International Journal of Cardiology 194 (2015) 23–27

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Letter to the Editor

Lower cardiovascular mortality with atorvastatin and rosuvastatin vs simvastatin: Data from "moderate-intensity" statin users in an observational registry on chronic heart failure (Daunia Heart Failure Registry)

Natale Daniele Brunetti [a,*], Michele Correale [a], Antonio Totaro [a], Armando Ferraretti [a], Ilenia Monaco [a], Tommaso Passero [a], Luisa De Gennaro [a,b], Matteo Di Biase [a]

[a] Cardiology Department, University of Foggia, Foggia, Italy
[b] Department of Cardiology, Ospedale San Paolo, Bari, Italy

ARTICLE INFO

Article history:
Received 11 April 2015
Accepted 7 May 2015
Available online 9 May 2015

Keywords:
Statins
Chronic heart failure
Moderate-intensity
Atorvastatin
Rosuvastatin
Simvastatin

The efficacy of statins in subjects with chronic heart failure (CHF) is still controversial. Despite encouraging findings from observational studies, randomized trials failed to demonstrate that lipid lowering drugs such as rosuvastatin may significantly reduce outcomes and improve survival in CHF [1,2]. Nevertheless, some interesting findings showed that atorvastatin may improve left ventricular systolic function and serum markers of inflammation in nonischemic heart failure [3]. Data from meta-analyses support the hypothesis that all-cause mortality is significantly reduced with atorvastatin therapy compared with placebo in CHF patients, with similar results in cardiovascular mortality and sudden cardiac death [4].

The global framework in the statin therapy was recently changed by latest guidelines issued by the joint American Heart Association and the American College of Cardiology [5] which classified available statins on the basis of their capacity in reducing cholesterol levels [6,7] into high-, moderate- or low-intensity statins.

We therefore aimed to ascertain whether different statins within the same intensity class are associated with different outcomes in a clinical registry on CHF.

Patients with CHF from the Daunia HF Registry were enrolled in the study and underwent clinical evaluation. The Daunia HF Registry enrolls outpatients with CHF, at least one hospitalization for HF, and in stable clinical conditions [8,9] from Daunia region (South-Eastern Italy, capital city Foggia, where our University Hospital is located).

A direct clinical follow-up was performed every 6 months. Clinical follow-up was anticipated in the case of occurrence of acute HF (AHF). Medical history, heart rate, systolic blood pressure, body mass index, NYHA class, and medications were recorded. All patients underwent conventional 2D and TDI echocardiography in ambulatory setting and under resting conditions. The rate of incidence of re-hospitalization for worsening HF was also recorded: worsening HF was defined as signs and symptoms of HF requiring either hospitalization or treatment with intravenous diuretics, vasodilators or positive inotropes, mechanical fluid removal, or intra-aortic balloon pump. When direct clinical examination was not possible, direct telephonic contact was held with the patients or a next of a kin.

We therefore focused on subjects assuming statins, excluding from the analysis both those not in treatment with statins and those treated with low-intensity and high-intensity statins.

Remaining subjects were divided into 3 groups: those assuming atorvastatin, those assuming rosuvastatin, those assuming simvastatin. The incidence of cardiovascular death (CVD) was therefore recorded.

All participants gave a written informed consent. The study was approved by Local Ethics Committee and complies with Helsinki declaration.

Continuous variables were expressed as mean ± standard deviation and compared with Student's *t*-test, categorical variables as percentages and compared with χ^2 test. Trends were analyzed by χ^2 test. Logistic regression analysis was performed to calculate odds ratio (OR) with 95% confidence intervals (C.I.). Event-free survival was shown with Kaplan–Maier curves and assessed with Log-rank test as intention to treat. Univariate results were tested in a multi-variate Cox analysis for age, gender, diabetes and principal bias factors. A $p < 0.05$ was considered statistically significant.

Given a type-I error probability associated with this test of this null hypothesis of 0.05, a minimum accrual interval of 12 months, an additional follow-up after the accrual interval of 6 months and previously

* Corresponding author at: Viale Pinto n.1, 71100 Foggia, Italy.
E-mail address: natale.brunetti@unifg.it (N.D. Brunetti).

http://dx.doi.org/10.1016/j.ijcard.2015.05.041
0167-5273/

reported survival medians and hazard ratio [10], we will need to study at least 55 experimental subjects and the same number of control subjects to be able to reject the null hypothesis that the experimental and control survival curves are equal with probability (power) 80%.

661 subjects with CHF were enrolled in the Daunia HF Registry (Fig. 1); statins were used in the 62% of subjects, and moderate-intensity statins in 62% of patients assuming statins (135 atorvastatin 10–20 mg, 61 simvastatin 20–40 mg, 27 rosuvastatin 5–10 mg). Incidence of cardiovascular death was ascertained in a median 1021 (±1256 interquartile range)-day follow-up Population's characteristics are given in Table 1.

The use of either atorvastatin or rosuvastatin was associated with lower mortality rates when compared with simvastatin (4%, 4% and 15% respectively, Fig. 2, Log rank $p < 0.01$, <0.05 respectively, Fig. 3). The Cox' hazard ratio was 0.20 (95% C.I. 0.06–0.70, $p < 0.05$) for atorvastatin, 0.04 (95% C.I. 0.01–0.77, $p < 0.05$) for rosuvastatin. Results remained significant even after correction for age, gender, left ventricular ejection fraction, and coronary artery disease in multivariable Cox' analysis.

In a subgroup analysis, the use of atorvastatin vs simvastatin was associated with a lower mortality at logistic regression (OR 0.22, 95% C.I. 0.07–0.69, $p < 0.01$), even in diabetic (OR 0.08, 95% C.I. 0.01–0.68, $p < 0.05$) and hypertensive (OR 0.15, 95% C.I. 0.04–0.63, $p < 0.01$) subjects with coronary heart disease (OR 0.19, 95% C.I. 0.05–0.79, $p < 0.05$), LVEF >35% (OR 0.10, 95% C.I. 0.01–0.96, $p < 0.001$), male patients (OR 0.19, 95% C.I. 0.05–0.79, $p < 0.05$), and those older than 70 years (OR 0.07, 95% C.I. 0.01–0.58, $p < 0.05$) (Fig. 4).

Results were not statistically significant in other subgroups presumably because of small number of patients. Subgroup analysis was not possible with rosuvastatin, given the small number of subjects enrolled in the registry and treated with such statin.

To the best of our knowledge, these are among the first data from a relatively large registry reporting on clinical efficacy of different statins with the same presumed efficacy in reducing cholesterol levels, according to the recently issued AHA/ACC Guidelines on CV risk prevention. We therefore found a lower CV mortality in subjects treated with atorvastatin and rosuvastatin in comparison with those treated with simvastatin.

Such results are not unexpected. In prior studies we found that the use of atorvastatin in real world nonrandomized registry may be associated with lower rates of adverse events at follow-up [10]. Also data from small randomized studies seem to confirm such a higher efficacy in preventing CV event with atorvastatin rather than other statins; atorvastatin therapy may reduce the incidence of sudden cardiac death in patients with advanced CHF [11]. Data from meta-analysis showed a lower mortality in patients with CHF treated with atorvastatin [4]. In a recently published meta-analysis atorvastatin was significantly more effective than simvastatin for secondary prevention of major coronary events [12].

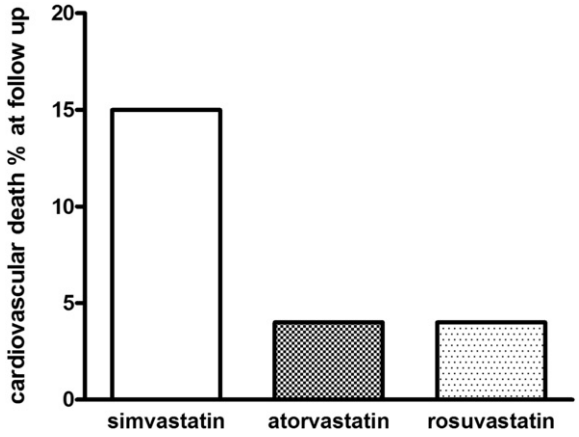

Fig. 2. Rates of incidence of cardiovascular death according to statin treatment.

Most studies aimed to compare clinical efficacy of different available statins in different clinical scenarios, with contrasting conclusions [13,14]. These results, however, are utterly biased by not comparable efficacy of doses selected for different drug comparisons.

The rationale for comparing different drugs with different intrinsic efficacies in reducing cholesterol levels but with a comparable activity in cholesterol levels is actually based on two observations.

First, Weng et al. showed that different statins induce different reduction in cholesterol levels: therefore any quantitative comparison between statins should be mandatory based on doses eliciting a comparable cholesterol reduction, as reported in latest guidelines on cholesterol treatment [6].

On the other hand, Hsia et al. showed that the main driver in clinical efficacy of statins, beyond ancillary effects of statins which should not be neglected, is the reduction of cholesterol levels [15].

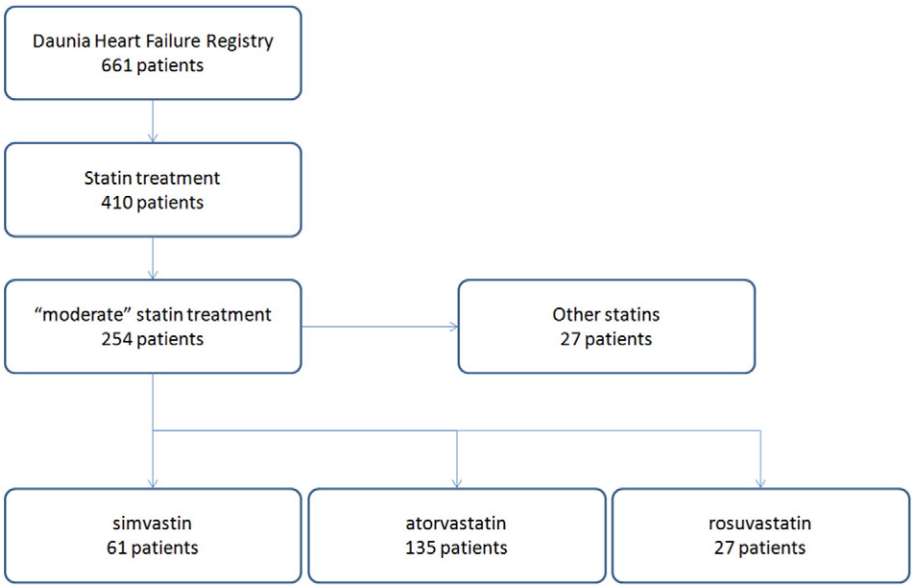

Fig. 1. Population selection.