Original Article

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Combining rosuvastatin with angiotensin-receptor blockers of different PPARγ activating capacity: Effects on platelet indices associated with cardiovascular disease

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Abstract

Introduction: Platelets play an important role in atherosclerosis development and progression. Various platelet indices have been associated with cardiovascular disease risk. The effect of combined treatment with a potent statin plus angiotensin receptor inhibitors with different PPARγ activating capacity is unknown.

Methods: Patients (n=151) with hypertension, dyslipidemia and impaired fasting glucose were randomly allocated to rosuvastatin (10 mg/day) plus telmisartan 80 mg/day (RT group, n=52) or irbesartan 300 mg/day (RI group, n=48) or olmesartan 20 mg/day (RO group, n=51). After 6 months of treatment, changes in common platelet indices were evaluated.

Results: After 6 months of treatment, platelet count, mean platelet volume, platelet distribution width and platelet larger cell ratio remained unchanged in all groups. Moreover, no difference between groups was observed.

Conclusions: The combination of rosuvastatin with sartans of different PPARγ activating capacity was not associated with any changes in common platelet indices.

Key words: rosuvastatin; telmisartan; olmesartan; irbesartan; platelets; cardiovascular disease

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1. Introduction

The development of atherosclerosis is a complex process mainly involving interactions between lipids, macrophages, platelets, cytokines and the vasculature. Indeed, platelets through their pro-inflammatory and pro-thrombotic properties are an integral component of atherosclerotic plaque development process. As a result, many researchers have postulated a correlation between the number, volume and activation of platelets and the development of atherosclerosis[1]. Indeed, several studies have shown an association between platelet indices and cardiovascular disease (CVD) [2-4]. Moreover, common platelet indices such as mean platelet volume (MPV), platelet distribution width (PDW) and platelet larger cell ratio (P-LCR) are easily measured by automatic analyzers. As a result, these indices could help identify patients with increased CVD risk through easy and inexpensive methods.

There are conflicting results regarding the effect of statin treatment on platelet indices. Indeed, findings range from no effect to a decrease of the previous platelet markers after statin therapy [5, 6]. Moreover, there is a scarcity of data regarding the effect of angiotensin receptor blockers (ARBs) on platelet indices. The peroxisome proliferator-activated receptor gamma (PPARγ) are ligand-activated transcription factors and members of the nuclear hormone receptor superfamily. These receptors are known to modify the transcription of numerous metabolic related genes. However, the presence of PPARγ is not limited in the cell nucleus where they regulate gene transcription. Indeed, studies have shown that PPARγ is also found in the cytoplasm of cells such as platelets [7, 8]. Furthermore, cytoplasmic PPARγ is biologically active and binds proteins in the cytoplasm independently of their gene transcription regulation role [9, 10].

A few ARBs, mainly telmisartan and to a lesser degree irbesartan, have the ability to partially activate PPARγ [11]. This trait of some ARBs may differentiate their effect on platelet function and morphology. The present study evaluated the effects of combining a statin with ARBs of different PPARγ activating capacity on common platelet indices in patients with mixed dyslipidemia, hypertension and prediabetes.

2. Subjects and Methods

2.1 Subjects

Study details have been previously described [12]. In brief, patients attending the Outpatient Lipid Clinic of the University Hospital of Ioannina, Greece, were recruited. Eligible patients were those with impaired fasting plasma glucose (IFG), mixed dyslipidemia and stage 1 hypertension. Patients were excluded if they had any of the following: (1) history of diabetes, (2) history of CVD, (3) elevated triglycerides (TG) (>400 mg/dL; 4.52 mmol/L), (4) renal disease, (5) hypothyroidism, (6) liver dysfunction, (7) receiving lipid-lowering or antihypertensive treatment in the last 3 months prior to recruitment and (8) females that did not take sufficient contraceptive measures. All participants gave written informed consent and the study protocol was approved by our institutional ethics committee.

2.2 Study design

All patients (n=159) received a 12-week dietary intervention in accordance with the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) guidelines and the Dietary Approaches to Stop Hypertension (DASH) diet. Patients (n=151) who continued to meet the inclusion criteria after the dietary intervention period were randomly allocated to open-label: i) rosuvastatin (10 mg/day) plus an ARB with partial PPARγ activating capacity (telmisartan 80 mg/day; n=52; RT group), ii) rosuvastatin (10 mg/day) plus an ARB with weak partial PPARγ activating capacity (irbesartan 300 mg/day; n=48; RI group) or iii) rosuvastatin (10 mg/day) plus an ARB without PPARγ activating capacity (olmesartan 20 mg/day; n=51; RO group). The doses of each drug were the usual starting doses in clinical practice.

Compliance with study medication was assessed at week 24 by counting taken tablets; patients were considered compliant if they took 80-100% of the prescribed number of tablets.

2.3 Biochemical parameters

All laboratory determinations were carried out af-

Table 1. **Baseline demographic characteristics of study participants***

Characteristic	RT Group	RI Group	RO Group	*p*
N (females/males)	25/27	26/22	27/24	NS
Age (years)	60 ± 10	60 ± 10	58 ± 12	NS
Smokers (%)	22	27	23	NS
Body mass index (kg/m^2)	29 ± 4	29 ± 5	28 ± 4	NS
Waist circumference (cm)	101 ± 9	101 ± 11	100 ± 8	NS
Systolic blood pressure (mm Hg)	153 ± 14	152 ± 11	151 ± 11	NS
Diastolic blood pressure (mm Hg)	91 ± 10	90 ± 9	93 ± 8	NS

RT: rosuvastatin + telmisartan, RI: rosuvastatin + irbesartan, RO: rosuvastatin + olmesartan, NS: not significant
**Values are expressed as mean ± SD*

ter an overnight fast and performed blindly with regard to treatment allocation. All blood analysis was performed in the laboratory of the University Hospital of Ioannina. Regarding the measurement of platelet indices, the same EDTA standardized tubes were used and all blood samples were analyzed within 2 hours after venipuncture in order to avoid bias due to EDTA-induced platelet swelling. All samples were processed in an automated hematology analysis system (Sysmex X 2100, Kobe, Japan). Levels of fasting plasma glucose, total cholesterol (TC), high density lipoprotein-cholesterol (HDL-C) and TGs were determined enzymatically using an Olympus AU 600 analyser (Olympus Diagnostica GmbH, Hamburg, Germany). Low-density lipoprotein cholesterol (LDL-C) was calculated by using the Friedewald formula (LDL-C=TC - TGs/5 - HDL) (provided that TGs were <400 mg/dL; 4.52 mmol/L). HOMA-IR (HOmeostasis Model Assessment Insulin Resistance) was calculated as follows: HOMA-IR= Fasting insulin (mU/L) × Fasting glucose (mg/dL)/405 [13].

2.4 Statistical analysis

Values are given as mean ± standard deviation (SD) and median (range) for parametric and non-parametric data, respectively. Continuous variables were tested for lack of normality by the Kolmogorov-Smirnov test and logarithmic transformations were accordingly performed for non-parametric variables. The paired-sample t-test was used for assessing the effect of treatment in each group. Analysis of covariance (ANCOVA), adjusted for baseline values, was used for comparisons between treatment groups. Analyses were performed using the Statistical Package for the Social Sciences (SPSS) 15.0 (SPSS Inc, Chicago, IL).

3. Results

A total of 159 patients (76 males, mean age 60) were enrolled. After the dietary intervention, 151 patients (73 males) continued to meet the inclusion criteria and were randomized to the 3 groups. No significant differences regarding baseline data were found across groups (**Table 1**). No patient dropped out and compliance was >80% in all patients.

The effect of all treatment combinations on metabolic parameters has been previously described [12]. In brief, after study end all groups had similar changes in blood pressure (**Table 2**). Regarding lipid profile, in all groups significant and similar reductions in TC (RT -35%, RI -37%, RO -36%; for all groups $p<0.001$ vs baseline), TGs (RT -25%, RI -28%, RO -23%; for all groups $p<0.001$ vs baseline) and LDL-C (RT -42%, RI -44%, RO -46%; for all groups $p<0.001$ *vs.* baseline) were noticed, while HDL-C remained unchanged. However, HOMA-IR decreased only in the RT group (-29%; $p<0.05$ *vs.* baseline; $p<0.01$ *vs.* RI and $p<0.05$ *vs.* RO), while an increase was observed in the other 2 regimens (RI +16%, RO +14%; both $p<0.05$ *vs.* baseline).

The effects of study treatment on platelet indices

Table 2. Serum metabolic parameters and blood pressure at baseline and after 6 months of treatment*

	Baseline*	6 months*	Percentage change
Total cholesterol [mg/dL (mmol/L)]			
RT Group	271 ± 29 (7.0 ± 0.8)	177 ± 28 (4.6 ± 0.7)	-35%‡
RI Group	269 ± 23 (7.0 ± 0.6)	170 ± 30 (4.4 ± 0.8)	-37%‡
RO Group	274 ± 27 (7.0 ± 0.7)	175 ± 32 (4.5 ± 0.8)	-36%‡
Triglycerides [mg/dL (mmol/L)]			
RT Group	180 (152-290) [2.0 (1.7-3.3)]	135 (81-270) [1.5 (0.9-3.1)]	-25%‡
RI Group	173 (151-276) [3.3 (1.7-3.1)]	125 (77-252) [1.4 (0.9-2.9)]	-28%‡
RO Group	187 (153-289) [2.1 (1.7-3.3)]	147 (76-210) [0.9 (1.7-2.4)]	-23%‡
HDL-C [mg/dL (mmol/L)]			
RT Group	55 ± 7 (1.4 ± 0.2)	56 ± 7 (1.4 ± 0.2)	+1%
RI Group	58 ± 11 (1.5 ± 0.3)	59 ± 15 (1.5 ± 0.4)	+1%
RO Group	53 ± 9 (1.4 ± 0.2)	54 ± 10 (1.3 ± 0.3)	+2%
LDL-C [mg/dL (mmol/L)]			
RT Group	182 ± 23 (4.7 ± 0.6)	105 ± 28 (2.7 ± 0.7)	-42%‡
RI Group	176 ± 23 (4.6 ± 0.6)	99 ± 22 (2.6 ± 0.6)	-44%‡
RO Group	183 ± 22 (4.7 ± 0.6)	99 ± 31 (2.6 ± 0.8)	-46%‡
Fasting plasma glucose [mg/dL (mmol/L)]			
RT Group	112 ± 10 (6.2 ± 0.6)	113 ± 9 (6.3 ± 0.5)	+1%
RI Group	110 ± 10 (6.1 ± 0.6)	112 ± 7 (6.2 ± 0.4)	+2%
RO Group	114 ± 11 (6.3 ± 0.6)	114 ± 8 (6.3 ± 0.4)	0%
HOMA-IR			
RT Group	2.6 (0.6-6.6)	1.8 (0.5-5.1)	-29%†,¶,§
RI Group	2.5 (0.5-6.2)	2.9 (0.5-8.1)	+16%†
RO Group	2.4 (0.5-7.9)	2.7 (0.5-5.2)	+14%†
Systolic blood pressure (mm Hg)			
RT Group	153 ± 14	136 ± 19	-11%†
RI Group	152 ± 11	135 ± 15	-11%†
RO Group	151 ± 11	134 ± 14	-11%†
Diastolic blood pressure (mm Hg)			
RT Group	91 ± 10	81 ± 13	-11%†
RI Group	90 ± 9	82 ± 9	-9%†
RO Group	93 ± 8	83 ± 7	-13%†

RT: rosuvastatin + telmisartan, RI: rosuvastatin + irbesartan, RO: rosuvastatin + olmesartan, HDL-C: high density lipoprotein cholesterol, LDL-C: low density lipoprotein cholesterol, HOMA-IR: Homeostasis model assessment insulin resistance

**Values are expressed as mean SD [except for triglycerides and HOMA-IR that are expressed as median (range)]*

†p<0.05 vs baseline, ‡p<0.001 vs baseline, ¶p<0.01 vs RI group, §p<0.05 vs RO group

as assessed by platelet count, MPV, PDW and P-LCR are shown in **Table 3**. No changes *vs.* baseline were observed in any group. Moreover, changes of platelet indices were similar between groups (p=NS for all comparisons between groups).

4. Discussion

In the present study, we evaluated the effects of combining rosuvastatin with ARBs of different PPARγ activating capacity on platelet indices in hypertensive patients with mixed dyslipidemia and impaired fasting plasma glucose. No significant change in platelet count, MPV, PDW or P-LCR was observed after study end compared with baseline values in

Table 3. Common platelet indices at baseline and after 6 months of treatment*

	Baseline*	6 months*
Platelets (X10³/μL)		
RT Group	229 ± 41	229 ± 46
RI Group	267 ± 80	259 ± 81
RO Group	248 ± 46	243 ± 55
PDW (fL)		
RT Group	14.0 ± 1.6	14.3 ± 1.4
RI Group	13.3 ± 2.0	13.2 ± 1.8
RO Group	13.1 ± 1.3	13.4 ± 1.8
MPV (fL)		
RT Group	11.3 ± 0.8	11.4 ± 0.8
RI Group	11.0 ± 1.1	10.9 ± 1.0
RO Group	10.9 ± 0.8	11.0 ± 0.9
P-LCR (%)		
RT Group	36.0 ± 6.4	37.2 ± 6.1
RI Group	31.0 ± 10.8	32.1 ± 8.1
RO Group	32.3 ± 6.4	32.6 ± 7.3

RT: rosuvastatin + telmisartan, RI: rosuvastatin + irbesartan, RO: rosuvastatin + olmesartan
*PDW: Platelet distribution width, MPV: **Mean platelet volume**, P-LCR: Platelet larger cell ratio*
**Values are expressed as mean ± SD*

any group. Moreover, no differences between the 3 groups were noticed with regard to changes of these parameters.

Platelets are heterogeneous in size and density with larger platelets being metabolically and enzymatically more active and with higher aggregation [14-16]. The most commonly used marker of platelet size is MPV and is positively associated with other markers of platelet activity, such as increased platelet aggregation, thromboxane synthesis and expression of adhesion molecules[15]. Similarly, PDW (which is a measure of the variability in platelet size) and P-LCR (which refers to the percentage of large platelets) represent additional markers of platelet activation. The association of MPV with higher CVD risk is also corroborated by studies which showed elevated values of MPV in patients with diabetes mellitus, hypertension, hypercholesterolemia, smoking, and obesity[17-21]. Moreover, studies have shown that MPV is as an independent prognostic factor of outcomes in patients with CVD [22]. Similarly, PDW as well as P-LCR have been positively associated with the severity of coronary artery disease in CVD patients [23, 24].

There are limited studies evaluating the effect of rosuvastatin on platelet indices. A small study in primary dyslipidemic patients (n=30) showed that rosuvastatin 10 mg/day decreased MPV after 12 weeks of treatment compared with healthy controls [25]. Similarly, a single-treatment arm study evaluated the effects of high-dose rosuvastatin (40 mg/day) in diabetic patients after 6 months of treatment [26]. Rosuvastatin treatment was associated with a decrease of MPV without a correlation between the decrease of MPV and changes in lipid profile. However, the study had some important limitations. It was a retrospective study without a control group. Moreover, most patients received aspirin or clopidogrel, which may have affected MPV, although their dosages were unaltered during the study period. In addition, seasonal variations in MPV were not taken into account [27]. Indeed, it was shown that MPV has a seasonal variation with a peak in May/June [27].

The renin-angiotensin-aldosterone system is thought to play an important role in the enhancement of platelet aggregation. Indeed, angiotensin II can augment the epinephrine-induced plate-

let aggregation. Available data regarding the effect of ARBs on platelet function is scarce. Studies have shown that losartan decreased platelet aggregation by a thromboxane A2-dependent mechanism [28-30]. Similarly, both valsartan and telmisartan have shown a decrease of platelet activation in diabetic patients [31]. In addition, PPARγ activators have shown beneficial effects regarding platelet function. Indeed, pioglitazone has been associated with decreased platelet aggregation in diabetic patients [32]. On the other hand, no effect on platelet function was observed with pioglitazone in healthy subjects [33].

Our study did not show any difference between groups regarding common platelet indices. This could be attributed to a neutral effect of all treatment parameters on the measured platelet associated parameters. Moreover, the relatively small study population as well as the limited observation period could also contribute to the absence of differentiation between the 3 groups.

Common platelet indices could inform the clinician about the course of CVD. However, despite available literature these indices are not widely used in clinical practice. This may be due to the heterogeneity of results between different laboratories and variations in pre-analytical factors [34, 35]. Moreover, there are no evidence based data regarding the interpretation of platelet indices and the establishment of optimal cut-off levels for CVD risk stratification. In addition, there is no consensus regarding the best platelet index for predicting CVD risk, while many methods require specialized equipment and therefore cannot be implemented in everyday clinical practice. Furthermore, some studies have failed to demonstrate any association between common platelet indices and cardiovascular disease [36-38]. These conflicting results may be due to the aforementioned methodological differences and lack of measurement standards. As a result, larger and well-designed studies are needed to determine standardized reliable methods for the consistent measurement of platelet indices and identify their role in the estimation of CDV risk.

5. Study limitations

This was an open-label study with a relatively small number of patients and a short treatment observation period. However, endpoints were blindly assessed. A control group receiving rosuvastatin as monotherapy was not included since it was considered not ethical to further delay antihypertensive treatment in these patients. Moreover, changes in platelet indices associated with cardiovascular disease were not the primary endpoint of our study. Finally, seasonal variations of MPV were not considered, but this is the case in the vast majority of studies using MPV.

6. Conclusion

The combination of rosuvastatin with ARBs of different PPARγ activating capacity for 6 months was not associated with any changes in common platelet indices in hypertensive patients with mixed dyslipidemia and impaired fasting plasma glucose.

Conflict of Interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript. Some of the authors have given talks, attended conferences and participated in trials and advisory boards sponsored by various pharmaceutical companies.

Περίληψη

Η επίδραση σε δείκτες καρδιαγγειακού κινδύνου σχετιζόμενους με αιμοπετάλια του συνδυασμού ροσουβαστατίνης με αποκλειστές των υποδοχέων ΑΤ1 της αγγειοτενσίνης ΙΙ που διαθέτουν διαφορετική ικανότητα ενεργοποίησης των PPARγ υποδοχέων

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Εισαγωγή: Τα αιμοπετάλια διαδραματίζουν σημαντικό ρόλο στην εμφάνιση και την εξέλιξη της αθηροσκλήρωσης. Διάφοροι μορφολογικοί δείκτες των αιμοπεταλίων έχουν συσχετιστεί με τον κίνδυνο εμφάνισης καρδιαγγειακής νόσου. Η επίδραση της χορήγησης μίας αποτελεσματικής στατίνης μαζί με σαρτάνες που έχουν διαφορετική ενδογενή δυνατότητα διέγερσης των PPARγ υποδοχέων σε αυτούς τους δείκτες δεν είναι γνωστή.

Μέθοδοι: Ασθενείς (n = 151) με υπέρταση, δυσλιπιδαιμία και διαταραχή γλυκόζης νηστείας τυχαιοποιήθηκαν σε ροσουβαστατίνη (10 mg/ημέρα) μαζί με τελμισαρτάνη 80 mg/ημέρα (ομάδα RT, n = 52) ή ιρμπεσαρτάνη 300 mg/ημέρα (ομάδα RI, n = 48) ή ολμεσαρτάνη 20 mg/ημέρα (ομάδα RO, n = 51). Μετά από 6 μήνες θεραπείας αξιολογήθηκαν οι μεταβολές των μορφολογικών δεικτών των αιμοπεταλίων.

Αποτελέσματα: Μετά από 6 μήνες θεραπείας ο αριθμός των αιμοπεταλίων, ο μέσος όγκος αιμοπεταλίων, το εύρος κατανομής των αιμοπεταλίων και το ποσοστό των μεγάλων αιμοπεταλίων παρέμειναν αμετάβλητα σε όλες τις ομάδες. Επιπλέον, δεν παρατηρήθηκε καμία διαφορά μεταξύ των ομάδων.

Συμπεράσματα: Ο συνδυασμός της ροσουβαστατίνης με σαρτάνες που έχουν διαφορετική ικανότητα ενεργοποίησης των PPARγ υποδοχέων δεν συσχετίστηκε με μεταβολές στους μορφολογικούς δείκτες των αιμοπεταλίων.

Λέξεις ευρετηρίου: ροσουβαστατίνη, τελμισαρτάνη, ολμεσαρτάνη, ιρβεσαρτάνη, αιμοπετάλια, καρδιαγγειακός κίνδυνος

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