

Diyaliz Hastalarında Dislipidemi ve Tedavisi

DR. GÜLTEKİN GENÇTOY

Cardiovascular mortality in the general population (NCHS) and in kidney failure treated by dialysis or transplant (USRDS)

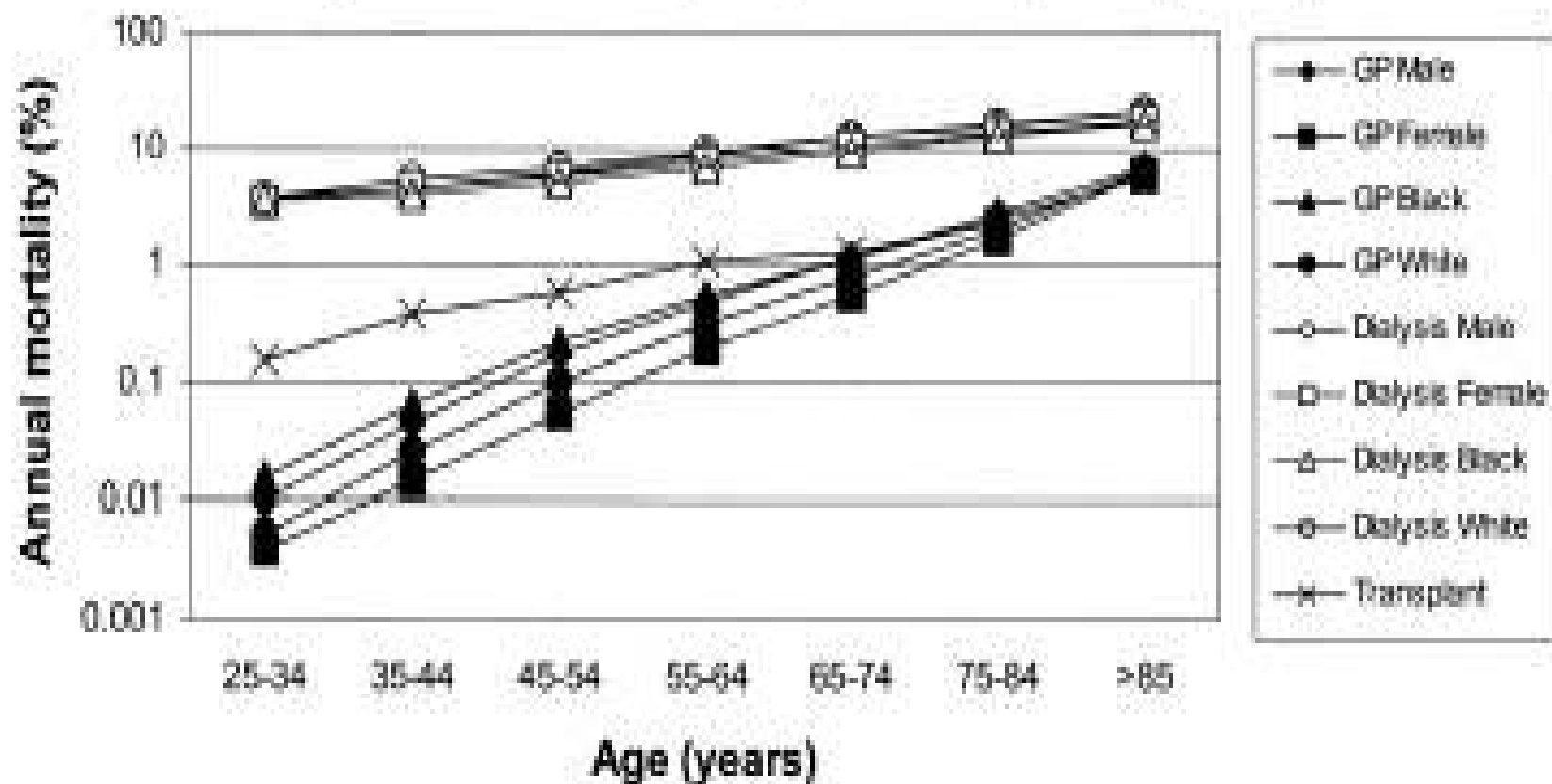


Table 2 Cardiovascular Event Rates* In 2000 and 2001

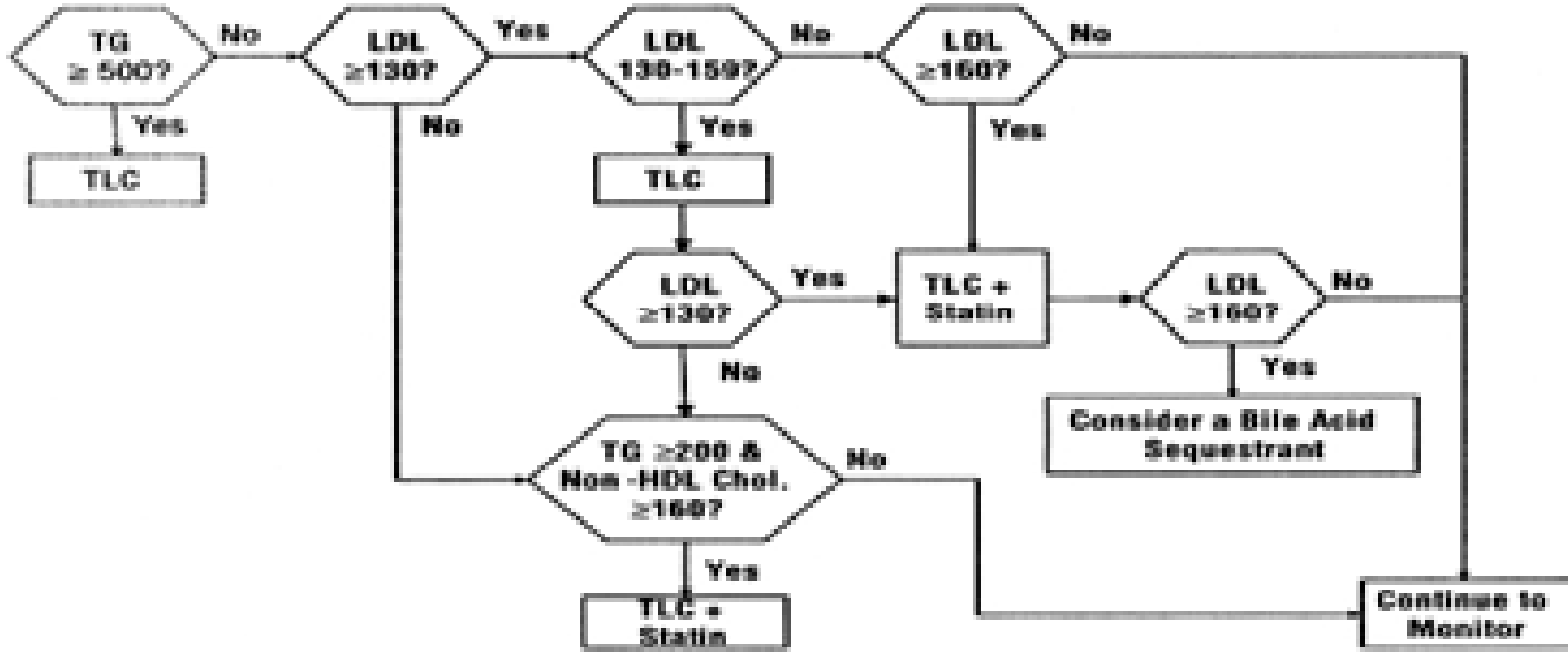
Group	AMI	CVA/TIA	PVD	ASVD	Death
Nondiabetes/non-CKD	1.6	7.6	6.9	14.1	5.5
Diabetes/non-CKD	3.2	13.1	12.8	25.3	8.1
Nondiabetes/CKD	3.9	16.6	19.9	35.7	17.7
Diabetes/CKD	6.9	22.0	26.6	49.1	19.9

Adapted from Foley et al. (8). *Rates are reported for 100 patient-years.

AMI = acute myocardial infarction; ASVD = atherosclerotic vascular disease; CKD = chronic kidney disease; CVA/TIA = cerebrovascular accident/transient ischemic attack; PVD = peripheral vascular disease.

- Son dönem böbrek yetmezliđi (SDBY) olan kiřilerin çođunluđu obezite, diyabet, hipertansiyon ve sigara gibi KVH için geleneksel risk faktörlerine uzun süreli olarak maruz kalmıřtır.
- Ancak tüm bunlar artmıř KV riski tam olarak açıklayamamaktadır
(ARIC Study; *J Am Soc Nephrol* 2005;16:529-538)

Figure 8 -The Approach to Treatment of Dyslipidemias in Adolescents With Chronic Kidney Disease Used in These Guidelines



TLC: Terapotik yaşam tarzı değişikliği

(KDOQI Clinical Practice Guidelines for Managing Dyslipidemias in Chronic Kidney Disease)

- KBH hastalarında spesifik çalışmalar eksik olduğundan, öneriler temelde Ulusal Kolesterol Eğitim Programı (NCEP) raporu (Adult Treatment Panel III) doğrultusunda TG > 500 mg / dL ve LDL > 100 mg/dL ise tedavi ek KV risk olmasa bile uygulanabilir.

Üremik Hastalarda Dislipidemi

- Hipertrigliseridemi
- HDL-K düzeyinde azalma, LDL/HDL oranı ↑
- Lipoprotein (a) ↑
- LDL oksidasyonunda artış
- Artık lipoproteinlerde artış
- sdLDL oranında artış
- Hastaların %10-45'inde LDL-K > 130 mg/dl

Table 3**Mechanisms of
Dyslipidemia in Chronic Kidney Disease**

Protein	Change	Effect on Plasma Lipids or LP
ApoA-1	↓	↓ HDL
LCAT	↓	↓ HDL-C, HDL-2/HDL-3
CETP	↑	↓ HDL-C
ACAT	↑	↑ VLDL-C, ↓ HDL-C
LPL	↓	↑ Trig (↑ delipidation of VLDL and CM)
VLDL receptor	↓	↑ VLDL, Trig
Hepatic lipase	↓	↑ IDL, CM remnants, HDL-TG, Trig, LDL-TG
LRP	↓	↑ IDL, CM remnants
ApoCII/CIII ratio	↓	↑ Trig (↑ LPL activity)
Pre-β HDL	↑	↑ Trig (↑ LPL activity)

Adapted from Vaziri (4).

↓ = decreases; ↑ = increases; ACAT = acyl-CoA (cholesterol acyl) transferase; Apo = apoprotein; CETP = cholesterol ester transferase protein; CM = chylomicron; DGAT = acyl-CoA diglycerol acyl transferase; HDL = high-density lipoprotein; HDL-C = high-density lipoprotein cholesterol; HDL-TG = high-density lipoprotein triglyceride; IDL = intermediate-density lipoprotein; LCAT = lecithin cholesterol acyl transferase; LDL-TG = low-density lipoprotein triglyceride; LP = lipoproteins; LPL = lipoprotein lipase; LRP = low-density lipoprotein receptor-related protein; Trig = triglyceride; VLDL = very-low-density lipoprotein; VLDL-C = very-low-density lipoprotein cholesterol; VLDL-TG = very-low-density lipoprotein triglyceride.

Table 4 Lipid-Modulating Clinical Trials in Patients With Chronic Kidney Disease

Study	Population	Design	Primary End Point	Duration (Months)	Treatment	RRR 95% CI	ARR
Statins trials							
KE (23)	n = 1,225, dialysis or hemodialysis	RCT	Cardiac death, total stroke, MACE, or stroke	68	Simvastatin 20 mg/day	8% 0.77-1.10 (p = 0.37)	NA
PROGRESS (24)	n = 1,476, nondialysis CKD >45	RCT, 2 × 2 factorial design	CV mortality and hospitalization	60	Pravastatin 40 mg/day	17% 0.88-1.07 (p = 0.009)	NA
SPR (25)	n = 1,076, G ₁ -G ₃ CKD, dialysis, or other end-stage renal disease	RCT subgroup, 2 × 2 factorial design	Overall mortality, major vascular event	60	Simvastatin 40 mg/day	26% (p < 0.005)	1.0%
CARD (26)	n = 1,711, CKD, GFR < 75, on dial	Post hoc subgroup of RCT	CHD death or symptomatic MACE	66.9	Pravastatin 40 mg/day	28% 0.95-1.09 (p = 0.007)	4%
ALERT (26)	n = 2,852, renal transplant recipients	RCT	Cardiac death, MACE, cardiac procedure	60	Fluvastatin 40-80 mg/day	17% 0.84-1.08 (p = 0.249)	NA
Nonstatin trials							
GLAGOL (26)	n = 1,046, non-dialysis CKD < 75, on dial	Post hoc subgroup of RCT	Primary death, MACE	60	Gemfibrozil 1,200 mg/day	17% 0.98-1.09 (p = 0.02)	0.3%
ORION (27)	n = 316, hemodialysis patients with CKD	RCT	Total CV events and death	24	n-3 PPAR- α 1.7 g/day	3% 0.73-1.68 (p = 0.80)	NA

ARR = absolute risk reduction; CKD = chronic kidney disease; G₁ = serum creatinine < 1.33 mg/dL; G₂ = creatinine clearance 30-59 mL/min; G₃ = creatinine clearance 15-29 mL/min; CV = cardiovascular; GFR = glomerular filtration rate; n-3 PPAR- α = omega-3 polyunsaturated fatty acids; NA = not applicable; MACE = medical myocardial infarction; RCT = randomized controlled trial; RRR = relative risk reduction.

4-D ve AURORA,

- **Diyaliz hastalarında** ölümcül olmayan MI ve inme ölüm kombine uç noktası
- Serum LDL-kolesterol düzeylerinde önemli bir azalma olmasına rağmen, her iki çalışmada statin tedavisinin **kardiyovasküler yarar sağlamadığı** görülmüştür.
 - (Wanner C, N Engl J Med 2005;353:238,
 - (Fellstrom BC et al. N Engl J Med 2009;360:1395-1407)

SHARP

- 9720 hasta; Pre-diyaliz KBH ve diyaliz hastaları dahil tüm çalışma kohortunda **statin ve ezetimib** kombinasyonunun KV yararını göstermiştir, ancak etki **diyaliz alt grubunda istatistiksel olarak anlamlı değil.** (Baigent C et al. Lancet 2011 Jun 25;377(9784):2181-92)

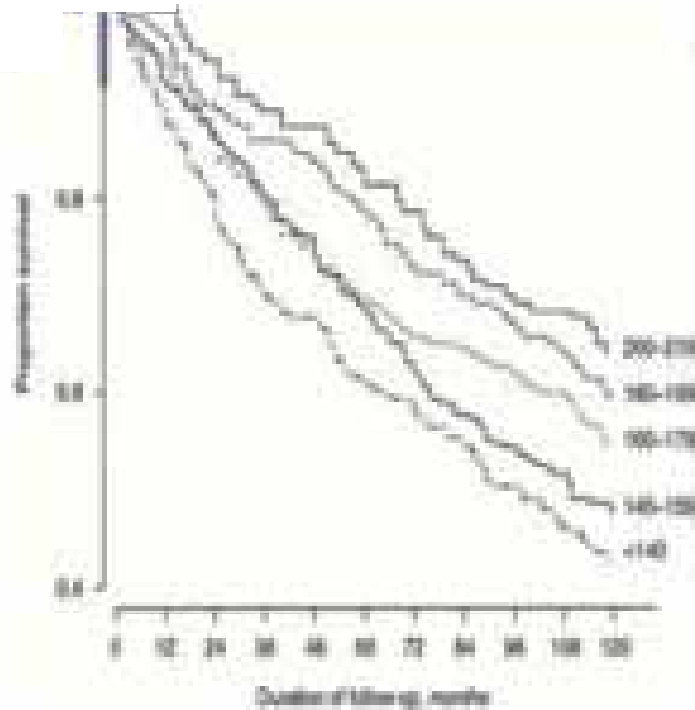
Lipid lowering in patients with chronic kidney disease: a SHARP turn in the wrong direction?

[Eur J Cardiovasc Prev Rehabil.](#) 2011

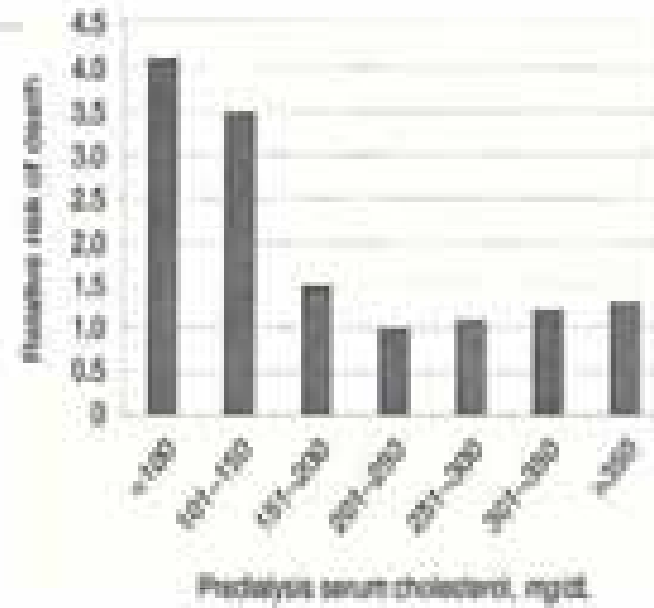
Dec;18(6):858-61.

- KV hastalık için %17 RR azaltımı var ancak survi üzerine etki yok.
- Ezetimib veya simvastatinden etkinin hangisine bağlı olduğu?

Hemodiyaliz hastalarında **hipokolesterolemi**, mortalite ilişkisi



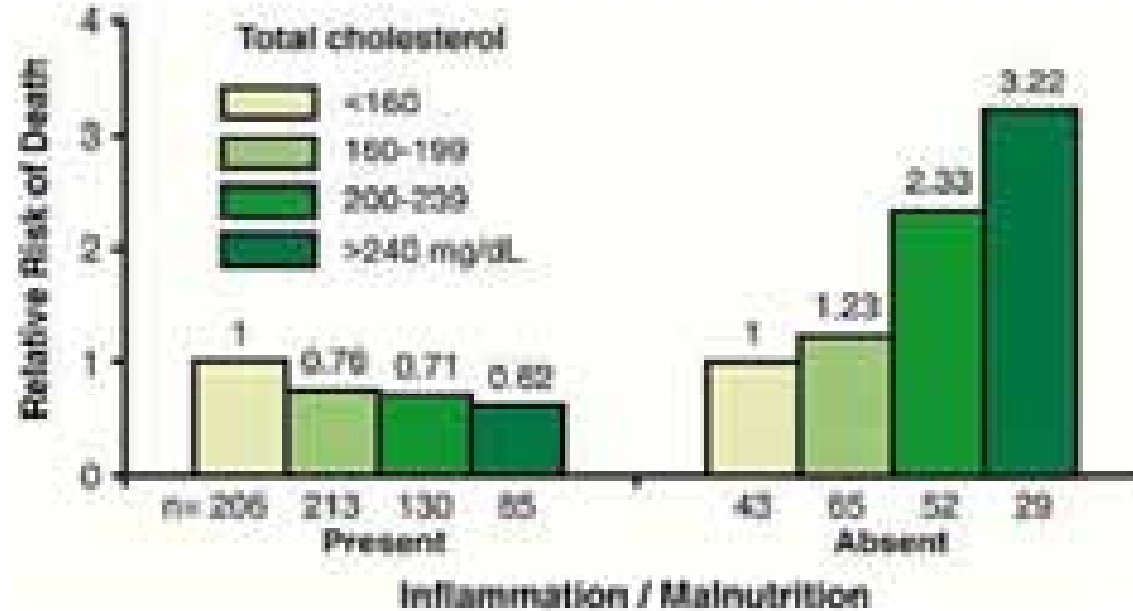
Iseki K, Kidney Int, 2002



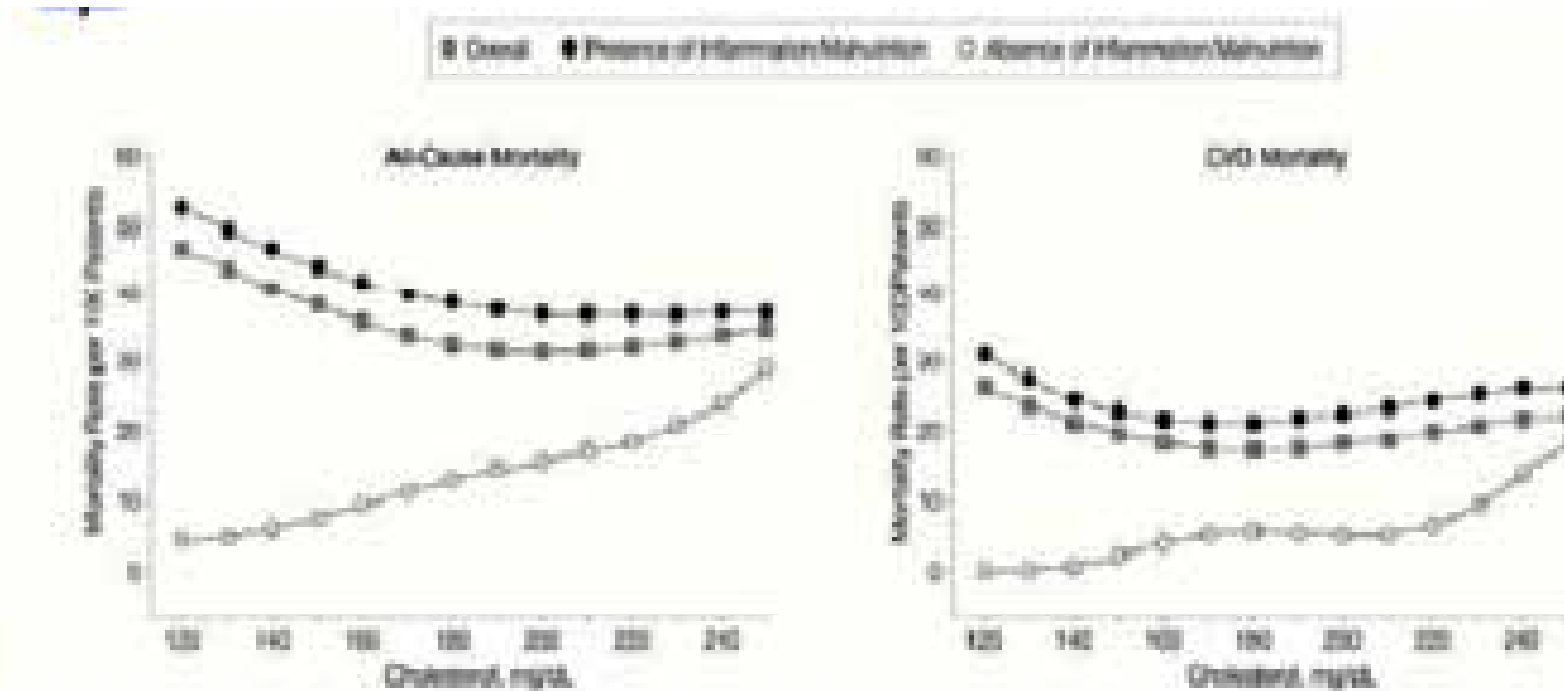
Lowrie EG, AJKD, 1990

İNFLAMASYON/MALNUTRİSYON VARLIĞINA GÖRE KOLESTEROL-MORTALİTE İLİŞKİSİ

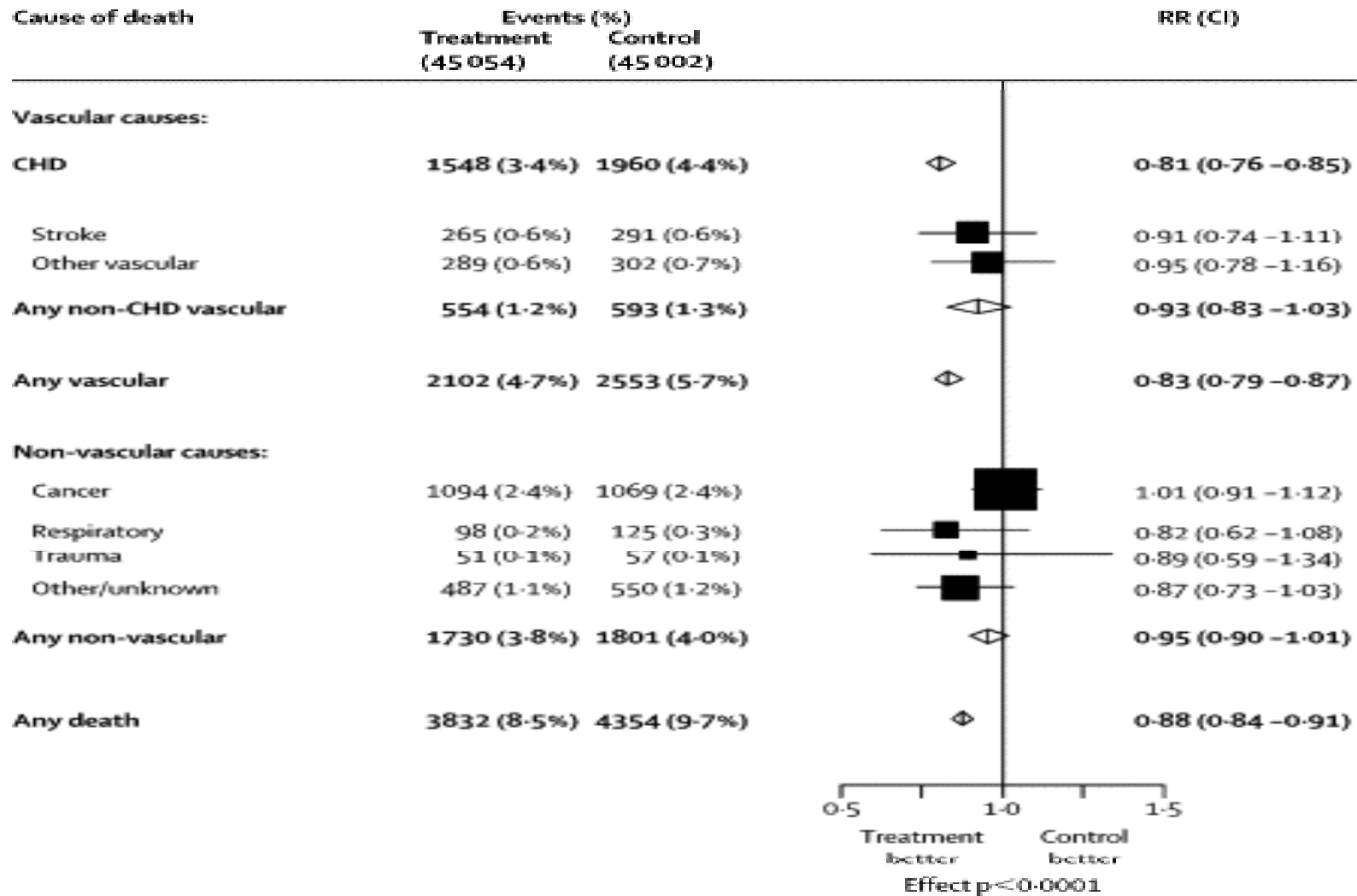
- Prospektif çalışma, Diyalize yeni başlayan 823 hasta; izlem süresi 2.4 yıl



Diyaliz Hastalarında Kolesterol/ Mortalite İlişkisi



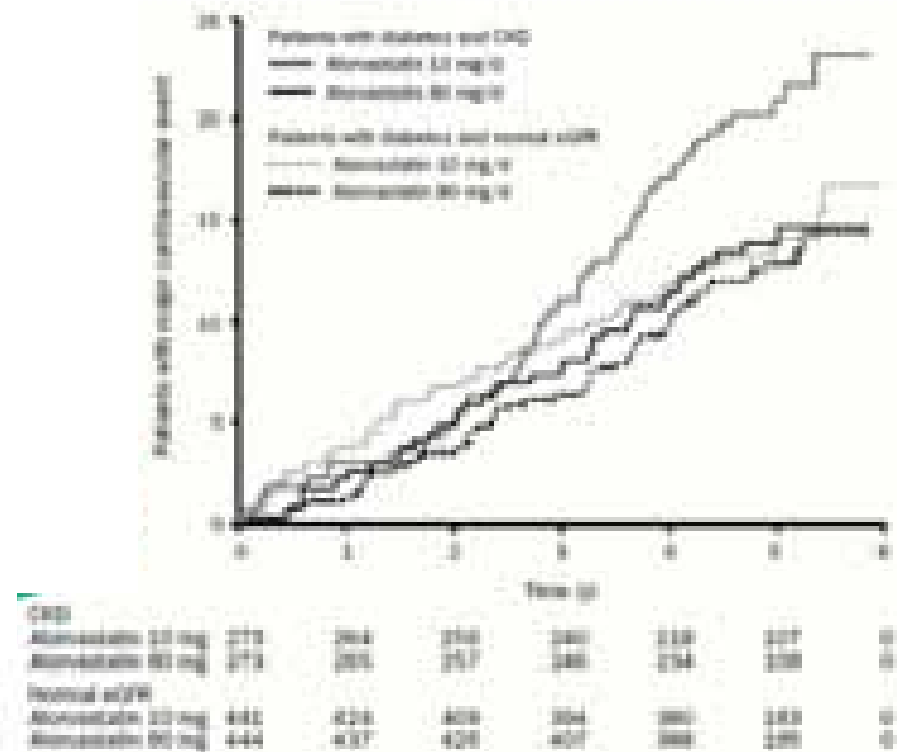
Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90056 participants in 14 randomised trials of statins

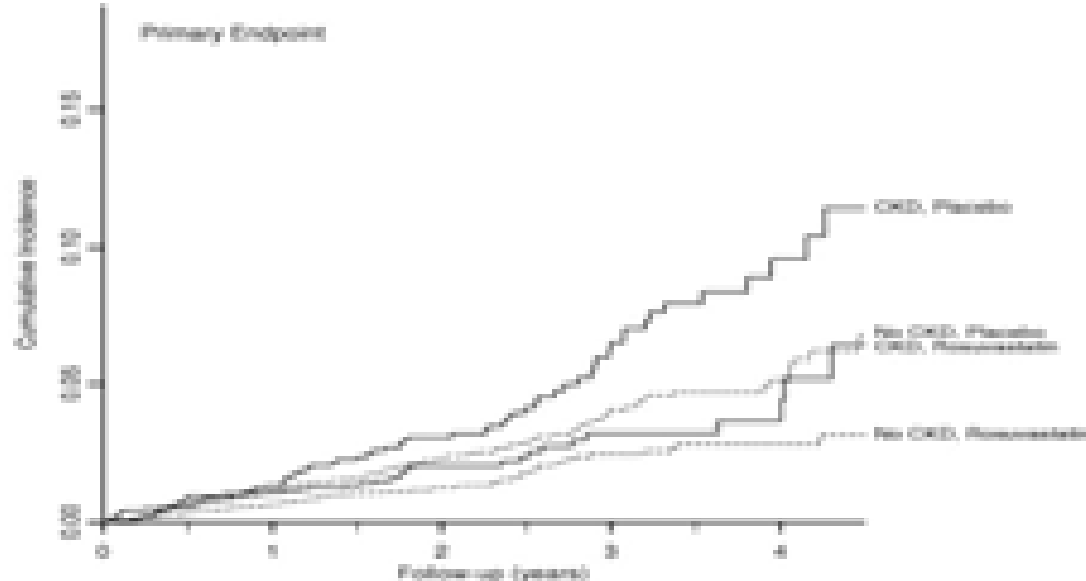


Baigent C, Lancet, 2005

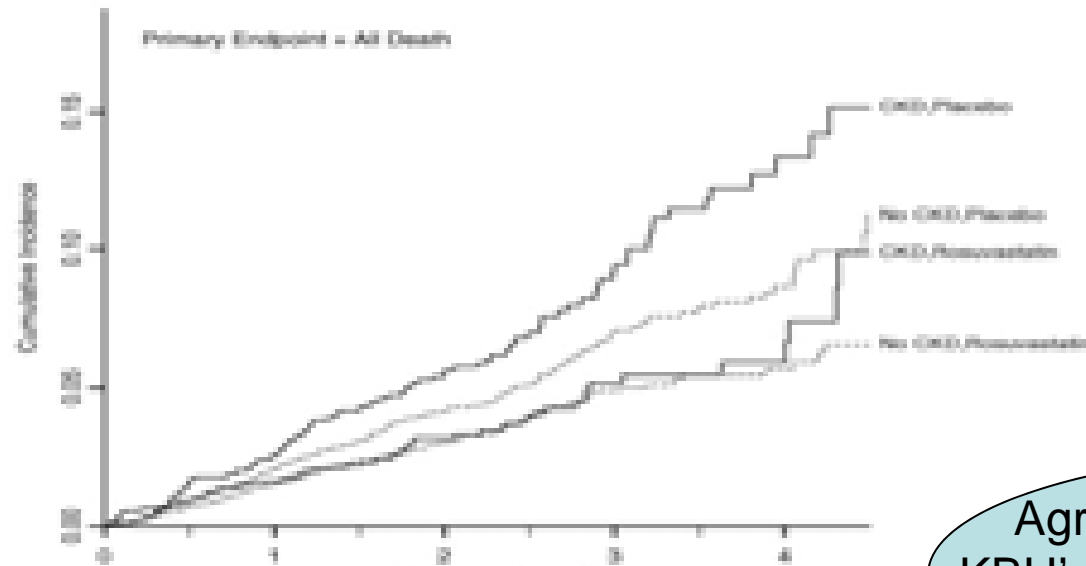
Diyabetik vs Diyabetik+KBH hastalarında Statin&KVH Üzerine Etkisi?

Shepherd J; Mayo Clin Proc. 2008;83(8):870-79.



A

No. at Risk	0	1	2	3	4
CVD, Placebo	1,000	1,000	1,000	1,000	1,000
No CVD, Placebo	1,000	1,000	1,000	1,000	1,000
CVD, Rosuvastatin	1,000	1,000	1,000	1,000	1,000
No CVD, Rosuvastatin	1,000	1,000	1,000	1,000	1,000

B

No. at Risk	0	1	2	3	4
CVD, Placebo	1,000	1,000	1,000	1,000	1,000
No CVD, Placebo	1,000	1,000	1,000	1,000	1,000
CVD, Rosuvastatin	1,000	1,000	1,000	1,000	1,000
No CVD, Rosuvastatin	1,000	1,000	1,000	1,000	1,000

**** Rosuvastatin**
LDL-C <130 mg / dl
ve yüksek hsCRP
düzeyine sahip orta
derece KBH'da ilk
kardiyovasküler
olay gelişimini ve
tüm nedenlere bağlı
mortaliteyi azaltır

A secondary analysis from the
JUPITER (Justification for
the Use of Statins in Prevention-
an Intervention Trial Evaluating
Rosuvastatin) trial.

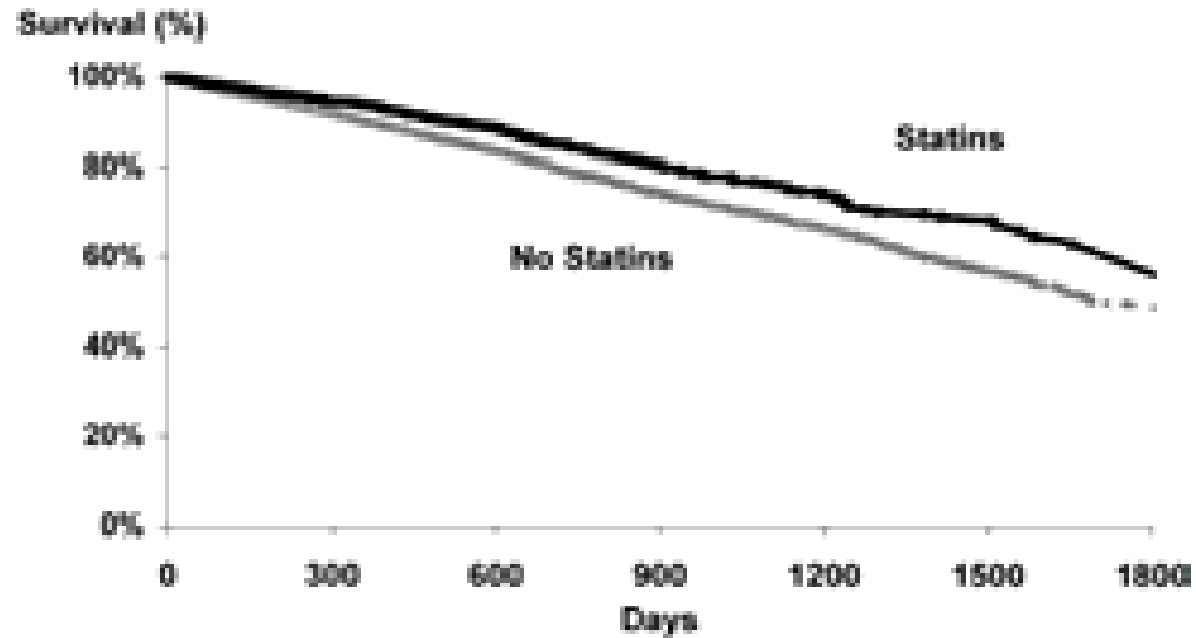
JACC 2010;55(12):1266-73.

Agresif lipid düşürücü tedavi
KBH'da KV olayları azaltmaktadır

HMG-coenzyme a reductase inhibitor use is associated with mortality reduction in hemodialysis patients

(DOPPS; Mason NA, Am J Kidney Dis, 2005;45:119)

- Gözlemsel çalışma
- 7365 hemodiyaliz hastası
- Tüm ölümlerde %31, Kardiak ölümlerde %23 azalma

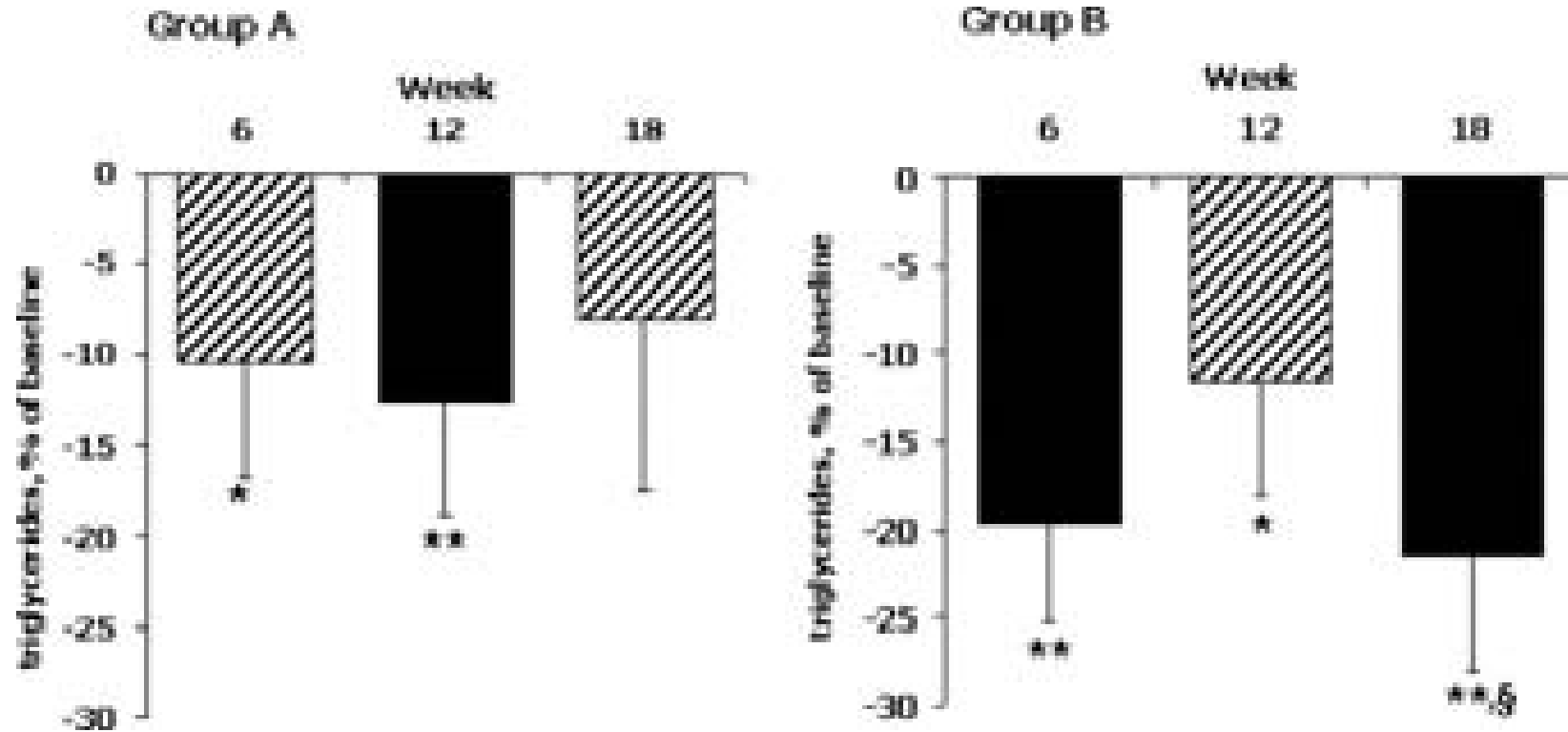


- Hemodiyaliz hastalarında statin tedavisi LDL-K ve CRP düzeylerini düşürmektedir ancak fatal veya non-fatal kardiyovasküler olaylar üzerine ekisi net değildir.
- Statinleri kullanalım mı?
- Statinleri hangi hastalarda kullanalım?
- Rabdomiyoliz, CK düzeyleri, karaciğer fonksiyonları açısından plaseboya göre farklılık saptanmamıştır.

Yüksek Akımlı (High-Flux)HD

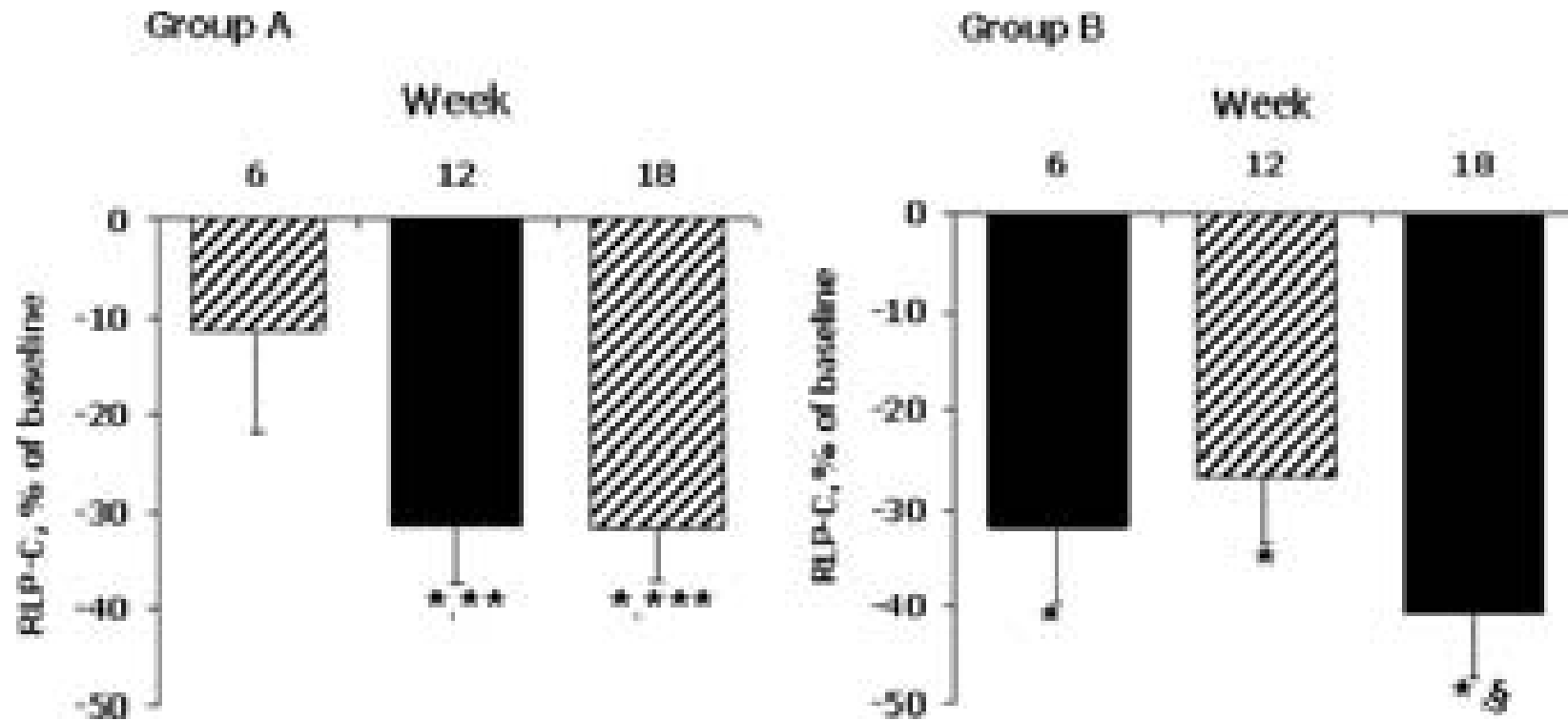
- 36 HD hastası düşük akımlı HD'den(modifiye sellüloz) yüksek akımlı (A: Polisulfon/ B:Modifiye sellülöz) HD'e geçildikten 6 hafta sonra...
- Kalıntı partikül kolesterol : B:% 32 (p <0.001) ve A: % 11 (NS)
- TG: % 20 ve % 10 (p<0.05) düşüş.
- Okside LDL sadece polisülfon grupta azalmış.
- Akut faz proteinleri, LDL-K ve HDL-K değişmemiş.
(Wanner C et al. Nephrol. Dial. Transplant. 2004;19:2570-2575)

Percentage difference of triglyceride levels from baseline in two groups of patients using a crossover design.



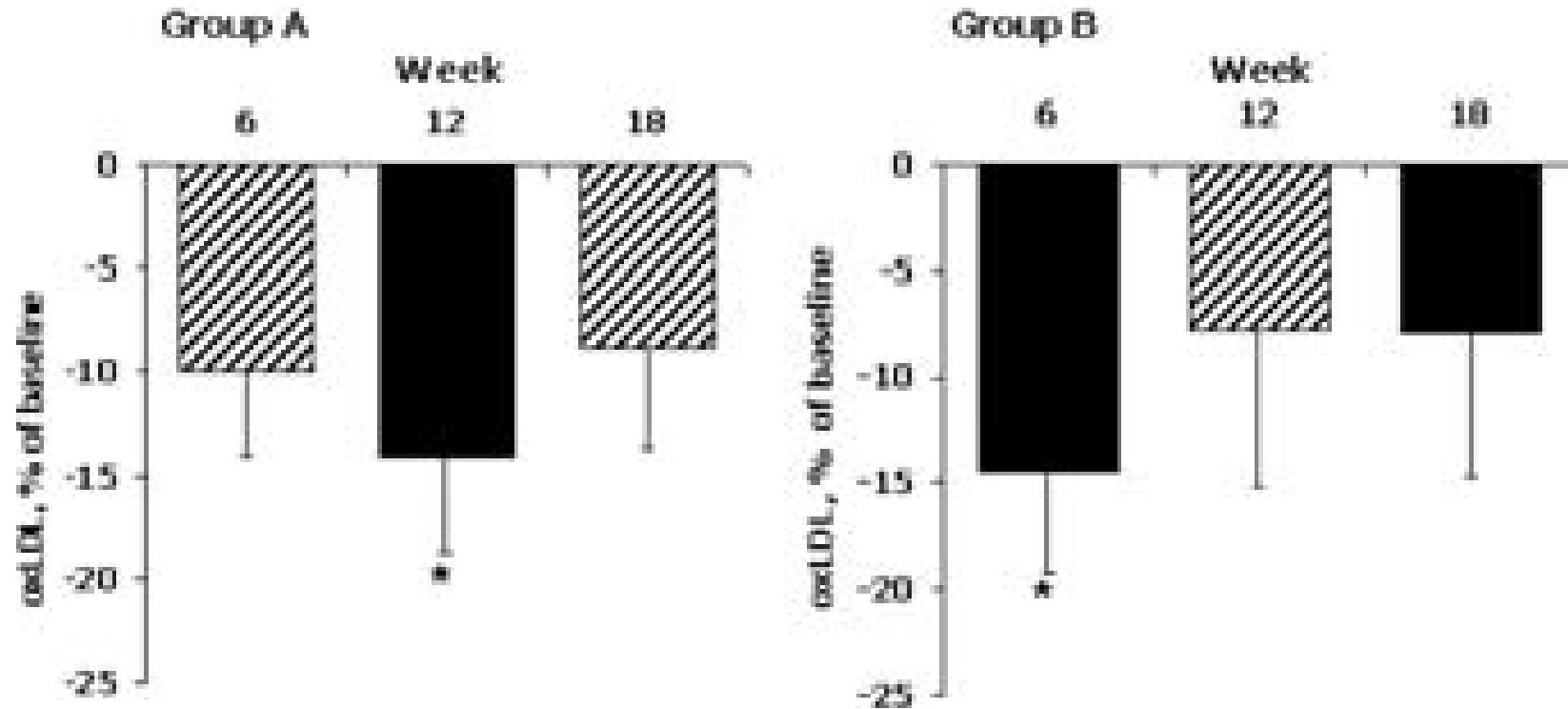
Wanner C et al. Nephrol. Dial. Transplant. 2004;19:2570-2575

Percentage difference of RLP-C levels from baseline in two groups of patients using a crossover design.



Wanner C et al. Nephrol. Dial. Transplant. 2004;19:2570-2575

Percentage difference of oxidized LDL levels from baseline in two groups of patients using a crossover design.



Wanner C et al. Nephrol. Dial. Transplant. 2004;19:2570-2575

FİBRATLAR

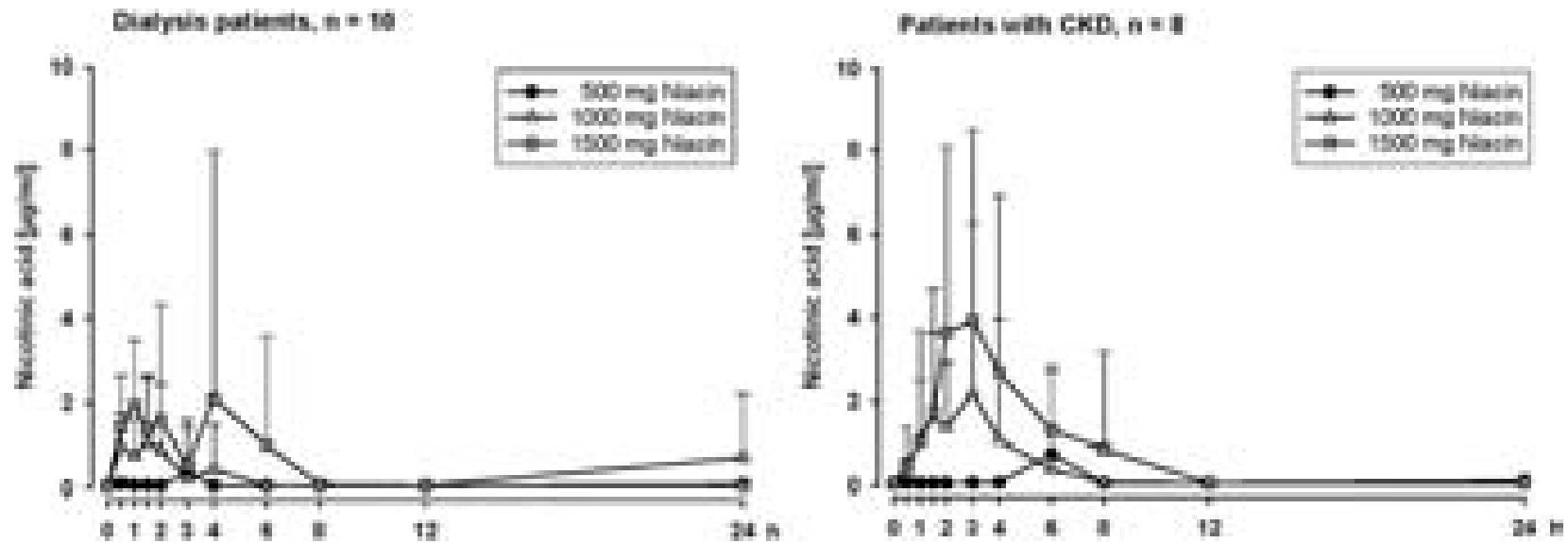
- Hemodiyaliz hastalarında fibratların etkisini gösteren kontrollü çalışma yok.
- Kreatinin klirensi ≤ 75 ml/dk olan 1046 hastada gemfibrozilin kardiyovasküler olayları %20 azalttığı gösterilmiştir.
(Tonelli M, *Kidney Int* 2004;66:1123)
- Statinler ile birlikte kullanımları yan etkilerini artırmaktadır.

NİASİN

- Nikotinik asit (niasin), B kompleks (B3 vitamini) suda eriyen bir vitamin olup dislipidemi tedavisin onlarca yıldır kullanılmaktadır.
- Yağ dokusundan yağ asidi mobilizasyonunu engelleyerek karaciğerde Tg, LDL-K ve VLDL-K sentezini engeller.
- Erişkin hasta grubunda KV olay gelişimini azaltmaktadır.
- Toplam kolesterol, TG ve LDL-K, Lp(a) düzeylerini düşürüp, HDL-K düzeyini artırmaktadır.

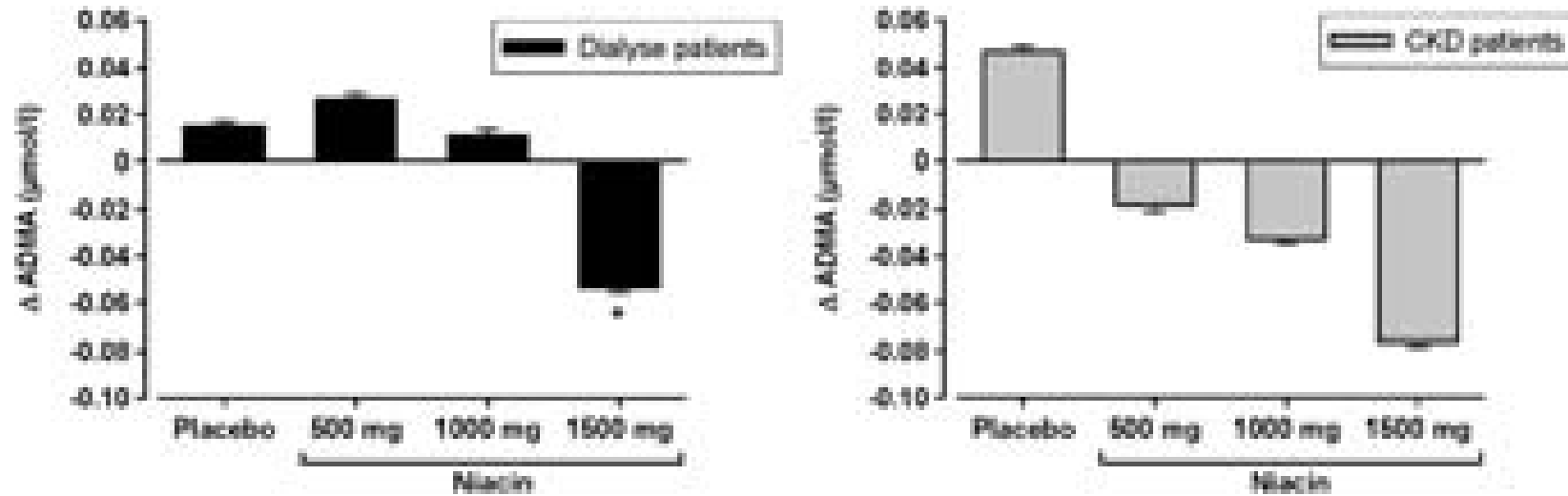
(Am J Health Syst Pharm. 2003 May 15;60(10):995-1005.)

Mean plasma concentration courses of nicotinic acid over 24 h on Day 4 after intake of an oral dose of 500 mg/day (black circle), 1000 mg/day (grey triangle) or 1500 mg/day (dark grey square) niacin; left: in dialysis patients; right: in patients with renal insufficiency.



Reiche I et al. Nephrol. Dial. Transplant. 2011;26:276-282

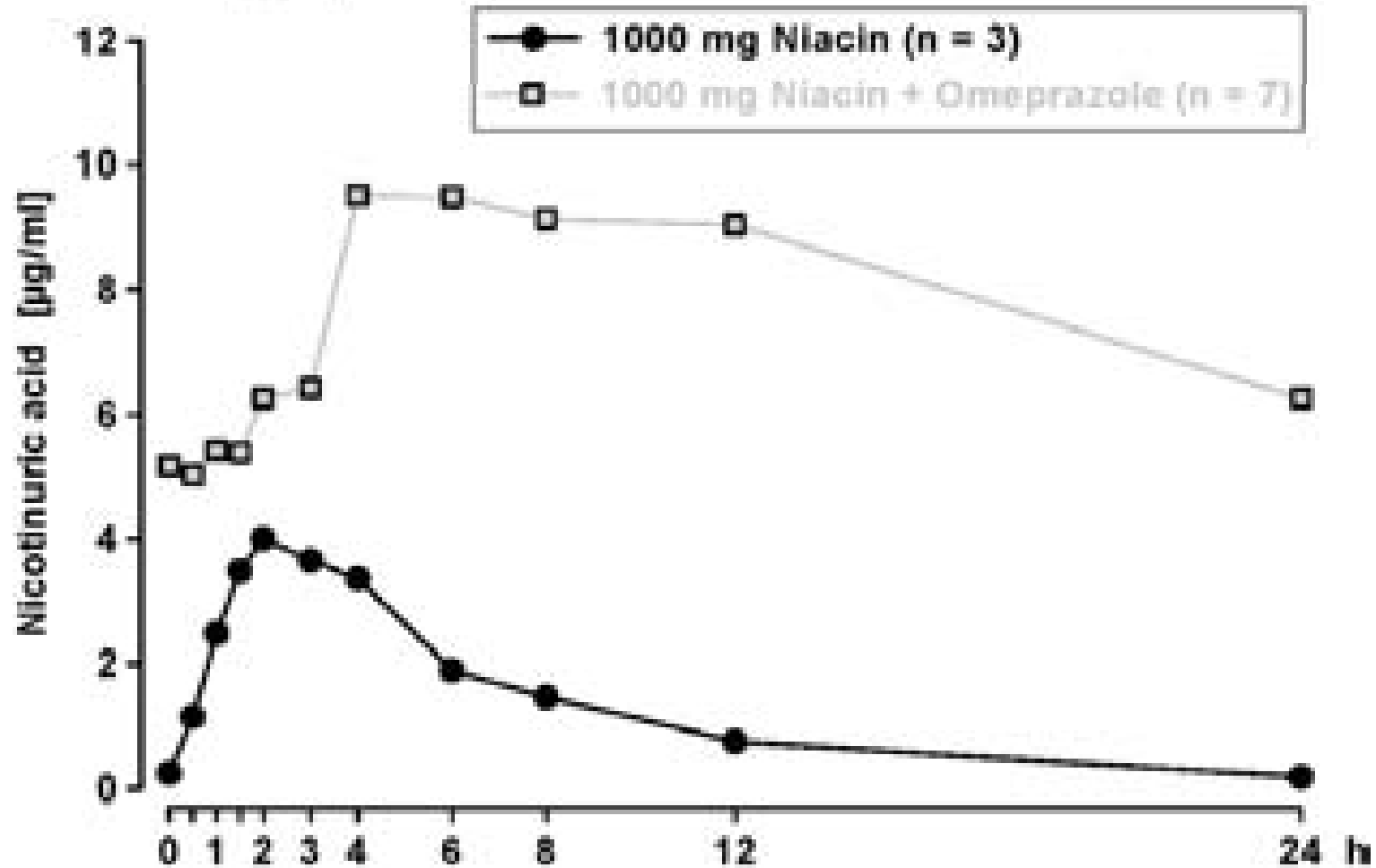
Effect of niacin treatment with 500, 1000 and 1500 mg and placebo for 1 week on ADMA concentrations versus baseline.



Reiche I et al. Nephrol. Dial. Transplant. 2011;26:276-282

Mean plasma concentration courses of the metabolite nicotinuric acid over 24 h on Day 4 after intake of an oral dose of 1000 mg/day niacin (black circle) and 1000 mg/day niacin under omeprazole therapy (grey square) in dialysis patients.

Dialysis patients



Reiche I et al. Nephrol. Dial. Transplant. 2011;26:276-282

İL AÇ TERCİHİ ?

- LDL-C yüksek olanlarda statinler kullanılmalıdır. Renal atılımı en az olanlar **atorvastatin ve fluvastatin**dir.
- Bilesik hiperlipidemide omega 3 yağ asitleri kullanılabilir. NKF GFR < 15 ml /dk olanlarda gemfibrozilin 600 mg/gün olarak kullanılabileceđi belirtilmektedir.
- Fluvastatin dısındaki statinler gemfibrozilin maksimum konsantrasyonunu artırır.

SONUÇ

- KBY de kardiyovasküler olayların gelişiminde dislipidemi dışında mekanizmalar da rol almaktadır.
- Diyaliz hastalarında optimal lipid düzeyleri bilinmemektedir.
- Yaygın olarak ölçülen TK, TG, LDL, HDL düzeyleri üremide gelişen lipid anormalliklerini artmış Lp(a), IDL, modifiye LDL, HDL alt grupları) saptamamaktadır.
- Statinlerin Lp(a), TG ve HDL üzerine etkileri zayıftır.
- Lipid anormallikleri KBY'nin erken dönemlerinden itibaren düzeltilmelidir.

STATE-OF-THE-ART PAPER

Managing Dyslipidemia in Chronic Kidney Disease

Charles R. Harpaz, MD, FACP,* Terry A. Jacobson, MD, FACP†

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The incidence of chronic kidney disease (CKD) in the U.S. continues to increase, and now over 10% of the U.S. population has some form of CKD. Although some patients with CKD will ultimately develop renal failure, most patients with CKD will die of cardiovascular disease before dialysis becomes necessary. Patients with CKD have major proatherogenic lipid abnormalities that are treatable with readily available therapies. The severe derangements seen in lipoprotein metabolism in patients with CKD typically results in high triglycerides and low high-density lipoprotein (HDL) cholesterol. Because of the prevalence of triglyceride disorders in patients with CKD, after treating patients to a low-density lipoprotein goal, non-HDL should be calculated and used as the secondary goal of treatment. A review of the evidence from subgroup analysis of several landmark lipid-lowering trials supports treating dyslipidemia in mild to moderate CKD patients with HMG-CoA reductase inhibitors. The evidence to support treating dyslipidemia in hemodialysis patients, however, has been mixed, with several outcome trials pending. Patients with CKD frequently have mixed dyslipidemia and often require treatment with multiple lipid-lowering drugs. Although statins are the cornerstone of therapy for most patients with CKD, differences in their pharmacokinetic properties give some statins a safety advantage in patients with advanced CKD. Although most other lipid-lowering agents can be used safely with statins in combination therapy in patients with CKD, the fibrates are renally metabolized and require both adjustments in dose and very careful monitoring due to the increased risk of rhabdomyolysis. After reviewing the safety and dose alterations required in managing dyslipidemia in patients with CKD, a practical treatment algorithm is proposed. (J Am Coll Cardiol 2008;51:2375-84)
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