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Scientific Update™

# Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA): The Role of Statins in Patients with Heart Failure and Systolic Dysfunction

*Originally presented by:* Åke Hjalmarson, MD

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**The role of statins in the management of patients with coronary artery disease and those at risk for cardiovascular events is well established. Patients with symptomatic heart failure, however, have been excluded from past placebo-controlled trials with statins and, therefore, the benefits and risks of statins in the treatment of heart failure remain controversial. The Swedish-based Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA) was designed to clarify the role of statin therapy in treating patients with heart failure with systolic dysfunction. This issue of *Cardiology Scientific Update* reviews the late-breaking results of CORONA, as well as their implications on the efficacy and safety of statins in the broad patient population.**

The benefits of statins are well established in a variety of patient groups.[1-8] Patients with heart failure (HF) have been excluded from past large-scale statin trials. Since a high proportion of patients with HF associated with left ventricular (LV) systolic dysfunction have coronary heart disease (CHD), the statins might be expected to provide benefits in these patients. Indeed, post-hoc subgroup analyses of randomized controlled trials (RCTs) and observational studies suggest that the statins may have beneficial effects in HF.[9,10] However, the benefits of statin therapy in large RCTs are largely due to the prevention of myocardial infarction (MI) since the reported rate of coronary events has been low in this patient population.[11,12] Furthermore, statins could have the potential to be harmful in HF.[12,13] No study thus far has provided definitive outcome data for the use of statins in patients with HF.

## The CORONA trial

CORONA was a multicentre, randomized, placebo-controlled study designed to clarify the role of statin therapy in treating patients with HF and systolic dysfunction.[14] The primary objective of CORONA was to determine whether rosuvastatin, when added to other medications prescribed for patients with HF, reduced the risk of the combined endpoint of death from a cardiovascular (CV) cause, nonfatal MI, or nonfatal stroke.

Details of the rationale and methodology of the study have been previously published.[15] Briefly, patients aged ≥60 years with symptomatic (New York Heart Association [NYHA] functional class II–IV) systolic HF of ischemic etiology and with an ejection fraction of ≤40% (≤35% if NYHA class II) were eligible. Subjects already on a statin (or another lipid-lowering drug) or considered by their own doctor to need (or have a contraindication to) a statin were excluded. The study design is illustrated in Figure 1. Patients who fulfilled the enrolment criteria at visit 2 received single-blind treatment with placebo once daily for 2 to 4 weeks. Thereafter, patients who fulfilled the inclusion and exclusion criteria were randomly allocated to rosuvastatin (10 mg) or matching placebo in a ratio of 1:1. The sample size was estimated in order to provide the number of events (based upon

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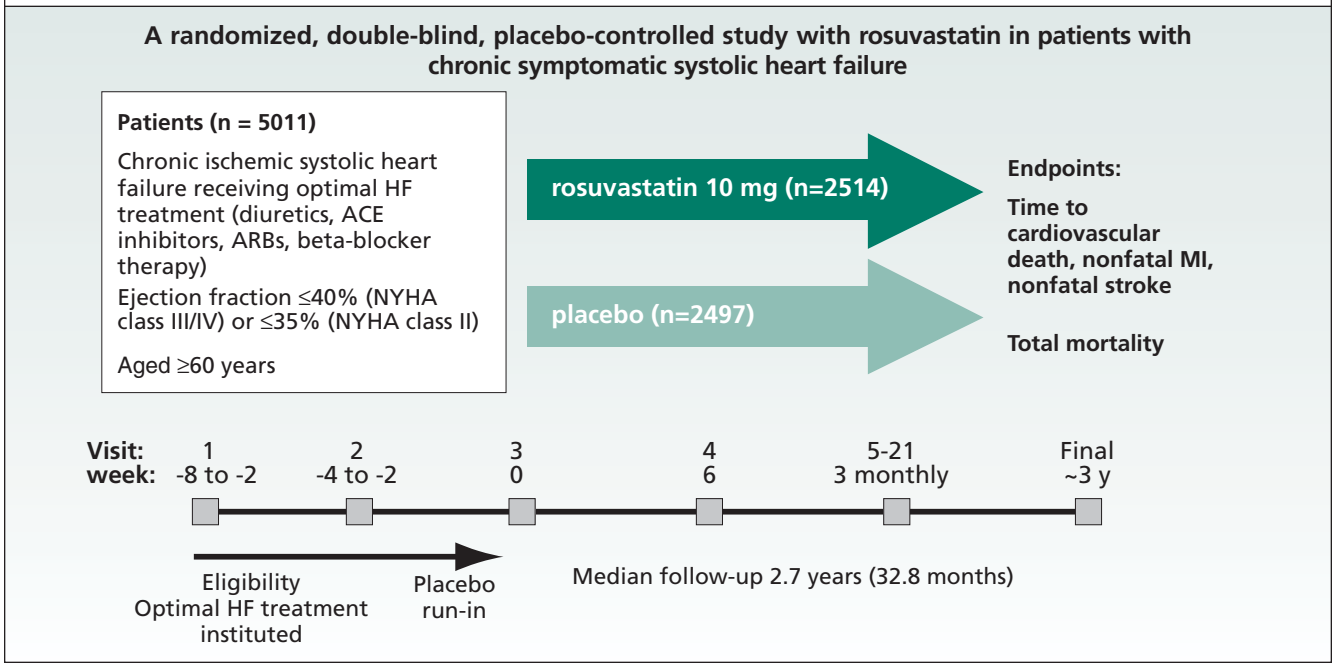
**Figure 1: CORONA – Study design**




ACE = angiotensin-converting enzyme; ARB = angiotensin-receptor blocker; NYHA = New York Heart Association

the combined primary endpoint of CV death, nonfatal MI, or stroke) needed to give power of at least 90% (p=0.10) to detect a significant difference between the treatment arms. The difference was tested using a two-sided significance level of 5% ($\alpha$ = 0.05), allowing for the alpha spent in 3 interim analyses before the final analysis.

A mean risk-reducing effect of rosuvastatin on the primary endpoint of 16.1% was assumed in the intention-to-treat population (taking into account withdrawals from randomized treatment). Based on assumptions of a 16-month recruitment period and 35 months of continued follow-up (a total study time of 51 months), it was estimated that 1,422 patients with the primary endpoint recruited from 4,950 subjects needed to be randomized. The primary outcome was the composite of death from CV causes, nonfatal MI, and nonfatal stroke. The secondary outcomes included death from any cause, any coronary event (defined as sudden death, fatal or nonfatal MI, percutaneous or surgical revascularization, ventricular defibrillation by an implantable cardioverter-defibrillator, resuscitation after cardiac arrest, or hospitalization for unstable angina), death from CV causes, and the number of hospitalizations for CV causes, unstable angina, or worsening HF.

## Primary results

From September 15, 2003, to April 21, 2005, a total of 5,459 patients entered the placebo run-in period, and 5,011 patients subsequently underwent randomization at 371 sites in 19 European countries, Russia, and South Africa. Of those patients, 2,514 were assigned to receive rosuvastatin and 2,497 to receive placebo. The median follow-up time was 32.8 months. Selected baseline characteristics are shown in Table 1. The two groups had similar characteristics at study entry. Patients had a mean age of 73 years, and 41% were at least 75 years old. There was a high prevalence of a history of hypertension, diabetes mellitus, and chronic kidney disease, and patients had been well-treated for HF.

As compared with the placebo group, patients in the rosuvastatin group had:

- decreased levels of low-density lipoprotein cholesterol (LDL-C); difference between groups, 45.0%, P<0.001;
- decreased high-sensitivity C-reactive protein (hsCRP); difference between groups, 37.1%, P<0.001;
- increased high-density lipoprotein cholesterol (HDL-C); difference, 5%, P<0.001).

The primary composite outcome occurred in 692 patients in the rosuvastatin group (11.4 per 100 patient-years of follow-up) and in 732 patients in the placebo group (12.3 per 100 patient-years of follow-up), with a hazard ratio (HR) in the rosuvastatin group of 0.92 (95% confidence interval [CI], 0.83 to 1.02; P=0.12); (Figure 2). Results of treatment on components of the composite primary endpoint are shown in Table 2. In addition, there were 728 deaths (11.6 per 100 patient-years) in the rosuvastatin group and 759 deaths (12.2

**Table 1: CORONA – Baseline characteristics**

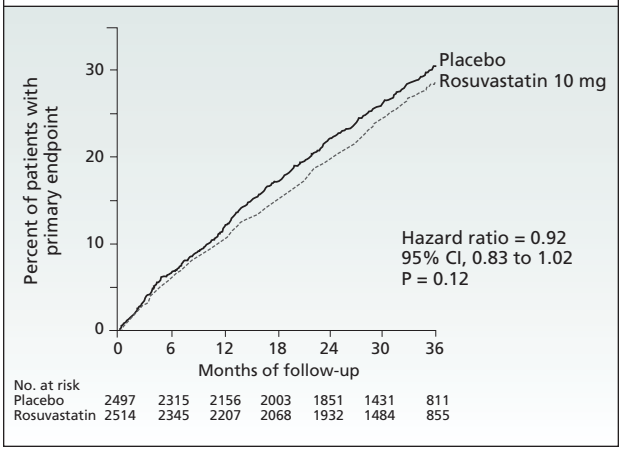
| Variable | Placebo (n=2497) | Rosuvastatin (n=2514) | *P* value |
|---|---|---|---|
| Age | | | |
| Mean year | 73±7.0 | 73±7.1 | 0.99 |
| ≥75 yr — no. (%) | 1029 (41) | 1035 (41) | 0.98 |
| Female sex — no. (%) | 587 (24) | 593 (24) | 0.95 |
| NYHA class — no. (%) | | | 0.61 |
| II | 918 (37) | 939 (37) | |
| III | 1540 (62) | 1541 (61) | |
| IV | 39 (1.6) | 34 (1.4) | |
| Ejection fraction | 0.31±0.07 | 0.31±0.07 | 0.94 |
| Body mass index | 27±4.6 | 27±4.5 | 0.54 |
| Blood pressure — mm Hg | | | |
| Systolic | 129±17 | 129±17 | 0.52 |
| Diastolic | 76±8.9 | 76±8.8 | 0.12 |
| Heart rate — beats/min | 72±11 | 72±11 | 0.61 |
| Current smoker — no. (%) | 206 (8) | 224 (9) | 0.41 |
| Medical history — no. (%) | | | |
| Myocardial infarction | 1494 (60) | 1510 (60) | 0.87 |
| Past or current angina pectoris | 1807 (72) | 1831 (73) | 0.71 |
| CABG or PCI | 638 (26) | 660 (26) | 0.57 |
| Hypertension | 1581 (63) | 1594 (63) | 0.95 |
| Diabetes mellitus | 734 (29) | 743 (30) | 0.90 |
| Atrial fibrillation or flutter on ECG | 585 (23) | 609 (24) | 0.51 |
| Stroke | 309 (12) | 315 (13) | 0.87 |
| Pacemaker | 299 (12) | 262 (10) | 0.08 |
| Implantable cardioverter–defibrillator | 64 (2.6) | 72 (2.9) | 0.51 |

CABG = coronary artery by pass graft;
PCI = percutaneous coronary intervention

per 100 patient-years) in the placebo group, with an HR of 0.95 in the rosuvastatin group (95% CI, 0.86 to 1.05; P=0.31). A coronary event occurred in 554 patients in the rosuvastatin group (9.3 per 100 patient-years) and in 588 patients in the placebo group (10.0 per 100 patient-years). This resulted in an HR in the rosuvastatin group of 0.92 (95% CI, 0.82 to 1.04; P=0.18). Results for the total number of hospitalizations, a secondary endpoint, are shown in Figure 3. There were significantly fewer hospitalizations for patients on rosuvastatin compared to those on placebo, whether due to any cause (p=0.007), CV causes (p<0.001), or for worsening HF (P=0.01). There was no difference in the number of hospitalizations for unstable angina or for non-CV causes.

Tolerability and safety data are shown in Table 3. Although the CORONA study population was an elderly HF population with renal impairment, rosuvastatin was well-tolerated. The number of patients who discontinued the study drug was significantly lower in the rosuvastatin group than in the placebo group (P=0.03), with significantly fewer

**Figure 2: CORONA – Primary endpoint**




study drug discontinuations due to adverse events in the rosuvastatin group than in the placebo group (P=0.004).

## Discussion and clinical implications

In the CORONA trial, rosuvastatin 10 mg daily reduced LDL-C by 44% and hsCRP by 32%. These parameters directly and independently correlate with CV risk and decreases of this magnitude have been associated with significant reductions in CV events in other studies. Nevertheless, the composite primary outcome of non-fatal MI, nonfatal stroke, or death from CV causes was not decreased significantly (HR=0.92, 95% CI, 0.83 to 1.02, p=0.12) in this trial, in which the statin was added to extensive background medications used to treat moderate-to-severe systolic HF.

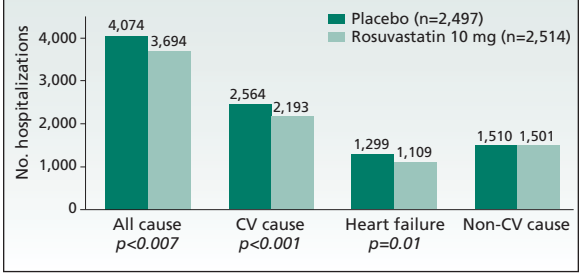
**Table 2: Components of primary endpoint**

Number of patients suffering any of the components of the primary endpoint

| | Placebo [n=2497] n (rate)[1] | Rosuvastatin [n=2514] n (rate)[1] | HR | 95% CI | *p* value |
|---|---|---|---|---|---|
| **Primary endpoint** *(CV death, nonfatal MI, nonfatal stroke)* | **732** (12.3) | **692** (11.4) | **0.92** | 0.83-1.02 | **0.12** |
| **CV deaths** | **487** | **488** | | | |
| Sudden death | 284 | 284 | | | |
| Worsening HF | 157 | 161 | | | |
| MI | 8 | 9 | | | |
| Stroke | 11 | 14 | | | |
| Pulmonary embolism | 7 | 1 | | | |
| Acute aneurysm | 5 | 0 | | | |
| Other | 15 | 19 | | | |
| **Nonfatal MI** | **141** | **115** | | | |
| **Nonfatal stroke** | **104** | **89** | | | |

[1] Events per 100 patient-years of follow-up
HR = Hazard Ratio; CI = Confidence interval; MI = Myocardial infarction

**Figure 3: Secondary endpoints – total number of hospitalizations[14]**




The CORONA trial evaluated a population that had not been previously studied in any of the major statin trials since it enroled an older and more severely-ill population, with a condition that has a particularly poor prognosis (eg, moderate-to-severe ischemic systolic HF). This fact needs to be emphasized as it is the most plausible explanation for the results of the trial. In fact, this was the sickest population ever studied in a major statin trial. In general, the mortality seen in patients with moderate-to-severe systolic HF is approximately 10% per year, which is 3 to 5 times higher than that observed in previous statin studies not focused on HF patients, in which MI, unstable angina, and coronary revascularization are the most common endpoints. In contrast, in HF, the majority of the events would be expected to be worsening HF and sudden cardiac death, as was seen in the CORONA trial.

Furthermore, overall risk was also enhanced by the fact that the mean age of the patients was 73 years and they were at least 60 years of age, which is significantly older than in most of the previous trials of statins in secondary prevention and much older than in the primary prevention trials.

Nevertheless, despite the fact that this was an older and sicker population with renal impairment and muscle fatigue, it was very encouraging to see that rosuvastatin was associated with an excellent safety profile and that the number of adverse events in patients receiving this medication was not higher than in placebo-treated patients. Additionally, despite the fact that the primary endpoint was not significantly reduced, there were consistently fewer primary events with rosuvastatin in most of the high-risk subgroups analyzed. In fact, the CIs around the primary endpoint (0.83 to 1.02) were consistent with a relative risk reduction of as much as 17% in the endpoints of nonfatal MI, nonfatal stroke, or CV death, which would amount to a nearly 2% absolute risk reduction. An absolute benefit of this degree would be clinically significant since it would result in a number needed to treat of 50 patients, which would be quite acceptable in this population.

**Table 3: Tolerability and safety data**

| | Placebo [n=2497] no. of pts | Rosuvastatin [n=2514] no. of pts |
|---|---|---|
| **Discontinuation of study drug[1]** | 546 | 490 |
| Adverse event[2] | 302 | 241 |
| Patient unwilling to continue | 162 | 187 |
| Other reason | 82 | 62 |

[1] Hazard ratio 0.88; (95% CI, 0.78 to 0.99; p=0.03)
[2] Hazard ratio 0.78; (95% CI, 0.66 to 0.92; p=0.004)

## Comparing PROSPER and CORONA

Comparing the results of the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) provides a helpful perspective on the CORONA study.[8] PROSPER was a statin trial that enrolled patients who were similar to those in CORONA in several respects. The mean age in PROSPER was 75 years (compared to 73 years in CORONA) and the mean follow-up was 38 months (compared to 32.8 months in CORONA). PROSPER enrolled 5,804 patients with a history of, or risk factors for, vascular disease who were randomized to pravastatin 40 mg or placebo. The primary endpoint was a composite of coronary death, nonfatal MI, and fatal or nonfatal stroke. Pravastatin lowered LDL-C levels by 34% and significantly reduced the incidence of the primary endpoint (HR=0.85). CHD death and nonfatal MI risk were also significantly reduced (HR=0.81). The absolute risk reduction was similar to the 2% absolute risk reduction seen in CORONA (27.5% of the patients randomized to rosuvastatin had a primary event compared to 29.3% of the patients randomized to placebo).

A comparison of CORONA with PROSPER is also helpful because of the differences between the populations studied in the 2 trials. This is particularly relevant because of differences in the distribution of the outcomes. For instance, the rate of nonfatal MI in the CORONA study was approximately one-quarter that reported in PROSPER. Therefore, although patients with moderate-to-severe ischemic systolic HF have high rates of adverse outcomes, it is possible that their risk of ischemic CV events – the outcome most likely to be prevented by the statins – are less frequent than in other patients with CHD. In fact, nonfatal stroke was also relatively uncommon in the CORONA population.

## The results of CORONA

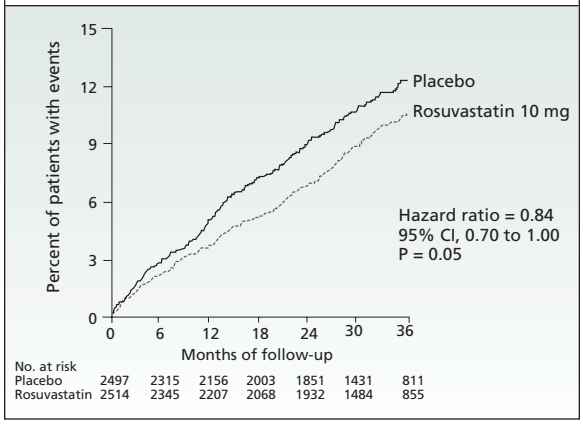
In the CORONA study, death from CV causes accounted for the majority of the primary events and

sudden death was responsible for the majority of these deaths. Rosuvastatin had no effect on the rate of death from CV causes or on sudden death and it is likely that many of these events were primarily arrhythmic, as would be expected in a population with severe LV dysfunction and a mean ejection fraction of only 31%.

In previous statin trials, the rate of sudden death was probably reduced by preventing the rupture of vulnerable coronary plaques, myocardial ischemia, and infarction.[5,16] In HF, sudden death is more likely to be caused (as mentioned) by a primary electrical event related to LV dilatation. Additionally, patients in both arms of the trial were treated equally aggressively with drugs known to reduce the risk of sudden death, such as angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, and aldosterone antagonists; however, the statins would not be expected to have an effect on primarily electrical events. As well, another major mode of death in patients with advanced systolic HF is death from the progression of HF; statins would not be expected to decrease this progression and, in fact, it has actually been speculated that statins have the potential to worsen HF. This topic and how this speculation has been put to rest by the CORONA trial, will be discussed in a subsequent section.

Interestingly, and most importantly, a post hoc analysis of CORONA evaluated the rate of nonfatal or fatal MI or stroke – events more clearly identifiable with an ischemic etiology – and found a significant reduction in these outcomes which occurred in 9% of the patients on rosuvastatin and in 10.6% of the patients randomized to placebo (16% relative risk reduction, p=0.05) (Figure 4). In other words, rosuvastatin prevented events that a statin would be expected to prevent and it may have been somewhat unrealistic, in hindsight, to expect that it would also prevent events related to terminal arrhythmias or progressive pump failure. Consequently, and despite the fact that the other major trials did not focus on HF patients, there is enough favourable information from the previous trials and from CORONA to justify the continued use of statins in patients who have HF of an ischemic etiology.

**Figure 4: CORONA – Post-hoc analysis of the number fatal/nonfatal MI or stroke in the primary endpoint*[14]**




* Data on file

It is also encouraging to note that a subgroup analysis suggested preferential statin benefits in patients who were younger, had less severe HF, and were in better general health. This is compatible with the hypothesis that giving statins earlier in the natural history of ischemic HF may result in greater benefit.

Additionally, treatment with rosuvastatin resulted in a decrease in the pre-specified secondary endpoint of total number of hospitalizations for HF, possibly because it prevented the occurrence of some acute coronary episodes that could have contributed to an exacerbation of HF. Another possibility is that rosuvastatin reduced myocardial ischemia by ameliorating endothelial or microvascular dysfunction or by an effect on the cardiac myocytes through some of the pleiotropic effects of the statins.[11,12,17] Irrespective of the mechanism, the most important implication of this result is that it refutes previous speculation that statins may worsen HF by possibly reducing the synthesis of coenzyme Q10, a cofactor in the mitochondrial-electron transport chain, and the production of selenoproteins. These proteins are involved in redox regulation of intracellular signaling and redox homeostasis and are connected with a protective activity against free radicals, among other functions.[13,18,19] These findings also suggest that the hypothetical detrimental effects of statins on skeletal and cardiac muscle function do not have clinical consequences in most patients.

Since HF is a chronic condition, patients may require multiple hospitalizations during its course to treat its decompensated states, which translates into a significant cost to the healthcare system. Therefore, a reduction in the number of hospitalizations for HF is broadly considered to be an important endpoint from a health economics perspective.

Other important findings with respect to the safety of rosuvastatin in this extremely-ill population deserve to be emphasized. There was no significant excess in the number of muscle-related symptoms or increased levels of creatine kinase in patients receiving rosuvastatin. As well, there were no more instances of significant elevations in hepatic aminotransferase levels or worsening of renal function in the patients receiving rosuvastatin compared to the group randomized to placebo. In fact, there were fewer treatment discontinuations and fewer deaths from non-CV causes in the rosuvastatin group, a reassuring finding, even if the clinical significance is uncertain.

The CORONA trial did not investigate 2 other important groups of patients with HF, namely patients with non-ischemic HF and those with preserved ejection fraction. Patients from those 2 groups are being investigated in the *Gruppo Italiano per lo Studio della Sopravivenza nell'infarto Miocardico Trial* (GISSI) Heart Failure Trial, which is comparing rosuvastatin with placebo and n-3 polyunsaturated fatty acids with placebo in 6,975 patients, of whom 4,574 have been enrolled in the rosuvastatin arm of the trial.[20] This study is expected to be completed in 2008.

## Conclusion

The CORONA trial demonstrated that treatment with rosuvastatin (10 mg daily) did not reduce the composite outcome of death from CV causes or nonfatal MI or stroke in very ill, elderly patients with ischemic systolic HF who were being extensively treated with other CV medications. However, rosuvastatin treatment resulted in a significant reduction in the secondary endpoint of hospitalization due to CV causes. Additionally, there were signals of preferential benefit in younger patients with less severe HF. Furthermore, a post-hoc analysis focusing on the definite ischemic endpoints of nonfatal or fatal MI or stroke demonstrated a significant 16% relative risk reduction in these endpoints with rosuvastatin treatment.

**References**


1. Randomized trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994;344:1383-1389.
2. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomized placebo-controlled trial. *Lancet* 2002;360:7-22.
3. Colhoun HM, Betteridge DJ, Durrington PN, et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomized placebo-controlled trial. *Lancet* 2004;364:685-696.
4. Pedersen TR, Faergeman O, Kastelein JJP, et al for the Incremental Decrease in End Points Through Aggressive Lipid Lowering (IDEAL) Study Group. High-Dose Atorvastatin vs Usual-Dose Simvastatin for Secondary Prevention After Myocardial Infarction: The IDEAL Study: A Randomized Controlled Trial. *JAMA* 2005;294:2437-2445.
5. Sacks FM, Pfeffer MA, Moye LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. *N Engl J Med* 1996;335:1001-1009.
6. Sever PS, Dahlof B, Poulter NR, et al. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA): a multicentre randomized controlled trial. *Lancet* 2003;361:1149-1158.
7. Shepherd J, Cobbe SM, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. *N Engl J Med* 1995;333:1301-1307.
8. Shepherd J, Blauw GJ, Murphy MB, et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomized controlled trial. *Lancet* 2002;360:1623-1630.
9. Kjekshus J, Pedersen TR, Olsson AG, Faergeman O, Pyorala K. The effects of simvastatin on the incidence of heart failure in patients with coronary heart disease. *J Card Fail* 1997;3:249-254.
10. Go AS, Lee WY, Yang J, Lo JC, Gurwitz JH. Statin therapy and risks for death and hospitalization in chronic heart failure. *JAMA* 2006;296:2105-2111.
11. Bohm M, Hjalmarson A, Kjekshus J, Laufs U, McMurray J, van Veldhuisen DJ. Heart failure and statins--why do we need a clinical trial? *Z Kardiol* 2005;94:223-230.
12. Krum H, McMurray JJ. Statins and chronic heart failure: do we need a large-scale outcome trial? *J Am Coll Cardiol* 2002;39:1567-1573.
13. Marcoff L, Thompson PD. The role of coenzyme Q10 in statin-associated myopathy: a systematic review. *J Am Coll Cardiol* 2007;49:2231-2237.
14. Kjekshus J, Apetrei E, Barrios V, et al. Rosuvastatin in older patients with systolic heart failure. *N Engl J Med* 2007;357:1304-1316.
15. Kjekshus J, Dunselman P, Blideskog M, et al. A statin in the treatment of heart failure? Controlled rosuvastatin multinational study in heart failure (CORONA): study design and baseline characteristics. *Eur J Heart Fail* 2005;7:1059-1069.
16. Pedersen TR, Kjekshus J, Berg K, et al. Randomized trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S)1994. *Atheroscler Suppl* 2004;5:81-87.
17. Cleland JG, Loh H, Windram J et al. Threats, opportunities, and statins in the modern management of heart failure. *Eur Heart J* 2006;27:641-643.
18. Moosmann B, Behl C. Selenoproteins, cholesterol-lowering drugs, and the consequences: revisiting of the mevalonate pathway. *Trends Cardiovasc Med* 2004;14:273-281.
19. Moosmann B, Behl C. Selenoprotein synthesis and side-effects of statins. *Lancet* 2004;363:892-894.
20. Tavazzi L, Tognoni G, Franzosi MG, et al. Rationale and design of the GISSI heart failure trial: a large trial to assess the effects of n-3 polyunsaturated fatty acids and rosuvastatin in symptomatic congestive heart failure. *Eur J Heart Fail* 2004;6:635-641.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