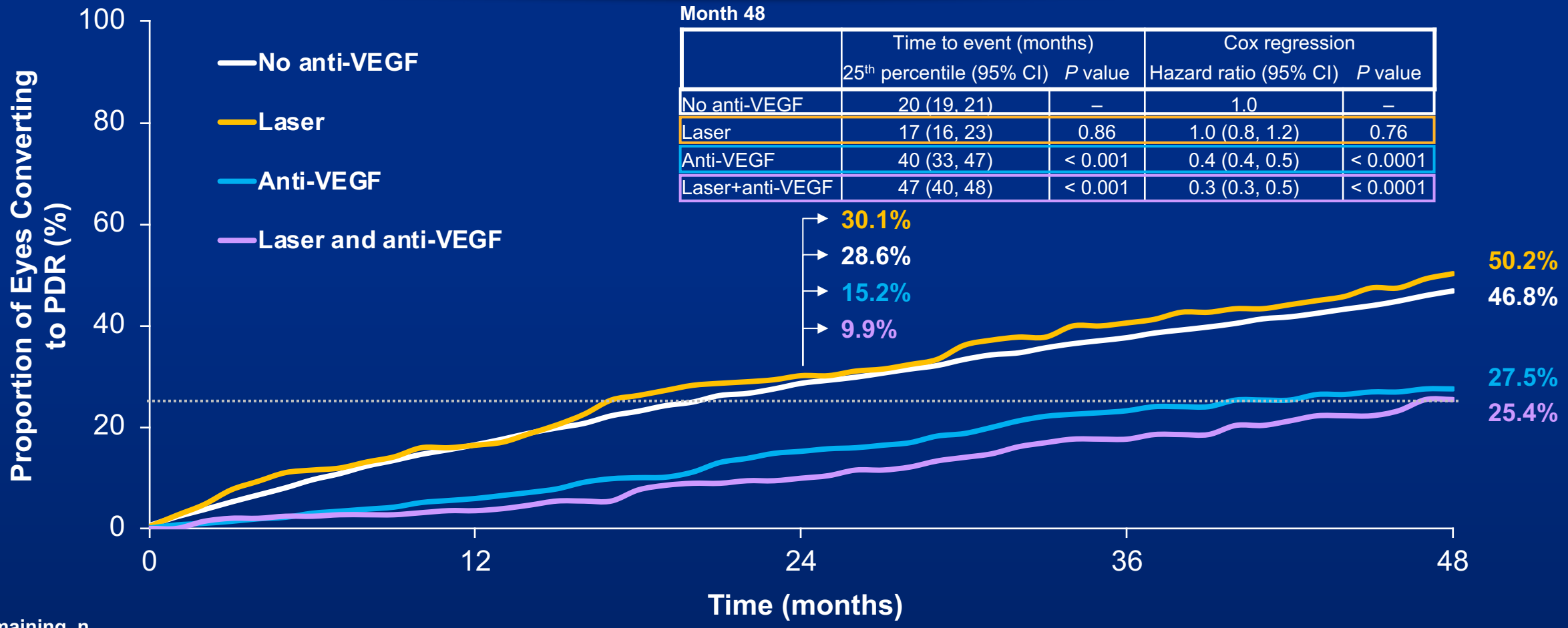
Month 48

	Time to event (months)		Cox regression	
	25th percentile (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
No anti-VEGF	NE	–	1.0	–
Laser	NE	< 0.05	0.8 (0.7, 1.0)	< 0.05
Anti-VEGF	NE	< 0.001	0.4 (0.4, 0.5)	< 0.0001
Laser+anti-VEGF	NE	< 0.001	0.5 (0.4, 0.7)	< 0.0001

Eyes remaining, n

No anti-VEGF	39,116	15,265	8,967	5,218	2,998
Laser	1,028	794	566	378	263
Anti-VEGF	2,237	1,804	1,291	860	532
Laser+anti-VEGF	726	663	575	401	273

Cumulative Incidence of Conversion to PDR By Baseline NPDR Severity and Treatment: Severe NPDR



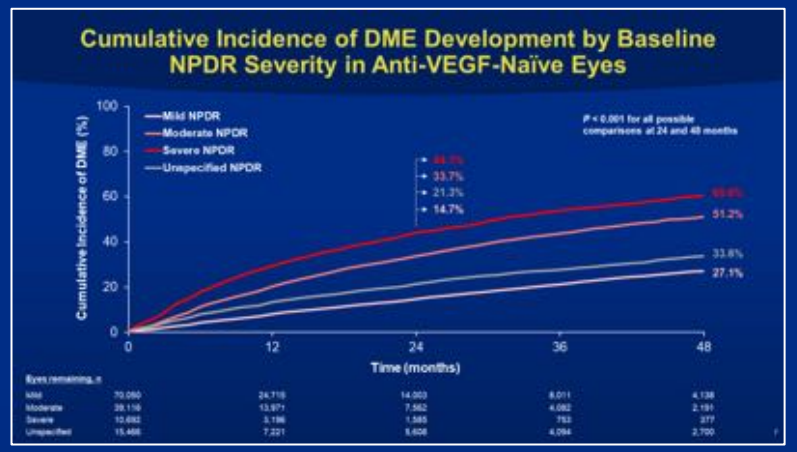
Month 48

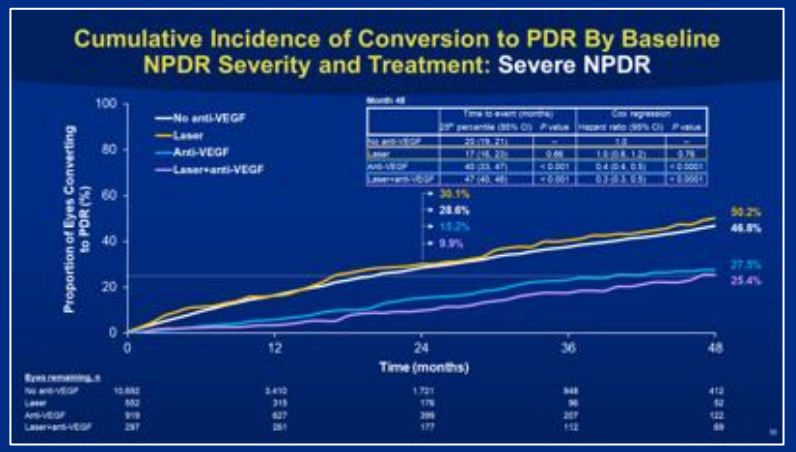
	Time to event (months)		Cox regression	
	25th percentile (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
No anti-VEGF	20 (19, 21)	–	1.0	–
Laser	17 (16, 23)	0.86	1.0 (0.8, 1.2)	0.76
Anti-VEGF	40 (33, 47)	< 0.001	0.4 (0.4, 0.5)	< 0.0001
Laser+anti-VEGF	47 (40, 48)	< 0.001	0.3 (0.3, 0.5)	< 0.0001

Eyes remaining, n

No anti-VEGF	10,692	3,410	1,721	848	412
Laser	552	315	176	96	52
Anti-VEGF	919	627	399	207	122
Laser+anti-VEGF	297	261	177	112	69

Conclusions





- Rates of DME development and progression to PDR were increased with increasing severity of NPDR at baseline
- Consistent with previous landmark studies, baseline NPDR severity was a strong predictor of progression to PDR
- These findings suggest that, when left untreated, nearly half of eyes (46.8%) with severe NPDR progressed to PDR within 4 years in the US routine clinical practice
- Rate of progression to PDR was substantially lower in eyes with severe NPDR treated with anti-VEGF compared to those not treated with anti-VEGF