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Improving Arterial Wall Characteristics in Patients After Myocardial Infarction with a Very Low Dose of Fluvastatin and Valsartan: A Proof-of-Concept Study

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Data Interpretation D
Manuscript Preparation E
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Background: We tested the concept of improving arterial wall characteristics by treatment with a very low-dose combination of fluvastatin and valsartan (low-flu/val) in stable, post-myocardial infarction (MI) patients.

Material/Methods: We enrolled 36 post-MI middle-aged males in the treatment (n=20) or control (n=16) group receiving low-flu/val (10 mg/20 mg) or placebo, respectively. The parameters of endothelial function (flow-mediated dilatation (FMD), reactive hyperemia index), and arterial stiffness (carotid-femoral pulse wave velocity (cf-PWV), local carotid PWV, and beta stiffness coefficient) were measured before and after 30 days of therapy, and 10 weeks later.

Results: Treatment with low-flu/val improved FMD from 3.1±1.3% to 4.8±1.5% ($p<0.001$; by 54.8%) and cf-PWV from 7.8±1.1 to 6.7±1.5 m/s ($p<0.01$; by 14.1%) without affecting either lipids or blood pressure. In the treatment group, FMD and/or cf-PWV significantly improved in 17 patients, but the improvements did not correlate. The benefits obtained were still detectable 10 weeks after complete treatment cessation. No changes were obtained in the control group. No other vascular parameters changed.

Conclusions: Low-flu/val added "on top of" optimal therapy substantially improves endothelial function and arterial stiffness in post-MI patients. Since these improved parameters are well-known predictors of future coronary events, such treatment could decrease cardiovascular risk. Further studies are therefore warranted.

MeSH Keywords: Myocardial Infarction • Pulse Wave Analysis • Vascular Stiffness

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Background

Coronary artery disease is associated with generalized changes of arterial function and structure. Thus, endothelial dysfunction as noninvasively determined by impaired flow-mediated dilatation (FMD) is well-documented in patients with coronary artery disease and linked to an increased risk of cardiovascular events [1–3]. The same is reported for increased arterial stiffness, a major marker of which is increased carotid-femoral pulse wave velocity (cf-PWV) [4–6].

Secondary prevention medications after myocardial infarction (MI) are well established by the guidelines [7]. It should be emphasized that a substantial proportion of patients show no improvement in arterial wall characteristics despite following the proposed conventional therapy. Accordingly, studies report persistently impaired FMD in 41% and PWV in 53% of patients with coronary artery disease after 6 months of optimized therapy. Furthermore, it has been shown that coronary artery disease patients who were poor responders in terms of FMD and PWV improvement (as the result of conventional therapy, risk factors modification and lifestyle) had clearly worse cardiovascular prognosis [8,9]. Hence, novel approaches specifically targeting functional and structural arterial wall impairments and consequently reducing residual cardiovascular risk after MI are highly desired.

Prior studies conducted by our research group have shown improvement of endothelial function and arterial stiffness by using a combination of very low, sub-therapeutic doses of fluvastatin and valsartan (low-flu/val) in middle-aged apparently healthy men and in diabetes mellitus type 1 and type 2 patients, without affecting either lipids or blood pressure [10–12]. Based on these clinical findings as well as animal studies [13,14], we hypothesized that similar beneficial pleiotropic effects of low-flu/val could be also generated in patients after MI. Importantly, "on top of" treatment with low-flu/val has already been applied in diabetes mellitus type 2 patients and the beneficial effects have clearly been demonstrated independent of concomitant use of therapeutic doses of angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs) and statins [15]. Therefore, we assumed that a similar effect could be achieved in already optimally-treated post-MI patients.

Overall, the aim of the present double-blind randomized study was to explore whether endothelial function and arterial stiffness in patients after MI could be improved by low-flu/val added "on top of" regular post-MI therapy.

Material and Methods

Participants

Thirty-six males aged under 55 years with a history of MI in the last 0.5 to 5 years were included. They suffered from MI type 1 presenting with ST-segment elevation (STEMI, 12 participants) or without persistent ST-segment elevation (NSTE-ACS, 14 participants) that was followed by percutaneous coronary intervention and revascularization of the target lesion. They were all receiving stable therapy as recommended by the guidelines [7]. Exclusion criteria were diabetes mellitus, manifest peripheral artery disease or carotid artery disease, acute infection, chronic diseases (infectious, autoimmune, and malignant) and present therapy with fluvastatin and/or valsartan. The average age of participants was 47.5±5.2 years, 7 (19.4%) were current smokers, 29 (80.6%) of the participants were receiving ACE inhibitors, 4 (11.1%) were receiving ARBs, and 35 (97.2%) were receiving statins, predominantly at moderate doses. The average percentage of used doses as a fraction of maximal doses was: 45%, 38%, and 49%, for ACE inhibitors, ARBs and statins, respectively. Furthermore, all included participants (100%) were taking acetylsalicylic acid, 17 (47.2%) were taking clopidogrel, prasugrel, or ticagrelor, and 30 (83.3%) were taking beta blockers as part of their regular therapy. Baseline characteristics are shown in Table 1.

Study design

A randomized, double-blind pilot study was conducted. The study was approved by the National Medical Ethics Committee of Slovenia, and is therefore compliant with the Declaration of Helsinki and its later amendments. The participants were recruited among attendees of the post-MI rehabilitation program at the University Medical Center Ljubljana. All participants signed informed consent. They were randomly divided into 2 groups: the treatment group that received 10 mg of fluvastatin and 20 mg of valsartan per orally (n=20) for 30 days (low-flu/val), and the control group that received a placebo (n=16). Low-flu/val and placebo were given in the form of tablets identical in appearance that were packed in opaque containers by an independent pharmacist. Computerized random numbers were then allocated to containers and the key was stored in the safe deposit box of the pharmacist. The participants were also assigned computerized random numbers and then got the container with the corresponding number. The key with numbers allocation was revealed by the pharmacist after the complete data collection. The participants' compliance was checked by interview and counting pills remaining in the container at the second visit. All participants were completely compliant to the regimen.

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Table 1. Baseline characteristics of the treatment and the control group.

	Treatment group (n=20)	Control group (n=16)	
Age, years	46.7±5.0	48.5±5.5	ns
Body mass index, kg/m^2	30.2±3.3	29.0±4.1	ns
Heart rate, bpm	57.0±8.2	57.4±9.0	ns
Time after myocardial infarction at inclusion, months	25.1±19.4	27.2±16.7	ns
ACE inhibitors in regular therapy, No. of participants	16	13	ns
Ramipril	4	3	
Perindopril	11	8	
Zofenopril	1	2	
Angiotensin II receptor blockers in regular therapy, No. of participants	3	1	ns
Candesartan	2	0	
Telmisartan	1	1	
Statins in regular therapy, No. of participants	19	16	ns
Atorvastatin	8	5	
Simvastatin	1	0	
Rosuvastatin	10	11	
Flow mediated dilatation, %	3.1±1.3	3.2±1.5	ns
Beta stiffness coefficient, U	8.6±3.0	7.9±1.8	ns
Carotid pulse wave velocity, m/s	6.3±1.2	6.0±0.8	ns
Carotid-femoral pulse wave velocity, m/s	7.8±1.1	7.1±1.0	ns
Reactive hyperemia index	1.9±0.5	1.9±0.5	ns

The values are mean ±SD or number (No.) of participants. ns – no significance.

All measurements were performed at the beginning of the study, after 30 days, and at 10 weeks after treatment discontinuation. The participants were systematically asked about any abnormality or adverse effect on every visit. Visits were always scheduled at the same time of the day. Participants were instructed to refrain from food or nicotine intake for 8 h, from caffeine or alcohol intake for 12 h, and from strenuous physical activity for 24 h before the visit. They were also asked not to change their lifestyle habits throughout the study. No changes to their regular post-MI therapy were made. Prior to measurement they laid supine for 10 min to allow standard acclimatization. Peripheral blood pressure was measured using an automated sphygmomanometer (Wellch & Allyn; Skaneateles Falls, USA) on the contralateral arm on which measurements of endothelial function were performed. The following primary endpoints were assessed: FMD, reactive hyperemia index (RHI), carotid pulse wave velocity (c-PWV), beta stiffness coefficient, and cf-PWV. Ultrasound parameters (FMD, beta stiffness coefficient, and c-PWV) were determined using an Aloka Pro-Sound Alpha 10 echo-machine (Hitachi Aloka Medical America, Inc.) with an integrated high-resolution e-Tracking system. Cf-PWV was measured using a SphygmoCor device (AtCor Medical Inc., Sydney, Australia) with CvMS software, while RHI was obtained using an Endopat 2000 device (Itamar Medical Ltd, Caesarea, Israel).

Assessment of arterial wall parameters

Brachial artery flow-mediated dilatation (FMD)

FMD measurements were taken in accordance with the established guidelines [16]. The participants laid supine, with their right arm extended on a foam cushion. The right brachial artery was visualized approximately 5–10 cm above the antecubital fossa and paired cursors were placed on its anterior and posterior wall. Continuous recording of arterial diameter was conducted in baseline conditions (for 1 min), during compression of the forearm by an inflated cuff to 50 mmHg above the systolic pressure (for 4 min), and during the reactive hyperemia phase following rapid cuff deflation (for 3 min). Continuous recording of arterial diameter and automatic calculation of FMD (ratio of maximal diameter during reactive hyperemia and baseline diameter) was enabled by use of the e-Tracking software.

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Carotid pulse wave velocity (c-PWV) and carotid beta stiffness coefficient

Measurements were performed on the right common carotid artery of participants in a supine position with the head tilted 30° to the left and elevated by approximately 45°. Paired cursors were placed on the posterior and anterior wall of the common carotid artery (approximately 2 cm before the bifurcation) to allow continuous pulse wave analysis. Beta stiffness coefficient and c-PWV were automatically deduced from 12 consecutive pulse wave amplitudes calculated from the relation between systemic blood pressure and changes in artery diameter [5].

Carotid-femoral pulse wave velocity (cf-PWV)

Cf-PWV measurement was performed with a SphygmoCor device following the Consensus document on arterial stiffness determination [17]. With patients in the supine position, pulse waveforms were acquired at the right carotid and right femoral artery. Cf-PWV was automatically calculated by dividing the distance traveled by the transit time. The distance traveled was determined as the difference between the distance from the sternal notch to the measuring site on the femoral artery and from the sternal notch to the measuring site on the carotid artery.

Reactive hyperemia index (RHI)

RHI was obtained by plethysmographic recording of the finger arterial pulse wave amplitude using an Endopat device as previously described [18]. The participants were in a semi-sitting position with extended forearms on a foam arm-rest under a 40° angle. Pneumatic probes were placed on both index fingers. The probes were inflated to 70 mmHg and the signal in baseline conditions was acquired for 5 min. Then, the cuff (which was now positioned on the left forearm) was inflated to 60 mmHg above the systolic pressure for 5 min. After the cuff was rapidly deflated, the signal was acquired for another 5 min. The RHI was automatically calculated from the ratio of average pulse wave amplitudes on the tested and control arm during the reactive hyperemia phase and baseline phase.

Laboratory parameters

Fasting venous blood samples were collected from all participants at their inclusion in the study and after 30 days of treatment. Blood serum concentrations of electrolytes, total cholesterol, high-density lipoprotein cholesterol, and triglycerides were determined through a VITRO 5.1FS Chemistry System (Ortho Clinical Diagnostics Inc.). The low-density lipoprotein cholesterol values were calculated using the Friedewald formula.

Statistical methods

The values are expressed as mean ± standard deviation (SD). The initial values in the treatment group and control group were compared through the *t* test for independent samples (for ratio values) or through the chi-square test (for nominal values). The *t* test for independent samples was also used for the comparison of absolute change of FMD and relative change of cf-PWV as follows: between the treatment and control group, between subgroups of the treatment group with cholesterol at and above target level, and between subgroups of the treatment group taking moderate- *vs.* high-intensity statins in regular therapy. The change in parameters after 30 days and 10 weeks was analyzed through the paired *t* test. Pearson correlation coefficient was calculated for FMD and cf-PWV. *P*-values below 0.05 were considered statistically significant. Statistical analysis was performed using SPSS 22.0 software.

Power analysis of the difference between the placebo and low-flu/val groups for FMD was performed. The parameters needed for the power analysis (the number of participants, mean values, and standard deviations of both groups) were estimated from the sample. A power of 91% was attained when existent FMD change was used as a response.

Results

There were no significant baseline differences in blood pressure, blood lipid levels, and vascular parameters between the treatment group and control group. Additionally, there was no significant difference in demographic characteristics between the 2 groups (Tables 1, 2). No significant changes either in blood pressure or in blood lipid levels were obtained after therapy in either group (Table 2). No adverse effects, including possible myalgia, were registered during the study. The parameters of kidney function (urea, creatinine, and potassium level) did not change significantly after 30 days of treatment in either group (Table 2).

Upon inclusion in the study, 78% of participants had FMD lower than 4%. In the treatment group, FMD increased significantly from 3.1% to 4.8% ($p<0.001$; Figure 1A) after 30 days. Initial RHI was below 1.5 in 17% of participants, but the average value was within normal limits. After 30 days, no significant change in RHI was observed in either group (Figure 1B). cf-PWV was significantly reduced by low-flu/val treatment from 7.8 m/s to 6.7 m/s ($p<0.01$; Figure 2A). cf-PWV and FMD remained unchanged in the control group. The absolute change of FMD was statistically different between the treatment group (1.70±0.96) and the control group (–0.04±0.43), as was the relative change of cf-PWV (%, –12.5±17.0 in the treatment group *vs.* –0.17±13.2 in the control group).

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Table 2. Blood pressure, lipid levels and parameters of kidney function in treatment and control groups at inclusion and after 30 days.

	Treatment group (n=20)			Control group (n=16)		
	Day 0	Day 30		Day 0	Day 30	
Systolic BP, mmHg	120±7.6	118±7.6	ns	120±11.4	119±10.8	ns
Diastolic BP, mmHg	73.1±8.6	73.4±6.7	ns	73.4±9.4	73±8.8	ns
Total cholesterol, mmol/l	3.8±0.6	3.7±0.6	ns	3.9±0.9	4.1±1.2	ns
HDL cholesterol, mmol/l	1.2±0.2	1.1±0.2	ns	1.3±0.3	1.3±0.3	ns
LDL cholesterol, mmol/l	2.0±0.4	1.8±0.5	ns	1.9±0.7	1.9±0.5	ns
Triglycerides, mmol/l	1.5±0.8	1.6±0.7	ns	1.7±1.3	2.2±2.9	ns
Urea, mmol/l	5.3±0.8	5.4±1.5	ns	5.5±1.3	6.0±1.0	ns
Creatinine, µmol/l	75.5±11.1	75.0±10.8	ns	83.2±10.5	82.5±10.4	ns
Potassium, mmol/l	4.8±0.3	4.8±0.4	ns	4.8±0.3	5.0±0.8	ns

The values are mean ±SD. BP – blood pressure; HDL – high density lipoprotein; LDL – low density lipoprotein; ns – no significance. ns refers to the comparison between the treatment and control groups at inclusion (Day 0) and to the comparison between Day 0 and Day 30 within the treatment and control group.

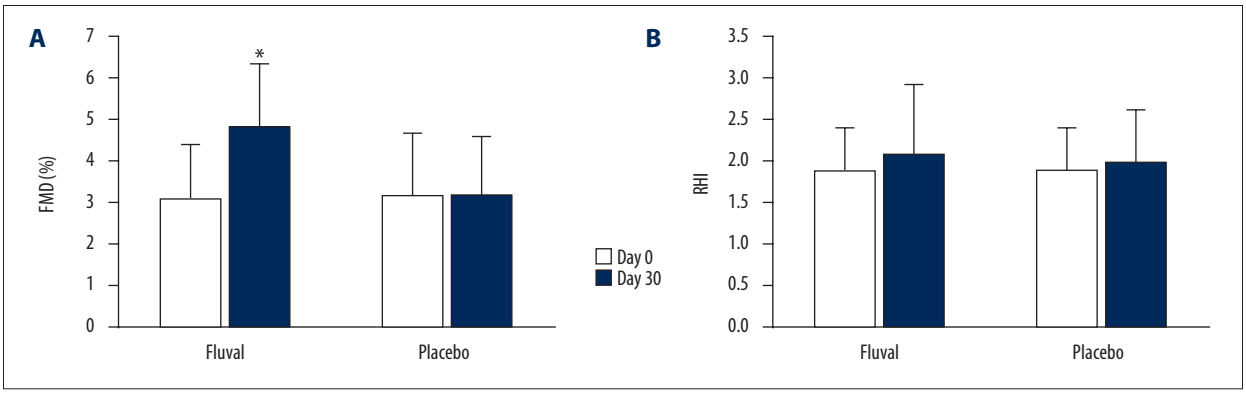

Figure 1. Influence of low-flu/val *vs.* placebo on flow-mediated dilatation (FMD) and reactive hyperemia index (RHI). Mean values ±SD of FMD (**A**) and RHI (**B**) at the inclusion (Day 0, white bars) and after 30 days of treatment (Day 30, blue bars) are presented. * p<0.001, refers to change of parameter after treatment.

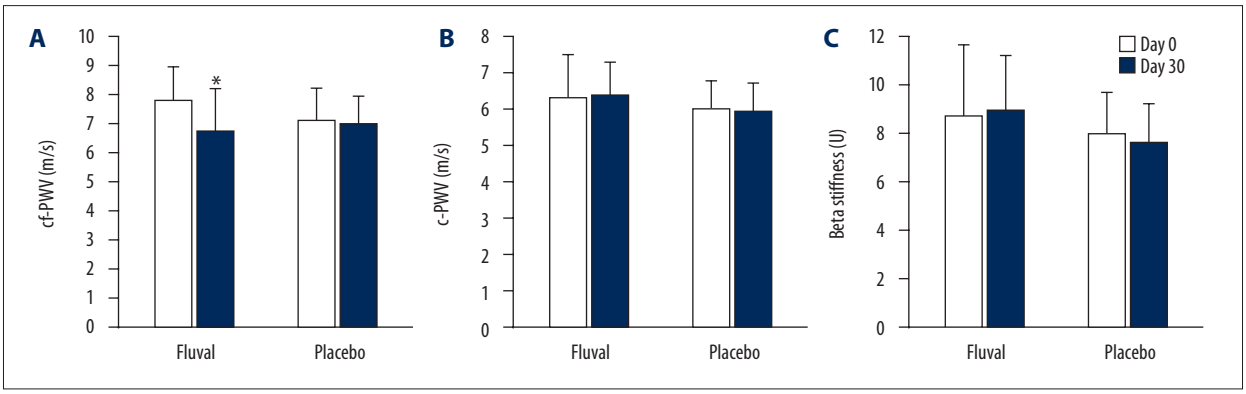

Figure 2. Influence of low-flu/val *vs.* placebo on carotid-femoral pulse wave velocity (cf-PWV), carotid pulse wave velocity (c-PWV), and beta stiffness coefficient. The mean values ±SD of cf-PWV (**A**), c-PWV (**B**), and beta stiffness (**C**) at the inclusion (Day 0, white bars) and after 30 days of treatment (Day 30, blue bars) are presented. * p<0.01, refers to change of parameter after treatment.

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Table 3. FMD and cf-PWV at inclusion, after 30 days of treatment and 10 weeks after treatment cessation.

	Day 0	Day 30	10 weeks	
FMD, %				
Benefit – absolute value	3.1±1.3	4.8±1.5	3.7±1.4	p<0.01
Relative benefit of improvement	–	100%	35.3%	
cf-PWV, m/s				
Benefit – absolute value	7.8±1.1	6.7±1.5	7.2±0.7	ns
Relative benefit of improvement	–	100%	54.5%	

Absolute values are mean ±SD. Relative residual improvement (%) of both parameters is presented. p-value refers to the comparison between initial value of FMD and cf-PWV and their values 10 weeks after treatment cessation. FMD – flow mediated dilatation; cf-PWV – carotid-femoral pulse wave velocity; ns – no significance.

No significant changes in c-PWV and beta stiffness were noted in both groups (Figure 2B, 2C). In relative terms, FMD increased by 54.8% and cf-PWV decreased by 14.1% in the treatment group.

Since not all patients presented with therapeutic levels of LDL-cholesterol, we performed further analysis of efficacy of low-flu/val in different subgroups of patients according to their LDL-cholesterol level (below *vs.* above target LDL-cholesterol of 1.8 mmol/l) and use of moderate- *vs.* high-intensity statins in regular therapy. No significant differences were revealed by the analysis: the absolute change of FMD was 1.65±0.64 *vs.* 1.73±1.13 and the relative change of cf-PWV (%) was –14.8±19.1 *vs.* –11.4±16.6 for the subgroups of the treatment group with LDL at *vs.* above the target value, respectively. The majority of patients (68.6%) were treated by high-intensity statins (rosuvastatin 20 or 40 mg, atorvastatin 40 or 80 mg). When comparing the subgroups taking moderate- *vs.* high-intensity satins, the absolute change of FMD was 1.85±1.3 *vs.* 1.62±0.81 and the relative change of cf-PWV (%) –11.6±22.6 *vs.* –12.6±14.5, all comparisons being insignificant.

At least a 25% increase of initial FMD was defined as a relevant response. Such a response was obtained in 16 out of the 20 treated patients and in 1 patient in the control group. Similarly, a relevant response defined as at least 0.5 m/s decrease of cf-PWV was obtained in 12 out of the 20 treated patients and 6 in the control group. Seventeen of the 20 treatment group patients responded in terms of FMD or/and cf-PWV improvement. Furthermore, there was no correlation between improved FMD and cf-PWV (r=–0.381, p=0.097) or between initial values of FMD and cf-PWV (r=0.076, p=0.757) in the treatment group. Benefits persisted 10 weeks after treatment cessation and were at 35% and 54.5% of the maximal benefit (after 1 month) for FMD and cf-PWV, respectively (Table 3).

Discussion

The present pilot study has revealed that adding a very low-dose combination of fluvastatin and valsartan (low-flu/val) "on top of" standard therapy in middle-aged post-MI men substantially improves endothelial function and arterial stiffness characterized by FMD and cf-PWV. The improvement was achieved by 30 days' treatment and the beneficial effects were still detectable 10 weeks after treatment discontinuation. Lipids and blood pressure remained unchanged.

Several validated methods were used in the present study – at least 2 for each arterial wall characteristic. FMD, mainly reflecting arterial macrovascular function, improved significantly (by 54.8%). On the other hand, RHI, which reflects microvascular function, remained unchanged. Furthermore, cf-PWV, primarily reflecting aortic stiffness, also improved significantly, decreasing by 14.1%, while no significant changes in carotid PWV and beta stiffness coefficient (indicators of local carotid wall characteristics) were observed. No effect on RHI, c-PWV, and beta stiffness could be explained by the well-known fact that atherosclerosis processes (obviously present in post-MI patients) primarily affect the endothelium in elastic arteries and aortic stiffness [5].

Since low-flu/val achieved the benefits without affecting lipids or blood pressure, its action should be attributed to pleiotropic efficacy. A few studies have addressed the effects of statins or ARBs on the arterial wall in coronary artery disease patients and show some improvement, which is attributed mainly to their therapeutic action on hypercholesterolemia and/or hypertension [19–24]. Importantly, very low doses that do not affect lipids or blood pressure have not been tested so far. The concept of using low doses of known drugs for other purposes is not new at all, with acetylsalicylic acid being the best-known example. For example, low doses of statins have been shown to increase angiogenesis and activation of mature and

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progenitor endothelial cells, in contrast to high doses that exert antiangiogenic effects [25–27].

Our research group previously explored low-flu/val in apparently healthy middle-aged males and in diabetes mellitus type 1 and type 2 patients, following the same 30-day treatment protocol. In those studies, FMD similarly significantly improved. Additionally, significant improvement of beta stiffness and c-PWV was also attained. Similarly, no effect on lipids and/or blood pressure was revealed, highlighting the unique low-flu/val pleotropic vascular capacity. In all studied groups, at least partial residual effects were observed 10 weeks after treatment [10,11,15]. The lasting effect of low-flu/val could have an important potential application, allowing for cyclic, intermittent treatment with short-term (e.g., 1 month) treatment periods, followed by longer (e.g., 3 months) non-treatment periods. The rationale behind this cyclic approach has already been described [28]. The mechanism behind sustained beneficial effects after low-flu/val withdrawal cannot be explained at present. It might be that treatment with low-flu/val induces favorable gene expression in endothelial cells and vascular smooth muscle cells that results in sustained and prolonged effects. This remains to be clarified in further mechanistic studies.

As post-MI patients are considered at very high cardiovascular risk, their relative comparative gain from the described treatment would likely be the greatest when compared to our previously studied groups. The obtained effect on FMD and cf-PWV seems to be clinically relevant and meaningful. Thus, the reduction of cf-PWV by 1.1 m/s achieved after 30 days of treatment holds important prognostic information. Such a reduction could be extrapolated to a nearly 14% reduction in cardiovascular risk according to the Vlachopoulos meta-analysis [4]. In addition, meta-analysis of prospective endothelial dysfunction studies revealed that 1% higher FMD reduces the risk for cardiovascular events by 13% [29]. Accordingly, the 1.7% improvement of FMD in the treatment group of our study would correspond to a 22% cardiovascular risk reduction. That shows some real-life applications of the study and is of particular importance in the studied group of post-MI patients with an average age of 47.5±5.2 years.

This study did not aim to explore the mechanism of action of low-flu/val, but was conceived as a "proof-of-concept" study aiming to establish whether low-flu/val could improve endothelial dysfunction and arterial stiffness. Therefore, the mechanisms of low-flu/val pleiotropic action can only partially be elaborated at this stage. The explanation below also explains why low doses of fluvastatin and valsartan in particular were chosen for this study. We assume that low-flu/val directly improves the function of both endothelial cells and vascular smooth muscle cells (VSMC) by clearly decreasing their intracellular oxidative stress. This assumption is based on our observation that low-flu/val increases telomerase activity, obviously due to decreased intracellular oxidative stress. Furthermore, increased telomerase activity is correlated with both endothelial function and arterial stiffness [30,31]. In the present study, we found that improvements in FMD and cf-PWV did not correlate. This suggests that improvements were achieved by distinct mechanisms or distinct targets (potentially the endothelial cells and VSMC) rather than by common mechanism(s). The intracellular renin-angiotensin system is a known important accelerator of intracellular oxidative stress. Since angiotensin I is intracellularly converted to angiotensin II by chymase, ACE inhibitors are intracellularly ineffective [32]. In contrast, valsartan effectively inhibits intracellular angiotensin II in the cytosol and nucleus of endothelial cells and VSMC [33]. On the other hand, fluvastatin has specific oxygen free radicals scavenging capacity, with antioxidant effects similar to those mediated by α-tocopherol [34,35]. Thus, fluvastatin (and its metabolites), in contrast to other statins, decrease intracellular oxidative stress by effectively scavenging oxygen free radicals. Furthermore, valsartan's intracellular inhibition of angiotensin is increased by interaction with fluvastatin [36]. Importantly, an appropriate intracellular oxy/redox state can be achieved only by fine-tuning between intracellular production and scavenging of oxygen free radicals that may be achieved by very low doses of effective drugs. Due to its specific, independent nature of action, low-flu/val is effective in patients already receiving ("on top of") ACE inhibitors, ARBs, and statins in therapeutic doses. Overall, evidently low-flu/val acts as different drug than ACE inhibitors, ARBs and statins. Undoubtedly, the mechanism of action of low-flu/val deserves to be studied in detail.

Conclusions

In conclusion, low-flu/val seems to act as an independent drug and its addition to regular post-MI therapy significantly improved arterial function (a well-known predictor of future coronary events) in middle-aged post-MI men. Although our pilot study is limited by the relatively low number of patients, we found a high response rate for both FMD and cf-PWV. The clinical value of our results should be validated in a study assessing the major cardiovascular events as the primary endpoints. Overall, further studies are needed to explore the clinical relevance of this encouraging approach, which might lead to decreased coronary risk in post-MI patients and potentially in other patients with coronary artery disease.

Conflicts of interest

None.

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