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Long-term effect of molsidomine, a direct nitric oxide donor, as an add-on treatment, on endothelial dysfunction in patients with stable angina pectoris undergoing percutaneous coronary intervention: Results of the MEDCOR trial

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ABSTRACT

Objective: The MEDCOR trial is a double-blind, randomized study aiming at demonstrating the superiority of molsidomine (direct NO donor) over placebo, used as add-on treatments, on improving endothelial function (EF) after 12 months, in stable angina patients undergoing percutaneous coronary intervention.
Methods: EF was assessed by peripheral vasodilator response (i.e. Endoscore) using arterial tonometry and by several biomarkers, in terms of changes versus baseline after a one-year treatment.
Results: The change in Endoscore was +75 ± 130% in placebo group and +39 ± 145% in molsidomine group ($p = 0.143$). There was a decrease in sICAM-1 with molsidomine (−6%) and an increase with placebo (+6%). The MPO activity/antigen ratio slightly increased with placebo (+9%) and strongly decreased with molsidomine (−42%) ($p = 0.020$).
Conclusion: The MEDCOR trial was not able to demonstrate significant differences between molsidomine and placebo for all parameters, except the MPO activity/antigen ratio which significantly decreased with molsidomine ($p = 0.020$ versus placebo).

1. Introduction

One of the mechanisms underlying a potential improvement of endothelial dysfunction (ED) in atherosclerosis relies upon the bioavailability of nitric oxide (NO) [1].

Molsidomine [2,3] is a direct NO donor that compensates for its loss of production by the injured vascular endothelium in patients with coronary artery disease (CAD). Molsidomine has been associated with vascular plaque stabilization and reduction of oxidative stress in cholesterol-fed rabbits [4]. In patients with established CAD, a significant improvement of endothelial dysfunction ($p = 0.020$) was reported after 48 h of molsidomine administration [5]. Moreover, a one-year molsidomine administration has been demonstrated to significantly reduce episodes of angina and to

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Table 1
Comparisons of demographics, disease history, Endoscore, biomarkers and microparticles between the placebo and the molsidomine groups at baseline.

	Placebo (N = 28)			Molsidomine (N = 20)			P value
	n	Mean or %	SD	n	Mean or %	SD	
Age (year)	28	64.1	9.9	18	62.4	10.2	0.612
BMI (kg/m^2)	28	28.0	2.9	18	29.2	4.4	0.386
Disease duration (year)	28	4.0	5.8	18	4.7	6.4	0.392
Endoscore	28	0.17	0.17	18	0.19	0.14	0.919
Endothelial MP (/μL plasma)	27	17.5	13.7	16	18.5	15.7	0.890
Platelet MP (/μL plasma)	27	3994	8569	16	2524	2577	0.669
Leukocyte MP (/μL plasma)	27	203	141	16	210	176	0.624
sICAM-1 (ng/mL)	28	233	99	18	210	66	0.589
hs-CRP (mg/L)	28	3.3	6.6	17	4.0	9.9	0.725
MOX-LDL (μg/mL)	28	1.46	0.89	17	1.52	1.07	0.888
MPO antigen (ng/mL)	28	52.7	58.9	17	33.6	9.4	0.761
MPO activity (ng/mL)	28	8.61	6.38	17	10.03	4.95	0.171
MPO activity/antigen ratio	28	0.22	0.15	17	0.30	0.15	0.075
Gender (male)	23	82.1		16	88.9		0.688
Smoking status							
- Non-smoker	9	32.1		5	27.8		0.269
- Previous smoker	14	50.0		6	33.3		
- Smoker	5	17.9		7	38.9		
Randomization stratification							
- Statin (yes)	25	89.3		17	94.4		1.000
- DES (yes)	21	75.0		14	77.8		1.000
- ACEI (yes)	6	21.4		9	50.0		0.354
Cardiac revalidation (yes)	7	25.0		8	44.4		0.208

SD = Standard deviation; BMI = Body Mass Index; MP = microparticles; sICAM-1 = Soluble Intercellular Adhesion Molecule-1; hs-CRP = high sensitivity-C-Reactive Protein; MOX-LDL = Myeloperoxidase Oxidized-Low Density Lipoprotein; MPO = Myeloperoxidase; DES = Drug-Eluting Stent; ACEI = Angiotensin-Converting Enzyme Inhibitor. P values were determined by Mann–Whitney's tests for continuous variables, and by chi-square or Fisher's exact tests (as appropriate) for discrete variables.

Table 2
Relative changes of the Endoscore, endothelial biomarkers and microparticles (%) at month 12 versus mean baseline in the placebo and molsidomine groups.

	Placebo (N = 28)			Molsidomine (N = 20)			P value
	n	Mean (%)	SD (%)	n	Mean (%)	SD (%)	
Endoscore	28	+75	130	18	+39	145	0.143
Endothelial microparticles	26	−40	42	16	−40	75	0.623
Platelet microparticles	26	−22	252	16	+0	101	0.623
Leukocyte microparticles	26	−37	29	16	−39	83	0.501
sICAM-1	25	+6	47	18	−6	51	0.522
hs-CRP	25	−35	163	17	−50	237	0.555
MOX-LDL	25	+41	83	17	+11	80	0.288
MPO antigen	24	−32	128	17	−1	19	0.255
MPO activity	24	+8	149	17	−43	51	0.112
MPO activity/antigen ratio	24	+9	68	17	−42	60	0.020

SD = Standard deviation; sICAM-1 = Soluble Intercellular Adhesion Molecule-1; hs-CRP = high sensitivity-C-Reactive Protein; MOX-LDL = Myeloperoxidase Oxidized-Low Density Lipoprotein; MPO = Myeloperoxidase. P values determined by Mann–Whitney's tests.

decrease the levels of soluble intercellular adhesion molecule-1 (sICAM-1), a well-known biomarker of endothelial damage [6].

The objective of the MEDCOR trial [7] was to demonstrate the superiority of molsidomine, as an add-on treatment to best of care medical therapy, over placebo on improving the endothelial function (EF) after 12 months of treatment in stable angina patients undergoing elective percutaneous coronary intervention (PCI).

2. Methods

The design of the MEDCOR trial (ClinicalTrials.gov NCT01363661) has previously been published [7]. Briefly, patients who underwent PCI for stable angina pectoris were included in this double-blind, parallel-group, randomized, multicenter and placebo-controlled study, if they fulfilled the following inclusion criteria: aged at least 18 years, no treatment with molsidomine and/or long-acting nitrates (oral or patches) for more than 48 h during the month preceding PCI and no treatment with these same drugs within 3 days before PCI, and written informed consent. In addition, to be included in the MEDCOR trial, patients needed to have an Endoscore index <0.40 (EndoPAT, Itamar Medical Ltd., Israel) after the PCI [8].

Patients were assigned to molsidomine (Coruno® 16 mg) or placebo once daily during one year (randomization 1:1). They were used as add-on treatments. Cardiac revalidation and all the other medications were allowed, except drugs directly interacting with NO.

The endothelial biomarkers sICAM-1, high sensitivity-C reactive protein (hs-CRP), myeloperoxidase (MPO) (antigen, activity and activity/antigen ratio) and myeloperoxidase oxidized-LDL (MOX-LDL) were analyzed at CHU Vésale, Montigny-le-Tilleul, Belgium, in sera samples, using ELISA kits and the MPO activity assay kit. The endothelial, platelet and leukocyte microparticles (MPs) were analyzed at OLVZ, Aalst, Belgium, in plasma samples, using flow cytometry [9–18].

The study was conducted in accordance with the International Conference on Harmonization Guideline for Good Clinical Practice and the Declaration of Helsinki. The protocol was submitted to Independent Ethics Committees for approval.

Results were analyzed in terms of relative changes versus mean baseline after one year of treatment [19]. The primary endpoint was