targets was associated with significantly improved cardiovascular outcomes in comparison with those meeting neither target after multivariable adjustment. Even though the addition of ezetimibe increased the likelihood of targets attainment, the benefit in risk reduction for those meeting both targets was similar by treatment arm. These results clearly indicate that the risk reduction was essentially driven primarily by simvastatin action, the only drug present in both randomized groups.

Therefore, change in plaque composition irrespective of the LDL lowering action of rosuvastatin (1) should be interpreted as the confirmation that statins in part exert their beneficial effects in reducing cardiovascular risk through their pleiotropic action, and that cardiovascular prevention should no more be considered simply a "cholesterol issue."

*Luca Mascitelli, MD
Mark R. Goldstein, MD
*Comando Brigata Alpina "Julia"/Multinational Land Force Medical Service
8 Via S. Agostino
Udine 33100
Italy
E-mail: lumasci@libero.it

http://dx.doi.org/10.1016/j.jacc.2016.05.095

Please note: Both authors have reported that they have no relationships relevant to the contents of this paper to disclose.

REFERENCES

1. Park S-J, Kang S-J, Ahn J-M, et al. Effect of statin treatment on modifying plaque composition: a double-blind, randomized study. J Am Coll Cardiol 2016;67:1772–83.

2. Colantonio LD, Bittner V, Reynolds K, et al. Association of serum lipids and coronary heart disease in contemporary observational studies. Circulation 2016;133:256–64.

3. Hayward RA, Krumholz HM. Three reasons to abandon low-density lipoprotein targets: an open letter to the Adult Treatment Panel IV of the National Institutes of Health. Circ Cardiovasc Qual Outcomes 2012;5:2–5.

4. Versmissen J, Oosterveer DM, Yazdanpanah M, et al. Efficacy of statins in familial hypercholesterolaemia: a long term cohort study. BMJ 2008;337:a2423.

5. Bohula EA, Giugliano RP, Cannon CP, et al. Achievement of dual low-density lipoprotein cholesterol and high-sensitivity C-reactive protein targets more frequent with the addition of ezetimibe to simvastatin and associated with better outcomes in IMPROVE-IT. Circulation 2015;132:1224–33.

STABLE Versus Non-STABLE Studies

Effects of Rosuvastatin on Modifying Coronary Plaques

Park et al. (1) report the STABLE (Statin and Atheroma Vulnerability Evaluation) study, which has been the only randomized trial using rosuvastatin to evaluate compositional changes so far. This study showed significant reduction of necrotic core and plaque volume and a decrease in thin-cap fibroatheromas. There is conflicting data previously reported in the literature using rosuvastatin.

First, the radiofrequency intravascular ultrasonography defined percent necrotic core volume (%) significantly decreased after high-dose rosuvastatin therapy in the STABLE study and in IBIS-3 (Integrated Biomarkers and Imaging Study-3) (2). Conversely, the percent volume did not decrease in the IBIS-4 study (3) and in the SATURN-VH (Study of Coronary Atheroma by Intravascular Ultrasound: Effect of Rosuvastatin Versus Atorvastatin) study (4), which included patients with acute ST-segment elevation myocardial infarction and mixed stable and acute coronary syndrome (ACS), respectively. In a meta-analysis of studies with various statins, plaque composition did not change significantly (5). Of note, the necrotic core volume did increase in the HORIZONS-AMI (Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction) study with usual statin therapy. The summary of these studies, which showed inconsistent results of rosuvastatin on plaque composition, are presented in **Table 1**.

Second, is there a real differential effect of rosuvastatin in STABLE versus non-STABLE patients? All studies that enrolled stable patients (except SATURN-VH, which is a small study) showed more decrease in necrotic core volume than in studies that included patients with ACS. Further, all studies with stable patients had more frequent changes from thin-cap fibroatheroma to a thick one than in patients with ACS. The intensive rosuvastatin therapy seems to be more effective in stable patients and stabilizes the plaque in the composition and the morphology.

In primary prevention studies, such as JUPITER (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin), which include healthy persons without hyperlipidemia but with elevated high-sensitivity C-reactive protein levels, rosuvastatin significantly reduced the incidence of major cardiovascular events (hazard ratio: 0.56; $p < 0.00001$). Also, in the HOPE-3 (Heart Outcomes Prevention Evaluation) trial, treatment with rosuvastatin significantly lowered the risk of cardiovascular events (hazard ratio: 0.76; $p = 0.002$). These studies showed that treatment with rosuvastatin prevented future cardiovascular events in patients with "stable" disease and intermediate risk. The STABLE study provides a plausible mechanistic

TABLE 1 Studies for Effect of Statins on Plaque Burden, Morphology, and Composition

	ORION		Kubo et al.		SATURN-VH		STABLE		IBIS-3		IBIS-4		HORIZONS VH		Meta-Analysis (Statins)	
	p Value		p Value		p Value		p Value		p Value		p Value		p Value		p Value	
Sample size	33		99		71*		225		164		82		63		830 (9 studies)	
Follow-up (months)	24		12		24		12		12		13		13		6-24	
Clinical presentation	Carotid artery disease		SA (77%) ACS (23%)		SA (66%) ACS (34%)*		SA (58%) ACS (42%)		SA (59%) ACS (41%)		STEMI (100%)		STEMI (100%)		Various	
Imaging modality	1.5-T MRI		VH-IVUS		VH-IVUS		VH-IVUS		VH-IVUS		VH-IVUS		VH-IVUS		VH-IVUS	
Statin use (%) and dose	Rosuvastatin (100%) 40/80 mg		Statins (70%)		Rosuvastatin 40 mg or atorvastatin 80 mg (100%)		Rosuvastatin 40 mg (100%)		Rosuvastatin 40 mg (100%)		Rosuvastatin 40 mg (100%)		Statins (98%)		Atorvastatin, pitavastatin, rosuvastatin, fluvastatin	
Change of percent atheroma volume (%)					-1.58	<0.001	-1.0	0.018			-0.9	0.007			-0.14	0.023
Change of necrotic core volume (%)	-41.4	0.005	-8†		1.9	<0.001	-3.2	<0.001	-1.4	0.006	-0.05	0.926	4.0	<0.0001	0.01	0.892
Change of VH-TCFA			↓↓↓		↓↓↓	0.001	↓↓↓	<0.001			↓		↓			

*Original SATURN study, not applicable in SATURN VH. †Only patients with TCFA.

↓ = minimal change; ↓↓↓ = important change; ACS = acute coronary syndrome; HORIZONS-VH = Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction; IBIS = Integrated Biomarkers and Imaging Study; IVUS = intravascular ultrasonography; MRI = magnetic resonance imaging; ORION = Outcome of Rosuvastatin treatment on carotid artery atheroma: a magnetic resonance Imaging ObservatioN; SA = stable angina; SATURN-VH = Study of Coronary Atheroma by Intravascular Ultrasound: Effect of Rosuvastatin Versus Atorvastatin; STABLE = Statin and Atheroma Vulnerability Evaluation study; STEMI = ST-segment elevation myocardial infarction; TCFA = thin cap fibroatheroma; VH = virtual histology.

explanation of the results observed in the JUPITER and HOPE-3 trials.

Sang Yeub Lee, MD, PhD
Ron Waksman, MD
***Hector M. Garcia-Garcia, MD, PhD**
*MedStar Washington Hospital Center
110 Irving Street, NW
Suite 4B-1
Washington, DC 20010
E-mail: hector.m.garciagarcia@medstar.net

http://dx.doi.org/10.1016/j.jacc.2016.05.093

Please note: Dr. Waksman is a consultant to Abbott Vascular, Biotronik, Boston Scientific, Medtronic, and St. Jude Medical; is a member of the speakers bureau of AstraZeneca, Boston Scientific, and Merck; and has received grant support from AstraZeneca, Biotronik, and Boston Scientific. The other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

REFERENCES

1. Park SJ, Kang SJ, Ahn JM, et al. Effect of statin treatment on modifying plaque composition. J Am Coll Cardiol 2016;67:1772–83.

2. Simsek C, Garcia-Garcia HM, van Geuns RJ, et al. The ability of high dose rosuvastatin to improve plaque composition in non-intervened coronary arteries: rationale and design of the Integrated Biomarker and Imaging Study-3 (IBIS-3). EuroIntervention 2012;8:235–41.

3. Räber L, Taniwaki M, Zaugg S, et al. Effect of high-intensity statin therapy on atherosclerosis in non-infarct-related coronary arteries (IBIS-4): a serial intravascular ultrasonography study. Eur Heart J 2015;36:490–500.

4. Puri R, Libby P, Nissen SE, et al. Long-term effects of maximally intensive statin therapy on changes in coronary atheroma composition: insights from SATURN. Eur Heart J Cardiovasc Imaging 2014;15:380–8.

5. Banach M, Serban C, Sahebkar A, et al. Impact of statin therapy on coronary plaque composition: a systematic review and meta-analysis of virtual histology intravascular ultrasound studies. BMC Med 2015;13:229.

The Paradox of Heart Failure and Atrial Fibrillation

I have read the paper by Witte et al. (1) with great interest, recently published in the *Journal*. Witte et al. (1) reported that high-dose vitamin D supplementation is safe and well tolerated, although there were no effects on the primary endpoint for the 6-min walk distance associated with a clinically relevant improvement in cardiac function in chronic heart failure patients already taking current optimal therapies (1).

Prevalence of atrial fibrillation (AF) in patients with heart failure ranges from as low as 6% to 35% with the prevalence thought to increase in parallel with the severity of disease. In the Framingham study, the relative risk of developing AF in patients with heart failure was 4.5 and 5.9 for men and women, respectively (2).

The renin-angiotensin-aldosterone system strongly contributes to deterioration of cardiac function,