Statins and Thrombosis

Vishnu Venkitasubramony, Akshay Kulkarni, Priya Joshi and Prutha Pore, The GTF Group

Abstract

A few reports indicate that statins could be beneficial in the management of thrombosis. Our mission was to research if and how statins could reduce inflammation, and therefore incidence of development of thrombosis in Myocardial Infarction, and Stroke.

Our group researched a variety of clinical trials and reviews, and selected the following resources:

1. The JUPITER Trial (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin)

2. The CARE Trial (Cholesterol And Recurrent Events)

3. SPARCL Trial (The Stroke Prevention by Aggressive Reduction in Cholesterol Levels).

The 3 trials indicated that statins are distinctly beneficial in the management of thrombosis by reducing inflammation, and therefore the incidence of development of thrombosis in MI, and stroke.

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Introduction

"Statins", also known as HMG-CoA reductase inhibitors,
are a class of drugs that lower the level of cholesterol in the blood by reducing the production of cholesterol by the liver.

We have seen a few reports that statins could be beneficial in the management of thrombosis. Our mission was to research if and how statins could reduce inflammation and therefore incidence of development of thrombosis in MI and stroke.

Our research indicated that most of the work has been done in the area of statins and arterial thrombosis. Therefore, our discussion will therefore refer to statins and arterial thrombosis.

Cholesterol and Statins

Cholesterol is critical to the normal function of every cell in the body. Unfortunately, cholesterol also contributes to the development of atherosclerosis, a condition in which cholesterol-containing plaques form within arteries. These plaques block the arteries and reduce the flow of blood to the tissues the arteries supply. When the plaque ruptures, a blood clot forms on the

plaque, thereby further blocking the artery and reducing the flow of blood. When blood flow is reduced sufficiently in the arteries that supply blood to the heart, the result is angina (chest pain) or a heart attack. If blood flow is reduced by plaque in the arteries of the brain, a stroke can occur. However, if the flow is reduced in the arteries of the leg, they can cause intermittent claudication (pain in the legs while walking). By reducing the production of cholesterol, statins are able to slow the formation of new plaque and occasionally can reduce the size of plaque that already exist. In addition, through mechanisms that are not well understood, statins may also stabilize plaque and make them less prone to rupturing and develop clots.

Cholesterol has a chemical structure that resembles a steroid nucleus with a cyclopentanoperhydrophenanthrene ring (Figure 1).

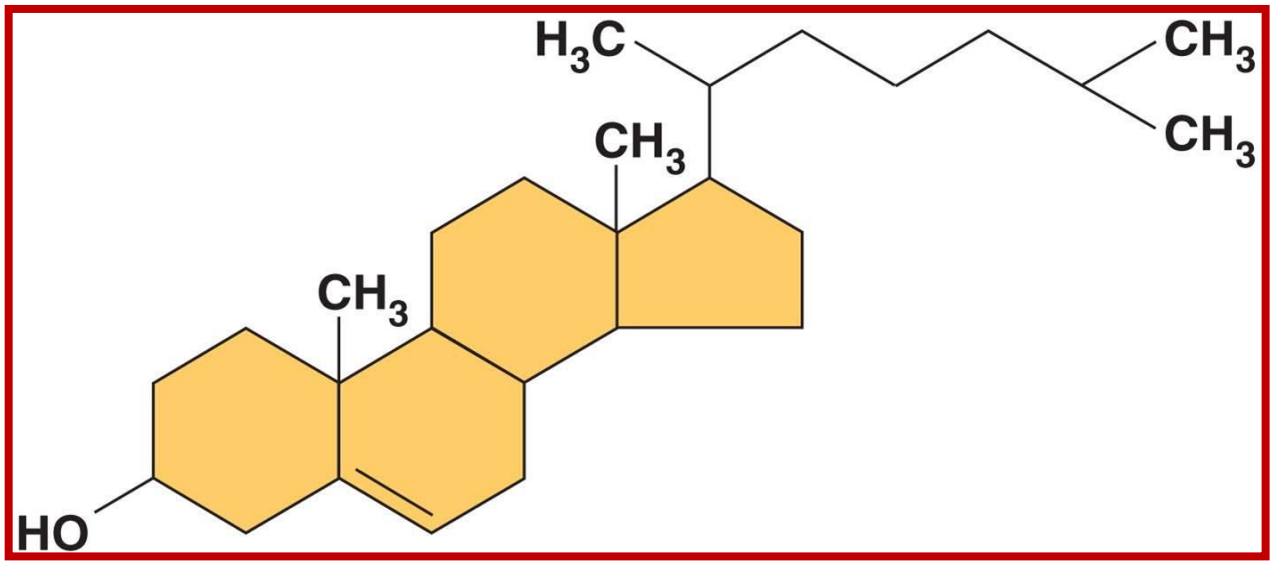

Figure 1: Structure of Cholesterol

The important role of cholesterol in the genesis of atherosclerosis is widely accepted. Atherosclerosis is a complex process that involves more than just cholesterol. Inflammation in the walls of the arteries may be an important factor in the development of atherosclerosis and hence blood clots.

When given to patients, statins have been found to be effective in reducing the risk of heart attack or stroke. These drugs have been proven to "reduce the risk of heart attack, stroke, and even death from heart disease."

Statins lower cholesterol levels and reduce inflammation, which could beneficially affect atherosclerosis and blood clots. This reduction of inflammation does not depend on statins' ability to reduce cholesterol.

Mechanism of Action of Statins

Statins act by blocking the enzyme hydroxy methyl glutaryl coenzyme A reductase (HMG-CoA reductase) in the liver that is responsible for making cholesterol.

Statins have a chemical structure that mimics the substrate molecule that HMG-CoA binds with, and is a competitive inhibitor that when binds to the enzyme also prevents the formation of Mevalonate. This is the molecule that is the intermediate in the synthesis of Cholesterol.
The cholesterol pathway is inhibited by HMG-CoA, thereby reducing cholesterol or the "bad cholesterol" (Low Density Lipoprotein, or LDL) production, thus lowering the risk atherosclerosis and other symptoms of VTE.

Types of statins

The following is a list of important, commonly used statins:

1. Atorvastatin (Lipitor)
2. Lovastatin (Mevacor, Altoprev)
3. Pitavastatin (Livalo, Nikita): Unlike most statins, Pitavastatin is less likely to interact with certain other drugs. Pitavastatin is processed differently in the body than some of the most commonly prescribed statins. Because of this difference, Pitavastatin may be less likely to cause certain unpredictable drug interactions.
4. Pravastatin (Pravachol): It is the most water soluble one of all the statins, is safe to use over a long period of time and has a lower incidence of side effects as well.
5. Rosuvastatin (Crestor)
6. Simvastatin (Zocor)

Side Effects of statins

- Muscle pain and debilitation
- Fever
- Dark urine
- Diarrhea

Research on statins and thrombosis

Our group researched in a variety of clinical trials and reviews, and selected the following resources:

1. The JUPITER Trial (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin, by Ridker, Danielson, Fonseca, et al, New Engl J Medicine, 2008).

2. The CARE Trial (Cholesterol And Recurrent Events by Sacks, Pfeffer, Moye, et al, New Engl J Med 1996).

3. SPARCL Trial (The Stroke Prevention by Aggressive Reduction in Cholesterol Levels by Amarenco, Bogousslavsky, Callahan, et al, New Engl J Med, 2006).

1. The JUPITER (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) Trial

This trial was conducted with the assumption that increased levels of the inflammatory biomarker high-sensitivity C-reactive protein (C-RP) predicts cardiovascular events. Since statins lower levels of high-sensitivity C-RP as well as cholesterol, it was thought that people with elevated high-sensitivity C-reactive protein levels but without hyperlipidemia might benefit from statin treatment.

A total of 17,802 apparently healthy men and women with low-density lipoprotein (LDL) cholesterol levels of less than 130 mg per deciliter and high levels of C-RP 2.0 mg per liter or higher were randomly assigned to rosuvastatin, 20 mg daily, or placebo and followed them for the occurrence of the combined primary end point of myocardial infarction, stroke, arterial revascularization, hospitalization for unstable angina, or death from cardiovascular causes.

Figure 2 shows that the cumulative incidence of primary endpoint was significantly lower in the rosuvastatin group, as compared to the placebo group (P <0.00001).

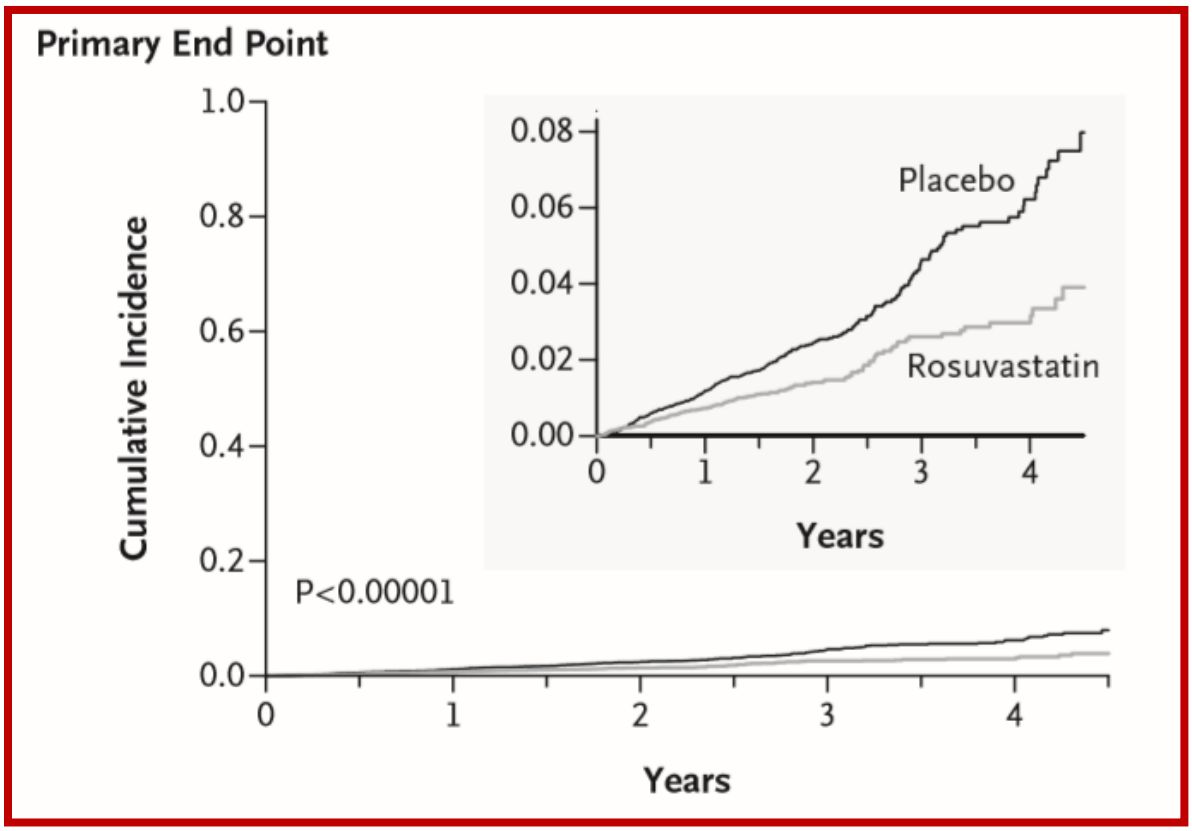

Figure 2

Figure 3 shows that the cumulative incidence of myocardial infarction, stroke and cardiovascular deaths was significantly lower in the rosuvastatin group, as compared to the placebo group (P <0.00001).

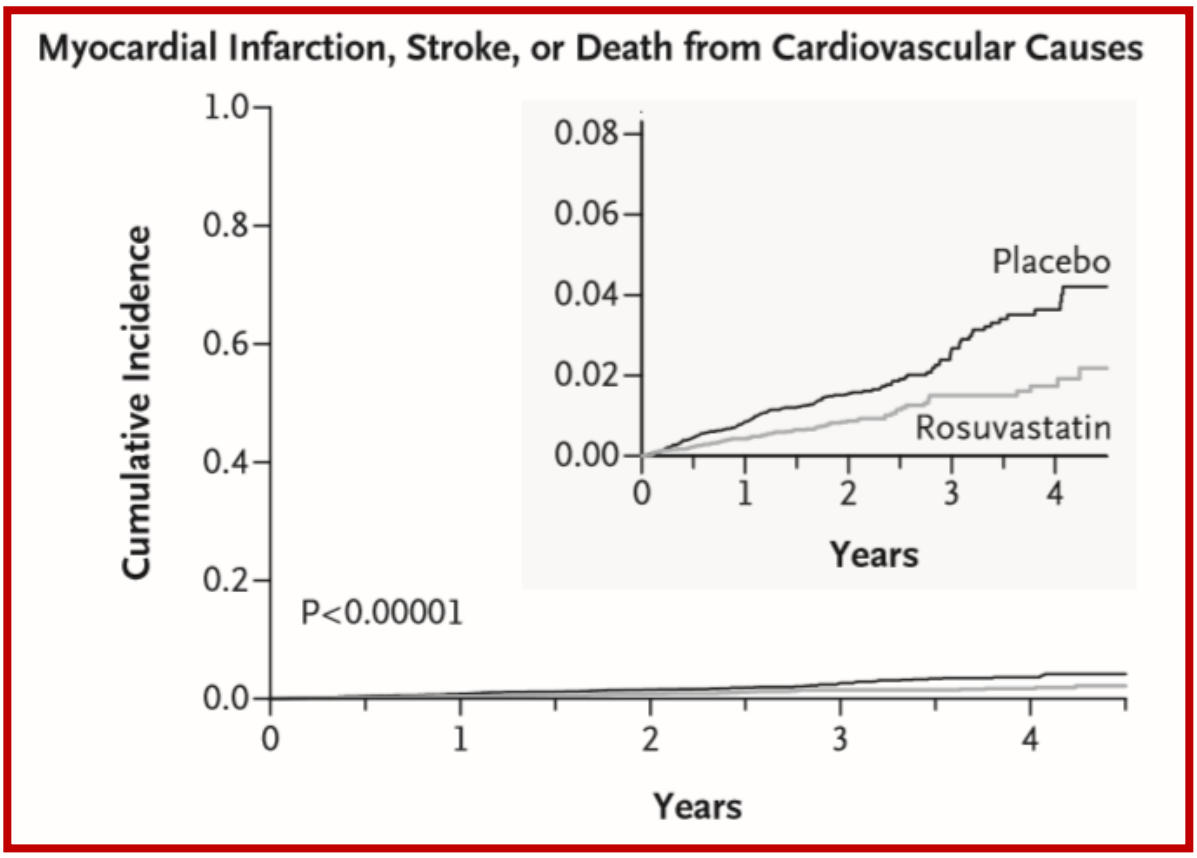

Figure 3

Figure 4 shows that the cumulative incidence of hospitalization for unstable angina was significantly lower in the rosuvastatin group, as compared to the placebo group (P <0.00001).

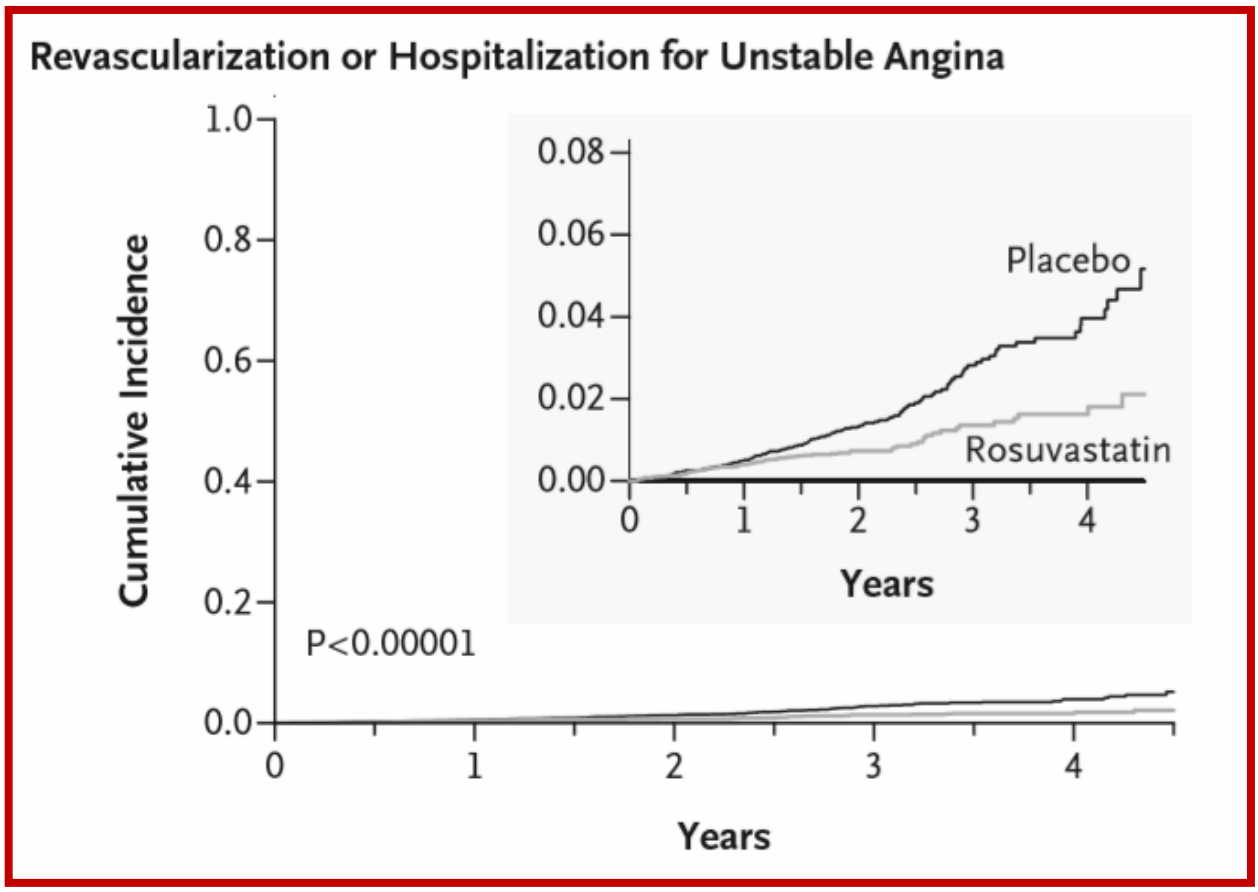

Figure 4

Figure 5 shows that the cumulative incidence of all cause mortality from any cause was significantly lower in the rosuvastatin group, as compared to the placebo group (P=0.02).

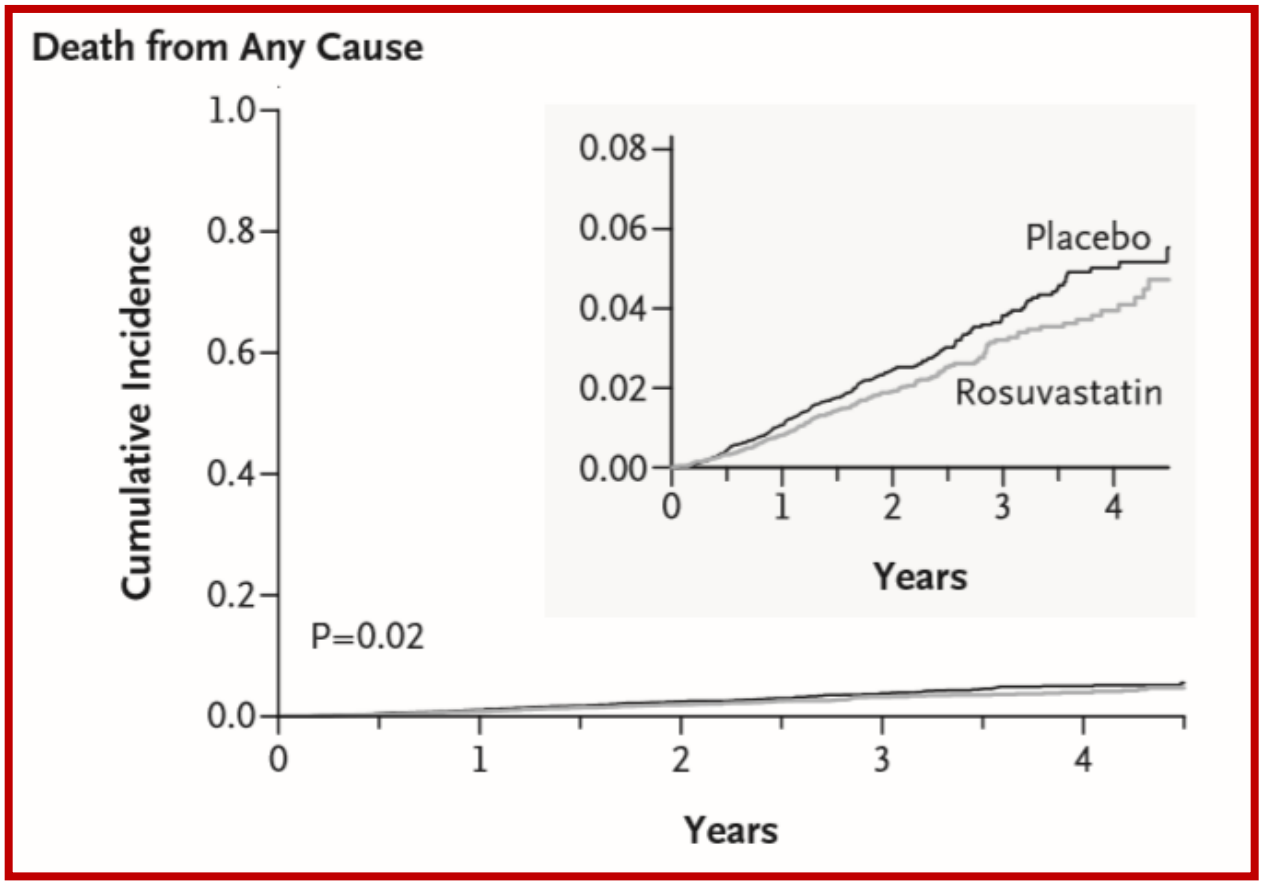

Figure 5

In summary, the JUPITER trial showed that rosuvastatin significantly reduced the incidence of major cardiovascular events.

2. The CARE (Cholesterol And Recurrent Events) Trial

It is not clear whether coronary events can be prevented by cholesterol-lowering therapy in patients who do not have hypercholesterolemia. This issue is of importance because the large majority of patients with coronary disease have elevated cholesterol levels.

The CARE trial was designed with an entry criteria of plasma total cholesterol level of less than 240 mg per deciliter and an LDL cholesterol level of 115 to 174 mg per deciliter to study the effectiveness in a typical population of lowering LDL cholesterol levels to prevent coronary events after myocardial infarction.

Patients were recruited in this double blind, randomized study, from 80 participating centers: 13 in Canada and 67 in the United States. Men and postmenopausal women were eligible if they had an acute myocardial infarction between 3 and 20 months before randomization, were 21 to 75 years of age, and had plasma total cholesterol levels of less than 240 mg per deciliter. Additionally, these patients had LDL cholesterol levels of 115 to 174 mg per deciliter, fasting triglyceride levels of less than 350 mg per deciliter, fasting glucose levels of no more than 220 mg per deciliter, left ventricular ejection fractions of no less than 25 percent, and no symptomatic congestive heart failure. Criteria for a qualifying myocardial infarction included typical symptoms and an elevated serum level of creatine kinase.

The patients were randomly assigned to receive either 40 mg of pravastatin once daily, or a matching placebo, determined by a telephone call from the data center. After randomization, visits to the clinic took place quarterly. Patients continued to take all prescribed medication, for cardiac and other conditions, that they had been receiving at baseline.

Plasma total cholesterol, high-density lipoprotein (HDL), and triglyceride levels were measured by the core laboratory at base line, at 6 and 12 weeks after randomization, at the end of each quarter during the first year, and semi annually thereafter.

Primary Endpoints

1. The primary outcome was the occurrence of a first major cardiovascular event, defined as nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina, an arterial revascularization procedure, or confirmed death from cardiovascular causes.

2. A symptomatic (unless during noncardiac surgery) nonfatal myocardial infarction confirmed by serum creatine kinase measurements.

Secondary Endpoints

Primary endpoints considered were: individually-arterial revascularization or hospitalization for unstable angina, myocardial infarction, stroke, or death from cardiovascular causes, and death from any cause.

A total of 4159 patients were randomly assigned to study groups (2078 to the placebo group and 2081 to the pravastatin group).

Pravastatin therapy lowered the mean Low Density Lipoproteins (LDL) level of 139 mg per deciliter by 32 percent and maintained mean levels of 97 to 98 mg per deciliter throughout the five-year follow-up. During follow-up, the LDL level was 28 percent lower in the pravastatin group than in the placebo group, the total cholesterol level was 20 percent lower, the HDL level was 5 percent higher, and the triglyceride level was 14 percent lower ($P<0.001$ for all comparisons).

Patients treated with pravastatin had a 24 percent lower incidence of the primary endpoint, fatal coronary heart disease or confirmed myocardial infarction, than patients in the placebo group (95 percent confidence interval, 9 to 36 percent; $P = 0.003$).

Figure 6: The incidence of fatal coronary disease or non-fatal MI was significantly greater in the pravachol group when compared to the placebo group (P=0.003).

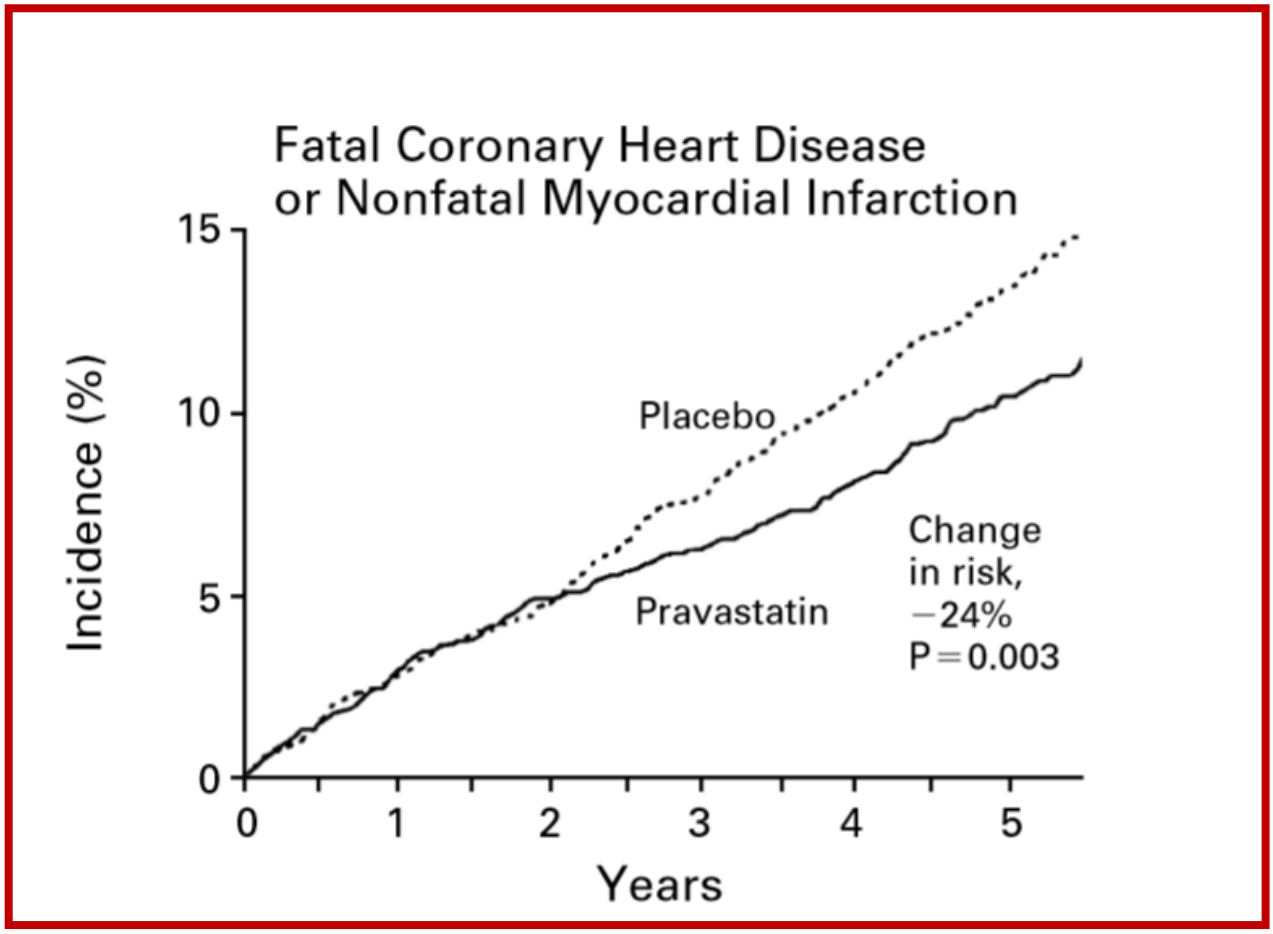

Figure 6

Figure 7: The incidence of coronary bypass surgery or angioplasty was significantly greater in the pravachol group when compared to the placebo group (P <0.001).

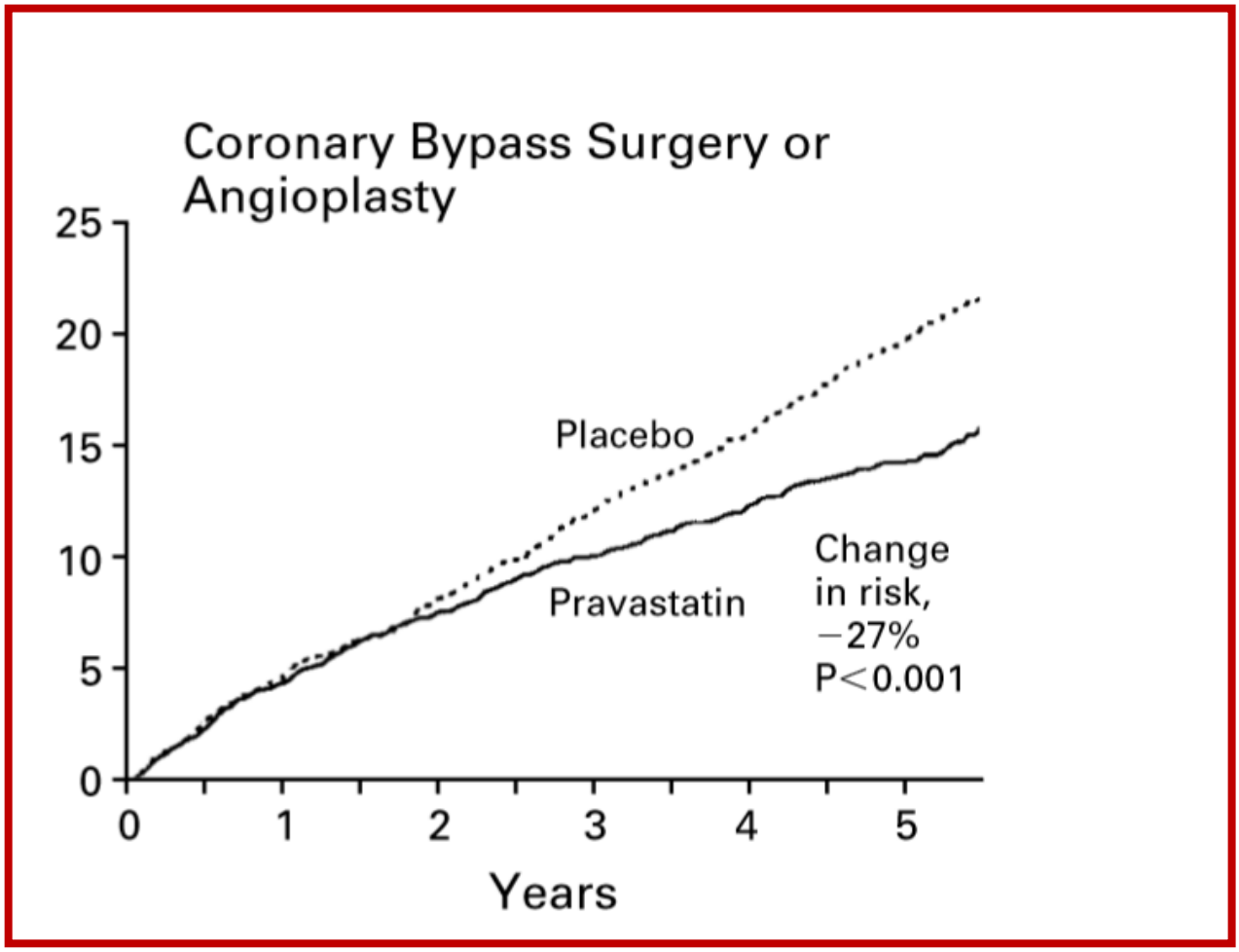

Figure 7

Figure 8: Incidence of % reductions in LDL over 5 years in patients with LDL levels of > 150 mg % (P=0.008)

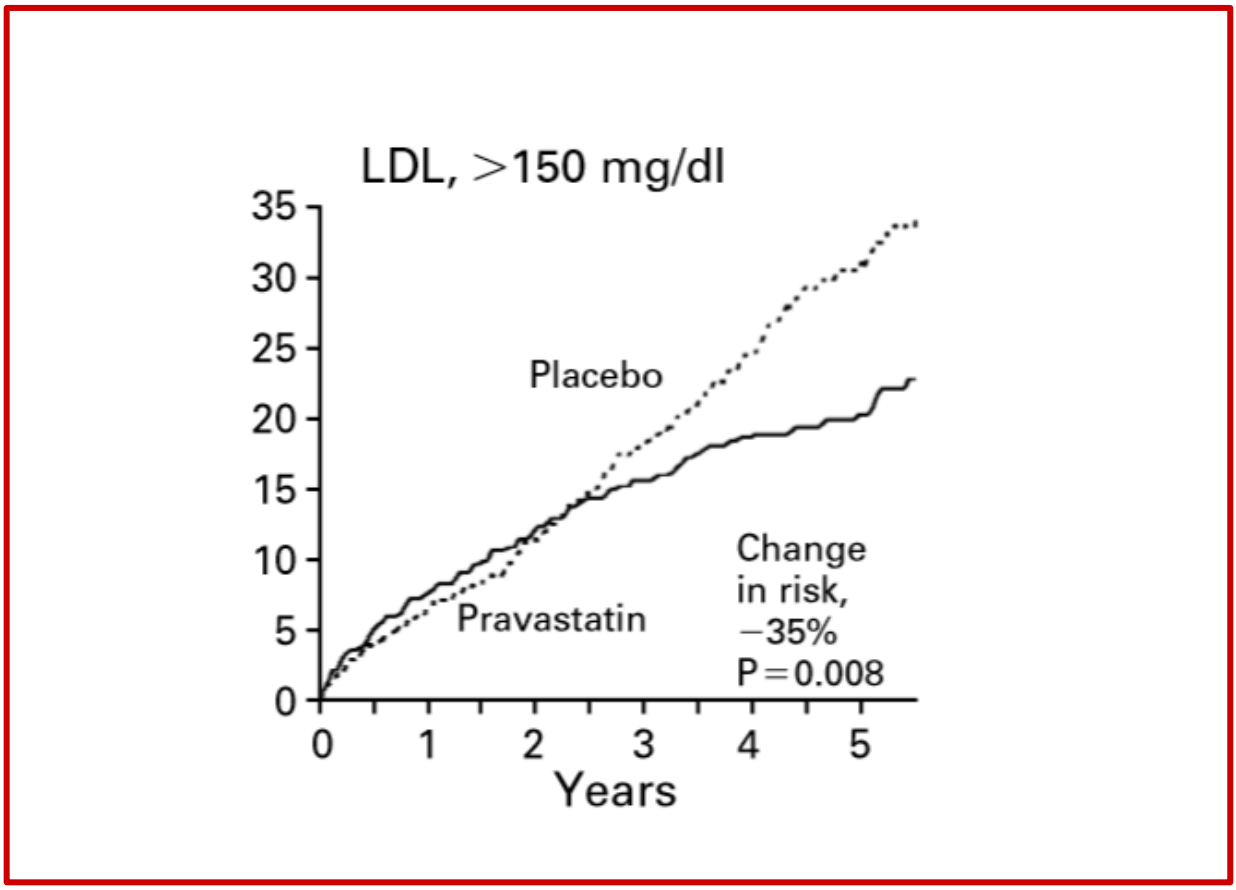

Figure 8

The reduction in the rate of coronary events with pravastatin was influenced by the pretreatment level of LDL. The patients with baseline LDL levels above 150 mg per deciliter (n = 953) had a 35 percent reduction in major coronary events, as compared with a 26 percent reduction in those with baseline levels of 125 to 150 mg per deciliter (n = 2355) and a 3 percent increase in those with baseline levels below 125 mg per deciliter (n = 851)

In patients with baseline LDL levels below the median, the following trend was observed: the lower the baseline value, the smaller the reduction in the risk. The rate of major coronary events was 23 percent lower in the pravastatin group than in the placebo group for patients with baseline LDL levels below the median (median, 137.5 mg per deciliter, but only 15 percent lower in patients with values in the lowest third (no more than 130 mg per deciliter, 10 percent lower in

the lowest quartile (less than 127 mg per deciliter, and 3 percent higher in the lowest quintile (less than 125 mg per deciliter).

These results also suggest that the pretreatment LDL level, at least within the CARE trial's eligibility range of 115 to 174 mg per deciliter, has an influence on the success of cholesterol-lowering therapy in preventing coronary events. In the upper part of the range, >150 to 175 mg per deciliter, the reduction in risk (35 percent) was similar to that achieved with reductase inhibitors in patients with hypercholesterolemia.

In the middle of the range, 125 to 150 mg per deciliter, the risk reduction remained substantial (26 percent); this range is at the center of the distribution of LDL values in contemporary populations with coronary heart disease.

In summary, stroke, a specified endpoint in the CARE trial, was reduced significantly (by 31 percent) in the pravastatin group. A reduction in cerebrovascular end points was found in post hoc analyses.

3. The SPARCL Trial (The Stroke Prevention by Aggressive Reduction in Cholesterol Levels)

This trial randomly assigned 4731 patients who had had a stroke or Transient Ischemic Attack (TIA) within one to six months before study entry, had LDL levels of 100 to 190 mg per deciliter, and had no known coronary heart disease to double-blind treatment with 80 mg of atorvastatin per day or placebo. The primary endpoint was a first nonfatal or fatal stroke.

Figure 9 shows a significant reduction in the incidence in the percent fatal or non-fatal stroke, with a nice separation between the placebo and the atorvastatin group, with p=0.03.

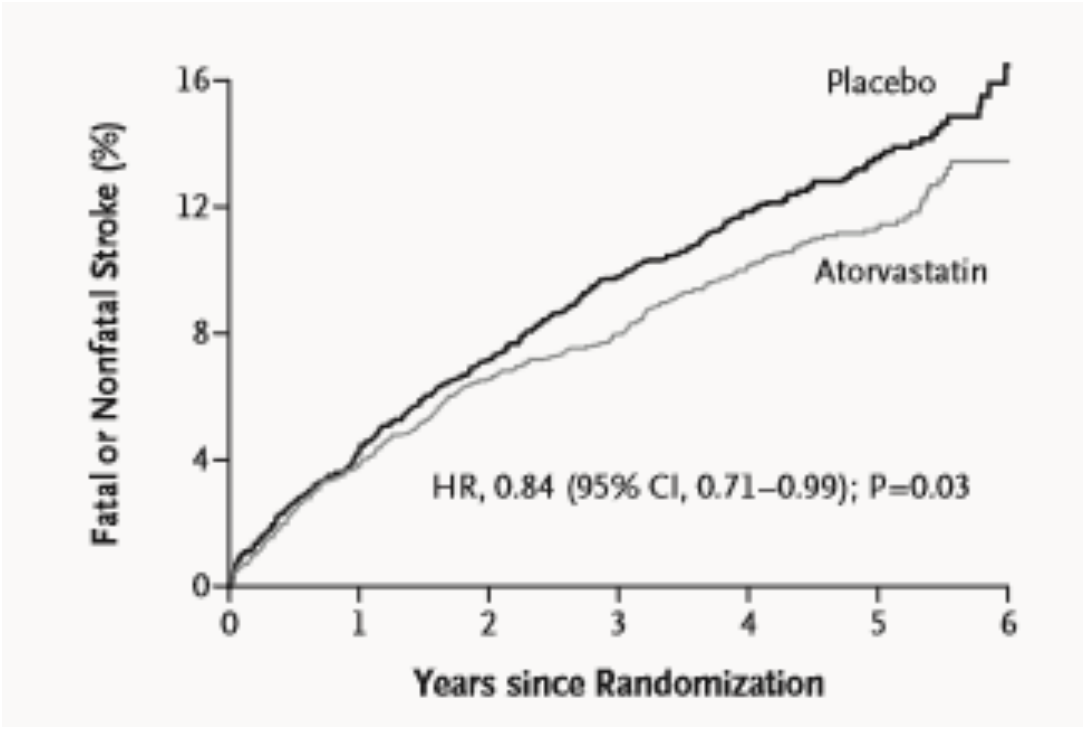

Figure 9

Figure 10 shows a significant reduction in the incidence in the percent fatal stroke, with a nice separation between the placebo and the atorvastatin group, with p=0.03.

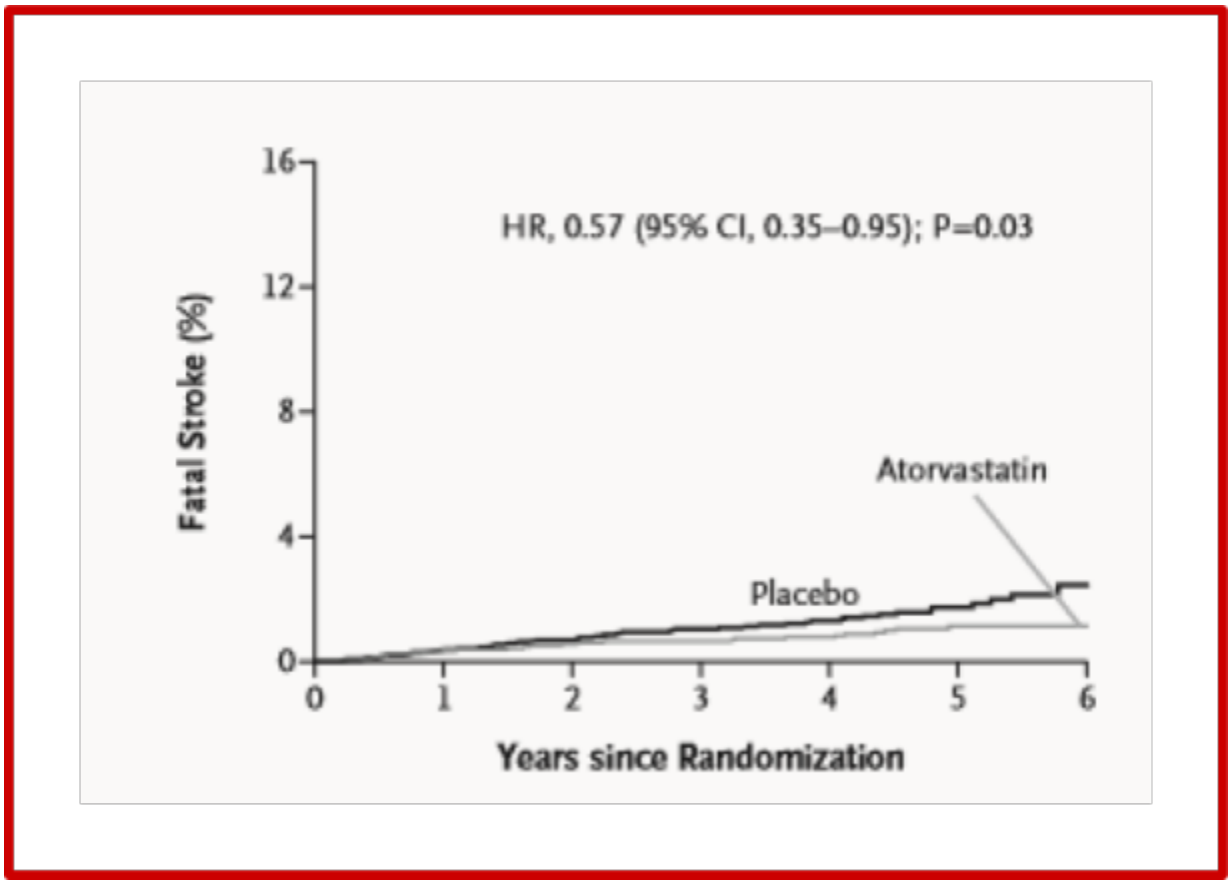

Figure 10

Figure 11 shows a reduction in the incidence in the percent non-fatal stroke, with a poor separation between the placebo and the atorvastatin group, with p=0.11.

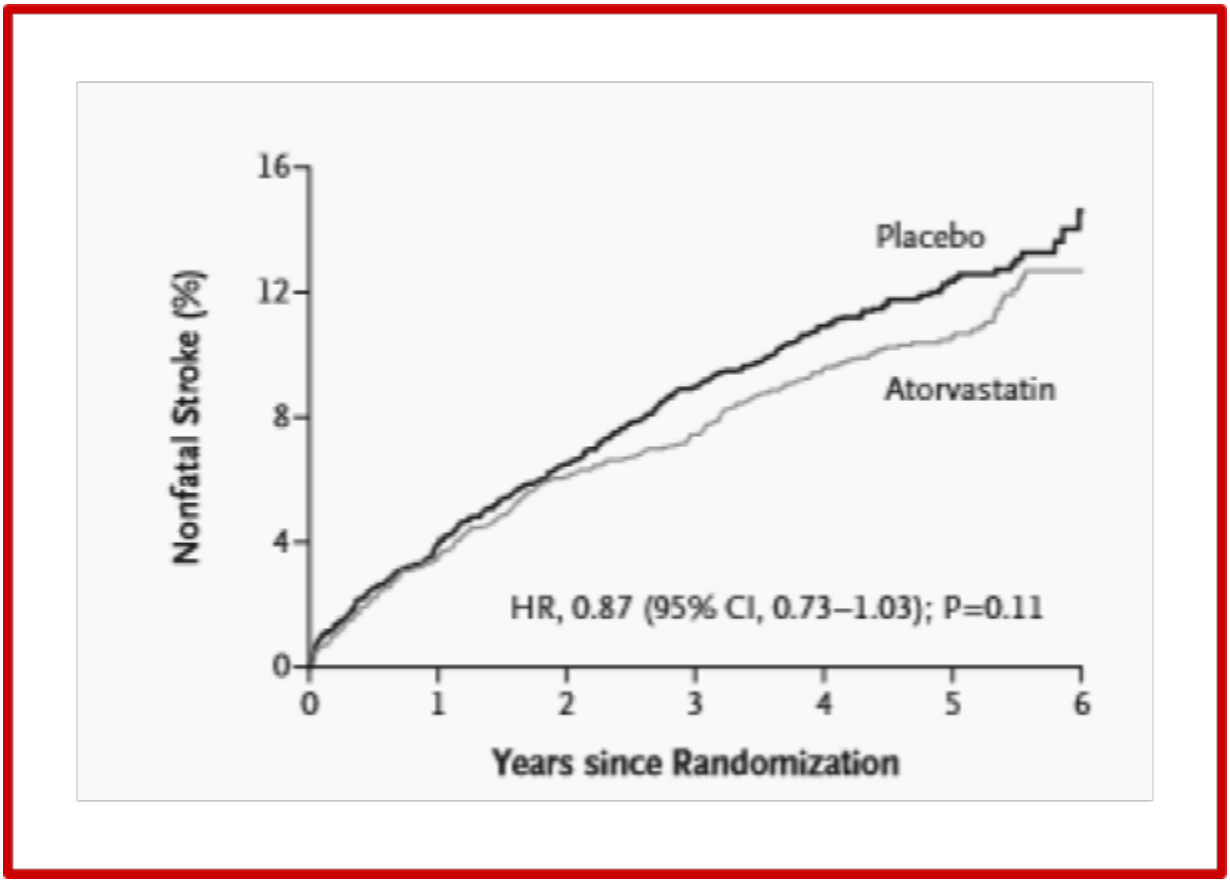
16
12
8
4
0
Nonfatal Stroke (%)
Placebo
Atorvastatin
HR, 0.87 (95% CI, 0.73–1.03); P=0.11
0
1
2
3
4
5
6
Years since Randomization

Figure 11

Figure 12 shows a significant reduction in the incidence in the percent stroke or TIA, with a nice separation between the placebo and the atorvastatin group, with p=0.001.

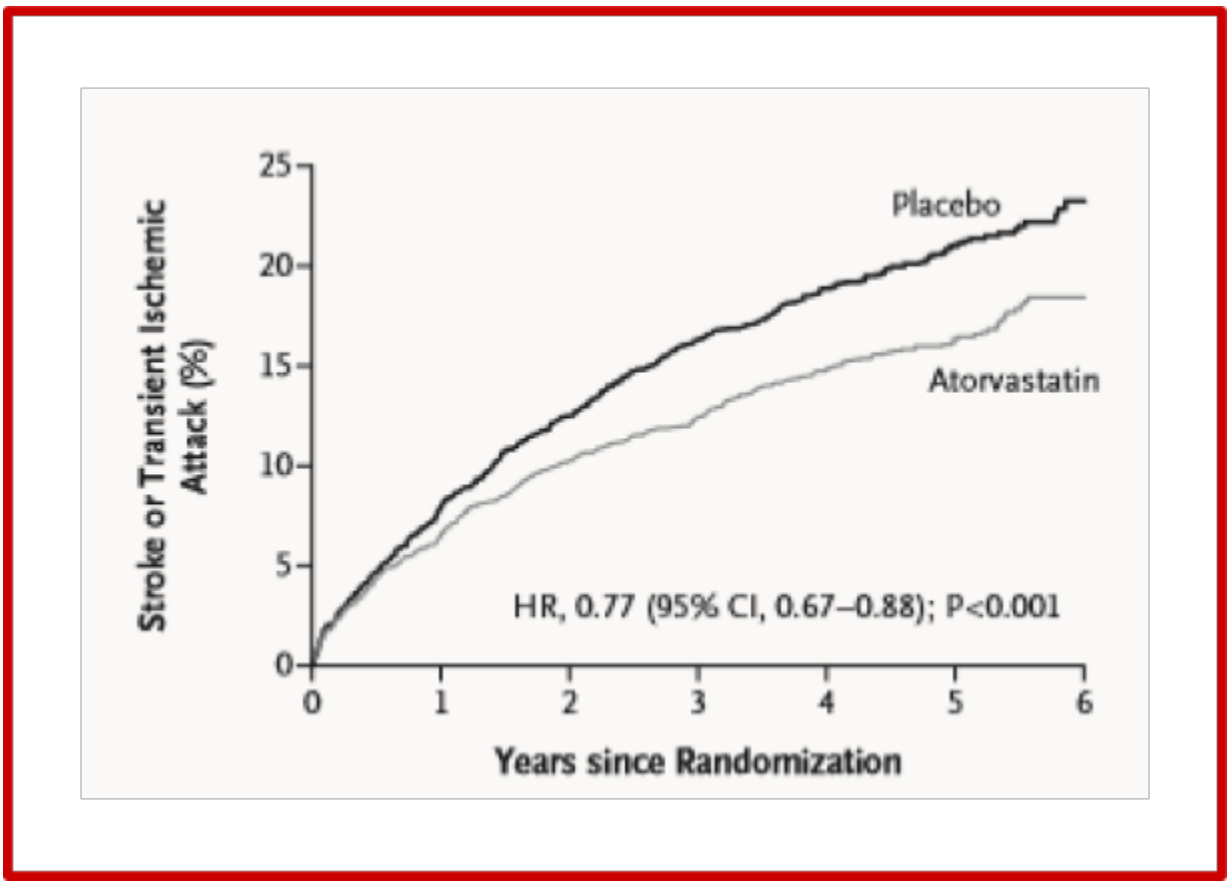

Figure 12

In summary, in patients with recent stroke or TIA and without known coronary heart disease, 80 mg of atorvastatin per day reduced the overall incidence of strokes and of cardiovascular events, despite a small increase in the incidence of hemorrhagic stroke.

In conclusion the results from the JUPITER Trial, the CARE Trial and the SPARCL Trial, conducted with different statins, indicate that the administration of statins clearly results in statistically significant reduction of the incidence of major cardiovascular events and coronary events. In patients with recent stroke or TIA without known coronary heart disease, there is a significant decrease in the overall incidence of strokes and of cardiovascular events with the use of statins.

Should statins be used for everyone?

This is a question that only a treating physician could respond to. No chemical is safe, every medication has some side effects. So are statins, with several, in some cases, serious side effects.

In general, a comment can be made by the authors that the use of statins in patients who are felt to benefit from their use represent a good return on investment and have a good risk to benefit ratio.

Summary and conclusions

The 3 trials cited here (The JUPITER Trial, The CARE Trial, and The SPARCL Trial) were very large multicenter trials, and indicated that statins are distinctly beneficial in the management of thrombosis by reducing inflammation, and therefore the incidence of development of thrombosis in MI, and stroke.

Acknowledgments

The authors we wish to acknowledge Rashmi Kulkarni, MD, for her expert critic and input in the preparation of this article.

One of the GTF members, Ms. Aryana Gavankar, conducted research on the topic of Statins and VTE, and published her preliminary research findings in e-thrombosis (https://natfonline.org/?s=aryana).
The current article is an extension of Aryana's research in going into a greater depth on statins and thrombosis. We acknowledge Aryana's contribution.

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