Journal of the American Society of Hypertension 8(2) (2014) 74–82

Research Article

Effects of renin-angiotensin-aldosterone system inhibitors and beta-blockers on markers of arterial stiffness

Charalambos Koumaras, MD[a], Konstantinos Tziomalos, MD, PhD[b], Eirini Stavrinou, MD[c], Niki Katsiki, MD, PhD[a], Vasilios G. Athyros, MD, PhD[a], Dimitri P. Mikhailidis, MD, FFPM, FRCP, FRCPath[d,*], and Asterios Karagiannis, MD, PhD[a]

[a]*Second Propedeutic Department of Internal Medicine, Medical School, Aristotle University of Thessaloniki, Hippokration Hospital, Thessaloniki, Greece;*

[b]*First Propedeutic Department of Internal Medicine, Medical School, Aristotle University of Thessaloniki, AHEPA Hospital, Thessaloniki, Greece;*

[c]*Department of Nephrology, Medical School, Aristotle University of Thessaloniki, Hippokration Hospital, Thessaloniki, Greece; and*

[d]*Department of Clinical Biochemistry (Vascular Disease Prevention Clinics), Royal Free Hospital Campus, University College London Medical School, University College London (UCL), London, UK*

Manuscript received July 26, 2013 and accepted September 11, 2013

Abstract

Antihypertensive agents may, even within the same class, exert variable effects on arterial stiffness variables. Nebivolol could have a better impact than atenolol on arterial stiffness, by increasing the bioavailability of endothelium-derived nitric oxide. Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) increase plasma renin activity (enhancing the production of angiotensin II via non-ACE-related pathways) whereas aliskiren does not, potentially affecting central hemodynamics differently. We compared the effects of two renin-angiotensin-aldosterone system (RAAS) inhibitors (quinapril and aliskiren) and 2 beta-blockers (atenolol and nebivolol) on arterial stiffness variables. Treatment-naïve patients (n = 72; 68.1% males; age, 47.6 ± 10.6 years) with uncomplicated stage I-II essential hypertension were randomly assigned to quinapril, aliskiren, atenolol, or nebivolol for 10 weeks. Central systolic and diastolic blood pressure (BP), central pulse pressure (PP), augmentation index (AIx), and pulse wave velocity (PWV) were measured at baseline, 2, and 10 weeks. The same measurements were performed in 20 normotensive subjects (65.0% males; age, 40.0 ± 8.9 years). Peripheral and central systolic and diastolic BP, peripheral PP, and PWV were significantly and similarly reduced by all agents. However, PWV continued to decline between the second and last visit in patients on quinapril and aliskiren but did not change in those on nebivolol or atenolol. Central PP and AIx decreased in patients on quinapril, aliskiren, and nebivolol but did not change in those taking atenolol. The decrease in central PP and AIx did not differ between patients on quinapril, aliskiren, and nebivolol. Despite similar reductions in peripheral BP, atenolol is less effective than nebivolol and RAAS inhibitors in improving central pulsatile hemodynamics. Aliskiren exerts similar effects on markers of arterial stiffness as quinapril. The clinical relevance of these differences remains to be established. J Am Soc Hypertens 2014;8(2):74–82. © 2014 American Society of Hypertension. All rights reserved.

Keywords: Antihypertensive treatment; central blood pressure; augmentation index; pulse wave velocity.

Conflict of interest: This study was conducted independently; no company or institution supported it financially. Some of the authors have attended conferences, given lectures, and participated in advisory boards or trials sponsored by various pharmaceutical companies.

Dr Koumaras was supported by an educational grant from the Hellenic Atherosclerosis Society.

*Corresponding author: Dimitri P. Mikhailidis, MD, FFPM, FRCP, FRCPath, Academic Head, Department of Clinical Biochemistry, Royal Free Hospital Campus, University College London Medical School, University College London (UCL), Pond Street, London NW3 2QG, UK. Tel: +44 20 7830 2258; fax: +44 20 7830 2235.

E-mail: MIKHAILIDIS@aol.com

1933-1711/$ - see front matter
http://dx.doi.org/10.1016/j.jash.2013.09.001

Introduction

Central blood pressure (BP) measurements and arterial stiffness are associated with higher risk for cardiovascular events[1–6] and appear to be stronger predictors of cardiovascular risk than peripheral BP.[5] Arterial stiffness has emerged as a potential treatment target, and several studies evaluated the effects of antihypertensive drugs on arterial stiffness variables.[2,7–11] It appears that differences exist regarding the effects on arterial stiffness variables not only among antihypertensive drug classes, but also between agents of the same class, even when comparable changes in peripheral BP are achieved.[9–11]

Inhibition of the renin-angiotensin-aldosterone system (RAAS) with angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) appears to reduce arterial stiffness more than other classes of antihypertensive drugs, despite similar lowering of peripheral BP.[10–14] In contrast, the effect on arterial stiffness of aliskiren, which directly inhibits renin, is less clear.[15–18] Even though both ACEIs and ARBs appear to be more effective than the classic cardioselective beta-blockers (eg, atenolol) in reducing markers of arterial stiffness,[10,11,19–25] it is unclear whether newer beta-blockers with vasodilating properties (ie, nebivolol and carvedilol) differ from other members of their class in their effect on arterial stiffness.[23–26]

The aim of the present study was to compare the effects of an ACEI (quinapril), aliskiren, a conventional cardioselective beta-blocker (atenolol), and a vasodilating beta-blocker (nebivolol) on markers of arterial stiffness in treatment-naïve patients with uncomplicated, stage I-II essential hypertension.

Methods

Treatment-naïve, adult patients (n = 72; 68.1% males; age, 47.6 ± 10.6 years) with uncomplicated, stage I-II, essential hypertension (mean sitting systolic BP, 140–180 mm Hg and/or mean sitting diastolic BP 90–110 mm Hg, confirmed on at least three occasions separated by a month) and 20 normotensive (systolic BP <140 mm Hg and diastolic BP <90 mm Hg) adults (65.0% males; age, 40.0 ± 8.9 years) were recruited from the Second Propedeutic Department of Internal Medicine of Aristotle University, at the Hippokration General Hospital in Thessaloniki. Patients with secondary hypertension, diabetes mellitus, dyslipidemia, severe obesity (body mass index >35 kg/m^2), metabolic syndrome, coronary heart disease, peripheral arterial disease, congestive heart failure (New York Heart Association class III and IV), arrhythmias, chronic obstructive pulmonary disease, sleep apnea syndrome, chronic kidney or liver disease were excluded from the study.

Patients were randomized to quinapril 20 mg once daily (n = 20), aliskiren 150 mg once daily (n = 18), atenolol 50 mg once daily (n = 17), or nebivolol 5 mg once daily (n = 17). Peripheral BP and markers of arterial stiffness were measured at baseline and after 2 and 10 weeks of treatment. The same parameters were measured at baseline in normotensive controls. All measurements were performed at the same time of the day for each patient. The drug doses could be adjusted (up to a maximum dose of quinapril 40 mg, aliskiren 300 mg, atenolol 100 mg, and nebivolol 10 mg) according to BP levels after the second visit (2 weeks of active therapy), in order to achieve the target peripheral BP of <140/90 mm Hg.

At each visit, peripheral BP was measured in the dominant arm using a validated mercury sphygmomanometer and an appropriate cuff size, after 15 minutes of supine rest in a quiet room, at controlled room temperature. Patients were asked not to have a meal or coffee and not to smoke within 3 hours before their visit. Measurements were repeated three times at 2-minute intervals, and the mean of the last two readings was recorded, provided that the readings did not differ by more than 10 mm Hg; otherwise, three additional BP measurements were performed.

After the last BP measurement, radial artery pressure waveforms at the wrist of the same arm were sampled over 20 seconds, and pulse wave analysis was performed using applanation tonometry with the SphygmoCor (Atcor Medical, Sydney, Australia). The system software generates an average peripheral and a corresponding central (ascending aorta) pressure waveform and central systolic BP, central diastolic BP, central pulse pressure, and both augmentation index (AIx) and AIx adjusted to heart rate (HR) of 75 beats per minute (AIx@HR75), which represents the percentage of central PP caused by the early return of the reflected wave in the aortic root, are calculated using a validated mathematical transfer function. Mean values were recorded after at least two consecutive measurements in each patient. Immediately afterwards, carotid to femoral pulse wave velocity (PWV) was assessed using the same device. Femoral artery followed by carotid artery electrocardiograph-gated waveforms were recorded over 20 seconds each, placing a sensor on femoral and carotid artery pulse, respectively. The surface distance from the suprasternal notch to the femoral site minus the surface distance from the suprasternal notch to the carotid site (both measured in mm with a tape measure) provided the path length to determine PWV. At least two consecutive measurements were obtained, and the mean value was recorded, provided that the difference between the measurements was below 0.5 m/s. Otherwise, a third PWV measurement was performed and the median value was recorded.

At baseline, serum total cholesterol, high-density lipoprotein cholesterol, triglycerides, glucose, uric acid, and creatinine levels were measured after an overnight fast.