Trakya Univ Tip Fak Derg 2010;27 Suppl 1:79-81

Review / *Derleme*

What Do We Know About Negative Statin Trials?

Negatif Statin Çalışmaları Hakkında Ne Biliyoruz?

Okan ERDOĞAN

Department of Cardiology Medical Faculty of Marmara University, İstanbul

The benefits of statins are well established in certain fields of cardiology. However, there are still unresolved issues in which statins are doubtfully effective in providing absolute benefit. Two large clinical trials showed that statins did not diminish the mortality rate in patients with heart failure. According to a randomized prospective clinical trial statins were also not able to halt the progression of aortic valve sclerosis. One large trial dictated that pravastatin did not significantly reduce either all-cause mortality or coronary heart disease when compared with usual care in older participants with well-controlled hypertension and moderately elevated low density cholesterol. Another study revealed that in patients undergoing hemodialysis, the initiation of treatment with rosuvastatin lowered the low density cholesterol level but had no significant effect on the composite primary end point of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke.

Key words: Statin; negative; trials; coronary; aortic; heart failure; mortality.

Statinlerin faydaları kardiyolojinin bazı alanlarında iyi anlaşılmış durumdadır. Fakat hala statinlerin mutlak yarar sağlamadaki etkinliğinin şüpheli olduğu çözülemeyen konular vardır. İki büyük klinik araştırma, statinlerin kalp yetersizliği olan hastalarda mortalite oranlarını düşürmediğini göstermiştir. Aynı zamanda, ileriye dönük randomize bir klinik çalışmaya göre, statinlerin aort kapağı sklerozunun ilerleyişini durduramadığı görülmüştür. Geniş bir çalışma, hipertansiyonu iyi kontrol edilmiş ve düşük yoğunluklu kolestrolü hafif yüksek yaşlı bireylerde, klasik tedavi görenlerle karşılaştırıldığında, pravastinin tüm nedenlere bağlı ölüm ya da koroner kalp hastalığını anlamlı şekilde azaltmadığını ortaya koymuştur. Diğer bir çalışma, hemodiyaliz tedavisi gören hastalarda, rosuvastatin tedavisinin düşük yoğunluklu kolestrolü azalttığını, fakat birleşik primer son noktalar üzerinde (kardiyovasküler nedenli ölüm, ölümle sonuçlanmayan miyokart enfarktüsü ya da inme) nedenlerden anlamlı etki göstermediğini ortaya koymuştur.

Anahtar sözcükler: Statin; negatif; çalışmalar; koroner; aort; kalp yetersizliği; mortalite.

It has been widely accepted that statins are going to be indicated in many aspects of medicine during the next subsequent years. However, trials have dictated that there are certain areas of medicine in which statins are of limited value and not be absolutely considered because of insufficient data of evidence. Some of the published negative randomized clinical statin trials are going to be summarized in the present article.

It is well known that statins exert their beneficial effects through anti-inflammatory, anti-atherogenic, antioxidant, plaque stabilising and anti-arrhythmic actions on the heart in patients with heart failure. However, recently published two randomized clinical statin trials did not reveal any significant benefit in terms of total mortality. In Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA) including 5011 patients with history of ischemic cardiomyopathy, New York Heart Association

Correspondence (İletişim adresi): Dr. Okan Erdoğan. Marmara Üniversitesi Tıp Fakültesi Kardiyoloji Anabilim Dalı, 34668 Haydarpaşa İstanbul.
Tel: 0216 - 336 32 05 Fax (Faks): 0212 - 572 79 05 e-mail (e-posta): okanerdogan@yahoo.com

(NYHA) functional class II-IV and ejection fraction less than 40% rosuvastatin 10 mg/day compared to placebo did not significantly impact the cardiovascular mortality, coronary events and stroke during a follow-up period of 33 months.[1] Besides that another important clinical trial, named as GISSI-HF trial included 4574 patients with heart failure, ejection fraction < 40% and NHYA II-IV functional status. Rosuvastatin 10 mg/day compared to placebo did not show any significant benefit in terms of mortality and admittance rate to hospital.[2]

Statins once thought to be of benefit in delaying operation time and progression of calcific aortic stenosis because of common characteristics with atherosclerosis, including hypercholesterolemia. In a double-blind, placebo-controlled trial, patients with calcific aortic stenosis were randomly assigned to receive either 80 mg of atorvastatin daily or a matched placebo. Aortic-valve stenosis and calcification were assessed with the use of Doppler echocardiography and helical computed tomography, respectively. The primary end points were change in aortic-jet velocity and aortic-valve calcium score. Progression in valvular calcification was 22.3±21.0%per year in the atorvastatin group, and 21.7±19.8% per year in the placebo group (p=0.93; ratio of posttreatment aortic-valve calcium score, 0.998; 95%confidence interval, 0.947 to 1.050). Hence, intensive lipid-lowering therapy did not halt the progression of calcific aortic stenosis or induce its regression.[3]

Studies have demonstrated that statins administered to individuals with risk factors for coronary heart disease (CHD) reduce CHD events. However, many of these studies were too small to assess all-cause mortality or outcomes in important subgroups. To determine whether pravastatin compared with usual care reduces all cause mortality in older, moderately hypercholesterolemic, hypertensive participants with at least 1 additional CHD risk factor a multicenter, randomized, nonblinded trial conducted in a subset of participants from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). Ambulatory persons (n=10 355), aged 55 years or older, with low density lipoprotein cholesterol (LDL-C) of 120 to 189 mg/dL (100 to 129 mg/dL if known CHD) and triglycerides lower than 350 mg/dL, were randomized to pravastatin (n=5170) or to usual care (n=5185). Baseline mean total cholesterol was 224 mg/ dL; LDL-C, 146 mg/dL; high-density lipoprotein cholesterol, 48 mg/ dL; and triglycerides, 152 mg/dL. Mean follow-up was 4.8 years. During the trial, 32% of usual care participants with and 29% without CHD started taking lipid-lowering drugs. At forth year, total cholesterol levels were reduced by 17% with pravastatin versus 8% with usual care; among the random sample who had LDL-C levels assessed, levels were reduced by 28% with pravastatin versus 11% with usual care. All-cause mortality was similar for the 2 groups (Relative Risk, 0.99; 95% Confidence Interval, 0.89-1.11; p=0.88), with six-year mortality rates of 14.9% for pravastatin versus 15.3% with usual care. Coronary heart disease event rates were not significantly different between the groups (Relative Risk, 0.91; 95% Confidence Interval, 0.79-1.04; p=0.16), with six-year CHD event rates of 9.3% for pravastatin and 10.4% for usual care. Pravastatin (40 mg/day) did not reduce either all-cause mortality or CHD significantly when compared with usual care in older participants with well-controlled hypertension and moderately elevated LDL-C. The results might have been due to the modest differential in total cholesterol (9.6%) and LDL-C (16.7%) between pravastatin and usual care compared with prior statin trials supporting cardiovascular disease prevention.[4]

Limited data are available evaluating how the timing and intensity of statin therapy following an acute coronary syndrome (ACS) event affect clinical outcome. To compare early initiation of an intensive statin regimen with delayed initiation of a less intensive regimen in patients with ACS an international, randomized, double-blind trial of patients with ACS receiving 40 mg/d of simvastatin for one month followed by 80 mg/d thereafter (n=2265) compared with ACS patients receiving placebo for four months followed by 20 mg/d of simvastatin (n=2232). The primary end point was a composite of cardiovascular death, nonfatal myocardial infarction, readmission for ACS, and stroke. Follow- up was for at least six months and up to 24 months. No difference was evident during the first four months between the groups for the primary end point (HR, 1.01; 95% CI, 0.83- 1.25; p=0.89), but from four months through the end of the study the primary end point was significantly reduced in the simvastatin only group (HR, 0.75; 95% CI, 0.60-0.95; p =0.02). The trial did not achieve the prespecified end point. However, among patients with ACS, the early initiation of an aggressive simvastatin regimen resulted in a favorable trend toward reduction of major cardiovascular events.[5] Twelve trials involving 13024 patients with ACS were included in a meta-analysis. The risk ratios for the combined end point of death, MI, and stroke for patients treated with early statin therapy compared with control therapy were 0.93 (95% CI, 0.80-1.09; p=0.39) at one month and 0.93 (95% CI, 0.81- 1.07; p=0.3) at four months following ACS. There were no statistically significant risk reductions from statins for total death, total MI, total stroke, cardiovascular death, fatal or nonfatal MI, or revascularization procedures (percutaneous coronary intervention or coronary artery bypass graft surgery). Sensitivity analyses with restriction to trials of high quality or with additional data from a large trial using cerivastatin indicated summary risk ratios even closer to 1. Based on available evidence, initiation of statin therapy within 14 days following onset of ACS does not reduce death, MI, or stroke up to four months.[6]

Statins reduce the incidence of cardiovascular events in patients at high cardiovascular risk. However, a benefit of statins in such patients who are undergoing hemodialysis has not been proved. An international, multicenter,

randomized, double-blind, prospective trial involved 2776 patients, 50 to 80 years of age, who were undergoing maintenance hemodialysis. Patients were randomly assigned to receive rosuvastatin, 10 mg daily, or placebo. The combined primary end point was death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. Secondary end points included death from all causes and individual cardiac as well as vascular events. During a median follow-up period of 3.8 years, 396 patients in the rosuvastatin group and 408 patients in the placebo group reached the primary end point (9.2 and 9.5 events per 100 patient-years, respectively; hazard ratio for the combined end point in the rosuvastatin group vs. the placebo group, 0.96; 95% Confidence Interval, 0.84 to 1.11; p=0.59). Rosuvastatin had no effect on individual components of the primary end point. There was also no significant effect on all-cause mortality (13.5 vs. 14.0 events per 100 patient-years; hazard ratio, 0.96; 95% CI, 0.86 to 1.07; p=0.51). In patients undergoing hemodialysis, the initiation of treatment with rosuvastatin lowered the LDL cholesterol level but had no significant effect on the composite primary end point of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke.[7] A multicenter, randomized, double-blind, prospective study included 1255 subjects with type 2 diabetes mellitus receiving maintenance hemodialysis who were randomly assigned to receive 20 mg of atorvastatin per day or matching placebo. The primary end point was a composite of death from cardiac causes, nonfatal myocardial infarction, and stroke. Secondary end points included death from all causes and all cardiac and cerebrovascular events combined. After four weeks of treatment, the median level of low-density lipoprotein cholesterol was reduced by 42% among patients receiving atorvastatin, and among those receiving placebo it was reduced by 1.3%. During a median follow-up period of four years, 469 patients (37%) reached the primary end point, of whom 226 were assigned to atorvastatin and 243 to placebo (relative risk, 0.92; 95% Confidence Interval, 0.77 to 1.10; p=0.37). Atorvastatin had no significant effect on the individual components of the primary end point, except that the relative risk of fatal stroke among those receiving the drug was 2.03 (95% Confidence Interval, 1.05 to 3.93; p=0.04). Atorvastatin reduced the rate of all cardiac events combined (relative risk, 0.82; 95% Confidence Interval, 0.68 to 0.99; p=0.03, nominally significant) but not all cerebrovascular events combined (Relative Risk, 1.12; 95%confidence interval, 0.81 to 1.55; p=0.49) or total mortality (Relative Risk, 0.93; 95%confidence interval, 0.79 to 1.08; P=0.33). Atorvastatin had no statistically significant effect on the composite primary end point of cardiovascular death, nonfatal myocardial infarction, and stroke in patients with diabetes receiving hemodialysis.[8]

In conclusion, before initiation of statin therapy in a particular patient one has to be convinced of its potential benefit in terms of total mortality and coronary event rates. A cost effectiveness analysis should also be performed in accordance with its widespread usage, long time treatment and variability of indications. An individualized treatment approach currently seems to be an appropriate option especially for patients who require primary prevention.

REFERENCES

1. Kjekshus J, Apetrei E, Barrios V, Böhm M, Cleland JG, Cornel JH, et al. Rosuvastatin in older patients with systolic heart failure. N Engl J Med 2007;357:2248-61.
2. Gissi-HF Investigators, Tavazzi L, Maggioni AP, Marchioli R, Barlera S, Franzosi MG, et al. Effect of rosuvastatin in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. Lancet 2008;372:1231-9.
3. Cowell SJ, Newby DE, Prescott RJ, Bloomfield P, Reid J, Northridge DB, et al. A randomized trial of intensive lipid-lowering therapy in calcific aortic stenosis. N Engl J Med 2005;352:2389-97.
4. ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. Major outcomes in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin vs usual care: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT). JAMA 2002;288:2998-3007.
5. de Lemos JA, Blazing MA, Wiviott SD, Lewis EF, Fox KA, White HD, et al. Early intensive vs a delayed conservative simvastatin strategy in patients with acute coronary syndromes: phase Z of the A to Z trial. JAMA 2004;292:1307-16.
6. Briel M, Schwartz GG, Thompson PL, de Lemos JA, Blazing MA, van Es GA, et al. Effects of early treatment with statins on short-term clinical outcomes in acute coronary syndromes: a meta-analysis of randomized controlled trials. JAMA 2006;295:2046-56.
7. Fellström BC, Jardine AG, Schmieder RE, Holdaas H, Bannister K, Beutler J, et al. Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. N Engl J Med 2009;360:1395-407.
8. Wanner C, Krane V, März W, Olschewski M, Mann JF, Ruf G, et al. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. N Engl J Med 2005;353:238-48.