DİYABETİK RETİNOPATİ VE LİPİDLER

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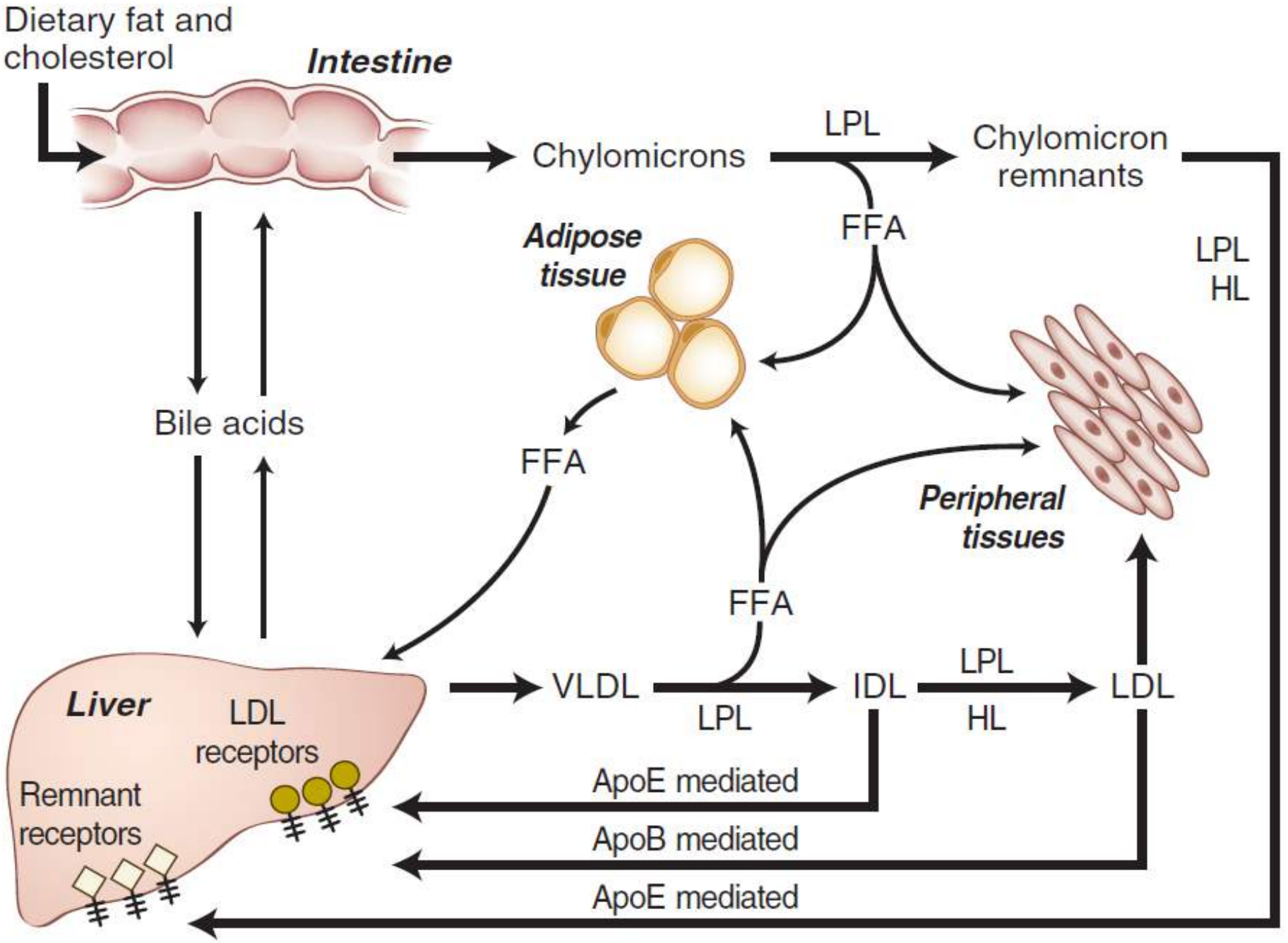
Endokrinoloji ve Metabolizma Hastalıkları BD
Adana


Dietary fat and cholesterol
Intestine
Chylomicrons
LPL
Chylomicron remnants
FFA
LPL
HL
Adipose tissue
Bile acids
FFA
Peripheral tissues
FFA
Liver
LDL receptors
Remnant receptors
VLDL
LPL
IDL
LPL
HL
LDL
ApoE mediated
ApoB mediated
ApoE mediated

Ophthalmology. 1991 Aug;98(8):1261-5.

The Wisconsin Epidemiologic Study of Diabetic Retinopathy. XIII. Relationship of serum cholesterol to retinopathy and hard exudate.

Klein BE[1], Moss SE, Klein R, Surawicz TS.

Author information

Abstract

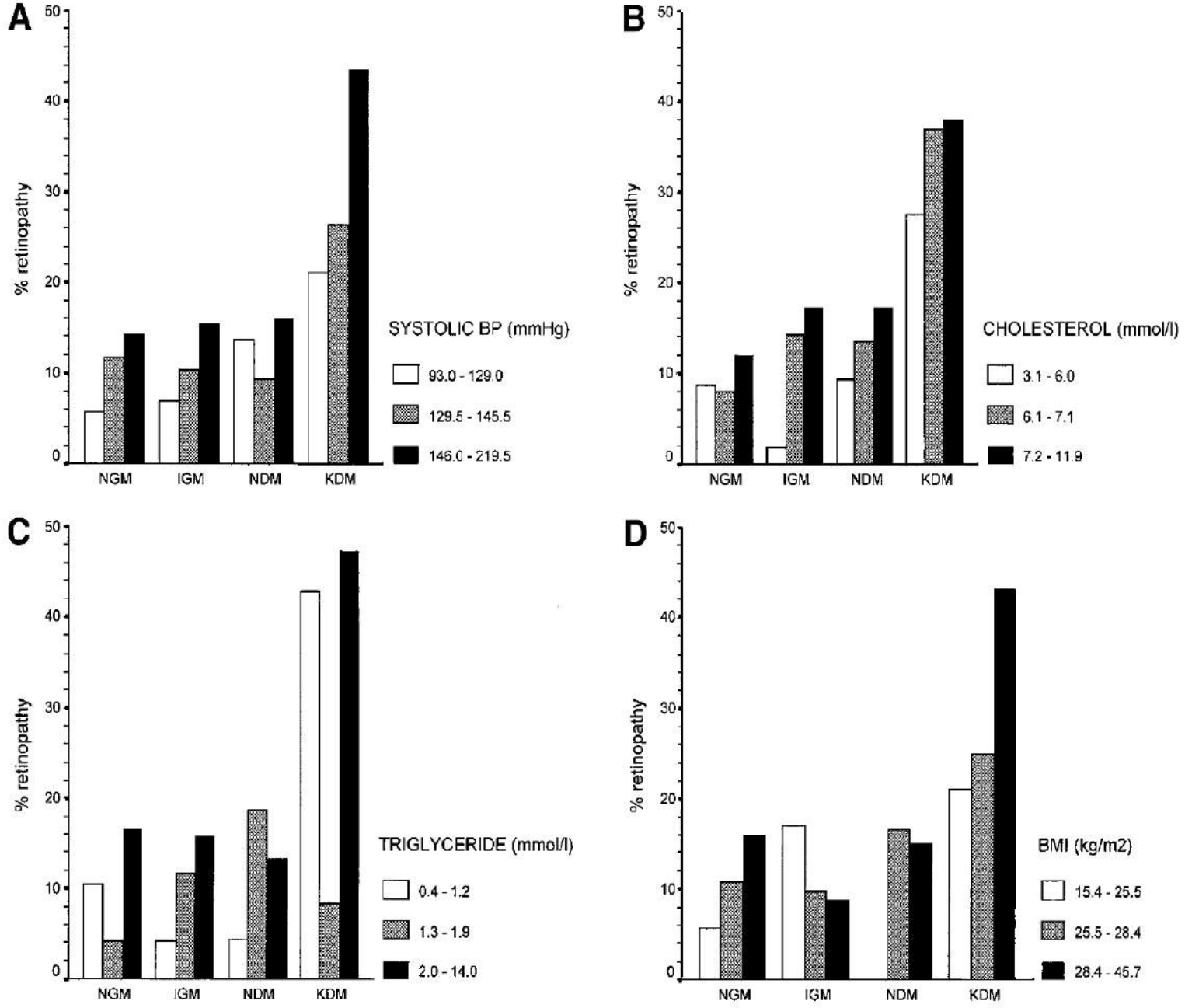
Serum total and high-density lipoprotein (HDL) cholesterol were measured in a sample of individuals examined between 1984 and 1986 for the Wisconsin Epidemiologic Study of Diabetic Retinopathy. There was a significant trend for increasing severity of diabetic retinopathy and of retinal hard exudate with increasing cholesterol in insulin-using persons. Cholesterol levels were not related to the severity of either ocular condition in older-onset patients. High-density lipoprotein-cholesterol was unrelated to the severity of either lesion. **In multiple logistic regression analyses, cholesterol was not a significant factor in describing the severity of retinopathy in any group but was a significant factor in describing the severity of retinal hard exudate**. Glycosylated hemoglobin and diastolic blood pressure were significant descriptors of the severity of retinopathy in younger-onset patients in these multivariate analyses. Diastolic blood pressure added significantly to explaining the severity of hard exudate in older-onset insulin users. These data support the current management strategies for diabetes, which include control of level of glycemia, blood pressure, and blood lipids.

Arch Ophthalmol. 1996 Sep;114(9):1079-84.

Association of elevated serum lipid levels with retinal hard exudate in diabetic retinopathy. EarlyTreatment Diabetic Retinopathy Study (ETDRS) Report 22.

n=2709, yaşlı tip 2 DM

Yüksek Total kolesterol ve LDL değerleri-----**SERT EKSUDA******

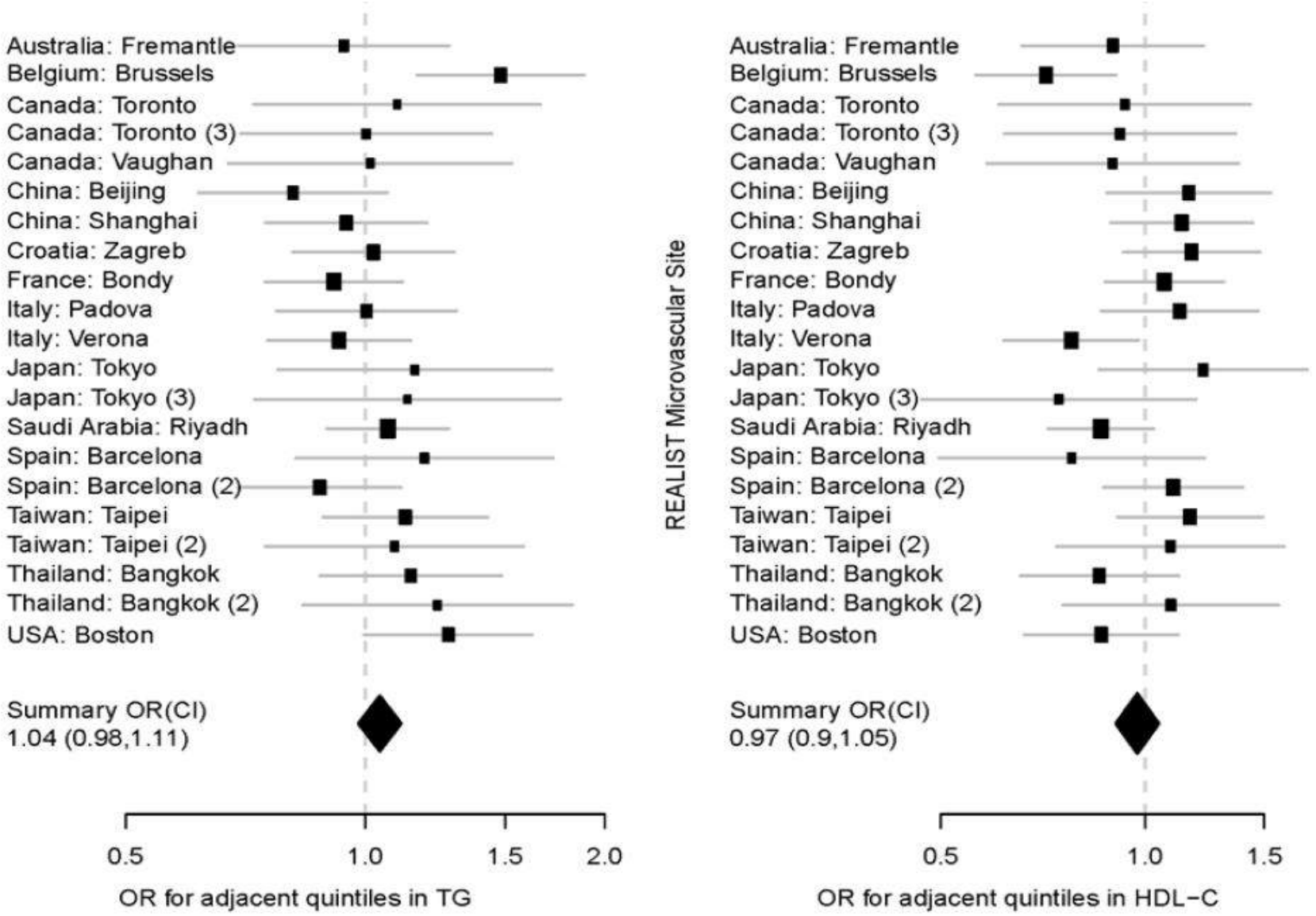


van Leiden HA, Diabetes Cre, 2002

Relationship of serum lipids with the development of retinal hard exudate*

Lipids (quintiles)	No. of events	Univariate model†	HbA_{1c} adjusted†‡
Total cholesterol (mg/dl)			
<148	19	1.0	1.0
148–165	39	1.27 (0.70–2.29)	1.22 (0.68–2.21)
166–181	32	2.12 (1.23–3.65)	2.03 (1.18–3.50)
182–203	38	2.27 (1.32–3.89)	2.14 (1.25–3.68)
≥204	48	2.46 (1.44–4.20)	2.23 (1.30–3.83)
P for trend	—	0.0008	0.002
LDL cholesterol (mg/dl)			
<86	21	1.0	1.0
86–99	32	1.58 (0.87–2.86)	1.52 (0.84–2.75)
100–114	41	1.64 (0.90–2.99)	1.57 (0.86–2.86)
115–132	35	2.62 (1.51–4.56)	2.45 (1.40–4.26)
≥133	47	2.93 (1.69–5.08)	2.68 (1.54–4.66)
P for trend	—	0.001	0.003
HDL cholesterol (mg/dl)			
<40	38	1.0	1.0
40–45	51	1.40 (0.90–2.17)	1.41 (0.91–2.20)
46–51	34	1.10 (0.69–1.74)	1.11 (0.70–1.76)
52–60	34	1.22 (0.77–1.92)	1.25 (0.79–1.97)
≥61	19	0.81 (0.47–1.38)	0.83 (0.48–1.43)
P for trend	—	0.18	0.22
Total–to–HDL cholesterol ratio			
≤2.803	15	1.0	1.0
2.804 to <3.283	27	1.77 (0.93–3.36)	1.72 (0.91–3.27)
3.283 to <3.777	36	2.30 (1.24–4.26)	2.19 (1.18–4.05)
3.777 to <4.429	48	3.22 (1.78–5.83)	2.99 (1.65–5.43)
≥4.429	50	2.73 (1.50–4.97)	2.49 (1.37–4.54)
P for trend	—	0.0003	0.001
Triglycerides (mg/dl)			
<52	13	1.0	1.0
52–63	31	2.08 (1.01–4.29)	2.06 (1.00–4.25)
64–76	37	3.11 (1.56–6.17)	3.01 (1.52–5.98)
77–99	43	2.94 (1.47–5.88)	2.74 (1.37–5.48)
≥100	52	3.28 (1.67–6.46)	2.91 (1.47–5.75)
P for trend	—	0.003	0.02

Miljanovic B, Diabetes 2004

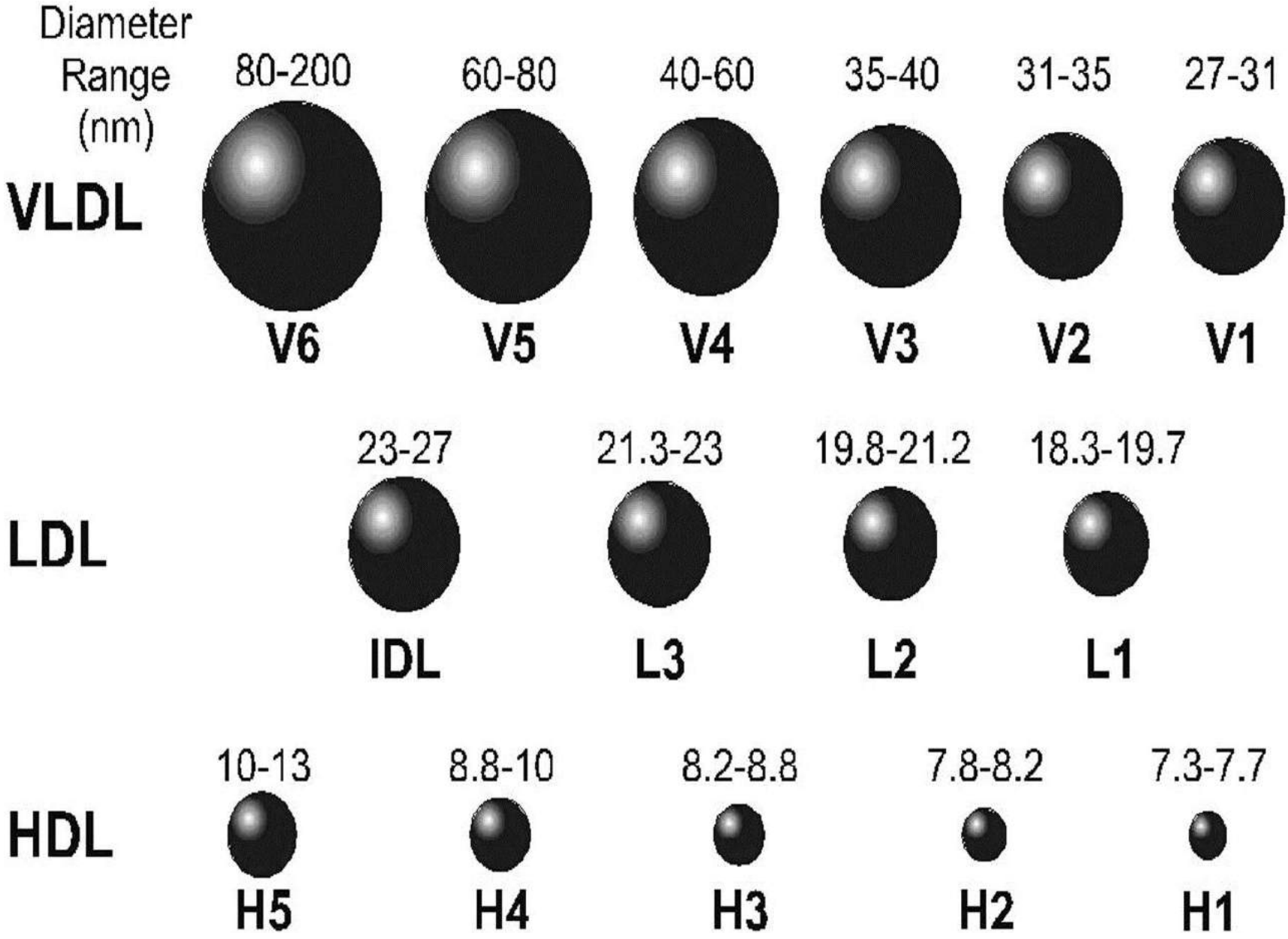


Sacks FM, Circulation 2014

Klein BE, JAMA Ophtalmol 2015

Prevalence analyses[b]

Covariate	WESDR 2 1984–1986 (N=392)	WESDR 3 1990–1992 (N=686)	WESDR 4 1994–1996 (N=513)	WESDR 6 2005–2007 (N=422)	WESDR 7 2012–2014 (N=306)	Overall (N=2319)
	Mean ±SD	Mean ±SD	Mean ±SD	Mean ±SD	Mean ±SD	Mean ±SD
Age, y	33.0 ±12.8	37.3 ±11.8	40.9 ±10.7	50.0 ±9.5	56.0 ±8.9	42.1 ±13.4
Diabetes duration, y	18.5 ±10.1	22.8 ±9.3	26.4 ±8.2	35.8 ±7.1	41.8 ±6.4	27.7 ±11.5
Glycosylated hemoglobin, %	9.5 ±1.9	9.3 ±1.6	8.9 ±1.5	7.6 ±1.4	7.8 ±1.2	8.7 ±1.7
Systolic blood pressure, mmHg	122.2 ±17.4	125.9 ±18.5	126.6 ±18.8	133.0 ±20.5	135.9 ±19.1	128.1 ±19.4
Diastolic blood pressure, mmHg	76.8 ±10.7	76.2 ±11.3	74.8 ±10.6	73.3 ±10.3	72.7 ±9.1	75.0 ±10.7
Body mass index, kg/m^2	24.7 ±4.0	25.8 ±4.0	26.7 ±4.4	28.7 ±5.5	29.0 ±5.6	26.8 ±4.9
Serum total cholesterol, mg/dL	202.8 ±50.4	197.1 ±45.6	196.7 ±42.9	166.9 ±37.9	163.7 ±37.0	188.1 ±46.1
Serum HDL cholesterol, mg/dL	51.0 ±16.0	46.7 ±14.1	49.7 ±14.4	56.6 ±17.5	61.5 ±17.9	51.8 ±16.5
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Sex						
Female	195 (49.7)	331 (48.3)	233 (45.4)	201 (47.6)	154 (50.3)	1114 (48.0)
Male	197 (50.3)	355 (51.7)	280 (54.6)	221 (52.4)	152 (49.7)	1205 (52.0)
Using statins						
No	392 (100.0)	672 (98.0)	478 (93.2)	213 (50.5)	88 (28.8)	1843 (79.5)
Yes	0 (0.0)	14 (2.0)	35 (6.8)	209 (49.5)	218 (71.2)	476 (20.5)
Smoking history						
Never	233 (59.4)	391 (57.0)	296 (57.7)	251 (59.5)	192 (63.0)	1363 (58.8)
Past	78 (19.9)	147 (21.4)	119 (23.2)	118 (28.0)	87 (28.5)	549 (23.7)
Current	81 (20.7)	148 (21.6)	98 (19.1)	53 (12.6)	26 (8.5)	406 (17.5)
End-stage renal disease						
Absent	372 (94.9)	640 (93.3)	464 (90.4)	361 (85.5)	265 (86.6)	2102 (90.6)
[illegible]						
Prevalent macular edema						
Absent	301 (85.3)	488 (77.0)	365 (75.1)	245 (70.6)	172 (71.1)	1571 (76.2)
Present	52 (14.7)	146 (23.0)	121 (24.9)	102 (29.4)	70 (28.9)	491 (23.8)
Prevalent PDR						
Absent	277 (70.7)	418 (60.9)	298 (58.3)	218 (51.7)	155 (51.0)	1366 (59.0)
Present	115 (29.3)	268 (39.1)	213 (41.7)	204 (48.3)	149 (49.0)	949 (41.0)


Diameter Range (nm)
VLDL
80-200
60-80
40-60
35-40
31-35
27-31
V6
V5
V4
V3
V2
V1
LDL
23-27
21.3-23
19.8-21.2
18.3-19.7
IDL
L3
L2
L1
HDL
10-13
8.8-10
8.2-8.8
7.8-8.2
7.3-7.7
H5
H4
H3
H2
H1

DCCT/EDIC Kohortu

RETİNOPATİ varlığı ile ilişki durumları

İlişki saptanmayanlar

Apo A1-Lipoprotein (a)-LDL oksidasyon yatkınlığı

Pozitif İlişki (yalnızca erkeklerde)

Küçük LDL-LDL partikül konsantrasyonu

apoB konsantrasyonu-küçük HDL

Negatif İlişki (yalnızca erkeklerde)

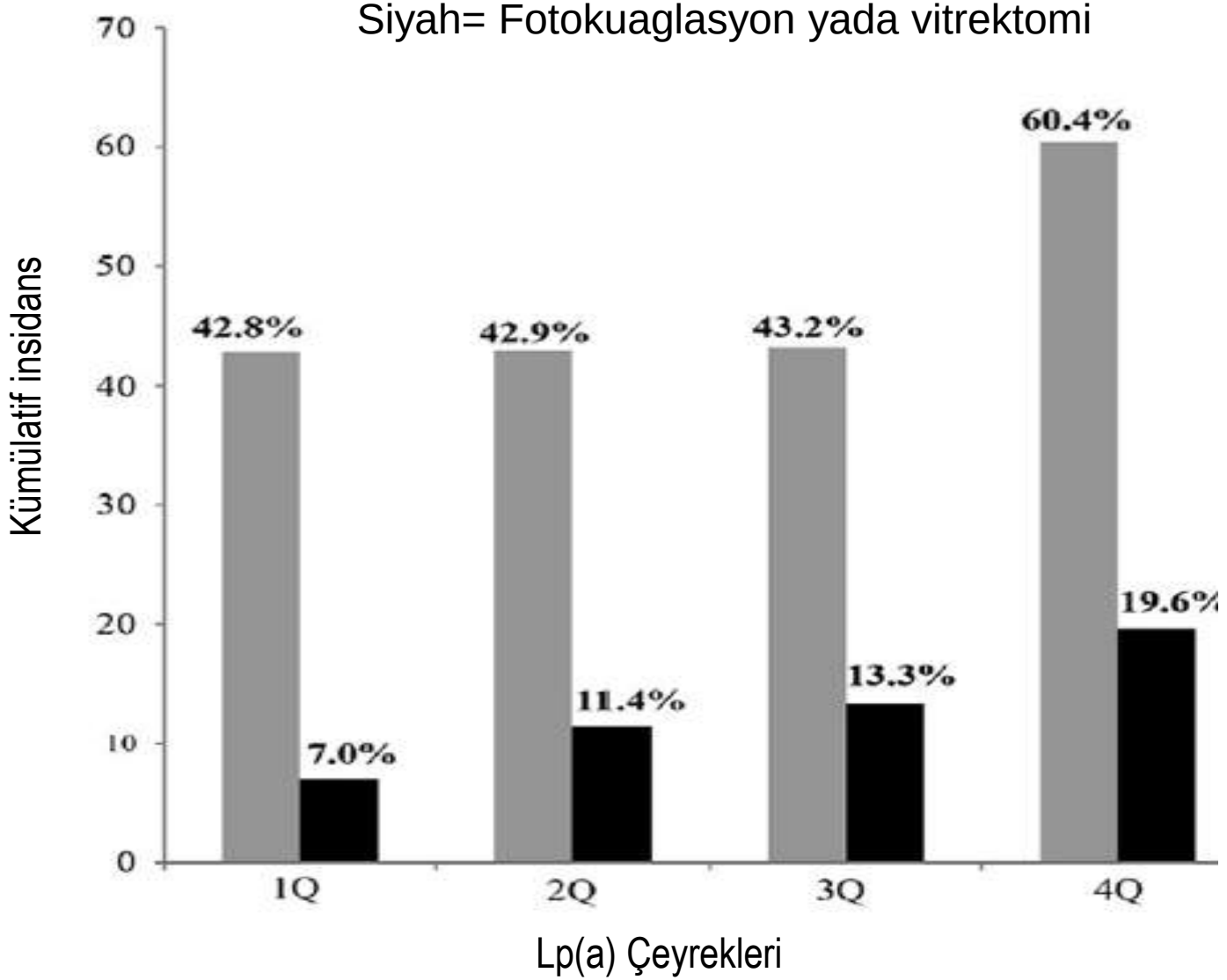
Büyük LDL-LDL boyutu-büyük HDL-HDL boyutu

Lyons TJ, IOVS, 2004

	Nonproliferative DR/non-CSME ($n = 115$)	Proliferative DR/non-CSME ($n = 34$)	Nonproliferative DR/CSME ($n = 45$)	Proliferative DR/CSME ($n = 14$)	p value
			Mean ± standard deviation		
Age (years)	67.3 ± 12.9	66.4 ± 9.9	67.2 ± 8.6	66.0 ± 11.2	0.772
Duration of DM (years)	13.5 ± 6.4	18.8 ± 8.8	15.2 ± 8.0	17.6 ± 6.9	**0.001**
BMI	30.9 ± 7.8	30.4 ± 6.7	30.2 ± 5.5	31.1 ± 6.9	0.981
			N (%)		
Male sex	61 (53.0)	25 (73.5)	30 (66.7)	5 (35.7)	**0.032**
Hypertension	41 (38.0)	22 (64.7)	31 (68.9)	10 (76.9)	**<0.001**
			Mean ± standard deviation		
Leptin (ng/mL)	27.2 ± 33.9	22.7 ± 24.4	21.8 ± 21.7	27.9 ± 20.6	0.391
Adiponectin (ng/mL)	10389.3 ± 6373.1	10566.7 ± 6165.8	11646.2 ± 7270.7	15712.1 ± 8702.9	0.179
Sialic acid (μM)	3365.8 ± 778.2	3139.7 ± 396.2	3052.3 ± 527.9	3613.7 ± 729	0.051
ApoA (g/L)	1.4 ± 0.5	1.5 ± 0.3	1.6 ± 0.3	1.6 ± 0.5	0.203
ApoB (g/L)	0.5 ± 0.5	0.8 ± 0.2	0.9 ± 0.3	0.8 ± 0.2	**0.0001**
ApoB/ApoA	0.39 ± 0.32	0.54 ± 0.18	0.57 ± 0.22	0.54 ± 0.17	**0.0003**
Vitamin D (ng/mL)	10.5 ± 10	9.5 ± 5.8	11.4 ± 5.9	10.1 ± 5.2	0.135
VEGF (pg/mL)	335.5 ± 235.3	431.0 ± 270.4	451.9 ± 283.6	508.7 ± 349.4	**0.017**
IL-1α (pg/mL)	12.2 ± 14.8	12.0 ± 12.7	16.7 ± 34.2	9.3 ± 6.7	0.734
IL-1β (pg/mL)	1.0 ± 1.3	0.7 ± 0.2	0.8 ± 0.7	0.9 ± 0.9	0.968
IL-1ra (pg/mL)	13.9 ± 22.6	10.8 ± 10.8	11.7 ± 16.9	11.3 ± 13.2	0.949
IL-4 (pg/mL)	10.0 ± 13.5	6.4 ± 11.4	8.5 ± 11.0	8.2 ± 12.7	0.052
IL-6 (pg/mL)	6.5 ± 14.9	3.6 ± 8	6.0 ± 10.0	3.2 ± 4.5	0.380
IL-10 (pg/mL)	3.6 ± 8.8	4.8 ± 12.3	3.6 ± 6.8	2.7 ± 3.3	0.821
TNF-α (pg/mL)	11.5 ± 9.4	15.3 ± 8.3	15.2 ± 11.2	17 ± 13.8	**0.003**

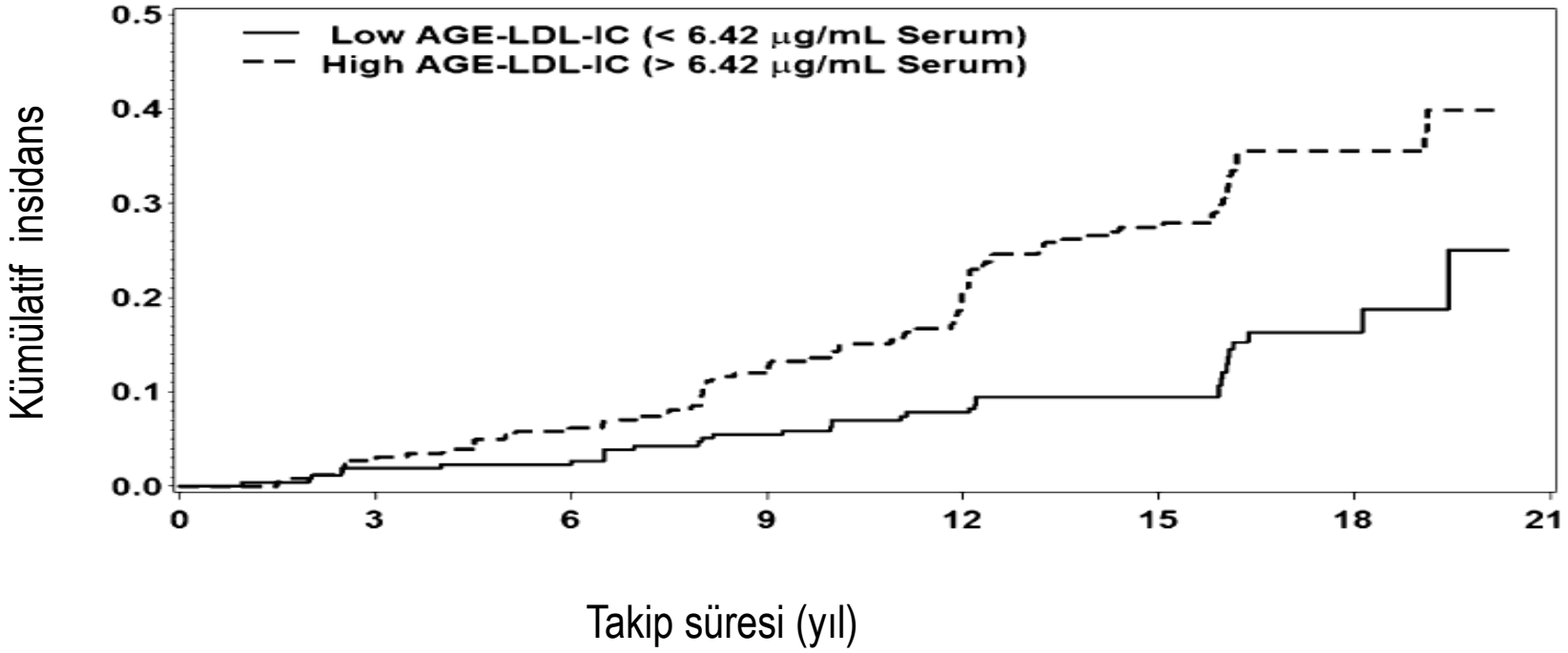
Crosby-Nwaobi R, J Diabetes Res, 2015

Gri= Retinopati geliştirme
Siyah= Fotokuaglasyon yada vitrektomi

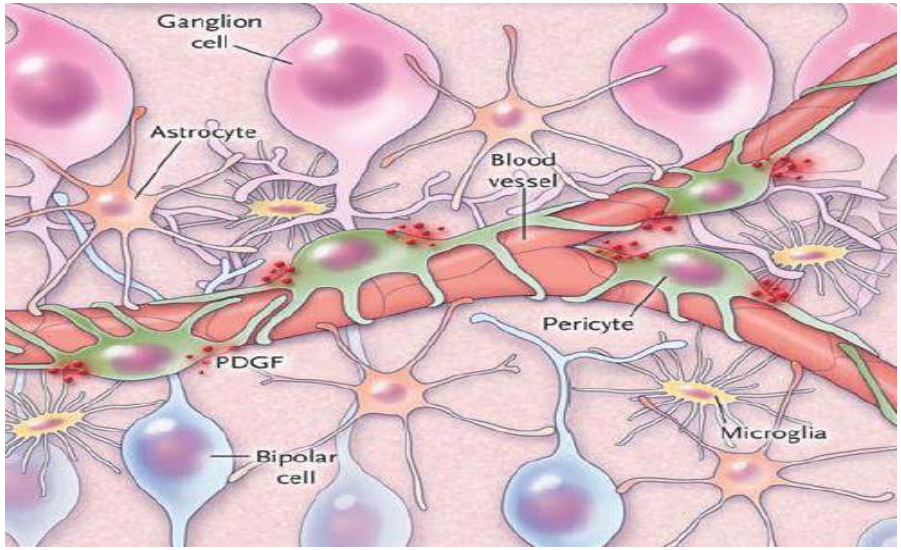


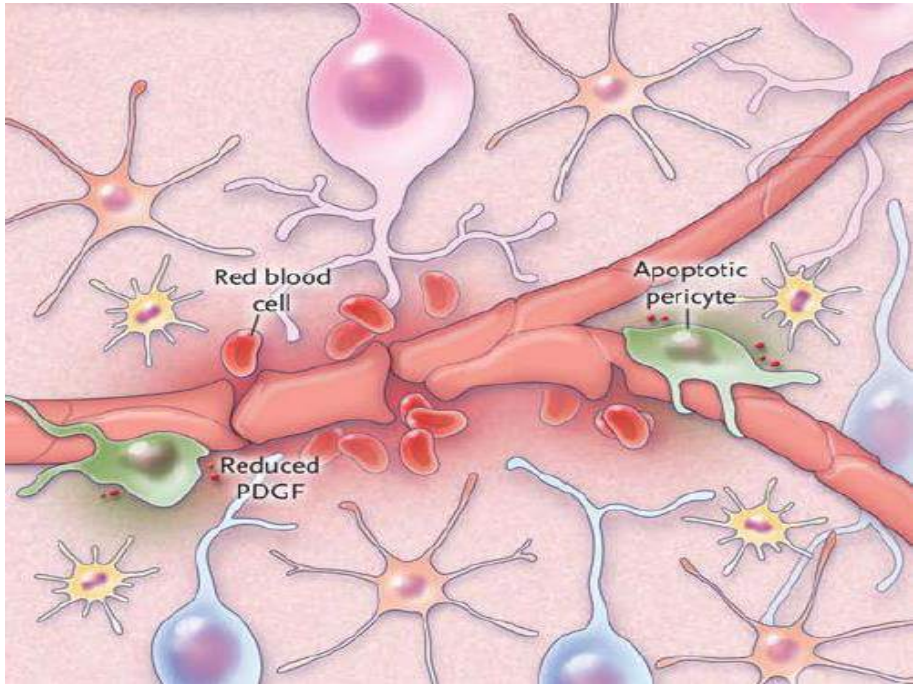
Yun JS, J Clin Lipidol, 2016

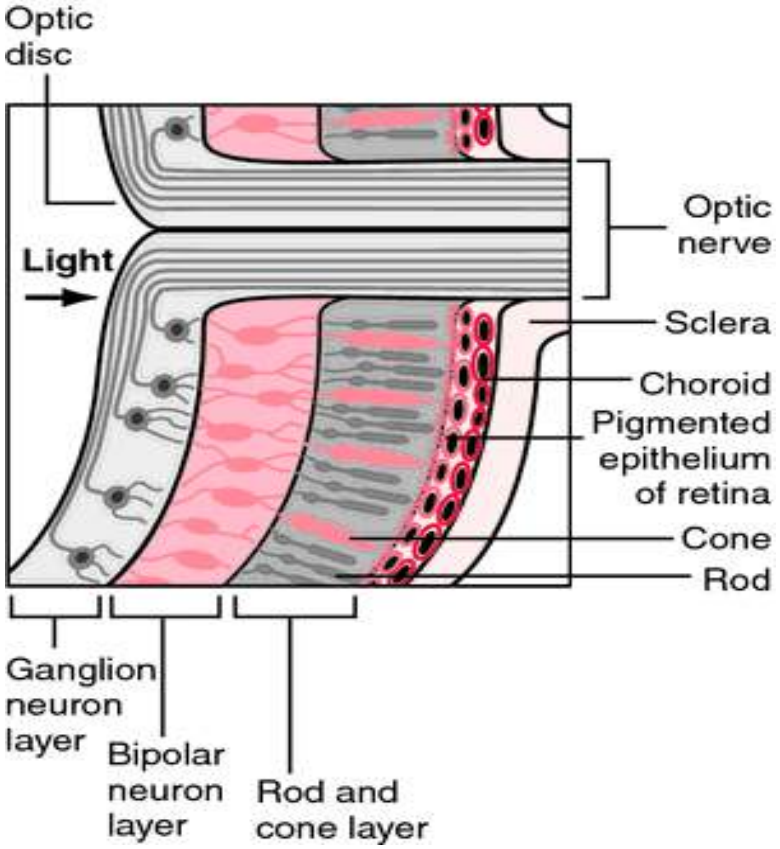
DCCT baseline characteristics	Primary prevention cohort			Secondary intervention cohort		
	Low AGE-LDL-IC (*n* = 131)	High AGE-LDL-IC (*n* = 102)	*P* value	Low AGE-LDL-IC (*n* = 126)	High AGE-LDL-IC (*n* = 156)	*P* value
Total cholesterol (serum, mg/dL)	167.5 ± 31.6	177.0 ± 35.4	**0.025**	174.5 ± 30.3	179.0 ± 33.7	0.277
Non–HDL cholesterol (serum, mg/dL)	114.5 ± 31.8	125.5 ± 32.9	**0.010**	122.7 ± 29.5	132.1 ± 32.2	**0.016**
Triglycerides (serum, mg/dL)	68.6 ± 27.7	76.1 ± 42.1	0.229	80.0 ± 32.7	90.4 ± 45.7	0.068
HDL cholesterol (serum, mg/dL)	52.9 ± 13.0	51.6 ± 12.9	0.436	51.7 ± 11.8	46.9 ± 10.7	**<0.001**
LDL cholesterol (serum, mg/dL)	100.8 ± 29.8	110.2 ± 30.2	**0.016**	106.8 ± 26.9	114.2 ± 28.3	**0.032**



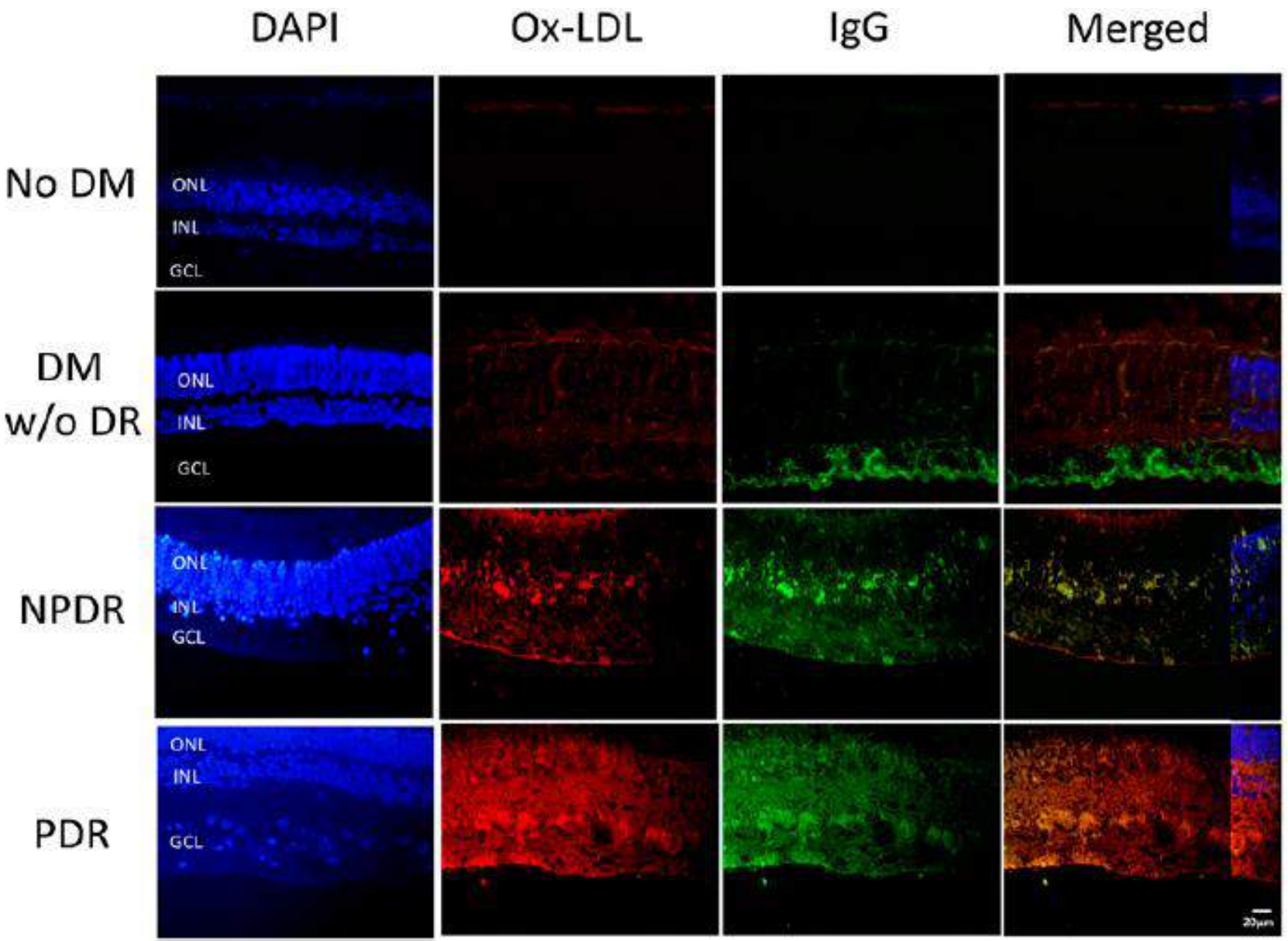
Lopes-Virella MF, Diabetes Care, 2012



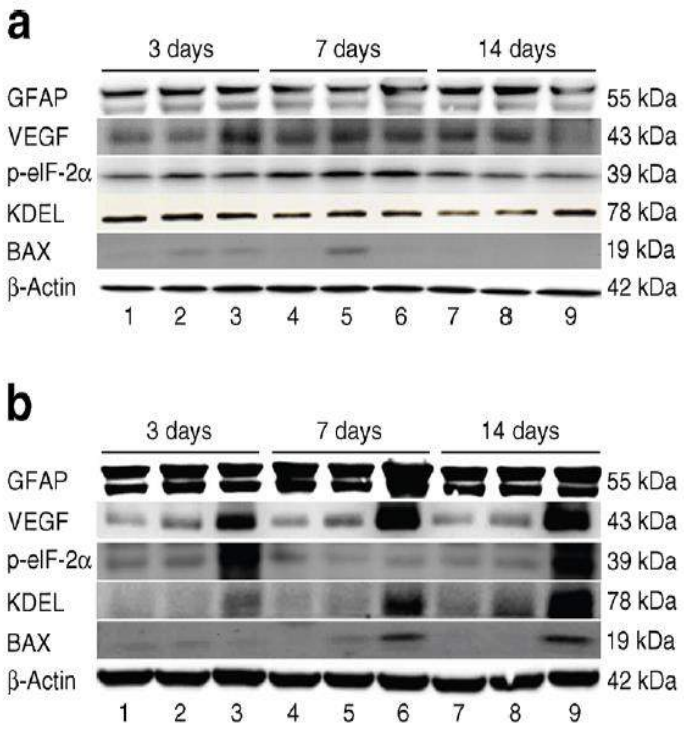


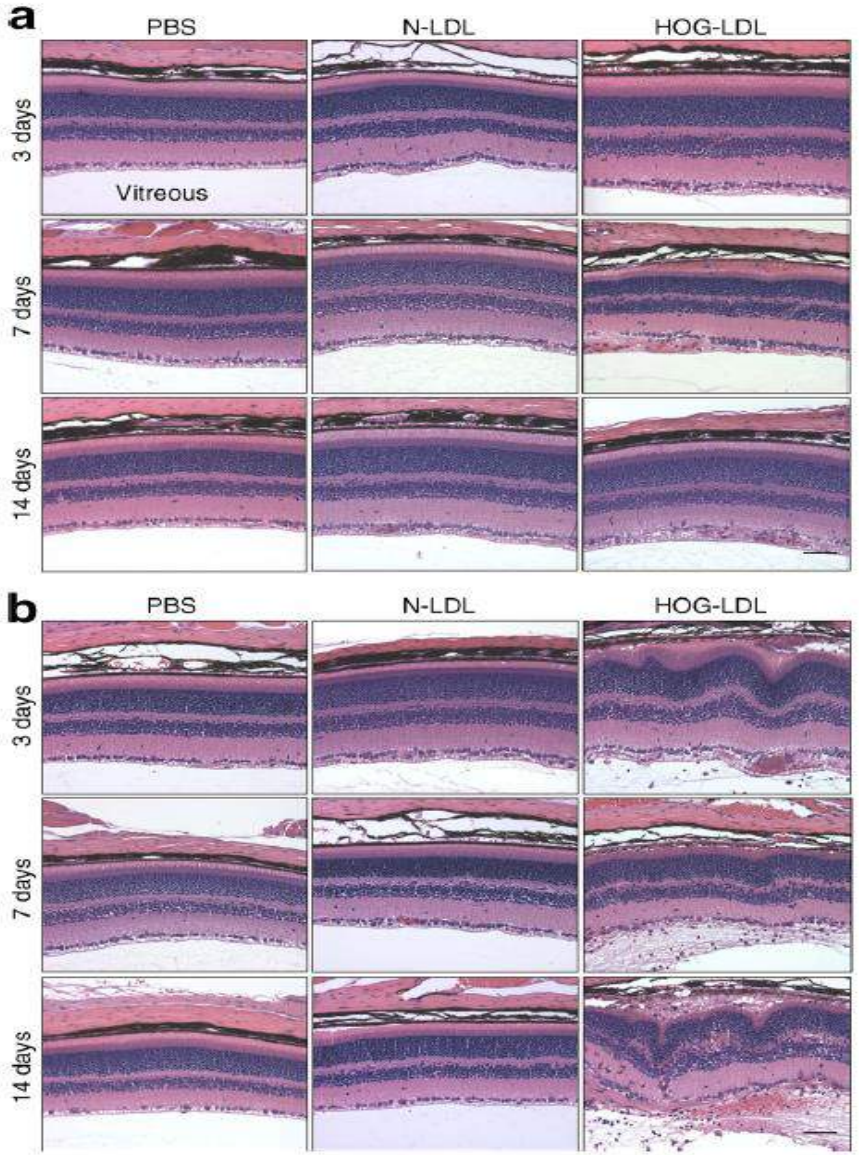


Antonetti DA; NEJM, 2012



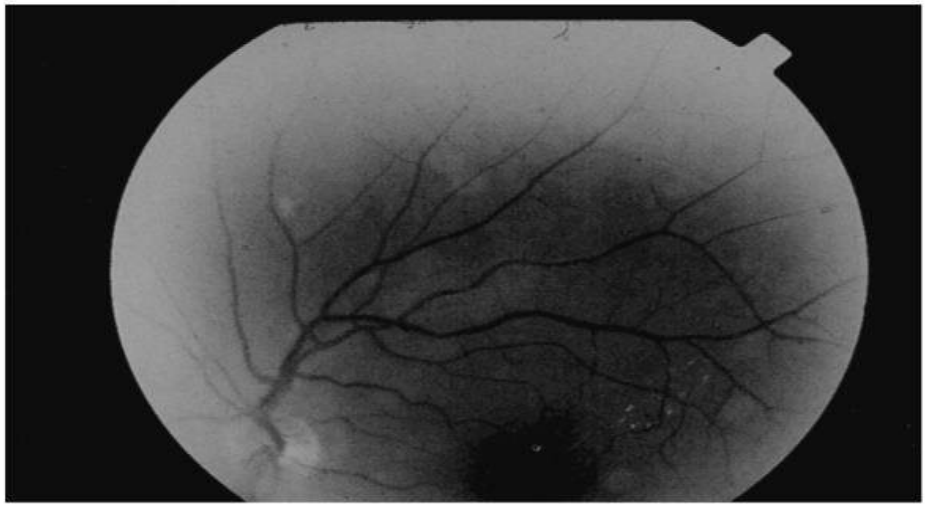
Dongxu F, J Lipid Res, 2014



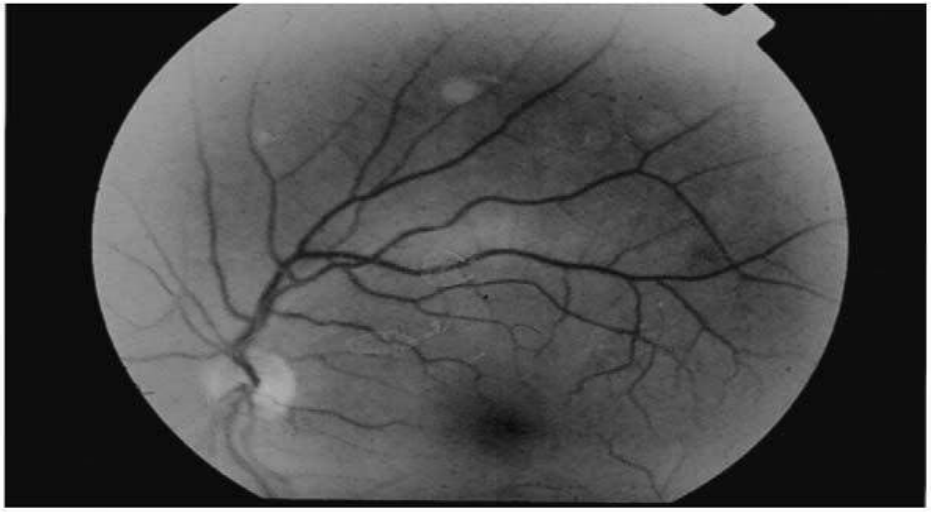


Yu JY, Diabetologia, 2016

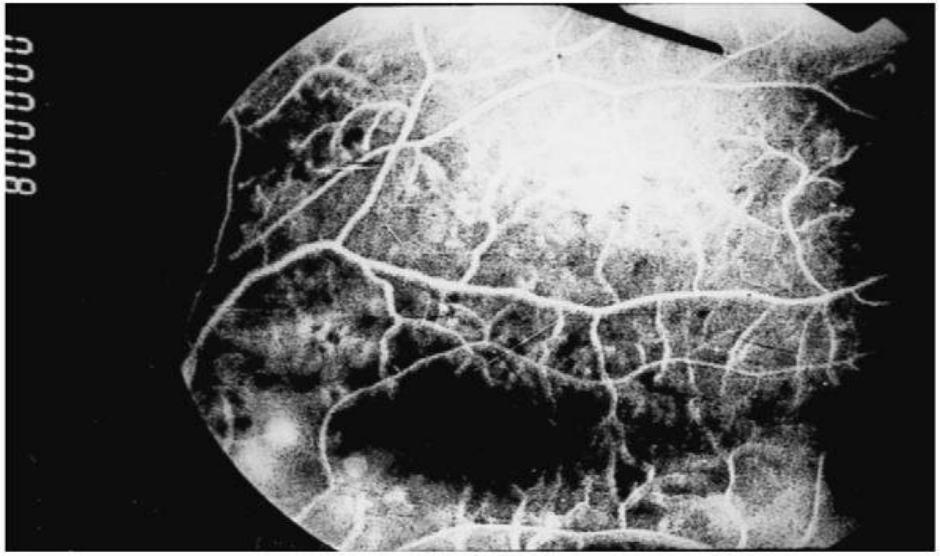
Diabetik Retinopati ve Hipolipidemik Tedavi



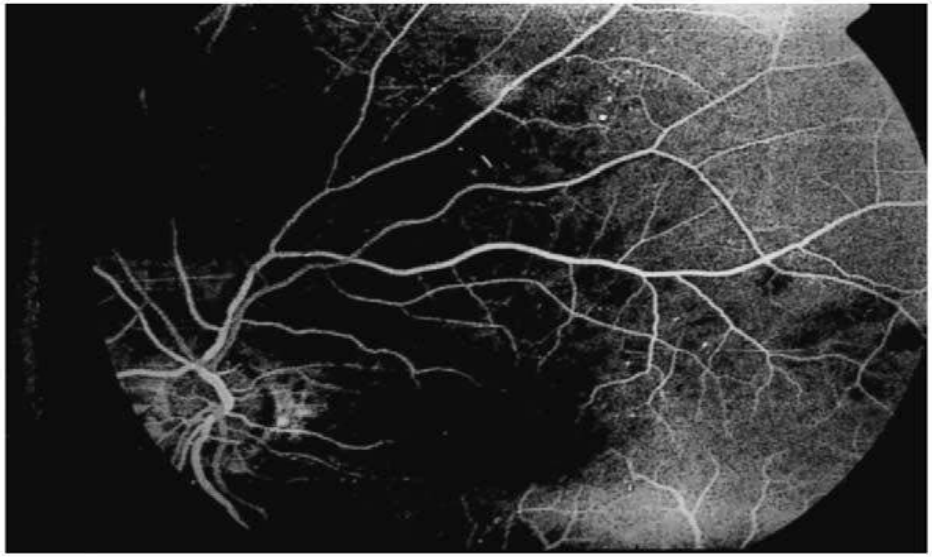
(a)



(c)



(b)



(d)

Sen K, Diab Res Clin Pract, 2002

Table 2. Changes in VEGI, VEGF, TNF-α, and IL-4 expression levels after 3 months.

Group	TNF-α (pg/mL)	VEGI (mg/L)	IL-4 (ng/L)	VEGF (mg/L)
Treatment group (a)	84.3 ± 4.5	33.4 ± 2.7	24.5 ± 9.7	25.9 ± 3.1
Control group (b)	97.2 ± 6.4	47.6 ± 2.5	36.2 ± 9.8	32.2 ± 2.8
Blank group (c)	76.5 ± 5.6	13.6 ± 2.6	16.5 ± 9.4	12.7 ± 2.6
T value	T value (a *vs* b) = 2.665; T value (a *vs* c) = 2.342; T value (b *vs* c) = 2.784	T value (a *vs* b) = 2.245; T value (a *vs* c) = 2.532; T value (b *vs* c) = 2.774	T value (a *vs* b) = 2.325; T value (a *vs* c) = 2.542; T value (a *vs* c) = 2.777	T value (a *vs* b) = 2.335; T value (a *vs* c) = 2.654; T value (a *vs* c) = 2.875
P value	$P < 0.05$; $P < 0.05$; $P < 0.05$	$P < 0.05$; $P < 0.05$; $P < 0.05$	$P < 0.05$; $P < 0.05$; $P < 0.05$	$P < 0.05$; $P < 0.05$; $P < 0.05$

Table 3. Changes in VEGI, VEGF, TNF-α, and IL-4 expression levels after 6 months.

Group	TNF-α (pg/mL)	VEGI (mg/L)	IL-4 (ng/L)	VEGF (mg/L)
Treatment group (a)	74.7 ± 2.1	13.1 ± 1.1	17.1 ± 7.8	13.7 ± 4.2
Control group (b)	95.4 ± 2.2	45.4 ± 1.9	33.2 ± 8.1	36.4 ± 4.7
Blank group (c)	75.7 ± 2.4	12.6 ± 1.7	16.8 ± 8.2	13.7 ± 4.5
T value	T value (a *vs* b) = 2.665; T value (a *vs* c) = 0.622; T value (b *vs* c) = 2.784	T value (a *vs* b) = 2.575; T value (a *vs* c) = 0.542; T value (b *vs* c) = 2.664	T value (a *vs* b) = 2.735; T value (a *vs* c) = 0.732; T value (a *vs* c) = 2.684	T value (a *vs* b) = 2.655; T value (a *vs* c) = 0.632; T value (a *vs* c) = 2.754
P value	$P < 0.05$; $P > 0.05$; $P < 0.05$	$P < 0.05$; $P > 0.05$; $P < 0.05$	$P < 0.05$; $P > 0.05$; $P < 0.05$	$P < 0.05$; $P > 0.05$; $P < 0.05$

Bi MC, Genet Mol Res, 2015

FIELD Çalışması

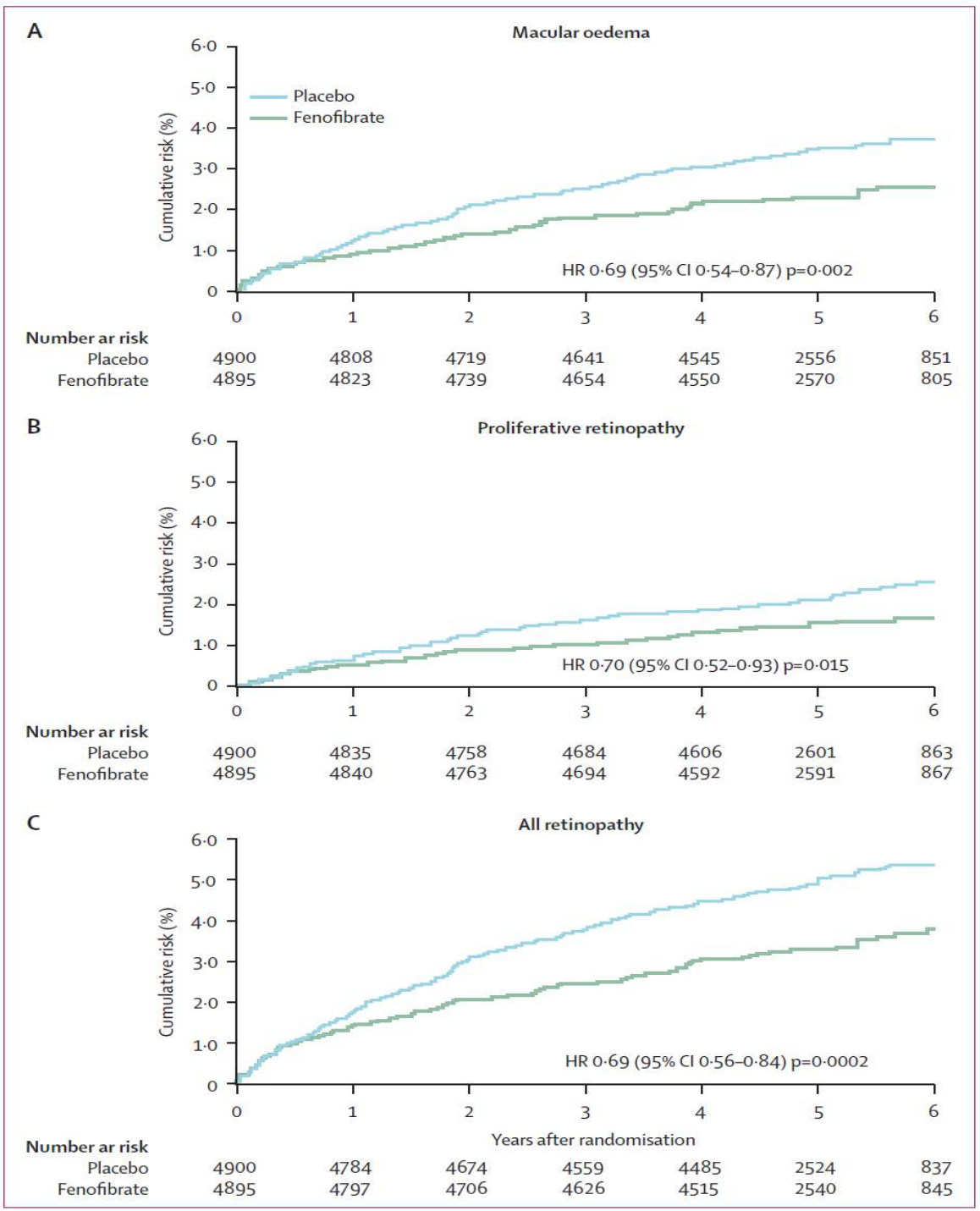
(Fenofibrate Intervention and Event Lowering in Diabetes)

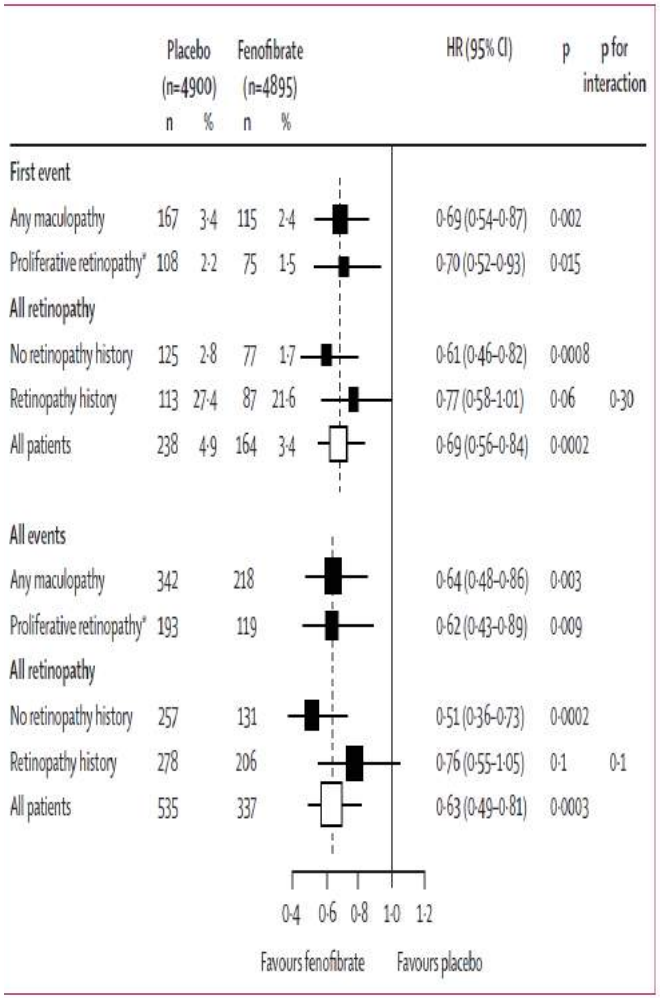
	No laser treatment (n=9393)	Laser treatment (n=402)	p value
Total cholesterol (mmol/L)	5·04 (0·70)	5·04 (0·69)	0·862
LDL cholesterol (mmol/L)	3·07 (0·65)	3·07 (0·68)	0·847
HDL cholesterol (mmol/L)	1·10 (0·26)	1·10 (0·27)	0·689
Triglyceride (mmol/L)	1·74 (1·34–2·33)	1·71 (1·33–2·27)	0·642

	Placebo (n=4900)		Fenofibrate (n=4895)	
	Number of patients (%)	Number of treatments	Number of patients (%)	Number of treatments
0	4662 (95%)	0	4731 (97%)	0
1	121 (2%)	121	85 (2%)	85
2	48 (1%)	96	38 (0·8%)	76
3	27 (0·6%)	81	17 (0·4%)	51
4	15 (0·3%)	60	9 (0·2%)	36
5	10 (0·2%)	50	8 (0·2%)	40
6–12	17 (0·3%)	127	7 (0·1%)	49
Cumulative total	238 (5%)	535	164 (3%)	337*

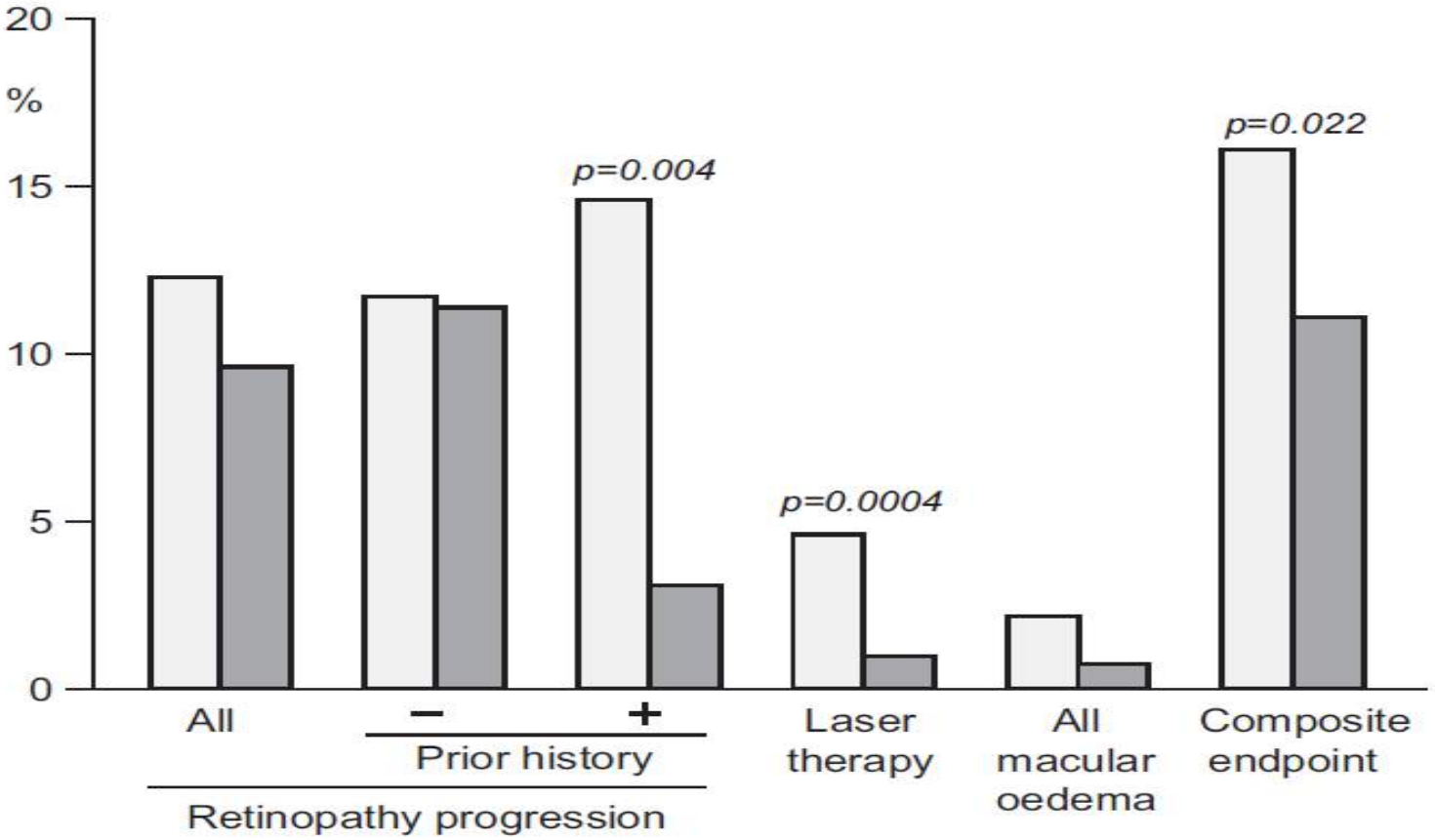
p=0.0003

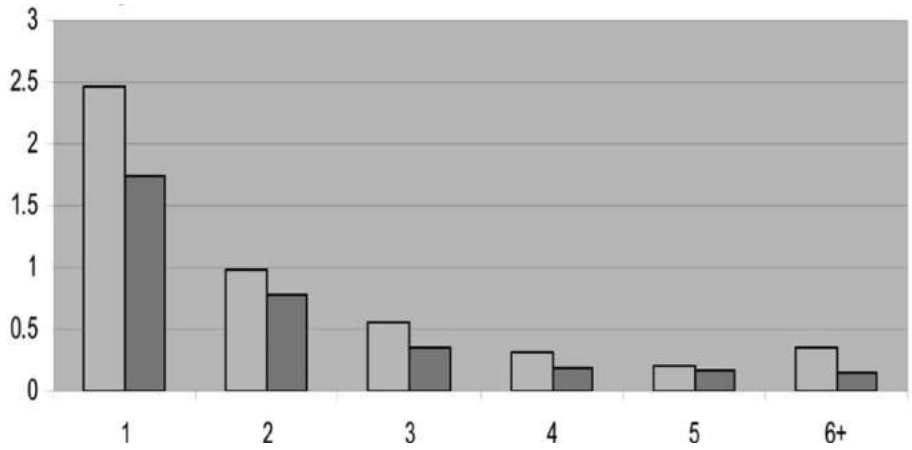
Keech AC, Lancet, 2007





Keech AC, Lancet, 2007





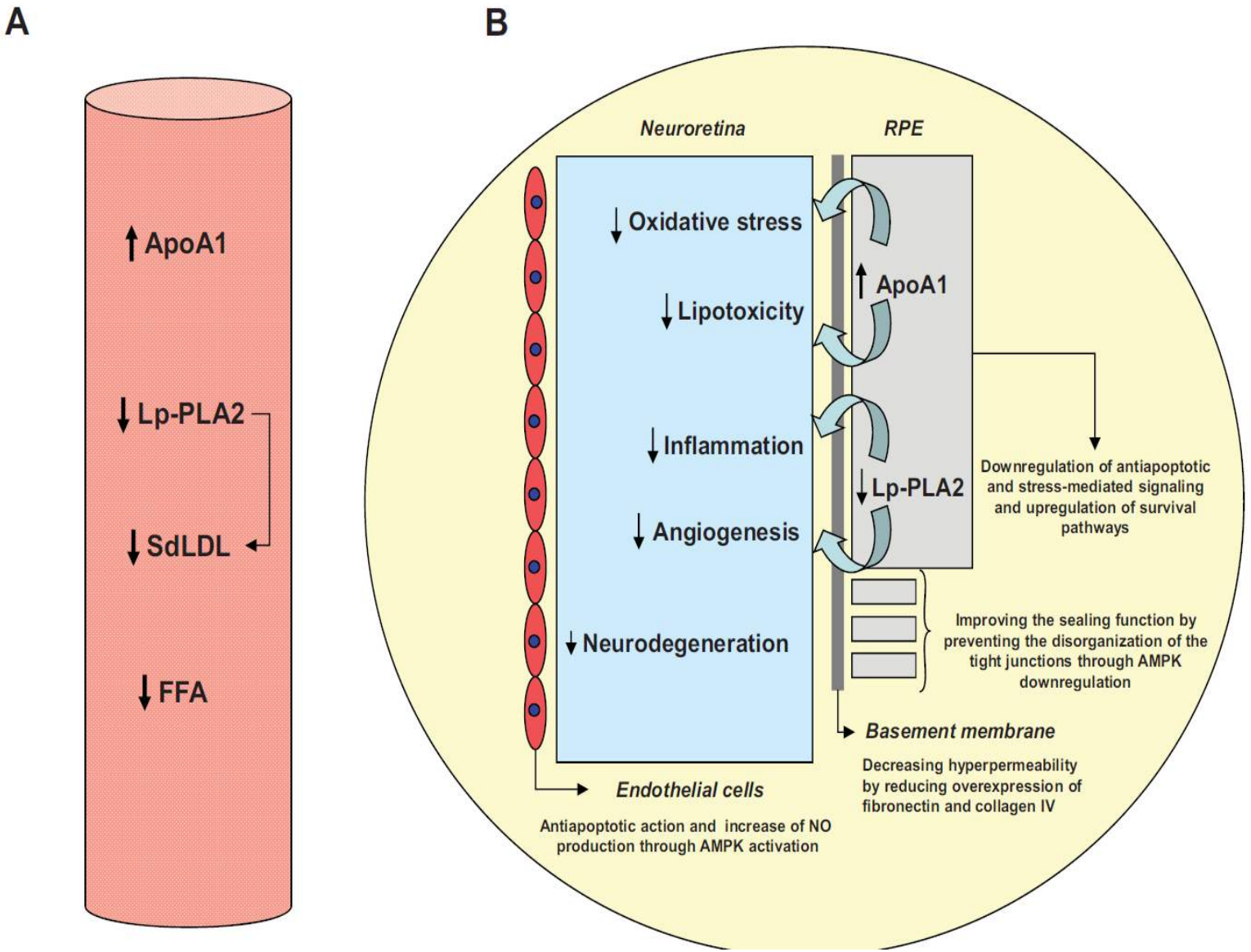
Plasebo, n=500

Fenofibrat, n=512

Keech AC, Lancet, 2007

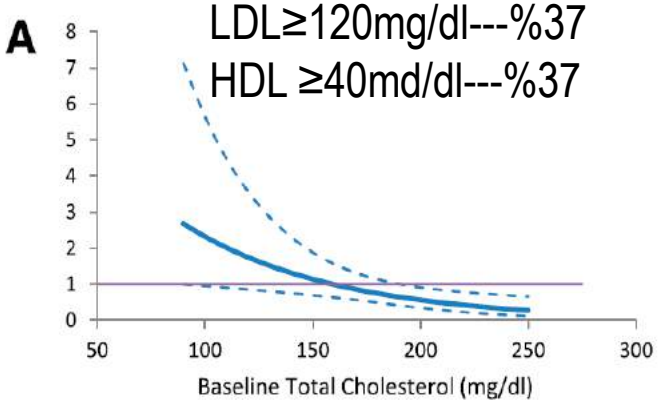
Treatment	Progression of Diabetic Retinopathy	Adjusted Odds Ratio (95% CI)	P Value	Moderate Vision Loss	Adjusted Hazard Ratio (95% CI)	P Value
	no./total no. (%)			*no./total no. (%)*		
Glycemia therapy		0.67 (0.51–0.87)	0.003		0.88 (0.77–1.01)	0.06
Intensive	104/1429 (7.3)			409/1715 (23.8)		
Standard	149/1427 (10.4)			457/1737 (26.3)		
Dyslipidemia therapy†		0.60 (0.42–0.87)	0.006		0.95 (0.79–1.14)	0.57
With fenofibrate	52/806 (6.5)			227/956 (23.7)		
With placebo	80/787 (10.2)			233/950 (24.5)		
Antihypertensive therapy		1.23 (0.84–1.79)	0.29		1.17 (0.96–1.42)	0.12
Intensive	67/647 (10.4)			221/798 (27.7)		
Standard	54/616 (8.8)			185/748 (24.7)		

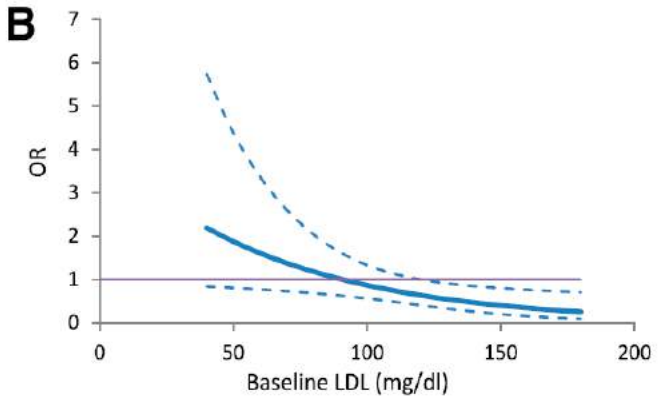
ACCORD Eye, NEJM, 2010

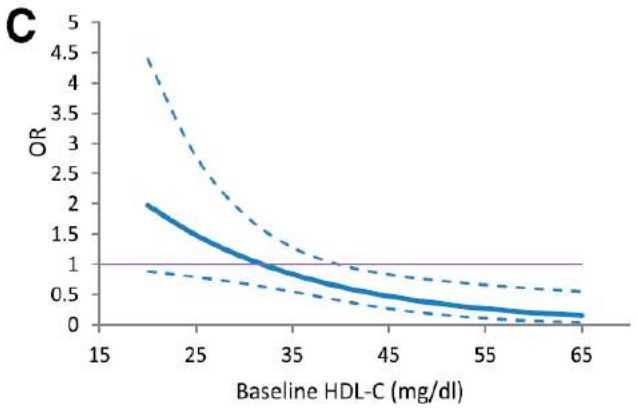


Simo R, Curr Med Chemistry, 2013

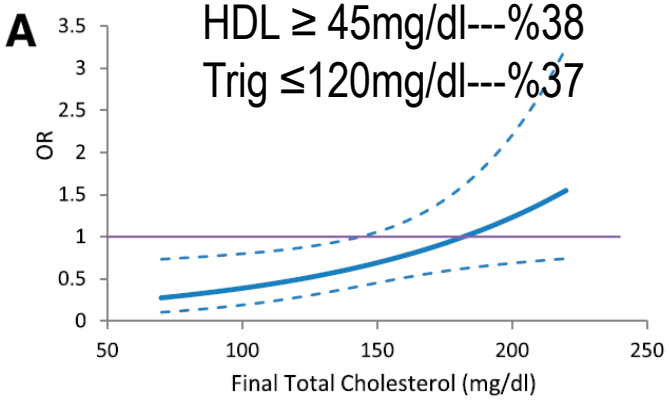
Tkol≥200mg/dl---%44
LDL≥120mg/dl---%37
HDL ≥40md/dl---%37

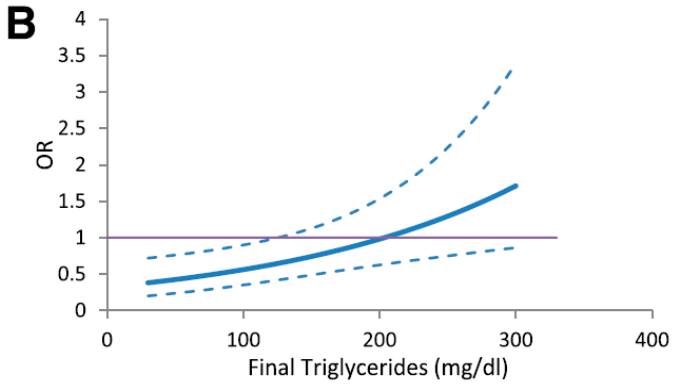


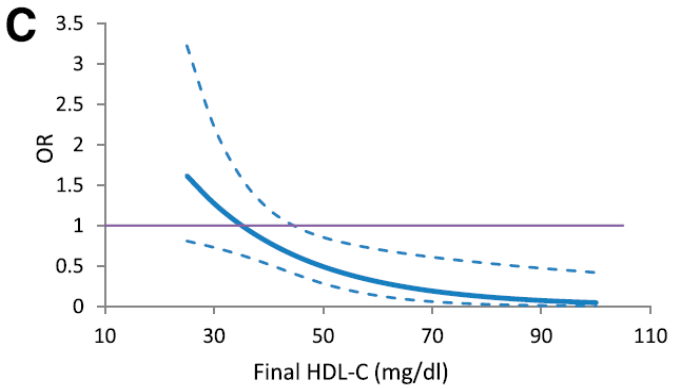




Tkol≤140mg/dl---%38
HDL ≥ 45mg/dl---%38
Trig ≤120mg/dl---%37







Azad N, Diabetes Care ,2016

SONUÇ

-Lipid subfraksiyonları

-AGE-okside lipid kompleksleri

-İyi glisemik kontrol önemli

-DR varlığında antihiperlipidemik tedavi; fenofibratlar****