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Pharmacokinetic interactions between clopidogrel and rosuvastatin: Effects on vascular protection in subjects with coronary heart disease ☆

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Significant decrease in outcomes with statins administration in the first 24 h of an acute myocardial infarction [1–4] and reduction of myocardial injury markers after high-dose statin given few hours before percutaneous interventions [5,6] were observed. These effects of statins take place before lipid changes [7,8]. Clopidogrel, a pro-drug largely prescribed for patients undergoing stent implantation, is metabolized in the liver via cytochrome P450 (CYP2C19 and CYP3A4) to form an active metabolite that inhibits the P2Y(12) ADP platelet receptor [9,10]. Rosuvastatin is partially metabolized by CYP2C9 and CYP2C19 [11]. Functional and anatomical changes of the endothelium, an inflammatory substrate and coagulation activation participate on the pathophysiology of acute coronary syndromes [12,13]. New biomarkers, such as endothelial and platelet microparticles (EMP and PMP), endothelial progenitor cells (EPC), platelet function tests and endothelial-dependent flow-mediated dilation (FMD) have been proposed for the evaluation of vascular homeostasis [14,15]. Thus, we examined possible pharmacokinetic interactions between clopidogrel and rosuvastatin, and the consequences on these biomarkers.

The protocol was in accordance with the ethical standards of the institution on human experimentation and was approved by the local ethics committee [16]. Patients ($n = 20$) aging 49 to 77 years, with stable coronary artery disease were included after having signed a written informed consent. Enrolled subjects were receiving a stable dose of statin for at least 3 months. We excluded patients with baseline LDL-C above 100 mg/dL to prevent possible consequences of statins withdrawal [17–20], those with uncontrolled metabolic disorders, genetic dyslipidemias, class III/IV heart failure [21], and with intolerance to the study drugs. Prior statin was discontinued for a week in the screening visit, when they were scheduled to baseline visit under use of aspirin 100 mg daily. Fig. 1 summarizes the study design. We evaluated early effects of rosuvastatin and clopidogrel, alone or combined. All drugs were supplied to the patients. Biochemistry and lipid profile analyses were performed in samples obtained after a 12-hour fasting period in a central laboratory of our university by standard techniques. EPCs, EMPs and PMPs were determined by flow cytometry, as previously reported [15]. Multiple electrode platelet aggregometer (Multiplate 5.0 Analyzer, Diapharma, Diapharma Group Inc., Munich, BV, Germany) tests were performed as reported before [22–24]. Aggregation was induced by collagen (COL), thrombin receptor activating peptide 6 (TRAP-6), adenosine-diphosphate (ADP), and arachidonic acid (ASP), performed in duplicate.

For pharmacokinetic studies blood samples were collected at 0, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 6.0, 8.0, 10.0, 12.0, 16.0 and 24.0 h post-dosing of the compound of reference. Plasma levels of rosuvastatin and clopidogrel were measured by using validated liquid chromatography with mass spectrometry as previously described [25,26]. FMD of the brachial artery was assessed at each visit by ultrasound (HP 5500) using a high-frequency transducer, as previously reported [27]. Variables were compared between time points using ANOVA-repeated measures followed by Tukey-test or Friedman test, when appropriate. Pharmacokinetic analyses were performed as previously described [26]. Tests were two-tailed and significance was set at a p-value <0.05.

Major characteristics of the study participants are shown in Table 1. Fig. 2 shows remarkable changes on LDL-cholesterol levels after statin withdrawal (+61%) and introduction (−39%). We observed lower platelet aggregation to ASP and COL (under aspirin), as well as to ADP tests (under clopidogrel alone or combined with rosuvastatin), whereas responses to TRAP-6 were unchanged (Fig. 3). Improvement in FMD was observed 24-h after rosuvastatin initiation and it was maintained up to

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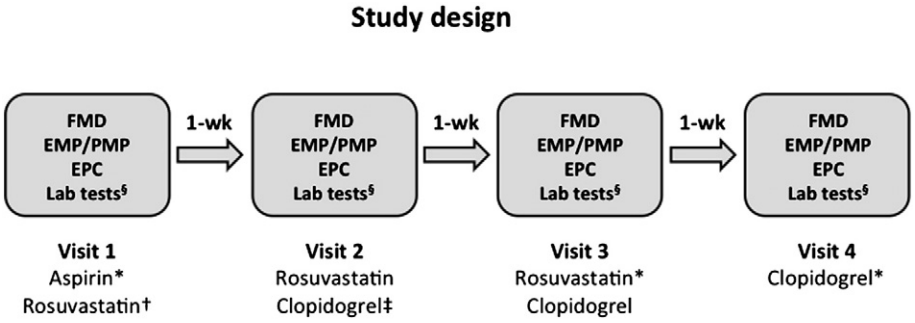

Fig. 1. Study design. FMD = flow mediated dilation of the brachial artery; EMP/PMP = endothelial microparticles/platelet microparticles; EPC = endothelial progenitor cells; §lab tests include platelet aggregation tests and pharmacokinetic studies for rosuvastatin and clopidogrel; *last dose; †starting dose; ‡loading dose. Rosuvastatin was given at daily dose of 40 mg; clopidogrel loading dose was 300 mg, followed by 75 mg daily. The FMD was performed at time 0 and after 24 h on each visit. Platelet aggregating tests in samples were obtained at each visit before initiation of therapy. All patients were under stable dose of statin in the last 3 months achieving LDL-C < 100 mg/dL. The statin therapy was stopped for a week prior to visit 1.

last visit (Fig. 4). We observed an interaction with clopidogrel, increasing the AUC_{last} and C_{max} of rosuvastatin; however, rosuvastatin did not modify clopidogrel pharmacokinetics (Table 2). There was a trend for higher levels of CD34 + /CD133 + subpopulation of EPCs on visit 3. After rosuvastatin withdrawal, an increase in the amount of PMP and a trend for increased levels of EMP were observed (Table 3).

Table 1
Baseline characteristics of study population.

Characteristic	Values
Patients, *n* (%)	20 (100)
Age, median (interquartile range)	58 (52–64)
Sex, *n* (%)	
Male	14 (74)
Female	6 (26)
Ethnicity, *n* (%)	
Caucasian	17 (85)
Afro descendant	3 (15)
Weight, kg, mean (SEM)	79.2 (3.1)
Body mass index, kg/m^2, mean (SEM)	29.3 (1.0)
Systolic blood pressure, mm Hg, mean (SEM)	121 (3)
Diastolic blood pressure, mm Hg, mean (SEM)	75 (2)
Medical history, *n* (%)	
Prior myocardial infarction	15 (75)
Unstable angina	1 (5)
Stable angina	3 (15)
Coronary artery bypass graft	3 (15)
Percutaneous coronary intervention	13 (65)
Hypertension	18 (90)
Diabetes mellitus	6 (30)
Active smokers	4 (20)
Medications, *n* (%)	
Statins	20 (100)
ACEIs/ARBs	15 (75)
β-blockers	15 (75)
Calcium channel blockers	7 (35)
Diuretics	8 (40)
Aspirin	20 (100)
Nitrates	2 (10)
Sulphonylureas/metformin	7 (35)
Insulin	2 (10)
Fasting glucose, mg/dL, mean (SEM)	104 (4)
Creatinine, mg/dL, mean (SEM)	0.98 (0.04)
CK, IU, mean (SEM)	137 (27)
ALT, IU, mean (SEM)	24 (2)

Baseline characteristics of the study population at visit 1. ACEIs = angiotensin-converting enzyme inhibitors; ALT = alanine aminotransferase; ARBs = angiotensin II receptor blockers; CK = creatine phosphokinase. Statins were withdrawn one-week before.

Our study reports interaction between clopidogrel and rosuvastatin, increasing rosuvastatin concentrations. As rosuvastatin is active independently of its metabolization [28], concomitant clopidogrel therapy does not reduce its benefits, as per the early and sustained lipid changes, and the impressive improvement in FMD 24-h after statin initiation. Abrupt statin withdrawal leads to an overshoot activation of HMG-CoA reductase, Rho and Rac with loss of the pleiotropic effects [29]. Rosuvastatin seems to act synergistically with clopidogrel. Riondino et al. [30] demonstrated neutral effects of rosuvastatin on platelet inhibition by clopidogrel. Our study showed, dynamically, the effects of rosuvastatin and clopidogrel introduction/withdrawal not only on platelet function, but also on EPCs mobilization and MPs release. In fact, rosuvastatin withdrawal increased the amount of PMP, suggesting augmented platelet consumption or apoptosis [31,32]. The observed trend for lower percentages of EPCs and higher levels of EMPs 1 week after rosuvastatin withdrawal, seems to imply the importance of the maintenance of combined therapy for a more comprehensive cardiovascular protection. Interestingly, the interaction between clopidogrel on plasma levels of rosuvastatin occurred exclusively after the loading dose (300 mg) and not with the 75 mg dose. On this view, some pleiotropic effects of statins in the first 24-h of myocardial infarction appear to play an important role in the early cardiovascular outcomes, and can be due to recovery of ischemic tissue in areas surrounding the necrotic core, probably due to the improvement of the microcirculation [33,34].

Most of the absorbed clopidogrel (~85%) is hydrolyzed by hepatic carboxylesterase to an inactive carboxylic acid metabolite, and the remaining ~15% is converted to an active thiol metabolite in a 2-step process [9,10]. CYP2C19, CYP1A2, and CYP2B6 isoenzymes are responsible for the first step, whereas CYP2C19, CYP2C9, CYP2B6, and CYP3A4 are responsible for the second step [9]. The extrapolation of our findings to statins that are pro-drugs seems premature. In addition, liver metabolization by other isoenzymes may produce other interactions and lack of synergistic effects with clopidogrel [35,36]. It is possible that changes in the amount of MPs and EPCs are more pronounced among statin naïve patients. We suggest a beneficial synergism between clopidogrel and rosuvastatin, determining a broader cardiovascular protection than that provided by each drug alone.

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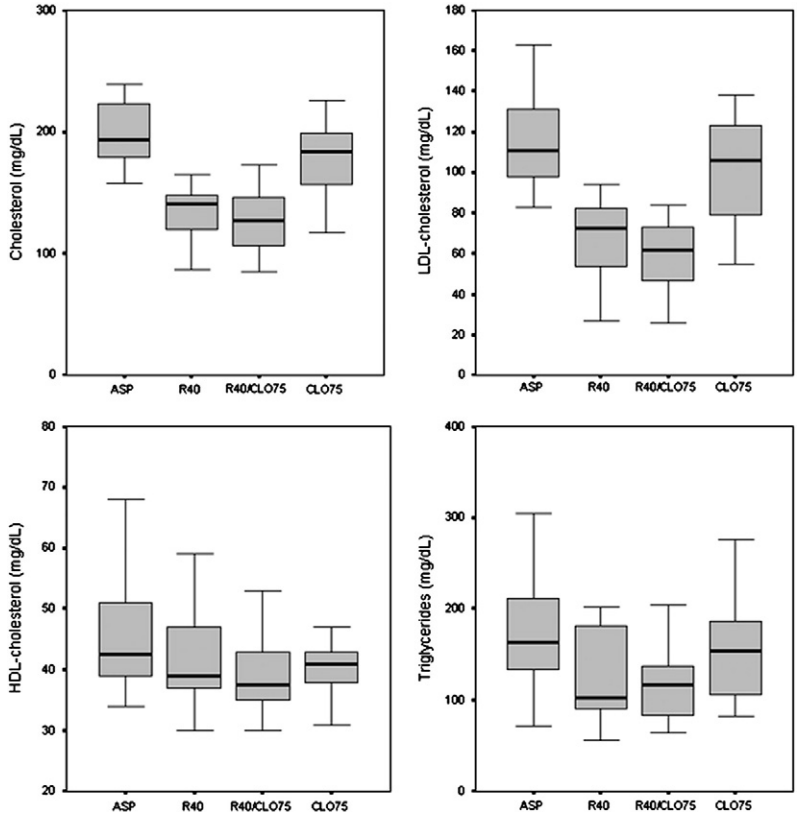

Fig. 2. Box-plots showing lipid changes by treatment at each visit. visit 1: ASP = aspirin 100 mg; visit 2: R40 = rosuvastatin 40 mg; visit 3: R40/CLO75 = rosuvastatin 40 mg + clopidogrel 75 mg; visit 4: CLO75 = clopidogrel 75 mg. Cholesterol serum levels at visit 1 > visit 2 and visit 3 ($p < 0.0001$); LDL-cholesterol serum levels at visit 1 > visit 2 and visit 3 ($p < 0.0001$); HDL-cholesterol and triglycerides serum values were not changed by treatments ($p = 0.44$ and $p = 0.17$, respectively). All analyses were made by ANOVA–Tukey.

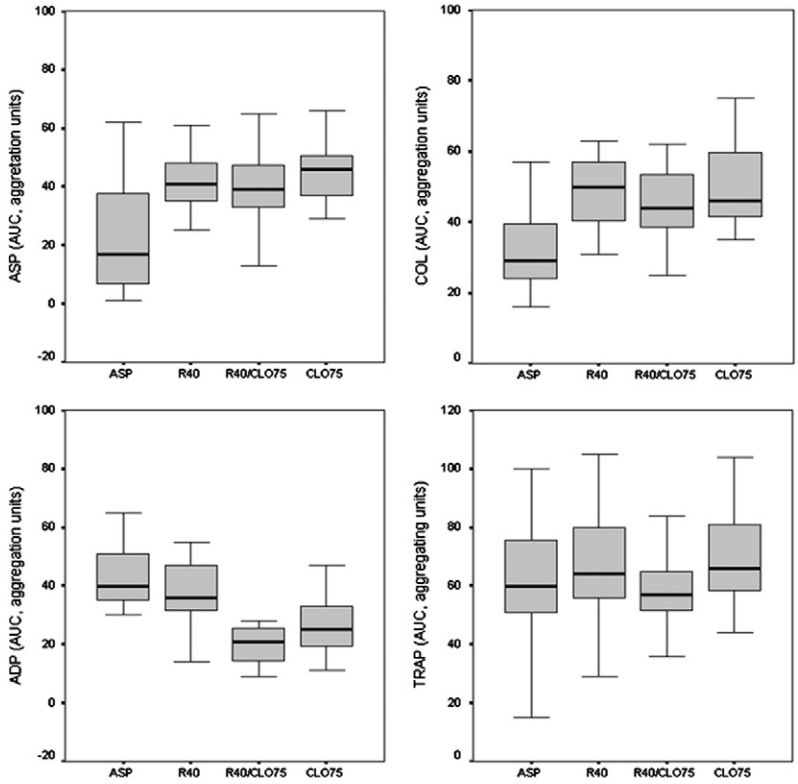

Fig. 3. Box-plots showing platelet aggregation tests by treatment. Visit 1: ASP = aspirin 100 mg; visit 2: R40 = rosuvastatin 40 mg; visit 3: R40/CLO75 = rosuvastatin 40 mg plus clopidogrel 75 mg; visit 4: CLO75 = clopidogrel 75 mg. All samples were obtained with the patients hospitalized immediately before drug administration. ASPtest—activation by arachidonic acid; COLtest—activation by collagen; ADPtest—activation by adenosine diphosphate; TRAPtest—activation by thrombin; AUC = area under the curve in aggregation units. ASPtest: visit 1 < visit 2, visit 3, and visit 4 ($p < 0.0001$); COLtest: visit 1 < visit 2, and visit 4 ($p = 0.008$); ADPtest: visit 1 and visit 2 > visit 3 and visit 4 ($p < 0.0001$); TRAPtest: unchanged between visits ($p = 0.53$). All analyses were made by ANOVA–Tukey.

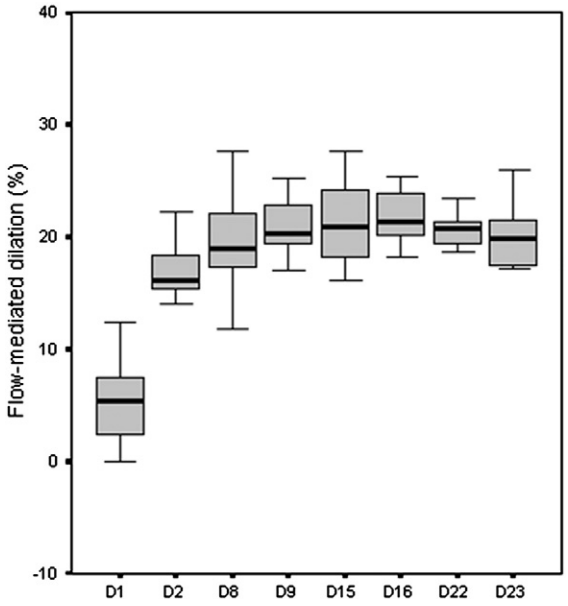

Fig. 4. Box-plots showing flow-mediated dilation (FMD) of the brachial artery by treatment. Values were obtained at each visit and 24 h after hospitalization; D = day. D1 = aspirin 100 mg; D2 = rosuvastatin 40 mg; D8 = rosuvastatin 40 mg; D9 = rosuvastatin 40 mg + clopidogrel 300 mg; D15 = rosuvastatin 40 mg + clopidogrel 75 mg; D16 = rosuvastatin 40 mg + clopidogrel 75 mg; D22 = clopidogrel 75 mg; D23 = clopidogrel 75 mg. FMD at visit 1 < FMD 24 h after the initiation of rosuvastatin 40 mg and all FMD dilation obtained in the subsequent visits ($p < 0.0001$, ANOVA–Tukey).

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Table 2
Pharmacokinetic parameters for clopidogrel and rosuvastatin, by treatment.

	Visit 1	Visit 2	Visit 3	Visit 4
	Rosuvastatin	Rosuvastatin + clopidogrel	Rosuvastatin + clopidogrel	clopidogrel
Rosuvastatin				
AUC_{last}, ng h/mL	178 (25)	304 (44)*	261 (41)*	NA
AUC_{inf}, ng h/mL	262 (41)	514 (83)	368 (54)	NA
C_{max}, ng/mL	22.9 (4.2)	29.8 (4.3)†	24.2 (3.1)	NA
T_{max}, h	4.37 (1.23)	3.26 (0.31)	3.50(031)	NA
T1/2, h	10.77 (1.28)	14.98 (1.59)	12.78 (1.31)	NA
Ke, 1/h	0.08 (0.01)	0.05 (0.00)	0.06 (0.01)	NA
Clopidogrel				
AUC_{last}, ng h/mL	NA	37 (10)	10 (3)	10 (2)
AUC_{inf}, ng h/mL	NA	42 (11)	13 (3)	10 (3)
C_{max}, ng/mL	NA	42 (11)	3.2 (0.7)	3.3 (0.7)
T_{max}, h	NA	1.45 (0.19)	1.53 (0.31)	1.21 (0.19)
T1/2, h	NA	6.27 (0.72)	6.02 (1.12)	6.37 (1.29)
Ke, 1/h	NA	0.14 (0.02)	0.28 (0.07)	0.30 (0.09)

Visit 1 = rosuvastatin 40 mg; visit 2 = rosuvastatin 40 mg + clopidogrel 300 mg; visit 3 = rosuvastatin 40 mg + clopidogrel 75 mg; visit 4 = clopidogrel 75 mg. AUC_{last} = the areas under the clopidogrel and rosuvastatin plasma concentration vs. time curves from 0 to the last detectable concentration; AUC_{inf} = extrapolation of these areas to infinity; C_{max} = maximal concentration; T_{max} = time to achieve the maximal concentration; T1/2 = half-life; Ke = the first-order terminal elimination rate constant; NA = not applicable. *$p < 0.0001$, ANOVA-repeated measures; visit 1 < visit 2, $p < 0.001$; visit 1 < visit 3, $p < 0.01$, Tukey–Kramer test. †$p = 0.0114$, ANOVA repeated measures; visit 1 < visit 2, $p < 0.05$, Tukey–Kramer test.

Table 3
Levels of endothelial progenitor cells and microparticles, by treatment.

Variable	Visit 1	Visit 2	Visit 3	Visit 4	*p*-Value
	Aspirin	Rosuvastatin	Rosuvastatin + clopidogrel	Clopidogrel	
Endothelial progenitor cells, %					
CD34 +/KDR +	0.11 (0.04)	0.08 (0.05)	0.06 (0.02)	0.13 (0.04)	0.66
CD34 +/CD133 +	0.03 (0.01)	0.02 (0.01)	0.030 (0.005)	0.023 (0.005)	0.059
CD133 +/KDR +	0.06 (0.05)	0.003 (0.003)	0.02 (0.02)	0.003 (0.003)	0.54
Microparticles, number per μL PPP					
Endothelial microparticles	1498 (489)	1397 (543)	2975 (790)	3737 (932)	0.059
Platelet microparticles	31,446 (8205)	26,050 (5797)	37,510 (10,049)	74,063 (16,070)	0.035

Visit 1 = rosuvastatin 40 mg; visit 2 = rosuvastatin 40 mg + clopidogrel 300 mg; visit 3 = rosuvastatin 40 mg + clopidogrel 75 mg; visit 4 = clopidogrel 75 mg.
Endothelial progenitor cells are expressed as % of the lymphocyte gate; microparticles as counts per μL of poor platelet plasma (PPP). Comparisons between treatments were made by the Friedman test.

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Strong link between basal and exercise-induced cardiac troponin T levels: Do both reflect risk?☆

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Elevated serum cardiac troponin (cTn) levels are not restricted to acute coronary syndrome (ACS), but are also frequently observed in healthy individuals during and after prolonged endurance-type exercise [1]. The magnitude of exercise-induced cTn release can vary tremendously among individuals, from virtually no response to more than ten times the diagnostic threshold for acute myocardial infarction (AMI) [2]. Studies to date have examined cTn levels in heterogeneous athlete populations during single or unstandardized ultra-endurance events, complicating the identification of factors involved, or the mechanisms underlying exercise-induced cTn elevations.

Using a homogeneous group of endurance-trained athletes, we examined exercise-induced cardiac troponin T (cTnT) elevations in a standardized laboratory-based setting to assess the reproducibility, identify predisposing factors and obtain evidence for a physiologic or pathologic nature of this phenomenon. This study was approved by the Medical Ethical Committee of the Maastricht University Medical Center and all participants gave written informed consent. Thirty-one male endurance-trained competitive cyclists (age 25 ± 5 years, bodyweight 73 ± 7 kg, maximal oxygen consumption (VO_{2max}) 60 ± 5 mL kg^{-1} min^{-1}, weekly training 11 ± 4 h) completed two identical standardized exercise trials, at a one week interval. The

Abbreviations: cTn, cardiac troponin; ACS, acute coronary syndrome; AMI, acute myocardial infarction; cTnT, cardiac troponin T; VO_{2max}, maximal oxygen consumption; W_{max}, maximum workload capacity; RCV, reference change value; CV_{tot}, median coefficient of total variation.

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