

Data that not support switching from Rosuvastatin to other statin increases the risk of myocardial infarction.

Alessandro Battaglia^{1*}, Andrea Scalisi², Alessandro Schivalocchi³, Alberto Donzelli⁴

¹Foundation Allineare Sanità e Salute, Tracanella via C.G. Merlo 3 - 20122, Milano, Italy

²General Practitioner, via Serradifalco-95 90145, Palermo, Italy

³Resident in Hygiene, Public Health and Preventive Medicine, University of Milan, Bicocca

⁴Executive Board of the Foundation, Allineare Sanità e Salute, Studio Tracanella, C.G. Merlo 3 - 20122, Milano

Keywords: Switching, Rosuvastatin, Confounding bias, Time-varying covariates, Myocardial infarction.

Accepted on March 29, 2017

Introduction

Rosuvastatin's patent will expire within year 2017: this heightens the manufacturer's need to demonstrate more advantages for the originator drug than for the other and generic statins. The observational cohort study [1], based on historical data analysis and funded by Astra Zeneca, seems intended for this purpose. The authors explored a large clinical database of Italian General Practitioners, following a cohort of 10,368 patients newly treated with Rosuvastatin for approximately two years. One fourth of these patients (23.6%) switched to another lipid-lowering drug, mostly (72.4%) to "medium" or "low intensity" statins [1]. The "switched" patients showed a higher risk of acute Myocardial Infarction (MI) (OR= 2.2; 95% CI 1.4-3.5, p=0.0001). The authors conclude that switching from Rosuvastatin to another non-equipotent lipid-lowering drug may increase the risk of MI and should be avoided. We describe here a critical appraisal of Colivicchi's work.

Colivicchi's work is an observational research, so for a valid comparison between groups, partly switching from Rosuvastatin to another therapy and partly not, the analysis needs to be balanced for any prognostic and/or confounding factor able to influence the outcome such as MI incidence or switching (exposition) 'per se'. Notably, a prognostic factor can influence only the outcome, while a confounding factor influences both the outcome and the exposition. In Colivicchi's work, the outcome corresponds obviously to acute MI while the exposition is represented by the switching.

Authors balanced their analysis through a multivariate proportional hazards regression (the classical COX model): particularly, much attention was paid in the adjustment of concomitant basal therapy (antihypertensive, antidiabetic, antiplatelet drugs), baseline risk factors (obesity, hypertension and diabetes) and other baseline disease (i.e., chronic kidney failure) that might represent potential predictors of MI. Cardiovascular diseases at baseline constituted a precise exclusion criterion for the whole cohort. This approach appears correct, but it must be noted that the exposition (i.e., the switching from Rosuvastatin to another lipid lowering treatment) was included by the Authors in their Cox model not as a dummy, but as a time-varying covariate. This approach, even if correct, introduces other methodological questions.

Being the 'switching' a time-varying covariate, the analysis represents a kind of 'per protocol' approach [2], making the model vulnerable to time-varying confounders. In this scenario, incident cardiovascular diseases other than MI and patients drug-adherence (both not considered by Colivicchi's analysis) constitute a virtually serious cause of bias due to confounding.

Discussion

First, CVD incident comorbidities represent not only a (obvious) prognostic factor for coronary events, but also a true confounder. We try to explain the reason: In presence of an incident CVD, physicians might have cautiously considered the opportunity of using another and better tested statin instead of Rosuvastatin. Indeed Rosuvastatin has not shown efficacy on major clinical endpoints in secondary prevention trials of coronary heart disease. In fact, in main trials Rosuvastatin showed better results only on lipid surrogate outcomes compared to atorvastatin; conversely, the efficacy of atorvastatin and simvastatin has been well documented on fatal and non-fatal major clinical endpoints (Table 1). These two statins represent together the 80.5% of all switched drugs in Colivicchi's study.

Thus, worse outcomes on MI in switched patients might be associated just to an anticipated worse prognosis regarding their CV risk. As mentioned, in Colivicchi's study another important cause of bias due to time-varying confounders may be due to a lower adherence of switched patients to their second-line drugs.

Indeed, there is evidence that switchers from a higher to a lower potency statin are 41% less adherent than patients allocated to an equipotent second-line drug [3]. This could be explained by previous experience of adverse events: these patients could have required a lower dose of statin and, together, might be less willing to continue a statin therapy [3]. Notably, the proportion of switched patients in Colivicchi's study (23.6% in about two years of follow-up) is very similar to the non-compliance rates reported in the trial JUPITER [4] (25.0% of the participants were not taking their study pills when the study was truncated - 1.9 years). Therefore, compliance to allocated treatments can be an important time-varying confounder. So the final prognosis reported in this study could be explained not by the interruption of Rosuvastatin, but rather by a lower exposure to second-line therapies, due to lower adherence. The authors emphasize the

Citation: Battaglia A, Scalisi A, Schivalocchi A, et al. Data that not support switching from Rosuvastatin to other statin increases the risk of myocardial infarction. *J Cardiovasc Med Ther.* 2017;1(1):7-10.

Table 1. Efficacy of Atorvastatin and Simvastatin on fatal and non-fatal major clinical end-points.

RCT	Year	Comparisons	Patients	Primary outcome	(follow-up) Result	References
RADAR	2005	Rosuvastatin 10 mg/die to 40 mg/die vs Atorvastatin 20 mg/die to 80 mg/die	Patients with cardiovascular diseases and HDL-C < 1 mmol/l	LDL-C/HDL-C ratio % change	(18 weeks) change from baseline -57.3% and -49.6% respectively p<0.001	Jukema JW, et al. <i>Curr Med Res Opin</i> 2005, 21(11):1865-1874
PULSAR	2006	Rosuvastatin 10 mg/die vs Atorvastatin 20 mg/die	Patients with high cardiovascular risk and hypercholesterolemia	LDL-C % change	(6 weeks) change from baseline -44.6% and -42.7% respectively p<0.05	Clearfield MB, et al. <i>Trials</i> 2006, 21(7):35
POLARIS	2007	Rosuvastatin 40 mg/die vs Atorvastatin 80 mg/die	Patients with high cardiovascular risk and hypercholesterolemia	LDL-C % change	(8 weeks) change from baseline -56% and -52% respectively p<0.001	Leiter LA, et al. <i>Atherosclerosis</i> 2007, 194(2):e154-64
DISCOVERY	2005	Rosuvastatin 10 mg/die vs Atorvastatin 10 mg/die	Statin-naïve and switched patients with fasting LDL-C ≥5 mg/dl above their NCEP ATP III goal	% of patients achieving their NCEP ATP III goal	(12 weeks) 71.2% vs 61.4% respectively p<0.001	Fonseca FA, et al. <i>Curr Med Res Opin</i> 2005, 21(8):1307-1315
ECLIPSE	2008	Rosuvastatin 10 to 40 mg/die vs Atorvastatin 20 to 80 mg/die	Patients with high cardiovascular risk	% of patients achieving their NCEP ATP III goal	(24 weeks) 83.6% vs 74.6% respectively p<0.001	Faergeman O, et al. <i>Cardiology</i> 2008, 111(4):219-228
MIRACL	2004	Atorvastatin 80 mg/die vs placebo	Patients with unstable angina or non-Q-wave acute myocardial infarction (allocation: between 24 and 96 hours after hospital admission)	Composite of death, nonfatal acute myocardial infarction, cardiac arrest with resuscitation, or recurrent symptomatic myocardial ischemia	(16 weeks) Risk Ratio= 0.84 (0.70-1.00) p=0.048	Kinlay S, et al. <i>Circulation</i> 2004, 110(4):386-391
GREACE	2002	Atorvastatin 10 mg/die to 80 mg/die vs usual medical care	Patients with established coronary heart disease	Primary endpoints of the study were : death, coronary morbidity (non-fatal myocardial infarction, unstable angina, congestive heart failure, revascularisation) and stroke	(3 years) Death Risk Ratio= 0.57 (0.39-0.78) p=0.0021 Coronary morbidity Risk Ratio=0.46 (0.25-0.71) p<0.0001 Stroke Risk Ratio=0.56 (0.30-0.82) p=0.034	Athyros VG, et al. <i>Curr Med Res Opin</i> 2002, 18(4):220-228
PROVE-IT	2004	Pravastatin 40 mg/die vs Atorvastatin 80 mg/die	Patients hospitalized for an acute coronary syndrome within the preceding 10 days	Composite of death from any cause, myocardial infarction, documented unstable angina requiring rehospitalization, revascularization (performed at least 30 days after randomization), and stroke	(2 years) Hazard Ratio Reduction in favour of atorvastatin = 0.16 (0.05 0.26) p=0.005	Cannon CP, et al. <i>N Engl J Med</i> 2004 350(15):1495-1504
ALLIANCE	2004	Atorvastatin 10 mg/die to 80 mg/die vs usual care	Coronary heart disease patients with hyperlipidemia	Composite of cardiac death, non-fatal MI, resuscitated cardiac arrest, cardiac revascularization, and unstable angina requiring hospitalization	(51.5 months) Hazard Ratio = 0.83 (0.71 to 0.97) p = 0.02	Koren MJ, et al. <i>Am Coll Cardiol</i> 2004, 44(9):1772-1779
IDEAL	2005	Atorvastatin 80 mg/die vs Simvastatin 20 mg/die	Men and women with a history of a definite myocardial infarction and who qualified for statin therapy according to national guidelines at the time of recruitment	Composite of coronary death, hospitalization for nonfatal acute myocardial infarction, or cardiac arrest with resuscitation	(4.8 years) Hazard Ratio = 0.89 (0.78-1.01) P=0.07	Pedersen TR, et al. <i>JAMA</i> 2005, 294(19): 2437-2445
TNT	2005	Atorvastatin 80 mg/die vs Atorvastatin 10 mg/die	Patients with clinically evident CHD and LDL cholesterol levels of less than 130 mg per deciliter	Composite of death from CHD, nonfatal non-procedure-related myocardial infarction, resuscitation after cardiac arrest, or fatal or nonfatal stroke	(4.9 years) Hazard Ratio = 0.78 (0.69 to 0.89) p<0.001	La Rosa JC, <i>N Engl J Med</i> 2005, 352(14):1425-1435
Colivicchi	2002	Atorvastatin 80 mg/die vs. conventional care	Patients with unstable angina pectoris or non-Q-wave acute myocardial infarction	Composite of cardiac death, nonfatal AMI, or recurrent symptomatic myocardial ischemia with objective evidence (electrocardiographic, echocardiographic, or scintigraphic) requiring emergency hospitalization	(1 year) Odds Ratio=0.33 (0.12 - 0.88) p = 0.025	Colivicchi F, et al. <i>Am J Cardiol</i> 2002, 90(8):872-874
4S	1994	Simvastatin 10 mg to 40 mg/die vs placebo	Patients with coronary heart disease	All-cause mortality	(5.4 years) Risk Ratio =0.70 (0.58-0.85)	No authors listed <i>Lancet</i> 1994, 19;344(8934):1383-9

MRC/BHF	2002	Simvastatin 40 mg/die vs placebo	Patients with coronary heart disease, other occlusive arterial disease, or diabetes	Primary outcomes were mortality (for overall analyses) and fatal or non-fatal vascular events	(5 years) All cause death Risk Ratio=0.87 (0.81-0.94) p=0.0003; Any major vascular event Risk Ratio =0.76 (0.72-0.81) p<0.0001	Heart Protection Study Collaborative Group Lancet 2002, 360:7–22
---------	------	----------------------------------	---	---	--	--

harmful consequences on lipid values of a “switched” therapy (which their dataset do not allow to analyze), but they perform no adjustment for any measures of adherence, even when obtainable from clinical records of IMS database [1].

Lacking of adjustment for these time-varying confounders might have seriously biased the authors’ conclusions, namely that switching from Rosuvastatin to a ‘lower potency’ statin can be dangerous, being associated to an increased risk of MI.

Rosuvastatin is a high-potency drug on lipid endpoints, showing in JUPITER trial a 50% decrease of LDL-C values compared to placebo [4]. Nevertheless, its efficacy on major clinical endpoints is proved only in two primary prevention studies (JUPITER [4] and HOPE-3 [5]). In JUPITER this drug was effective on all-cause mortality and on non-fatal endpoints (stroke, MI), but only in a high selected sample of elderly patients (mean age 66, all with LDL-C <130 mg/dl, but with high levels of CRP, more than 40% with metabolic syndrome) [4]. In HOPE-3 trial Rosuvastatin still showed some efficacy on the same endpoints (Stroke, MI), but not on all-cause or CVD deaths [5]. However, also atorvastatin has evidence of efficacy in primary prevention (ASCOT [6]), even on all-cause mortality and after an 11-year mortality follow-up [7].

Moreover, since only a part of statins’ efficacy is due to LDL-C lowering effect [8,9], than the drug choice should be mainly driven by experimental evidence of efficacy on major clinical endpoints, not on surrogate endpoints. Therefore, we do not consider correct to recommend the prosecution of Rosuvastatin, when a drug-switching could be clinically justified, more so because a cheaper and equipotent statin is practically always available. This statin is atorvastatin at an appropriate dose, about four times cheaper than patent Rosuvastatin in the Italian market. In fact, e.g. 20 mg or 40 mg of atorvastatin are equipotent to 10 mg or 20 mg of Rosuvastatin, respectively [10]. The minimal residual gap in LDL-C lowering can be easily closed with a handful of nuts [11], which have also strong evidence to reduce total, cardiovascular and non-cardiovascular mortality [12].

Finally, there are good clinical reasons to recommend an equipotent dose of atorvastatin, instead of Rosuvastatin, for nephropathic or diabetic patients [13,14].

Conclusion

In conclusion, we do not consider appropriate to rely on observational data prone to many confounders [1] to advise against a switch from Rosuvastatin to another statin, as long as the patient maintains the correct adherence. The authors in fact do not consider (neither adjust for) important confounders, leading to potentially biased results to support an alleged advantage of Rosuvastatin compared with alternatives cheaper and probably safer to preserve renal function.

Acknowledgments

We are grateful to librarians’ Dr. Silvia Sacchi and Dr. Massimo Flammini for their valuable help in researching the cited medical literature.

Conflict of Interest

None.

References

- Colivicchi F, Gulizia MM, Franzini L, et al. Clinical implications of switching lipid lowering treatment from rosuvastatin to other agents in primary care. *Adv Ther.* 2016;33(11):2049-58.
- Sterne JAC, Higgins JPT, Reeves BC. A Cochrane risk of bias assessment tool: For non-randomized studies of interventions. *ACROBAT-NRSI* 2014.
- Romanelli RJ, Segal JB. Predictors of statin compliance after switching from branded to generic agents among managed-care beneficiaries. *J Gen Intern Med.* 2014;29(10):1372-78.
- Ridker PM, Danielson E, Fonseca FA, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med.* 2008;359(21):2195-207.
- Yusuf S, Bosch J, Dagenais G, et al. Cholesterol lowering in intermediate-risk persons without cardiovascular disease. *N Engl J Med.* 2016;374(21):2021-31.
- Sever PS, Dahlöf 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 randomised controlled trial. *Lancet* 2003;361:1149-58.
- Sever PS, Chang CL, Gupta AK, et al. The Anglo-Scandinavian cardiac outcomes trial: A 11-year mortality follow-up of the lipid-lowering arm in the U.K. *Eur Heart J.* 2011;32(20):2525-32.
- Boekholdt SM, Arsenault BJ, Mora S, et al. Association of LDL cholesterol, non-HDL cholesterol, and apolipoprotein B levels with risk of cardiovascular events among patients treated with statins: A meta-analysis. *JAMA.* 2012; 28;307(12):1302-9. Erratum in: *JAMA.* 2012;307(18):1915. *JAMA.* 2012;307(16):1694.
- Hayward RA, Hofer TP, Vijan S. Narrative review: Lack of evidence for recommended low-density lipoprotein treatment targets: A solvable problem. *Ann Intern Med.* 2006;145(7):520-30. A review.

Citation: Battaglia A, Scalisi A, Schivalocchi A, et al. Data that not support switching from Rosuvastatin to other statin increases the risk of myocardial infarction. *J Cardiovasc Med Ther.* 2017;1(1):7-10.

10. AIFA – Agenzia Italiana del Farmaco. Modifica alla Nota 13 di cui alla Determina del 26 marzo 2013 http://www.aifa.gov.it/sites/default/files/Nota13_GU156_08072014.pdf.
11. Banel DK, Hu F. Effects of walnut consumption on blood lipids and other cardiovascular risk factors: A meta-analysis and systematic review. *Am J Clin Nutr.* 2009;90:56–63.
12. Aune D, Keum N, Giovannucci E, et al. Nut consumption and risk of cardiovascular disease, total cancer, all-cause and causespecific mortality: A systematic review and dose-response meta-analysis of prospective studies. *BMC Medicine* 2016;14:207.
13. De Zeeuw D. Different renal protective effects of atorvastatin and rosuvastatin in diabetic and non-diabetic renal patients with proteinuria. Results of the PLANET trials. 2010 European Renal Association-European Dialysis and Transplant Association Congress; June 27, 2010; Munich, Germany.
14. De Zeeuw D, Anzalone DA, Cain VA, et al. Renal effects of atorvastatin and rosuvastatin in patients with diabetes who have progressive renal disease (PLANET I): A randomised clinical trial. *Lancet Diabetes Endocrinol.* 2015;3(3):181-90.

***Correspondence to:**

Alessandro Battaglia
Foundation Allineare Sanità e Salute,
Tracanella via C.G. Merlo 3
Milano
Italy
E-mail: a.battaglia@libero.it