Concomitant administration of simvastatin with ivabradine in contrast to metoprolol intensifies slowing of heart rate in normo- and hypercholesterolemic rats

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Abstract

Introduction: β-Blockers play a significant role in therapeutic heart rate (HR) management and angina control. In patients who are unable to tolerate β-blockers ivabradine could be particularly useful. The aim of the study was to establish whether concomitant administration of simvastatin with ivabradine or metoprolol had any effect on rat HR and blood pressure (BP).

Material and methods: The experiments were performed in hyper- and normo-cholesterolemic outbred Wistar rats. Animals were divided into 2 groups: receiving during 4 weeks normal diet (normocholesterolemic rats) or diet with 5% cholesterol and 2.5% cholic acid (hypercholesterolemic rats). Then rats received placebo (0.1% methylcellulose), 2) metoprolol 30 mg/kg bw; 3) ivabradine 10 mg/kg bw; 4) simvastatin 10 mg/kg bw; 5) simvastatin 10 mg/kg bw + metoprolol 30 mg/kg bw; 6) simvastatin 10 mg/kg bw + ivabradine 10 mg/kg bw. Drugs were given during a 4-week period. HR and BP measure were provided by an Isotec pressure transducer connected to a direct current bridge amplifier. For the further lipid profile examination, 0.25 ml of blood samples were taken.

Results: After administration of ivabradine with simvastatin to normocholesterolemic and hypercholesterolemic rats the mean HR was significantly reduced as compared to rats receiving simvastatin (312.0 ±30.2 min⁻¹ vs. 430.7 ±27.8 min⁻¹, p < 0.05); (329.8 ±24.2 min⁻¹ vs. 420.5 ±9.2 min⁻¹, p < 0.05) or ivabradine alone (312.0 ±30.2 min⁻¹ vs. 350.2 ±16.0 min⁻¹, p < 0.05); (329.8 ±24.2 min⁻¹ vs. 363.0 ±21.7 min⁻¹, p < 0.05).

Conclusions: Concomitant administration of simvastatin with ivabradine intensified slowing of HR, although it did not influence BP in normo- and hypercholesterolemic rats. Statin-induced intensification of HR deceleration after metoprolol administration was not observed.

Key words: simvastatin, ivabradine, metoprolol, heart rate, rats.

Introduction

β-Adrenergic blocking drugs turned out to reduce both mortality and recurrent myocardial infarction in patients with a previous myocardial infarction [1]. Anti-anginal and anti-ischemic therapy with β-adrenergic blocking drugs in some patients with coronary artery disease might be complicated by contraindications and drug side effects [2-5]. Alternative pharmacotherapy by ivabradine – the novel selective for the If current lowering heart rate agent – seems to have beneficial effects in patients with...
stable coronary artery disease (CAD) [1, 6]. It reduces heart rate in the sino-atrial node and does not affect blood pressure, myocardial contractility, intracardiac conduction or ventricular repolarization [7]. In ischemic heart disease (IHD) patients the position of 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) inhibitors in primary and secondary prevention of cardiovascular events is well established [8, 9]. Their beneficial activity depends on limiting cholesterol synthesis as well as cholesterol independent “pleiotropic” effects [10]. The possible drug-drug interactions involving statins might limit the safety of concomitant therapy with potent CYP3A4 inhibitors [11-13]. Also it was established that simvastatin increased the area under plasma concentration time curve (AUC) ratio of other agents metabolized via the CYP3A4 pathway [14]. Moreover, HMG-CoA inhibitors turned out to interact with other drugs, probably by desensitization of β-adrenergic signaling resulting from reduced iso- prenylation of G-proteins [15]. Therefore in the present study we have examined whether concomitant administration of simvastatin and ivabradine or metoprolol to rats had any effect on the heart rate and blood pressure.

Material and methods

Animals

The study was approved by the Ethics Committee of the Medical University of Lodz (Poland) – 3/ŁB405/2008. The experiments were performed in 120, Wistar rats, outbred males, 200-260 g body weight (bw). A several day adaptation period was scheduled prior to the beginning of the experiment. After the adaptation period, animals were divided into 2 groups: receiving normal diet – granulated MIX “LSK” (normocholesterolemic rats) or normal diet with 5% cholesterol and 2.5% cholic acid (hypercholesterolemic rats). After a four-week period each group was divided into 6 subgroups receiving intragastrically (i.g.) during 4 weeks: 1) placebo (0.1% methylcellulose); 2) metoprolol 30 mg/kg bw; 3) ivabradine 10 mg/kg bw; 4) simvastatin 10 mg/kg bw; 5) simvastatin 10 mg/kg bw + metoprolol 30 mg/kg bw; 6) simvastatin 10 mg/kg bw + ivabradine 10 mg/kg bw.

All rats were provided with free access to food and water throughout the study. After 4 weeks of treatment, heart rate and hemodynamic parameters were measured. The surgery was performed 24 h after administration of the last drug dose and 10 h after the last feed supply. For the further surgical procedures, anesthesia was initiated by an intraperitoneal (i.p.) dose of pentobarbital sodium at 60 mg/kg bw. The anesthesia was maintained with intraperitoneal bolus injections of pentobarbital sodium at 10 mg/kg bw as needed. To measure the heart rate and blood pressure, catheters were implanted into the right carotid artery. The signals were provided by an Isotec pressure transducer connected to a direct current bridge amplifier (both Hugo Sachs Elektronik) for 20 min after the hemodynamic parameter stabilization period. For the further lipid profile examination, 0.25 ml of blood samples were taken. Surgical procedures, and heart rate and blood pressure recording were performed as described previously [16, 17].

Statistical analysis

All data are presented as means ± SD (standard deviation). Statistical comparisons among groups were performed using ANOVA, and post-hoc comparisons were performed with the LSD (least significant difference) test. Normal distribution of parameters was checked by means of Shapiro-Wilk test. If data were not normally distributed or the values of variance were different, ANOVA with Kruskal-Wallis and Mann-Whitney’s U test were used. All parameters were considered statistically significantly different if p < 0.05. The statistical analysis of heart rate and hemodynamic parameters were performed using Statgraphics 5.0 plus software.

Results

Metoprolol administration to normocholesterolemic rats heart rate resulted in significant decrease in comparison with control group (390.8 ±20.5 min⁻¹ vs. 429.8 ±19.5 min⁻¹, p < 0.05). Similar results were observed in hypercholesterolemic group, as well (384.3 ±21.9 min⁻¹ vs. 418.0 ±29.0 min⁻¹, p < 0.05). Statistically significant reduction of heart rate after ivabradine administration to normocholesterolemic rats (350.2 min⁻¹ ±16.0 vs. 429.8 ±19.5 min⁻¹), and hypercholesterolemic rats (363.1 ±21.7 min⁻¹ vs. 418.0 ±29.1 min⁻¹) as compared to control groups were noted, as well. Insignificant changes of heart rate were noted in normocholesterolemic (430.7 ±27.8 min⁻¹ vs. 429.8 ±19.5 min⁻¹) and hypercholesterolemic rats (420.5 ±9.2 min⁻¹ vs. 418.0 ±29.0 min⁻¹) receiving simvastatin at 10 mg/kg bw alone as compared to control groups. The mean heart rate after concomitant administration of metoprolol and simvastatin to normocholesterolemic rats statistically decreased as compared to the control group (370.5 ±15.5 min⁻¹ vs. 429.8 ±19.5 min⁻¹, p < 0.05) and as compared to the group receiving simvastatin alone (370.5 ±15.5 min⁻¹ vs. 430.7 ±27.7 min⁻¹, p < 0.05). Similar observations were made in hypercholesterolemic rats. Significant slowing of heart rate after concomitant administration of simvastatin with metoprolol as compared to control rats (386.5 ±22 min⁻¹ vs. 418.0 ±29.0 min⁻¹, p < 0.05) and as compared to rats receiving sim-
vastatin alone (386.5 ±22 min⁻¹ vs. 420.5 ±9.2 min⁻¹, \( p < 0.05 \)) were observed, as well. The concomitant administration of simvastatin with metoprolol to normocholesterolemic and hypercholesterolemic rats insignificantly influenced the mean heart rate as compared to rats receiving metoprolol alone (Table I, Figures 1, 2). After administration of ivabradine with simvastatin to normocholesterolemic and hypercholesterolemic rats the mean heart rate was significantly reduced as compared to the control group (312.0 ±30.2 min⁻¹ vs. 429.8 ±19.5 min⁻¹, \( p < 0.05 \)); (329.8 ±24.2 min⁻¹ vs. 418.0 ±29.0 min⁻¹, \( p < 0.05 \)) and as compared to rats receiving simvastatin (312.0 ±30.2 min⁻¹ vs. 430.6 ±27.8 min⁻¹, \( p < 0.05 \)); (329.8 ±24.2 min⁻¹ vs. 420.5 ±9.18 min⁻¹, \( p < 0.05 \)) or ivabradine alone (312.0 ±30.2 min–¹ vs. 350.2 ±16.0 min–¹, \( p < 0.05 \); (329.8 ±24.2 min–¹ vs. 363.0 ±21.7 min–¹, \( p < 0.05 \)) (Table I, Figures 1, 2).

Metoprolol, ivabradine, and simvastatin given alone or in combination (i.e. simvastatin with metoprolol; simvastatin with ivabradine) insignificantly influenced the mean, systolic and diastolic blood pressure in normocholesterolemic and hypercholesterolemic rats (Table II).

**Discussion**

Heart rate reduction is a major pharmacological effect of ivabradine. The probability of side effects such as symptomatic bradycardia during ivabradine therapy is very low – approximately 0.2%. However, these effects might be potentiated by concomitant administration of several inhibitors or substrates of cytochrome P450 isoenzyme CYP3A4 [14]. As it was shown in previous studies, statins in humans are substrates of the CYP3A4 isoenzyme [18-20]. Although simvastatin metabolism in rats is different to humans, similar interaction between simvastatin and ivabradine is very likely.

In this pathway ivabradine plasma concentration might result in potentiating the slowing of heart rate [14, 21]. Our observations of heart rate in rats after concomitant administration of simvastatin and ivabradine to normo- and hypercholesterolemic rats might be the result of the drug–drug metabolism interaction. In previous studies it was reported that HMG-CoA reductase inhibitors might decrease the inhibitory effect on the platelet aggregation of clopidogrel (mainly metabolized by CYP3A4), and they might decrease the clearance of midazolam (CYP3A4 substrate) [13, 16]. Hypercholesterolemic diet in our study did not seem to have an influence on the possible interaction after combined administration of simvastatin and ivabradine. Similarly to our previous observations, no impact of simvastatin during its combined admin-

**Table I.** Values of the mean heart rate [beats/min] in rats fed normo- and hypercholesterolemic diet measured after 4-wk administration of drugs.

| Group   | Mean Heart Rate [beats/min] |
|---------|-----------------------------|
| K       | 429.81 ±19.50               |
| K_H     | 418.03 ±29.05               |
| S       | 430.66 ±27.76               |
| S_H     | 420.51 ±9.18                |
| IW      | 350.18 ±16.02*              |
| IW_H    | 363.05 ±21.68*              |
| M       | 390.76 ±20.54               |
| M_H     | 384.28 ±21.87*              |
| SIW     | 312.02 ±30.25*a,b           |
| SIWH    | 329.83 ±24.16*a,b           |
| SM      | 370.54 ±15.55*a             |
| SM_H    | 386.50 ±22.20*a             |

K – normocholesterolemic control group, K_H – hypercholesterolemic control group, IW – normocholesterolemic group receiving ivabradine, IW_H – hypercholesterolemic group receiving ivabradine, S – normocholesterolemic group receiving simvastatin, S_H – hypercholesterolemic group receiving simvastatin, SIW – normocholesterolemic group receiving simvastatin with ivabradine, SIWH – hypercholesterolemic group receiving simvastatin with ivabradine, \( \cdot p < 0.05 \) as compared to control group, \( \cdot p < 0.05 \) as compared to rats receiving simvastatin alone, \( \cdot p < 0.05 \) as compared to rats receiving ivabradine alone.

**Figure 1.** Values of the mean heart rate in rats fed normo- and hypercholesterolemic diet measured after 4-wk administration of drugs.

\( \cdot p < 0.05 \) as compared to control group, \( \cdot p < 0.05 \) as compared to rats receiving simvastatin alone, \( \cdot p < 0.05 \) as compared to rats receiving ivabradine alone.

**Figure 2.** Baseline mean heart rate in rats fed normo- and hypercholesterolemic diet measured after 4-wk administration of drugs.

\( \cdot p < 0.05 \) as compared to control group, \( \cdot p < 0.05 \) as compared to rats receiving simvastatin alone.
isoprenylation of G-proteins of the Rho and Ras families of numerous signaling molecules, including those of the angiotensin II – type 1 receptor with reduced vasoconstrictor response to angiotensin II infusion [35]. Moreover, statins could improve systemic arterial compliance by reducing large artery stiffness and blood pressure in normolipidemic patients with isolated systolic hypertension [36, 37]. Although in vitro studies suggested a possible lowering effect of statins on blood pressure, in vivo observations have provided inconsistent results.

In conclusion, heart rate is an important predictor of all-cause and cardiovascular mortality in both subjects with and those without left ventricular dysfunction. Concomitant administration of simvastatin, well established in primary and secondary prevention of cardiovascular events, with ivabradine, a novel, alternative drug for patients with stable coronary artery disease with left ventricular systolic dysfunction, intensifies slowing of heart rate. No impact on blood pressure in normo- and hypercholesterolemic rats was observed, however. A similar simvastatin-induced intensification of heart rate deceleration during metoprolol therapy was not observed. However, no results of interaction between simvastatin and metoprolol in blood pressure changes were observed. We suggest that the possible explanation for such interaction between statins and ivabradine might be linked to a metabolic pathway. Further studies are required to confirm such interaction considering its clinical importance and safety with the possibility of changes in dosage regimen in patients with cardiovascular diseases receiving statin with ivabradine.

### Table II. Summary statistics (mean ± SD) for blood pressure [mm Hg] in normo- and hypercholesterolemic rats

|       | Diastolic  | Mean       | Systolic  |
|-------|------------|------------|-----------|
| K     | 84.11 ±6.96 | 93.38 ±5.51 | 104.88 ±6.31 |
| K_H   | 86.32 ±3.82 | 91.74 ±3.65 | 105.61 ±4.30 |
| S     | 85.99 ±2.41 | 91.38 ±3.92 | 105.08 ±4.12 |
| S_H   | 82.83 ±3.75 | 91.54 ±2.61 | 104.50 ±3.08 |
| IW    | 85.97 ±2.25 | 93.47 ±3.27 | 105.23 ±4.80 |
| IW_H  | 81.39 ±3.66 | 92.26 ±2.01 | 106.71 ±2.52 |
| M     | 83.89 ±4.22 | 92.68 ±2.70 | 105.18 ±3.03 |
| M_H   | 86.86 ±3.80 | 94.30 ±4.43 | 105.89 ±3.32 |
| SIW   | 83.56 ±3.57 | 92.93 ±2.61 | 107.16 ±5.15 |
| SIW_H | 81.83 ±2.92 | 92.51 ±2.51 | 107.43 ±3.26 |
| SM    | 80.68 ±3.14 | 89.35 ±2.27 | 106.49 ±5.72 |
| SM_H  | 86.22 ±2.34 | 92.90 ±2.75 | 106.94 ±4.10 |

Although concomitant administration of simvastatin with ivabradine seems to intensify slowing of heart rate, no impact on systolic, diastolic or mean blood pressure was observed. These observations are comparable with the previous studies [7]. The results of previous large clinical trials have not definitely proved the anti-hypertensive activity of statins. The authors of the UCSD Statin Study and the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA) suggest that HMG-CoA reductase inhibitors may have some blood-pressure-lowering properties in addition to their effect on lipids [27, 28]. However, in the CARE study no significant reduction of blood pressure with statin therapy was observed [29]. The anti-hypertensive activity of HMG-CoA inhibitors might be the result of their influence on endothelial function, and decrease of oxidative stress and inflammation [10, 30]. The possible mechanisms of statin BP-lowering effects might result from e.g. increased endothelial production of NO with up-regulation of endothelial NO synthase expression [31, 32], decreased level of vasoconstrictor endothelin-1 [33], reduced production of reactive oxygen species (e.g. superoxide anion and hydroxyl radicals) [34] or down-regulation of the angiotensin II – type 1 receptor with reduced vasoconstrictor response to angiotensin II infusion [35]. Moreover, statins could improve systemic arterial compliance by reducing large artery stiffness and blood pressure in normolipidemic patients with isolated systolic hypertension [36, 37]. Although "in vivo" studies suggested a possible lowering effect of statins on blood pressure, "in vitro" observations have provided inconsistent results.
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References

1. Ruff CT, Scirica BM, Morrow DA. Symptomatic treatment after ACS Anti-anginal therapy in patients after acute coronary syndrome: evaluation of newer agents. Arch Med Sci 2010; 6 (Suppl 1A): S83-8.
2. Fox K, Borer JS, Camm AJ, et al. Resting heart rate in cardiovascular disease. J Am Coll Cardiol 2007; 50: 823-30.
3. Lewis RV, Lofthouse C. Adverse reactions with beta-adrenoceptor blocking drugs: an update. Drug Saf 1993; 9: 272-9.
4. Reneland R, Alvarez E, Ansersson PE, et al. Induction of insulin resistance by beta blockade but not ACE-inhibition: long-term treatment with atenolol or trandolapril. J Hum Hypertens 2000; 14: 175-80.
5. Tottersfield AE. Respiratory function in the elderly and the effects of beta blockade. Cardiovac Drugs Ther 1991; 4: 1229-32.
6. Fox K, Ford I, Steg PG, Tendera M, Robertson M, Ferrari R. Relationship between ivabradine treatment and cardiovascular outcomes in patients with stable coronary artery disease and left ventricular systolic dysfunction with limiting angina: a subgroup analysis of the randomized, controlled beautiful trial. Eur Heart J 2009; 30: 2337-45.
7. Vilaine JP . The discovery of the selective If current inhibitor ivabradine. A new therapeutic approach to ischemic heart disease. Pharmacol Res 2006; 53: 424-34.
8. Tanaka N, Katayama Y, Katsumata T, Otori T, Nishiyama Y. Effects of long-term administration of HMG-CoA reductase inhibitor, atorvastatin, on stroke events and local cerebral blood flow in stroke-prone spontaneously hypertensive rats. Brain Res 2007; 1169: 125-32.
9. Chris J. Packard Risk factor modification after ACS benefits of lipid regulation in acute coronary syndrome. Arch Med Sci 2010; 6 (Suppl 1A): S76-82.
10. Jasińska M, Owczarek J, Orszulak-Michalak D. Statins: mechanisms and clinical relevance (EPAR), Procoralan [online]. Available from URL: http://www.emea.eu.int [Accessed 2008 Jan 14].
11. Jacobson TA. Comparative interaction profiles of pravastatin, simvastatin, and atorvastatin when coadministered with cytochrome P450 inhibitors. Am J Cardiol 2004; 94: 1140-6.
12. Neunov J, Jakovljevic KM, Brkic M. Simvastatin but not pravastatin is very susceptible to interaction with the CYP3A4 inhibitor itraconazole. Clin Pharmacol Ther 1998; 63: 322-32.
13. Neunov J, Nemi M, Backman JT. Drug interactions with lipid-lowering drugs: mechanisms and clinical relevance. Clin Pharmacol Ther 2006; 80: 565-81.
14. European Medicines Agency: Committee for Medicinal Products for Human European Public Assessment Report (EPAR), Procoralan [online]. Available from URL: http://www.emea.eu.int [Accessed 2008 Jan 14].
15. Mühlhäusler U, Zolk O, Rau T, Münnzel F, Wieland T, Eschenhagen T. Atorvastatin desensitizes beta-adrenergic signaling in cardiac myocytes via reduced isoformylation of G-protein gamma-subunits. FASEB J 2006; 20: 785-7.
16. Lau WC, Waskell LA, Watkins PB, et al. Atorvastatin reduces the ability of clopidogrel to inhibit platelet aggregation: a new drug drug interaction. Circulation 2003; 107: 32-7.
17. Owczarek J, Jasińska M, Orszulak-Michalak D. Dose-dependent influence of two-week administration of simvastatin and metoprolol injection on blood pressure in normocholesterolemic rats. Acta Pol Pharm 2008; 65: 147-51.
18. Ishigami M, Honda T, Takasaki W, et al. A comparison of the effects of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors on the CYP3A4-dependent oxidation of mexazolam in vitro. Drug Metab Dispos 2001; 29: 282-8.
19. Sakaeda T, Fujino H, Komoto C, Kakumo M, Jin J, Iwaki K. Effect of acid and lactone forms of eight HMG-CoA reductase inhibitors on CYP-mediated metabolism and MDRI-mediated transport. Pharm Res 2006; 23: 506-12.
20. Transon C, Leemann T, Dayer P. In vitro comparative inhibition profiles of major human drug metabolizing cytochrome P450 isozymes (CYP2C9, CYP2D6 and CYP3A4) by HMG-CoA reductase inhibitors. Eur J Clin Pharmacol 1996; 50: 209-15.
21. Savelieva I, Camm AJ. If inhibition with ivabradine electrophysiological effects and safety. Drug Saf 2008; 31: 95-107.
22. Owczarek J, Jasińska M, Orszulak-Michalak D. Interaction between different dosages of simvastatin after two-week administration and metoprolol injection on the heart rate in normocholesterolemic rats. Acta Pol Pharm 2008; 65: 141-5.
23. Nette AF, Abraham G, Ungemach FP, et al. Interaction between simvastatin and metoprolol with respect to cardiac beta-adrenoceptor density, catecholamine levels and peroperative catecholamine requirements in cardiac surgery patients catecholamine requirements in cardiac surgery patients. Naunyn Schmiedebergs Arch Pharmacol 2005; 372: 115-24.
24. Simonds WF, Butynski JE, Gautam N, Unson CG, Spiegel AM. Gproteins beta gamma dimmers. Membrane targeting requires subunit co expression and intact gamma C-A-A-X domain. J Biol Chem 1991; 266: 5363-6.
25. Chiloèches A, Lasa M, Brihuega F, Montes A, Toro MJ. Effects of lovastatin on adenylyl cyclase activity and G proteins in GH4C1 cells. FEBS Lett 1995; 361: 46-50.
26. Nusse O, Neer EJ. Localization of G alpha o to growth cones in PC12 cells: role of G alpha o association with receptors and G beta gamma. J Cell Sci 1996; 109: 221-8.
27. Golomb BA, Ritchie JB, Criqui MH, Dimsdale JE. Statins lower blood pressure: results from the UCSD Statin Study. Circulation 2004; 110: III-402.
28. Poulter N, Sever PS. Do statins lower blood pressure? Evidence from the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid-Lowering Arm (ASCOT-LLA). Circulation 2004; 110: III-402.
29. Sacks FM, Pfeffer MA, Moye LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. N Engl J Med 1996; 335: 1001-9.
30. Wierzbiicki AS, Chowienczyk PJ, Cockcroft JR, et al. Endothelial dysfunction is strictly connected with hypertension development and LDL-C levels. Cardiovascular risk factors and endothelial dysfunction. Clin Sci (London) 2004; 107: 609-15.
32. Strazzullo P, D’Elia L, Versiero M. Response to upregulation of nitric oxide, inhibition of oxidative stress, and antihypertensive effects of statins. Hypertension 2007; 49: 792-8.

33. Hernandez-Perera O, Perez-Sala D, Navarro-Antolin J, et al. Effects of the 3-hydroxy-3-methylglutaryl-CoA reductase inhibitors, atorvastatin and simvastatin on the expression of endothelin-1 and endothelial nitric oxide synthase in vascular endothelial cells. J Clin Invest 1998; 101: 2711-9.

34. Rikitake Y, Kawashima S, Takeshita S, et al. Anti-oxidative properties of fluvastatin, an HMG-CoA reductase inhibitor, contribute to prevention of atherosclerosis in cholesterol-fed rabbits. Atherosclerosis 2001; 154: 87-96.

35. Nickenig G, Baumer AT, Temur Y, Kebben D, Jockenhovel F, Bohm M. Statin-sensitive dysregulated AT1 receptor function and density in hypercholesterolemic men. Circulation 1999; 100: 2121-4.

36. Ferrier KE, Muhlmann MH, Baguet JP, et al. Intensive cholesterol reduction lowers blood pressure and large artery stiffness in isolated systolic hypertension. J Am Coll Cardiol 2002; 39: 1020-5.

37. Shige H, Dart A, Nestel P. Simvastatin improves arterial compliance in the lower limb but not in the aorta. Atherosclerosis 2001; 155: 245-50.