

UPDATES IN CARDIOLOGY

Percent reduction in LDL cholesterol following high-intensity statin therapy: potential implications for guidelines and the prescription of emerging lipid-lowering agents

Current guidelines for statin therapy in Europe and Canada argue obtaining a fixed LDL cholesterol target value or a reduction greater than 50% of it, while guidelines in the US advocate for a moderate (<50%) or high intensity (>50%) reduction. Instead, there is insufficient data to link these percentage decreases to the reduction of subsequent cardiac events, especially when it comes to high-intensity statin regimens.

The study presented in this article represents a second analysis of the data from the JUPITER (Justification for the Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) study. In short, this study involved 17 802 asymptomatic subjects, women >60 years and men >50 who had LDL levels <130 mg/dl (with a median baseline of 108 mg/dl), PCR high-sensitive <2 mg / l and triglycerides <500 mg/dl. Exclusion criteria included a history of diabetes, cardiovascular disease or lipid-lowering treatment.

By randomization, all participants received either 20 mg rosuvastatin daily or placebo and were followed for 5 years until the appearance of the the first cardiovascular event (defined as myocardial infarction, non-fatal stroke, acute non-fatal MI, hospitalization for unstable angina, cardiovascular revascularization procedure, or death from cardiovascular causes).

Using statistical methods the variability of LDL cholesterol levels was evaluated in response to a daily dose of 20 mg of rosuvastatin. The study also assessed the risk of a first cardiovascular event for a greater than 50% reduction of LDL cholesterol. Among subjects assigned to rosuvastatin, 3,640 of them (46.3) had a >50% decrease, of the 3365 subjects (42.8%) had a reduction between 0-50% and for 851 of them (10.8%) no reduction or even an increase in LDL cholesterol from baseline was observed.

These percentages relate directly to the risk of a first cardiovascular event; upon completion of the study, rates within the primary end-point were 11.2, 9.2, 6.7 and 4.8 per 1000 person / year respectively in the placebo group, the group without any reduction in LDL cholesterol, the group with a reduction <50% and the group with a >50% decrease.

In conclusion, the current data confirms a wide variation in the percentage reduction of LDL cholesterol using high intensity statin therapy and a direct relationship between the magnitude of the reduction percentage and proven clinical benefit. These data represent a general basis for introducing the concept of LDL cholesterol reduction percentage in current medical practice, with fixed targets for LDL value.

In addition, these data obtained by using statin therapy to achieve percentage reduction can be useful in the future in introduction of adjuvant therapy with PCSK9 inhibitors, if these agents prove to be effective in reducing cardiovascular events.

Ridker et al. Percent reduction in LDL cholesterol following high-intensity statin therapy: potential implications for guidelines and the prescription of emerging lipid-lowering agents. European Heart Journal (2016)37, 1373-1379. (IM, RM)

Patients with familial hypercholesterolemia are characterized by presence of cardiovascular disease at the time of death

Heterozygous Familial hypercholesterolemia is a genetic disease characterized by elevated plasma levels of LDL cholesterol, which represents a major risk factor for the development of cardiovascular disease. If not diagnosed and treated properly, the symptoms of cardiovascular disease begin manifesting in men in the fourth decade of life and in women in the fifth decade.

The study presented in this article retrospectively analyzed the medical records of 4688 patients who died in Norway, with known heterozygous familial hypercholesterolemia and aims at assessing the presence of cardiovascular disease, age at time of death, cause of death, lipid profile and the followed medical treatment.

Data was collected from 4688 patients in Norway with a molecular diagnosis of heterozygous familial hypercholesterolemia between 1989-the year of the first recorded death- and 2010- the year in which data collection ended. Information about gender, past medical history, the presence of cardiovascular disease, risk factors and clinical manifestations (xanthelasma, xanthomas, arcus senilis), and last known cholesterol lowering treatment and lipid profile values were collected.

Thus, the study results showed that the average age of death was 60 ± 13.2 years (between 33 to 94 years). Women accounted for 41% of all patients included in the study. 50% of the deaths were due to cardiovascular diseases, followed by cancer in a percentage of 32%. 93% of patients had an established diagnosis of cardiovascular disease at death. 86% of subjects had coronary artery disease and 69% of them had suffered one or more myocardial infarctions. The prevalence of atrial fibrillation was 19%. More than half of patients had hypertension, and 22% had diabetes. 91% received therapy with statin alone or combined on an average duration of 8 years of treatment.

Once it was established that the average age of death was 60 years, patients were divided into two groups (younger than 60 years-and-older than 60 years). It was found that among those under 60, where the average age at time of death was 51 years, 55% of them were smokers ($P = 0.001$), whereas only 10% of the other group (average age of death 71 years) were smokers.

It was observed that the values immediately prior to death of LDL cholesterol in the group of younger patients with familial hypercholesterolemia were significantly higher compared to the other group. No significant differences were identified for the presence of cardiovascular disease at the time of death between the 2 groups.

Assessing the presence of cardiovascular disease by gender, it was observed that fewer women with familial hypercholesterolemia were identified in the study group than men (84% versus 100%).

In conclusion, the study presented in this article demonstrates that most patients with familial hypercholesterolemia showed cardiovascular disease at the time of death which proved to be the cause of death in over half of them.

Krogh H et al., *Patients with familial hypercholesterolemia are characterized by presence of cardiovascular disease at the time of death. European Heart Journal (2016) 37, 1398-1405. (IM, RM)*

Safety and efficacy of LY3015014, a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 (PCSK 9): a randomized, placebo-controlled Phase 2 study

Reduction of plasma levels of LDL-cholesterol remains one of the main mitigation strategies in primary and secondary cardiovascular prevention. In spite of statin therapy reducing cardiovascular risk, residual risk still

remains considerable, which is why new adjuvant lipid-lowering therapies have been developed i.e proprotein convertase subtilisin /kexin type 9 (PCSK9). They play a major role in the metabolism of LDL cholesterol, acting by inhibiting the effect of LDL receptor recycling. These monoclonal antibodies are administered by subcutaneous injection and have been shown to be safe and effective in combination with other lipid-lowering therapies.

LY3015014 (LY) is a monoclonal antibody derived from a human immunoglobulin G4 (IgG4) with a comparatively longer life as demonstrated in a preclinical phase of some studies.

Based on this assumption the authors of this study have tried to demonstrate that the administration of LY every 8 weeks may be sufficient to reduce LDL cholesterol and may provide a significant advantage over other anti PCSK9 antibodies that require administration every 2 or 4 weeks.

Therefore, the aim of the study presented in this article was to evaluate the efficacy in reducing LDL cholesterol plasma levels following subcutaneous administration of LY for 4 or 8 weeks in patients with familial hypercholesterolemia, added to a pre-existing standard lipid-lowering treatment.

The study presented is a multicentre, randomized, double-blind, parallel, placebo-controlled trial conducted between 27 June 2013 and January 2, 2014 that included 527 patients aged 18-80 years with familial hypercholesterolemia defined as LDL-cholesterol >80 mg / dl and triglycerides <450 mg/dl.

The study was conducted over a period of 16 weeks and patients were randomized to receive either a subcutaneous dose of 20, 120 or 300 mg every 4 weeks (Q4w) either 100 or 300 mg every 8 weeks (Q8W) (alternating with placebo Q4w) or placebo Q4w. Efficacy was demonstrated by measuring the levels of LDL cholesterol, non HDL cholesterol, ApoB, HDL cholesterol, Lp (a), high sensitive C-reactive protein and PCSK9 free.

Most subjects were male (53.6%), white (68.6%) with a mean age of 58.4 years. Among all patients, 10% were treated with 40-80 mg atorvastatin or 20-40 mg rosuvastatin, 69.7% were treated with another statin or another dose and 20.2% did not use any statin. 13.9% of patients were treated with ezetimib. Lipid profile values were as following: average LDL cholesterol 136.3 mg/dl, HDL cholesterol 55.7 mg/dl, triglycerides 139 mg/dl.

The study has shown that administration of LY3015014 produced a significant dose-dependent de-

crease of levels of LDL cholesterol, non-HDL cholesterol, Apo B, and Lp (a). Using least squares regression, the mean reduction in LDL cholesterol from the beginning to the end of the study ranged from -14.9 to -50.5% with a dose of 20-300 mg every 4 weeks and -14.9 to -37.1% with dose from 100 to 300 mg every 8 weeks, compared with an increase of 7.6% in the placebo group.

In this study, the continued effect of reducing LDL cholesterol had a longer duration than has been observed in other trials with anti PCSK9. In addition a significant reduction of other atherogenic lipoproteins, including non-HDL, Apo B, and Lp (a) was observed and only a modest effect on triglyceride levels and HDL cholesterol was noted.

Regarding side effects, LY antibody did not result in the growth of transaminases or bilirubin or CK levels. The most common adverse event was rhino pharyn-

gitis. Also reported were local reactions at the site of subcutaneous administration, but these reactions were generally mild.

In conclusion, the study presented in this article showed that LY, a monoclonal anti PCSK9 antibody has proven an important and lasting reduction of LDL levels when administered every 4 or 8 weeks. Short-term safety of this antibody was shown similar to that described in other anti PCSK9. Evaluating the safety profile and efficacy on cardiovascular effects, however, requires further investigation.

Kastelein et al., Safety and efficacy of LY3015014, a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 (PCSK 9): a randomized, placebo-controlled Phase 2 study, European Heart Journal (2016), 37, 1360-1369. (IM, RM)

Rubrică realizată de Dr. Irina Macovei, Dr. Rugina Mihaela.