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EC CARDIOLOGY
Research Article

Male Vs Female Comparison of High Rosuvastatin and Atorvastatin Pretreatment in Patients Undergoing Elective PCI to Reduce the Incidence of Myocardial Periprocedural Necrosis. The ROMA II Gender Differences Sub-Study

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Received: November 12, 2016; **Published:** November 17, 2016

Abstract

Background: In ROMA II trials we ascertained that the reloading of statin, in stable patients on chronic statin therapy, decreases the incidence of periprocedural myocardial infarction (PMI) comparing with the standard treatment.

Objectives: We sought to investigate the impact of gender difference on the efficacy of statin reloading to reduce the PMI.

Methods: In ROMA II trial, patients who underwent elective PCI, were randomized to receive a pre-procedural loading dose of statin or the standard treatment. In this sub-analysis patients were divided in two groups according to gender differences.

Results: Twelve and 24-hours post-PCI Troponin T (TnT) elevation > 5 x 99th percentile URL frequency didn't show significant differences between men and female treated with a reloading dose of statin (respectively, at 12-h: 11.3% vs 8.3%; p = 0.22 and at 24-h: 16.7% vs 17.9%; p = 0.97). At 12-months follow-up the incidence of major adverse cardiovascular and cerebrovascular events (MACCE) did not show significant differences between men and female treated with reloading dose of statin (respectively, 5% vs 4%, p = 0.62, Log-rank test).

Conclusions: PMI is not correlated with sex in stable patients reloaded with statin.

Keywords: *Gender Differences; Periprocedural Myocardial Infarction; Elective Coronary Angioplasty; Atorvastatin; Rosuvastatin*

Abbreviations

PMI: Periprocedural Myocardial Infarction; MACCE: Major Adverse Cardiovascular and Cerebrovascular Events; Tnt: Troponin T; PCI: Percutaneous Coronary Intervention; ACS: Acute Coronary Syndromes; MI: Myocardial Infarction; TVR: Target Vessel Revascularization; GFR: Glomerular Filtration Rate; SVG: Saphenous Vein Graft; IMA: Internal Mammary Artery; CTO: Chronic Total Occlusions; TIMI Flow: Thrombolysis in Myocardial Infarction; ACT: Activated Clotting Time; BMS: Bare-Metal Stent; DES: Drug-Eluting Stent; ECG: Electrocardiogram; SD: Standard Deviation; FG: Female Group; MG: Male Group

Introduction

Percutaneous coronary intervention (PCI) is the most prevalent revascularization strategy in patients with coronary artery disease. Although this procedure is safe, peri-procedural myocardial infarction (PMI), assessed by cardiac marker elevation, occurs in 5% to 40%

of patients [1]. In the majority of patients, the PMI is diagnosticated only by elevated biomarker levels because the injury is due to small epicardial vessel occlusion or microvascular circulation damage [2].

Statins inhibit hepatic 3-hydroxy-3-methylglutaryl coenzyme A reductase, with a subsequent suppression of cholesterol biosynthesis. The lipid-lowering properties of statins have been suggested as the main reason for the reduction of morbidity and mortality rates [3-5]. However, multiple investigations have indicated the possibility that statins may evoke beneficial effects via LDL cholesterol-independent mechanisms by blocking the HMG-CoA reductase, not only cholesterol biosynthesis but also numerous additional intermediates are diminished. These factors, such as geranylgeranyl pyrophosphate, are involved in a wide array of cellular events which makes it conceivable that statins exert additional effects beyond cholesterol reduction [6,7]. The available data suggest that the administration of an high loading dose of statins either at least 3 - 7 days before and within 24 hours of elective PCI, reduces LDL cholesterol; this reduction reaches 50% for Atorvastatin and exceed 50% for Rosuvastatin [8-10]. In our previous study, the ROMA II [11], we compared the effect of a reloading dose with Rosuvastatin or Atorvastatin in terms of PMI reduction and the incidence of major adverse cardiovascular and cerebrovascular events (MACCE) in patients on chronic statin therapy underwent elective PCI, confirming the cardioprotective effects of both statins without significant differences between the two study groups.

Women and men with acute coronary syndromes (ACS) have been found to have different clinical profiles and presentation, with a smaller percentage of women than men presenting with ST-elevation myocardial infarction (MI), but more presenting with unstable angina [12].

This seems to be due to the protective effect of estrogens, in fact, in women the risk increases significantly after menopause, parallel to the hormones reduction. Estrogens induce a modulation of coronary vasoreactivity decreasing the basal vasomotor tone, the resistance and the abnormal coronary vasomotor responses to acetylcholine. This leads to an increased epicardial cross-sectional area and coronary flow [13]. Prior studies have reported significant gender differences in the procedural outcomes after elective PCI. Many of these differences have been explained by the presence of more comorbidities and worse clinical characteristics such as older age, unstable angina, congestive heart failure, diabetes mellitus, and hypertension in women than in men [14].

On the basis of this controversial data we sought to investigate the impact of gender differences on the efficacy of statin reloading to reduce the PMI and MACCE.

Materials and Methods

Aim of the study and definition

We performed a sub-analysis of ROMA II trial to assess the differences between male and female to reduce the PMI in patients underwent elective PCI, in chronic statin therapy receiving a reloading dose of statin. PMI was defined as cTn elevation > 5 x 99th percentile URL (normal referent value < 0.01 ng/dl) according to the third universal definition of myocardial infarction (type 4a) [15].

Although this study was not powered for clinical evaluation we estimated the incidence of MACCE, in terms of cardiac death, periprocedural myocardial infarction, spontaneous myocardial infarction, target vessel revascularization, stroke and rehospitalization at 12 months.

Spontaneous MI was defined following the consensus statement of the Joint European Society of Cardiology/American College of Cardiology Foundation/American Heart Association/World Heart Federation Task Force for the Redefinition of Myocardial Infarction for clinical trials on coronary intervention [16]. Target vessel revascularization (TVR) included both by-pass surgery and percutaneous revascularization of the previous treated vessel. Stroke was defined as permanent neurologic deficit adjudicated by a neurologist and confirmed by MRI control.

Study population and design

In this sub-study, we analyzed the Roma II Trial population and compared the female group and the men group treated with statin. As described in the previous study [11] the inclusion criteria were: age > 18 years, elective coronary angiography due to symptomatic coronary artery disease, "*de novo*" lesions in a native coronary artery and chronic statin therapy. Baseline troponin T had to be within the normal limits. Clinical exclusion criteria were: ACS with elevated cardiac markers; primary or rescue PCI, basal elevated cardiac markers, previous myocardial infarction; renal failure (defined as glomerular filtration rate -GFR- <60 ml/min/1.73 m2 for three months [serum creatinine concentration > 137 micromol/L in men, and > 104 micromol/L in women]); kidney damage ascertained by the presence of micro albuminuria [albumin to creatinine ratio >30 mg/g in two spot urine specimens at least]), left ventricular ejection fraction < 30%, basal elevated alanine aminotransferase and aspartate aminotransferase serum levels and inability to give informed consent.

Angiographic exclusion criteria were: restenotic lesions, saphenous vein graft (SVG) or internal mammary artery (IMA) and chronic total occlusions (CTO). Twenty-four hours before the procedure the eligible patients were randomized to receive the reloading dose of atorvastatin 80 mg or Rosuvastatin 40 mg, whereas a suitable number of control group patients on chronic statin therapy was also included. The randomization was performed by a 1:1 ratio using computer-generated random numbers.

Procedure and post-PCI treatment

Coronary angiography and stent implantation was performed according to the standard practice. Angiographic success was defined as final residual stenosis < 20% and Thrombolysis in Myocardial Infarction III flow grade (TIMI flow III). At the start of procedure all patients received intra-arterial bolus of unfractioned heparin (70 IU/kg) to achieve an activated clotting time (ACT) ≥ 250 sec. Platelet glycoprotein IIb/IIIa inhibitors were administered at operators' discretion. Standard therapy with a loading dose of clopidogrel (300 mg the previous day or 600 mg < 6h before the procedure) and aspirin (500 mg, if aspirin naive) was administered in all patients 24 hours before the coronary angiography. Moreover, patients randomized to Rosuvastatin group received a loading dose (40 mg) of the drug 24 hour before the procedure and patients randomized to Atorvastatin group received a loading dose (80 mg) of the drug 24 hours before the procedure. After coronary revascularization, aspirin was continued lifelong and clopidogrel administration 75 mg/day was recommended at least for 1 or 12 months if the patients were respectively treated with bare-metal stent (BMS) or drug-eluting stent (DES) implantation. Baseline standard myocardial markers (CK-MB and Troponin T) were collected at the admission time. Pre- and post-procedural electrocardiograms (ECG) were performed. Pre-procedural medical therapy was recorded. Pre-procedural values of total and LDL cholesterol were assessed. All patients were discharged on Rosuvastatin 20 mg/day or Atorvastatin 40 mg/day, according with the randomization group. Standard ischemic and anti-hypertensive therapies were prescribed according to patient conditions at discharge. Following the procedure, blood samples were collected at 12 and 24 h, for CK, CK-MB and Troponin T determination.

Clinical Follow Up was performed through direct visits or telephone interview at twelve months after the index procedure.

Statistical analysis

Statistical Analysis was performed with the SPSS software package for windows v.19 (SPSS Inc. Chicago IL, USA). All categorical variables are expressed as percentages and all continuous variables as mean ± standard deviation (SD). The differences between categorical variables were analyzed by the $\chi 2$ test. Kaplan-Meier plots of cumulative incidence freedom of overall MACCE were constructed from the index procedure to 12-months follow-up. A two-tailed p value < 0.05 was considered statistically significant.

Results

The population of the Roma II Trial was composed by 350 patients on chronic statin therapy who underwent elective PCI and received a loading dose of Atorvastatin or Rosuvastatin before the PCI. This population was divided in a female group (FG) formed by 63 patients and a male group (MG) formed by 287 patients. The flow chart of the study is represented in (Figure1).

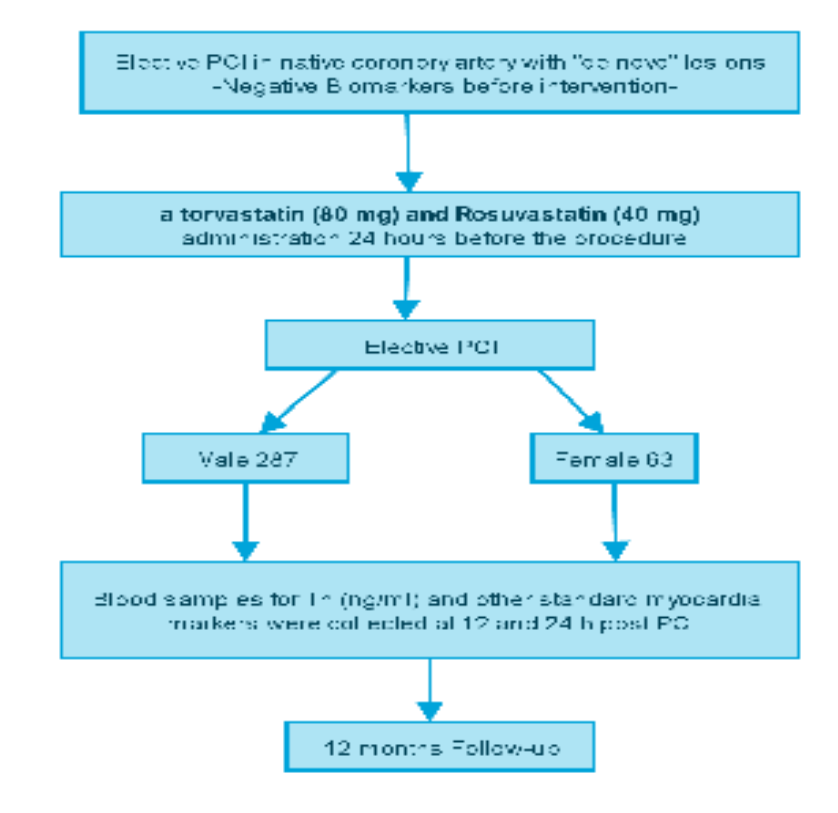

Figure 1: *Study Flow-chart.*

Clinical baseline characteristics and statin therapy before the procedure are showed in the table 1. The mean age was 67.8 ± 9.9 years old in the MG and 68 ± 9.4 years old in the FG (p = 0,89). The male patients had a worse clinical risk profile, in fact they had a higher rate of no insulin dependent diabetes mellitus: 99 (34.6%) vs 8 (12.7%) respectively in MG and in FG (p = 0.0.0007); hypertension percentages were 190 patients (66.2%) vs 18 patients (28.6%) in MG and FG (p = 0,0001); male were also more smokers than female patients (p = 0.05), they also had a family history for cardiovascular diseases (p = 0.0001) and a major incidence of prior PCI (p = 0.0001).

Variables	Male (287)	Female (63)	p
Age, mean ± SD	67.8 ± 9.9	68±9.4	0.89
Current smoker, pts (%)	117 (40.7)	11 (17.4)	0.05
Diabetes mellitus, pts (%)	110 (38,5)	27 (42.9)	0.5
NIDDM, pts (%)	99 (34.6)	8 (12.7)	0.0007
IDDM, pts (%)	11 (3.8)	0	0.11
Hypertension, pts (%)	190 (66.2)	18 (28.6)	0.0001
Hypercholesterolemia, pts (%)	169 (58.8)	34(53.9)	0.47
Family history of CAD, pts (%)	141 (49.1)	7 (11.1)	0.0001
Prior PCI, pts (%)	246 (85.7)	16 (25.4)	0.0001

LVEF, %±SD	52.7±5.7	53.9±5.2	0.16
Rosuvastatin, n (%)	143 (49,8)	32 (50,8)	0.89
Atorvastatin, n (%)	94 (32,7)	4 (6,3)	0.0001
Simvastatin, n (%)	39 (13,6)	21 (33,3)	0.0007
Fluvastatin, n (%)	0	6 (9,5)	0.0001
Pravastatin, n (%)	11 (3,8)	0	0.22

Table 1: *Clinical Baseline Characteristics.*

Variable (n = 350) Male Group (n = 287) Female Group (n = 63)

Angiographic and procedural features were similar between the two groups (Table 2). Coronary anatomy, lesion and procedural characteristics were similar in both groups. Atorvastatin loading dose was administered before PCI in 74,2% male (213 pts) versus 76,2% female (48pts) and Rosuvastatin loading dose in 25,8% male (74 pts) versus 23,8% female(15pts), without significant differences between groups (P = 0,87). Procedural success was achieved in all patients. In-hospital major complications (death or need urgent revascularization) were not found.

Variables	Male (287 pts)	Female (63 pts)	P value
AHA/ACC Type B_2/C, %	60.8	59.3	0.578
Mean lesion length, mm ± SD	23 ± 15.15	19.54 ± 16.5	0.071
Mean RVD, mm ± SD	2.92 ± 0.36	2.85 ± 0.51	0.163
Mean MLD, mm ± SD	0.56 ± 0.47	0.51 ± 0.39	0.308
Mean diameter stenosis, %±SD	80.7 ± 17.93	82.2 ± 12.62	0.394
Mean stent length, mm ± SD	26.5 ± 17.15	27.5 ± 12.9	0.562
Total vessels treated	340	75	-
Total lesion treated	369	82	-
Total implanted stent	383	85	-
DES implanted %	84.8 (325)	81.1 (69)	-
Left anterior descending, %	32.6	43.8	0.254
Left circumflex, %	21.7	21.7	0.542
Right coronary artery, %	30.4	28.5	0.752
Intracoronary thrombosis %	0	0	-
Angiographic success %	100	100	-
Complete revascularization %	100	100	-

Table 2: *Angiographic and Procedural Characteristics of the Two Groups:*

Abbreviations: *AHA/ACC: American American Association/American College of Cardiology; SD: Standard Deviation; RVD: Reference Vessel Diameter; MLD: Minimal Lumen Diameter; DES: Drug-Eluting Stent*

The TnT elevation (>5 x 99th percentile URL) frequency, at 12 and 24 h post PCI, did not show significant differences between men and female treated with a reloading dose of Atorvastatin or Rosuvastatin (respectively, at 12-h: 11.3% vs 8.2%; p = 0.22 and at 24-h: 16.7% vs 17.9%; p = 0.97) (Figure 2 and 3).

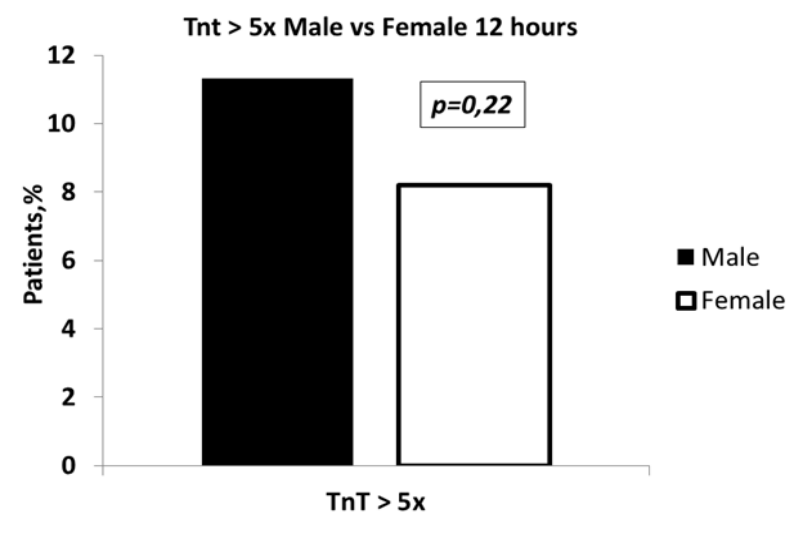

Figure 2: *Tnt > 5x Male vs Female 12 hours.*

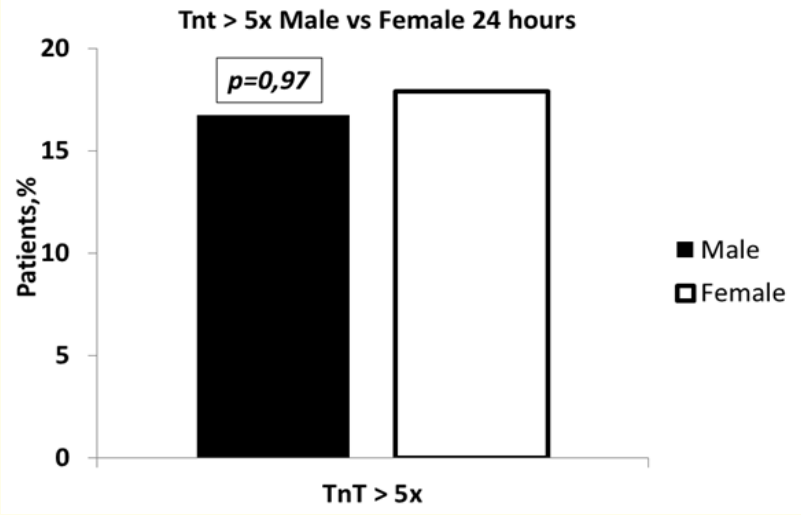

Figure 3: *Tnt > 5x Male vs Female 24 hours.*

No patients were lost at follow-up and after 12-month the incidence of cumulative MACCE, including spontaneous MI, stroke, rehospitalization, TVR and cardiac death, did not show significant differences between men and female treated with reloading dose of Atorvastatin/Rosuvastatin (respectively, 5% vs 4%, p = 0.62, Log-rank test) (Figure4).

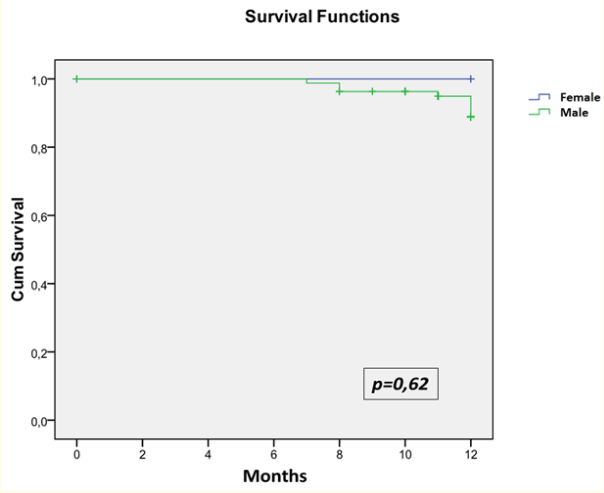

Figure 4: *Kaplan Mayer Male vs Female at 12 months.*

Discussion

This is the first analysis that investigated the impact of gender difference in patients treated with statin loading dose before elective coronary PCI. In this sub-study, as already demonstrated, we confirmed the cardioprotective effect of statins. In fact, a reloading high dose of both Rosuvastatin or Atorvastatin, administered within 24 hours before stent implantation, seems to similarly reduce the rise of myocardial markers after PCI. Furthermore, preprocedural reload of statins seems reduce the incidence of cumulative MACCE up to 12 months' follow-up. In this sub-analysis, the results showed that the sex did not influence the periprocedural and long-term outcomes in patients that assumed chronic statin therapy and that received a high dose of statin before elective PCI.

Previous studies have shown that statin therapy improved the outcome in patients underwent PCI, in particular, the ARMYDA-ACS trial was the first randomized study to assess the efficacy of statin loading dose before PCI in patients with ACS. The results of this trial indicated that 80 mg atorvastatin administered at 12h before PCI reduced post-procedural biomarker elevation and 30 days MACE [17].

The benefits of statins in cardiovascular diseases can be explained not only by their lipid-lowering potential but also by non-lipid-related mechanisms, the pleiotropic effects that results in a modification of endothelial function, inflammatory responses, plaque stability and thrombus formation, improving clinical outcomes after PCI [18,19].

Our target was to assess the impact of sex regarding PMI in patients underwent elective PCI. Our results showed a similar incidence of periprocedural MI and adverse clinical events between male and female. Considering the absence of data about gender difference and efficacy of statin therapy in patient with stable coronary disease, we compared our results with principal papers that analyzed the same target but in ACS patients. In support of our data, Perl., et al. [20] analyzed 5819 patients with ACS undergoing urgent PCI and compared according to sex. The first analysis showed a greater risk for adverse clinical outcomes following ACS in women especially in young and diabetic ones. These differences were not confirmed after correction for advanced age and comorbidities. Importantly, no differences were found in patients with diabetes mellitus or those younger than 60 years of age. This may reflect the importance of the administration of evidence-based therapeutics in women.

Tillmanns performed a prospective study [21] sought to investigate the clinical events during the early phase (30 days) and 1 - 4 years after primary PCI in STEMI women. Data were obtained in 178 consecutive and unselected women and 513 consecutive and unselected men who had undergone primary PCI. The procedure of the infarct–related artery was equally successful in both sexes (women 95%, men

94%). At 30 days follow-up there were not significant gender-related differences in early mortality. Total cumulative mortality during 1-4 years of follow–up was 12.5%, 14.5%, 18% and 23% in women, respectively, versus 9%, 10.5%, 12% and 15%, respectively, in men. The general trend for a higher post-discharge mortality in women became apparent after 3 years and reached significance after 4 years. After multivariate analysis, female gender was not independent risk factor of increased mortality. Long–term follow–up (4 years) also revealed no sex–related differences in mortality and cardiac morbidity after primary PCI.

On the contrary, Argulian., *et al*. [22], developed a prospective registry including all consecutive non-urgent PCI patients. In this analysis were included 3921 patients (2756 male and 1165 female) and the authors showed that in women, particularly younger women, were more likely than men to experience coronary vascular injury and bleeding complications unaccounted for by coronary artery size and other patient characteristics. In addition, Akhter [23], analyzing patients presented with acute coronary syndrome (UA/NSTEMI Men = 101961, Women = 55691 and STEMI men = 29703, Women = 12335), demonstrated the influence of gender about clinical presentation, angiographic features, antiplatelet therapies and higher procedural complications in women have undergone urgent PCI. In particular, women were prone to more vascular and bleeding complications than men, but there was no significant gender difference in adjusted in-hospital mortality rates.

Conclusions

In conclusion, this study confirms the cardioprotective effects of statins in patients undergoing to elective PCI. Rosuvastatin as Atorvastatin showed similar beneficial effects in both sexes on PMI incidence. This sub-analysis shows that the efficacy of treatment with statin before PCI is not gender-linked and PMI is not correlated with sex in stable patients reloaded with statin.

Limitations

Our study has some limitations: first of all, the small sample size and the missing sub-analysis in the female group according to the age, considering the hormonal changes following menopause and the protective role of estrogens.

Disclosures: none.

Acknowledgement: none.

Bibliography

1. Brener SJ., *et al*. "Frequency and long-term impact of myonecrosis after coronary stenting". *European Heart Journal* 23.11 (2002): 869-876.

2. Prasad A and Herrmann J. "Myocardial infarction due to percutaneous coronary intervention". *New England Journal of Medicine* 364.5 (2011): 453-464.

3. Sacks FM., *et al*. "The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators". *New England Journal of Medicine* 335.14 (1996): 1001-1009.

4. "The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels". *New England Journal of Medicine* 339.19 (1998): 1349-1357.

5. "Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial". *Lancet* 360.9326 (2002): 7-22.

6. Goldstein JL., *et al*. "Regulation of the mevalonate pathway". Nature 343.6257 (1990): 425-430.

7. Elsabrouty R., *et al*. "Sterol-induced dislocation of 3-hydroxy-3-methylglutaryl coenzyme A reductase from membranes of permeabilized cells". *Molecular Biology of the Cell* 24 (2013): 3300-3308.

8. Jones PH., et al. "STELLAR Study Group. Comparison of the efficacy and safety of rosuvastatin versus atorvastatin, simvastatin, and pravastatin across doses (STELLAR* Trial)". *American Journal of Cardiology* 92.2 (2003): 152-160.

9. Nicholls SJ., *et al*. "Meta-analysis of comparative efficacy of increasing dose of Atorvastatin versus Rosuvastatin versus Simvastatin on lowering levels of atherogenic lipids (from VOYAGER)". *American Journal of Cardiology* 105.1 (2010): 69-76.

10. Sardella G., *et al*. "ROsuvastatin pre-treatment in patients undergoing elective PCI to reduce the incidence of MyocArdial periprocedural necrosis. The ROMA trial". *Catheterization and Cardiovascular Interventions* 81.1 (2013): E36-E43.

11. Sardella G., *et al*. "Comparison of high reloading ROsuvastatin and Atorvastatin pretreatment in patients undergoing elective PCI to reduce the incidence of MyocArdial periprocedural necrosis. The ROMA II Trial". *International Journal of Cardiology* 168.4 (2013): 3715-3720.

12. Rosengren A., *et al*. "Sex, age, and clinical presentation of acute coronary syndromes". *European Heart Journal* 25.8 (2004): 663-670.

13. Reis SE., *et al*. "Ethinyl Estradiol Acutely Attenuates Abnormal Coronary Vasomotor Responses to Acetylcholine in Postmenopausal Women". *Circulation* 89.1 (1994): 52-60.

14. Presbitero P., *et al*. "Gender differences in the outcome of interventional cardiac procedures". *Italian Heart Journal* 4.8 (2003): 522-527.

15. Thygesen K. *et al*. "Joint ESC/ACCF/AHA/WHF Task Force for Universal Definition of Myocardial Infarction. Third universal definition of myocardial infarction". *Journal of the American College of Cardiology* 60.16 (2012): 1581-1598.

16. Thygesen K., *et al*. "on behalf of the joint ESC/ACCF/AHA/WHF task force for the redefinition of myocardial infarction. Universal definition of myocardial infarction". *Journal of the American College of Cardiology* 50.22 (2007): 2173-2195.

17. Patti G., *et al*. "Atorvastatin pretreatment improves outcomes in patients with acute coronary syndromes undergoing early percutaneous coronary intervention: results of the ARMYDA-ACS randomized trial". *Journal of the American College of Cardiology* 49.12 (2007): 1272-1278.

18. Sposito AC., *et al.* "Statin therapy in acute coronary syndromes. Mechanistic insight into clinical benefit". *Arteriosclerosis, Thrombosis, and Vascular Biology* 22.10 (2002): 1524-1534.

19. Takemoto M., *et al*. "Pleiotropic effects of 3-hydroxy-3-methylglutaryl coenzyme a reductase inhibitors". *Arteriosclerosis, Thrombosis, and Vascular Biology* 21.11 (2001): 1712-1719.

20. Perl L., *et al*. "Impact of female sex on long-term acute coronary syndrome outcomes". *Coronary Artery Disease* 26.1 (2015): 11-16.

21. Tillmanns H., *et al*. "Gender Differences in the Outcome of Cardiac Interventions". *Herz* 30.5 (2005): 375-389.

22. Argulian E., *et al*. "Gender differences in short-term cardiovascular outcomes after percutaneous coronary interventions". *American Journal of Cardiology* 98.1 (2006): 48-53.

23. Akhter N., *et al*. "Gender differences among patients with acute coronary syndromes undergoing percutaneous coronary intervention in the American College of Cardiology-National Cardiovascular Data Registry (ACC-NCDR)". *American Heart Journal* 157.1 (2009): 141-148.

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