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Therapeutic Update

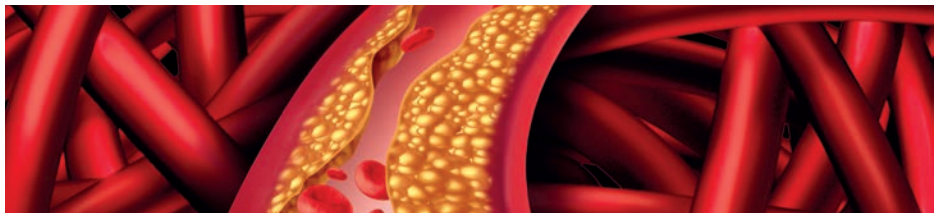
- Effects of a changeover from other angiotensin II receptor blockers to olmesartan on left ventricular hypertrophy in heart failure patients

  Since the development of LVH was found to be associated with progression to HF, interest has been high in treatment to reduce LVH in HF patients. A meta-analysis of the effects of treatment on LV mass in essential hypertension reported that angiotensin (Ang) II receptor blockers (ARBs), angiotensin-converting enzyme (ACE) inhibitors, and calcium channel blockers reduced LV mass by approximately 10–13 %

Clinical Pearls

- Efficacy study of olmesartan medoxomil on coronary atherosclerosis progression and epicardial adipose tissue volume reduction in patients with coronary atherosclerosis detected by coronary computed tomography angiography: study protocol for a randomized controlled trial

  A significant amount of clinical research has been conducted to investigate the link between EAT and coronary atherosclerosis. It was claimed that calcified plaque progression in patients without coronary artery disease and in patients with type 2 diabetes mellitus were associated with a larger EAT volume.



Practice Guide

- Comparison Among Recommendations for the Management of Arterial Hypertension Issued by Last US, Canadian, British and European Guidelines

  The management of hypertension is a key factor of primary and secondary cardiovascular disease (CVD) prevention strategies. Hypertension societies have a common goal; to help the medical community understand hypertension complexity and expand the medical knowledge assisting hypertension research.

- Drug Evaluation: Olmesartan Medoxomil + Rosuvastatin for the Treatment of Dyslipidemia and Concomitant Risk Factors: A Chance for Better Compliance?

  Among the established, most common, and well-controlled by pharmacotherapy risk factors of CVD remain high blood pressure and cholesterol abnormalities: increased serum concentration of low-density lipoprotein - cholesterol (LDL) and low levels of high-density lipoprotein – cholesterol (HDL). Commonly used drugs for the treatment of hypertension and dyslipidemia are angiotensin receptor blockers (ARBs) and HMGCoA reductase inhibitors (statins) respectively.

Clinical Vignette

- Patient with Essential Hypertension and Left Ventricular Enlargement

  A 51-year-old Caucasian male farmer was admitted to the outpatient clinic reporting a more than 2-year-long clinical history of uncontrolled essential hypertension and mild exertional dyspnoea.

Clinical Challenges

- A case report of malignant hypertension in a young woman

  Malignant hypertension is a condition characterized by severe hypertension and multi-organ ischemic complications. Incidence of malignant hypertension has remained stable over the years, although mortality and renal survival have improved with the introduction of antihypertensive therapy.

- A case of treatable hypertension: fibromuscular dysplasia of renal arteries

  Renovascular hypertension is due to renal artery stenosis (RAS) leading to reduced renal perfusion activating the renin angiotensin aldosterone system, resulting in hypertension. It accounts for 1–2 % of all cases of hypertension in the general population, and 5.8 % of secondary hypertension, but plays a major role in completely treatable causes of hypertension in the young.

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Effects of a changeover from other angiotensin II receptor blockers to olmesartan on left ventricular hypertrophy in heart failure patients

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Since the development of LVH was found to be associated with progression to HF, interest has been high in treatment to reduce LVH in HF patients. A meta-analysis of the effects of treatment on LV mass in essential hypertension reported that angiotensin (Ang) II receptor blockers (ARBs), angiotensin-converting enzyme (ACE) inhibitors, and calcium channel blockers reduced LV mass by approximately 10–13%.

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Introduction

Left ventricular (LV) hypertrophy (LVH) is an independent cardiovascular risk factor in the general population, and occurs in various types of heart failure (HF) patients such as those with HF with reduced ejection fraction (EF) (HFrEF) and HF with preserved EF (HFpEF) [1–3]. Since the development of LVH was found to be associated with progression to HF, interest has been high in treatment to reduce LVH in HF patients. A meta-analysis of the effects of treatment on LV mass in essential hypertension reported that angiotensin (Ang) II receptor blockers (ARBs), angiotensin-converting enzyme (ACE) inhibitors, and calcium channel blockers reduced LV mass by approximately 10–13 % [4]. ARBs are widely used in the treatment of hypertension, and large-scale clinical studies have shown that they have a variety of effects, not only their anti-hypertensive effect but also prevention of the progression of HF [5]. The renin–angiotensin system (RAS) plays a key role in LVH, and Ang II is a major determinant in this process [6]. Ang II stimulates LVH and fibrosis in HF patients, whereas Ang II blockade prevents development of LVH [7–10]. An ACE-related carboxypeptidase, known as ACE 2, was identified in the human heart, and ACE 2 degrades Ang I into Ang-(1–9) and Ang II into Ang-(1–7) [11–13]. Characterization of the actions of Ang-(1–7) has demonstrated that the RAS consists of an important biochemical arm which generates Ang II via the action of ACE on Ang I. In addition, the RAS possesses another important

biochemical arm which generates Ang-(1–7) from either Ang I or Ang II via enzymes other than ACE [14, 15]. The discovery of ACE 2 and the demonstration that its catalytic efficiency is approximately 400-fold higher with Ang II as a substrate than with Ang I [16], as well as the report that the ARB olmesartan is associated with high activity of ACE2 and increases Ang-(1–7) via ACE2 [17–21], suggest that olmesartan may have the capability to reduce LVH in HF patients more than other ARBs.

The objective of this study was, therefore, to investigate the effects on LVH in HF patients of a changeover from other ARBs to olmesartan.

Methods

Study population

Participants enrolled in this prospective trial were 64 outpatients with stable HF who had been treated with ARBs other than olmesartan for more than 1 year at Kobe University Hospital between December 2013 and March 2016. We excluded patients with (1) the development of HF within 3 months; (2) hypotension <90/50 mmHg; (3) severe types of renal dysfunction defined as serum creatinine level (Cr) >3 mg/dl; (4) atrial fibrillation; and (5) administration of ACE inhibitors. At the time of enrollment, all patients were in clinically stable condition. The trial was registered with the University Hospital Medical Information Network (UMIN) Clinical Trials Registry (registration number UMIN000011807), conformed to the principles outlined in the Declaration of Helsinki, and was performed with the approval of the Ethics Committee of Kobe University Hospital. Written informed consent was obtained from all patients.

Study protocol

Patients who had consented to their participation in this study switched from other ARBs to olmesartan on the basis of the findings of their most recent late phase II dose-finding studies to maintain blood pressure [22–26] (Table 1). Other drugs were not changed after the change to olmesartan. The physical examinations, blood tests, and echocardiography were performed on the same day at baseline and 6 months after administration of olmesartan. Blood pressure was measured after at least 15 min of rest in a supine position and before echocardiography by a physician (H.S.), and was determined by averaging two consecutive measurements (Terumo Elemano Blood Pressure Monitor; Terumo, Tokyo, Japan).

Echocardiographic examination

Two-dimensional echocardiography was performed using a commercially available ultrasound system (Aplio Artida; Toshiba Medical Systems, Tochigi, Japan). Digital routine grayscale two-dimensional cine loops from three consecutive heartbeats were obtained at end-expiratory apnea from the standard parasternal views and three apical views. Sector width was optimized to allow for complete myocardial visualization while maximizing the frame rate. LV measurements were obtained in accordance with the current guidelines of the American Society of Echocardiography/European Association of Cardiovascular Imaging [27]. The early diastolic (E) and atrial wave velocities (A) and the E-wave deceleration time were measured using the pulsed-wave Doppler recording from the apical four-chamber view. Spectral pulsed-wave Doppler-derived early diastolic velocity (e') was obtained from the septal mitral annulus, and the E/e' ratio was calculated to obtain an estimate of LV filling pressure [28]. LV mass was estimated from the formula proposed by Devereux et al., and LV mass index (LVMI) was calculated for each subject by dividing LV mass by body surface area [29]. LVH was defined as LVMI >95 g/m^2 for females and >115 g/m^2 for males [27].

Definitions of end point

The primary end point was defined as a change in LVMI between baseline and 6 months after the start of administration of olmesartan. The secondary end points comprised a change in brain natriuretic peptide (BNP), E/A, e' and E/e' between baseline and 6 months after the start of administration of olmesartan.

Statistical analysis

Continuous variables were expressed as mean ± SD or percentages, while categorical data were summarized as frequencies and percentages. The parameters of the two subgroups were compared by means of Student's t test or Wilcoxon rank sum test as appropriate. Assuming 30 % of patients with decreased LVMI 6 months after administration of olmesartan, an alpha error of 0.05, a beta error of 0.2, and statistical power of 80 %, and the sample size requirement was 44 patients. However, considering a potential 25 % dropout or loss to follow up rate, 58 will be considered. Statistical significance was basically defined as p value <0.05 for each step. MedCalc version 15.11.4 (MedCalc Software, Mariakerke, Belgium) was used for all analyses.

The discovery of ACE 2 and the demonstration that its catalytic efficiency is approximately 400-fold higher with Ang II as a substrate than with Ang I, as well as the report that the ARB olmesartan is associated with high activity of ACE2 and increases Ang-(1–7) via ACE2, suggest that olmesartan may have the capability to reduce LVH in HF patients more than other ARBs.

Results

Three initially eligible patients (4.7 %) were excluded from all subsequent analyses because of lost follow-up, so that the final study group consisted of 61 patients. There were no cardiac events or deaths during follow-up. The baseline clinical and echocardiographic characteristics of the 61

Table 1: The other ARBs-to-olmesartan conversion table

Other ARBs dose (mg/day)					Olmesartan dose (mg/day)
Losartan	Candesartan	Valsartan	Telmisartan	Azilsartan	
25	4	40	20	10	5
50	8	80	40	20	10
100	16	160	80	40	20

ARB angiotensin II receptor blocker

Table 2: Baseline characteristics of the patients	
Age, years	59 ± 13
Gender (female), n (%)	24 (39)
Body surface area, m^2	1.67 ± 0.21
Medications, n (%)	
Diuretics	21 (35)
β-Blockers	54 (89)
Spironolactone	24 (39)
Calcium channel blockers	7 (11)
ARBs, n (%)	61 (100)
Losartan	21 (35)
Candesaltan	24 (39)
Valsartan	11 (18)
Telmisartan	2 (3)
Azilsartan	3 (5)
Etiology of heart failure, n (%)	
HFpEF	23 (38)
EFrEF	38 (62)
Dilated cardiomyopathy	24 (39)
Cardiac sarcoidosis	7 (11)
Valvular heart disease	4 (7)
Ischemic cardiomyopathy	2 (3)
Cardiac amyloidosis	1 (2)

ARB angiotensin II receptor blocker, *HFpEF* heart failure with preserved ejection fraction, *HFrEF* heart failure with reduced ejection fraction

HF patients are summarized in Tables 2 and 3. Their mean age was 59 ± 13 years, LVEF was 46 ± 12 %, and 24 patients (39 %) were female. HFpEF was observed in 23 patients (38 %), and the remaining 38 patients (62 %) were classified as HFrEF.

No significant changes were observed in systolic and diastolic blood pressures and heart rate 6 months after administration of olmesartan (120 ± 20 vs. 121 ± 21 mmHg, $p = 0.9$; 70 ± 11 vs. 72 ± 13 mmHg, $p = 0.9$; 67 ± 11 vs. 67 ± 12 bpm, $p = 0.86$, respectively, Table 3).

Primary end point

LVMI showed significant decreases from 119 ± 38 to 110 ± 24 g/m^2 ($p = 0.007$) 6 months after administration of olmesartan (Fig. 1). In addition, LVMI showed significantly further decreased from 110 ± 24 to 103 ± 35 g/m^2 ($p = 0.0003$) of 51 patients 12 months after administration of olmesartan available (Fig. 1). Patients with LVH, defined as an LVMI >95 g/m^2 for female and >115 g/m^2 for male, were observed in 34 patients (56 %), and the remaining 27 patients (44 %) were classified as without LVH (Fig. 2). Reduction of LVMI for patients with LVH was significantly higher than that for patients without LVH both between baseline and 6 months after the start of administration of olmesartan (−24.1 ± 29.3 vs. 1.6 ± 26.9 g/m^2, $p < 0.001$), and between baseline and 12 months after the start of administration of olmesartan (−41.0 ± 44.0 vs. -5.7± 23.3 g/m^2, $p < 0.001$).

Secondary end point

The results of using the secondary end point are shown in Fig. 3. BNP tended to decrease 6 months after the start of administration of olmesartan from 52 pg/mL (17–182) to 40 pg/mL (19–129) ($p = 0.2$), but the difference was not statistically significant. No significant changes were observed in *E*/*A*, *e*′ and *E*/*e*′ 6 months after administration of olmesartan.

Other echocardiographic parameters

Other echocardiographic parameters, such as LV end-diastolic diameter, intra-ventricular septal thickness, and LV end-diastolic and end-systolic volumes, were also significantly reduced 6 months after the start of administration of olmesartan (Table 3).

Table 3: Changes of after administration of olmesartan			
	Baseline	**6 months after administration of olmesartan**	**p value**
Systolic blood pressure, mmHg	120 ± 20	121 ± 21	0.9
Diastolic blood pressure, mmHg	70 ± 11	72 ± 13	0.9
Heart rate, bpm	67 ± 11	67 ± 12	0.9
BNP, pg/mL	52, 17–182	40, 19–129	0.2
Echocardiographic parameters			
LV end-diastolic diameter, mm	54 ± 8	52 ± 8	<0.01
LV end-systolic diameter, mm	42 ± 11	41 ± 11	0.1
Intra-ventricular septal thickness, mm	9.8 ± 3.1	9.4 ± 2.6	0.02
LV posterior wall thickness, mm	9.5 ± 2.2	9.8 ± 1.8	0.4
LV end-diastolic volume, mL	124 ± 49	113 ± 39	<0.01
LV end-systolic volume, mL	72 ± 44	65 ± 35	<0.01
LV ejection fraction, %	46 ± 12	45 ± 11	0.8
Left arterial volume index, mL/m^2	40 ± 22	39 ± 20	0.6
Early diastolic wave velocity, cm/s	61 ± 22	61 ± 23	0.9
Arterial wave velocity, cm/s	65 ± 18	67 ± 18	0.4
E/A	0.99 ± 0.54	0.95 ± 0.57	0.6
e′, cm/s	6.0 ± 2.4	5.7 ± 2.1	0.1
E/e′	11.6 ± 7.0	11.4 ± 6.66	0.9
LV mass index, g/m^2	119 ± 38	110 ± 24	0.007

LV left ventricular, *E*/*A* early diastolic and atrial wave velocities ratio, *e*′ early diastolic septal mitral annulus velocity, *E*/*e*′ early diastolic and mitral annulus velocities ratio, *BNP* brain natriuretic peptide

Discussion

The findings of our study indicate that LVMI for HF patients, who had received other ARBs, significantly decreased 6 months after the changeover to olmesartan despite similar blood pressures and further decreased after 12 months. This reduction tended to be more prominent in patients with LVH. This is the first study to demonstrate the further reduction in LVH attainable with olmesartan as compared with that attained with ARBs.

Effect of olmesartan on of LV hypertrophy reduction

LVH is an independent cardiovascular risk factor in the general population and occurs in various types of HF patients [1–3]. The development of LVH has been associated with progression to HF as characterized by increased LV end-diastolic pressure and diminished LV contractility. A meta-analysis of the effects of treatment on LV mass in essential hypertension reported that ARBs, ACE inhibitors, and calcium channel blockers reduced LV mass by approximately 10–13 % [4]. The RAS plays a key role in LVH, and

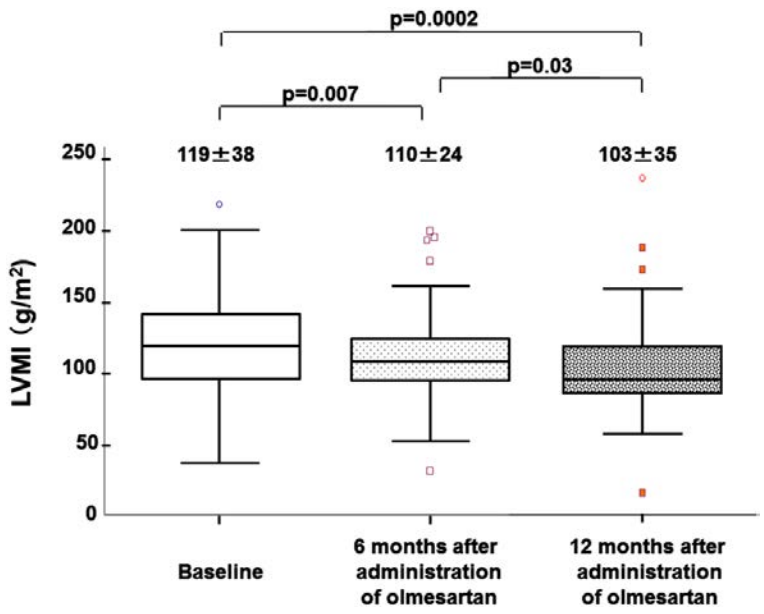

Fig. 1: Primary end point. Left ventricular mass index (LVMI) showed significant reductions 6 months after the start of administration of olmesartan, and had further decreased significantly 12 months after administration of olmesartan.

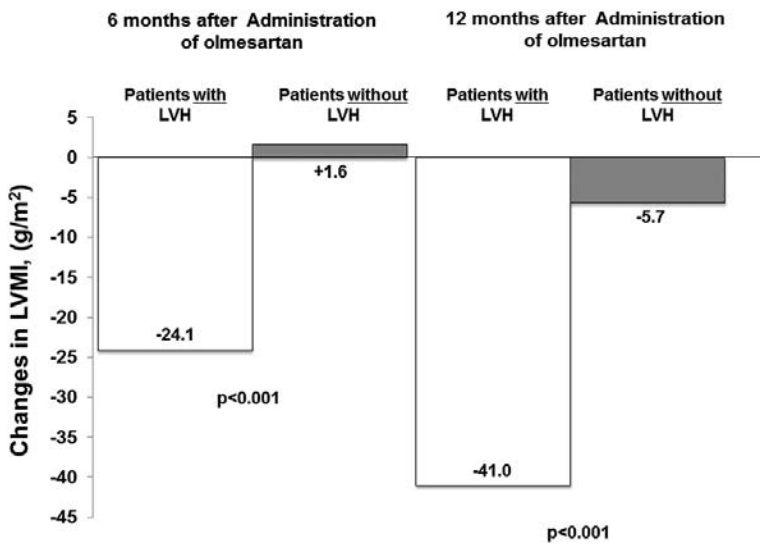

Fig. 2: Reduction in left ventricular mass index (LVMI) for patients with left ventricular hypertrophy (LVH) was significantly higher than that for patients without LVH both between baseline and 6 months after the start of administration of olmesartan, as well as between baseline and 12 months after the start of administration of olmesartan.

Ang II is a major determinant in this process [6]. Ang II stimulates LVH and fibrosis in HF patients, whereas Ang II blockade prevents development of LVH [7, 8]. Moreover, Ang II also causes LVH independent of its effect on blood pressure, whereas blockade of the RAS attenuates or reverses the cellular adaptations to pressure overload [30, 31]. An ACE-related carboxypeptidase, known as ACE 2 and identified in the human heart degrades Ang I into Ang-(1–9) and Ang II into Ang-(1–7) [11–13]. Characterization of the actions of Ang-(1–7) demonstrated that the RAS consists of two biochemical arms: one generates Ang II via the action of ACE on Ang I, and the second generates Ang-(1–7) from either Ang I or Ang II via enzymes other than ACE [14, 15]. The discovery of ACE 2 was followed by the demonstration that its catalytic efficiency is approximately 400-fold higher with Ang II as a substrate than with Ang I [16]. In this study, we showed that olmesartan may have the potential to exert a stronger reductive effect on LVH than any other ARBs. The reason for this is that olmesartan features a higher activity of ACE2 than other ARBs, and increases Ang-(1–7) via ACE2 more than do the other ARBs [17–21]. Several previous investigators have reported that the use of olmesartan was advantageous for attaining regression of LVH. Agata et al. reported that the long-term administration of olmesartan in an animal study caused an increase in renin activity, no changes in angiotensin II, and a decrease in aldosterone [32]. This resulted in reductions in LVMI,

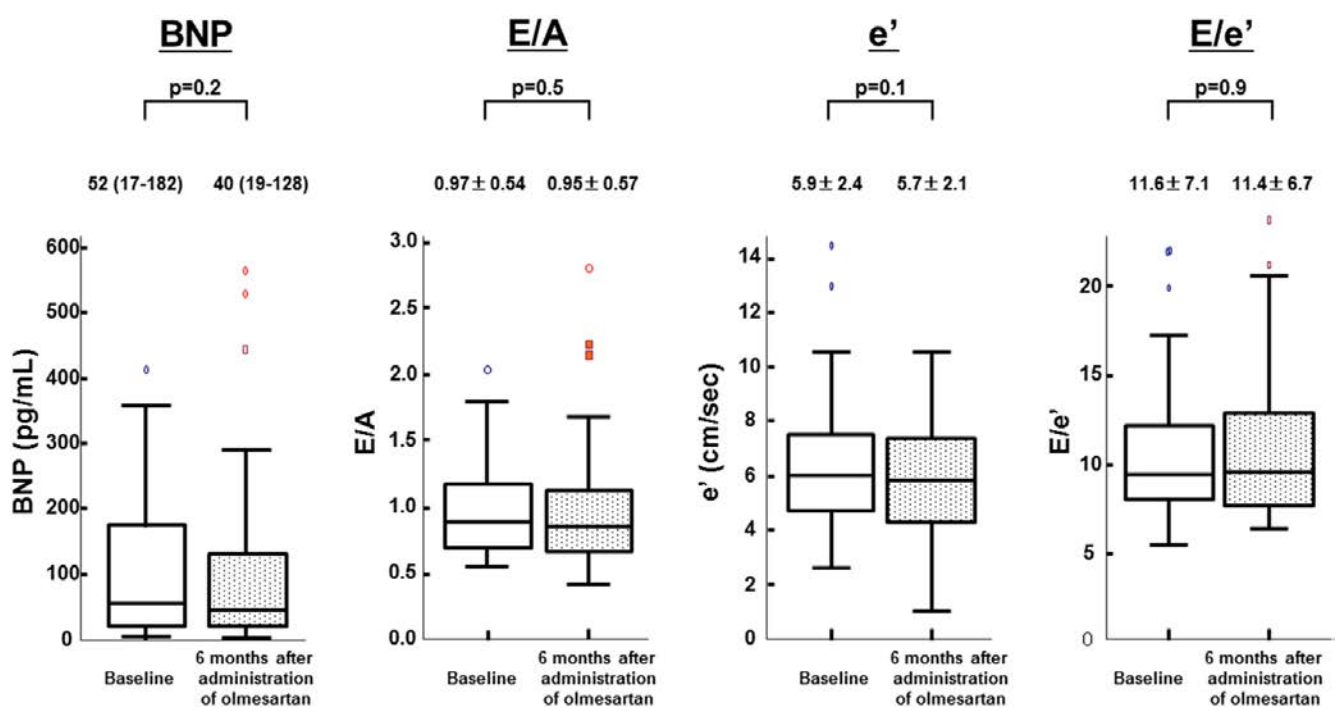

Fig. 3: Secondary end point. Brain natriuretic peptide (BNP) tended to decrease 6 months after the start of administration of olmesartan, but the difference was not statistically significant. No significant changes were observed either in *E*/*A*, *e*′ and *E*/*e*′ at the same point in time.

coronary arterial wall lumen ratio and perivascular fibrosis, as well as improvement in cardiovascular remodeling. Igase et al. reported that olmesartan reduced the thickness of the tunica media of the abdominal aorta and that this led to an increase in Ang-(1–7) [33]. Yokoyama et al. found that olmesartan showed definite inhibitory effects on LVH and mesenteric arterial hypertrophy, and that these effects on cardiovascular remodeling were due to factors related to hypotensive effects and also factors not dependent on blood pressure [34].

It has been suggested that the aldosterone breakthrough is an important risk factor for cardiovascular disease progression including the progression of LVH, despite the use of ACE inhibitors or ARBs [35–37]. Sezai et al. evaluated the effects of a changeover from candesartan to olmesartan on the renin–angiotensin–aldosterone system in 56 patients with essential hypertension found that angiotensin II and aldosterone are reduced by a changeover from candesartan to olmesartan. Furthermore, LVMI and BNP decreased 6 months and 12 months after the changeover [38]. In another clinical study which compared the effects of candesartan and olmesartan [39], Tsutamoto et al. found no difference between the effects of the two drugs on aldosterone, but Ang II was significantly lower for the group after 3 months to one year of olmesartan administration. The rate of reduction in the LVMI of the olmesartan group was significantly higher after 1 year of administration, and the rates for Ang II and LVMI reduction correlated [39]. Thus, olmesartan may be associated with a lower incidence of aldosterone breakthrough than attainable with other ARBs, so that this may be one of the reasons for the more pronounced regression of LVH.

Olmesartan may be associated with a lower incidence of aldosterone breakthrough than attainable with other ARBs, so that this may be one of the reasons for the more pronounced regression of LVH.

Clinical implications

As mentioned before, LVH is an independent cardiovascular risk factor for various types of HF patients. The use of ARBs has been highly recommended for HF patients, especially those with HFrEF [5]. On the other hand, there is no established pharmacological treatment for a better prognosis of patients with HFpEF. LVH was found to be present in the majority of patients with HFpEF, and LV mass to be independently associated with an increased risk of morbidity and mortality [40]. Our findings indicate that the use of olmesartan rather than other ARBs may lead to regression of LVH, and may result in a favorable clinical outcome for patients with HFrEF and HFpEF.

LVH of HF patients was reduced following the changeover from treatment with other ARBs to that with olmesartan. This finding may well have clinical implications for better management of HF patients.

Study limitations

There were certain limitations to this study. First, ACE2 and Ang-(1–7) were not measured in this study, so that we were not sure that LVH was determined by ACE2 and Ang-(1–7) to a greater than other factors such as hemodynamics. Second, the assessment of cardiopulmonary test, and cardiothoracic ratio in chest X-ray, and 12-lead electrocardiogram to evaluate the effects of a changeover from other ARBs to olmesartan was not part of this study. Finally, we used only echocardiography to assess LVH, and the assessment of LVH by means of cardiac magnetic resonance imaging was not part of this study.

Conclusions

LVH of HF patients was reduced following the changeover from treatment with other ARBs to that with olmesartan. This finding may well have clinical implications for better management of HF patients. This study covered a small number of patients in a single-center study, so that the future prospective studies of larger patient populations with randomly assigned to receive olmesartan or other ARBs or crossover study are necessary to validate our findings.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

Appendix and References available on request Healthcare.India@springer.com

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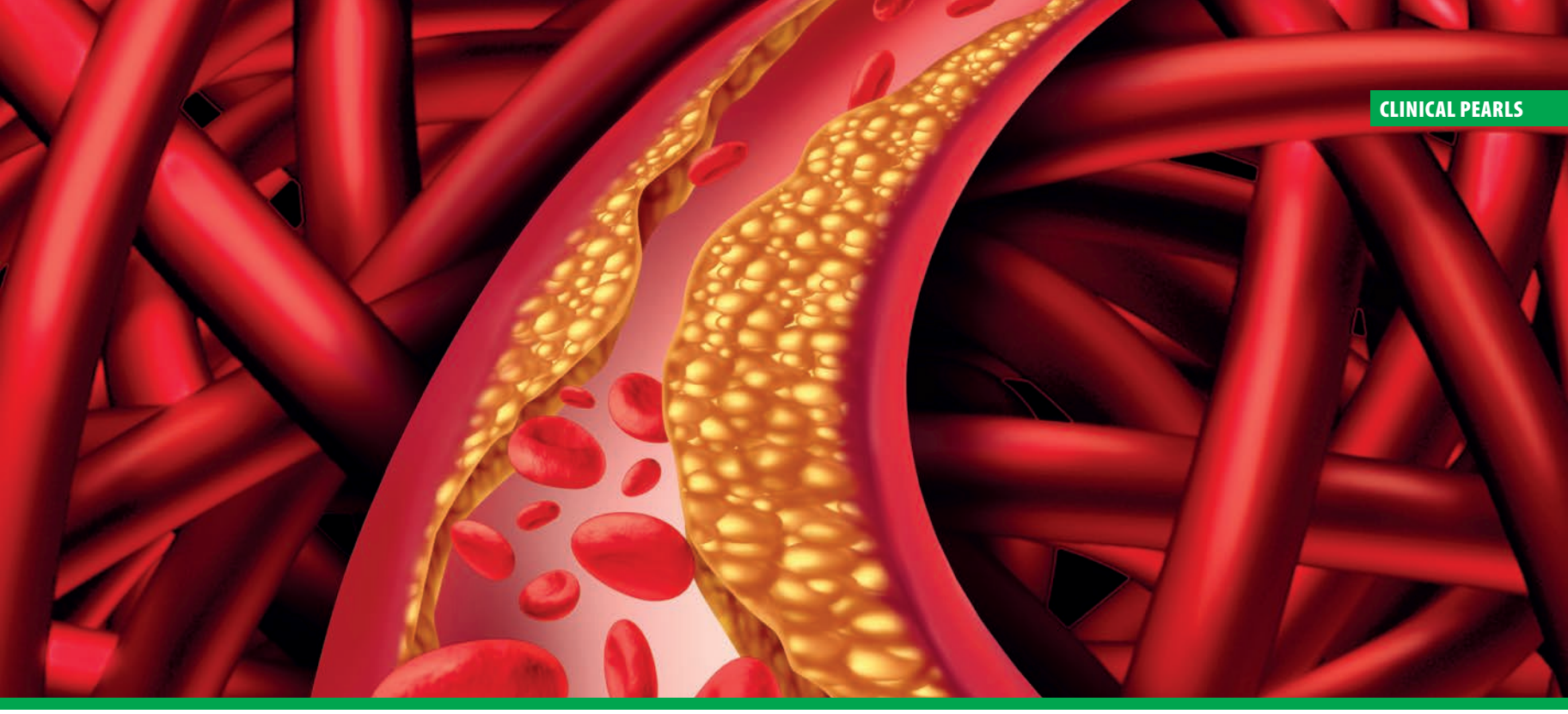

Efficacy study of olmesartan medoxomil on coronary atherosclerosis progression and epicardial adipose tissue volume reduction in patients with coronary atherosclerosis detected by coronary computed tomography angiography: study protocol for a randomized controlled trial

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> A significant amount of clinical research has been conducted to investigate the link between EAT and coronary atherosclerosis. It was claimed that calcified plaque progression in patients without coronary artery disease and in patients with type 2 diabetes mellitus were associated with a larger EAT volume.

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Background

Epicardial adipose tissue and coronary atherosclerosis

Epicardial adipose tissue (EAT) is directly deposited around the pericardium and coronary artery. By autocrine and paracrine means, EAT can generate various kinds of cytokines, inflammatory mediators and free fatty acids. These biological indicators can affect the state of coronary endothelial function and promote inflammation and oxidative stress, which finally aggravate the progression of coronary atherosclerosis [1–3]. A significant amount of clinical research has been conducted to investigate the link between EAT and coronary atherosclerosis. It was claimed that calcified plaque progression in patients without coronary artery disease and in patients with type 2 diabetes mellitus were associated with a larger EAT volume

[4, 5]. Epicardial adipose tissue is also an independent predictor of significant coronary stenosis and is independently associated with high-risk coronary plaque features, such as low CT attenuation plaque, thin-cap fibroatheroma and positive remodeling [6]. Not only is EAT, as a special visceral fat, correlated with the increased development of coronary artery atherosclerosis, but it is also associated with adverse coronary events [7].

Treatment of epicardial adipose tissue and coronary atherosclerosis

There are ample studies exploring the progression of coronary atherosclerosis following pharmacological manipulation. At the time of writing, the use of statins is recognized as an effective treatment; statins can result in decreases in plaque and necrotic core volume, and can also significantly reduce the progression of low attenuation plaque (<30 Hounsfield units) and non-calcified plaque [8, 9]. Other drugs, such as dipeptidyl-peptidase 4 inhibitors [10], a PPARγ agonist (pioglitazone) [11], atorvastatin plus ezetimibe [12], olmesartan [13], have also been reported to have antiatherosclerotic effects, although the effects have not been verified by large-scale studies. As studies show that EAT volume is associated with plaque progression and cardiovascular adverse events, treatments aimed at reducing EAT volume may finally achieve an antiatherosclerotic, preventive effect. However, at the time of writing, limited studies have aimed at reducing both EAT and plaque volume to achieve an antiatherosclerotic effect. A serial coronary computed tomography angiography (CCTA) study recently indicated that intensive statin therapy can reduce the EAT volume of Europeans, but the study failed to demonstrate a relationship among EAT volume reduction, coronary atherosclerosis progression and clinical prognosis [14]; moreover, intensive statin therapy might not be appropriate for Asians. The epidemiological studies and clinical researches show that Asians may have poorer tolerability and safety to intensive statins than white people, owing to genetic differences (variants in structure or polymorphisms) in pharmacokinetics and pharmacodynamics properties [15–17]. It has been claimed that polymorphic variants in cytochrome P450 (CYP450) families that were associated with statin metabolism might result in varying rates of metabolic clearance. CYP450 2C19 slow metabolizer phenotype was reported to be present in approximately 16 % of Asians compared with only about 3 % of white people [18]. Polymorphic variants in the predominant CYP450 isoform, CYP450 3A4, were reported to be associated with a functional decrease in the enzyme's activity in dyslipidemic Chinese patients [19]. The HPS2-THRIVE study recently also indicated that, using same-dose statin treatment, an excess of increased alanine aminotransferase was seen mainly among Chinese patients (more than three consecutive values above the upper limit of normal of 0.24 %/year compared with 0.02 %/year in Europe) [20]. Moreover, the morbidity of chronic hepatitis B was high in china with nearly 90 million infections. For these reasons, intensive statin therapy may result in higher hepatotoxicity in Asian populations than in white populations, so low- to moderate- dose statin therapy might be more appropriate for Asian populations [15, 16]. Subjects who undergo weight loss exercise, bariatric surgery, or low-dose aspirin therapy can also reduce EAT volume or inflammation, but the effects are weak and these treatments cannot achieve good results in patients with coronary atherosclerosis progression [21–24]. Our aim is to find a drug that reduces EAT volume while inhibiting the progression of coronary atherosclerosis.

In recent years, studies have confirmed that olmesartan medoxomil can improve endothelial function, resist thrombosis, improve tissue reconstruction, and resist oxidative stress to achieve atherosclerosis resistance [13, 25–28]. The latest research shows that olmesartan medoxomil can better inhibit rat epididymal adipose cell hypertrophy and inflammatory reactions [29]. Therefore, we hypothesized that olmesartan medoxomil may also reduce EAT volume, finally achieving an anti-atherosclerosis effect.

EAT and coronary atherosclerosis imaging with computed tomography

Compared with such invasive methods as intravascular ultrasound, virtual histology intravascular ultrasound, optical coherence tomography, and fractional flow reserve, CCTA has emerged as a noninvasive imaging method that analyzes both coronary atherosclerosis and EAT volume [14, 30]. To date, ample CCTA studies have explored the progression of coronary atherosclerosis following pharmacological manipulation. Thus, in this study, using CCTA as a noninvasive method to analyze both coronary atherosclerosis progression and EAT volume is of significant clinical value.

Aims of the main study

The purpose of this study is to determine whether olmesartan medoxomil is effective on both the treatment of coronary atherosclerosis progression and EAT volume reduction in patients with coronary atherosclerosis detected by CCTA.

Aims of the anti-atherosclerosis mechanism study

1. To explore the relationship between coronary atherosclerosis progression and EAT volume reduction.
2. To explore the effect of olmesartan medoxomil on serum levels of blood lipids, glucose, circulating surrogate markers of atherosclerosis inflammation, including high-sensitivity C-reactive protein, IL-6, monocyte chemotactic protein 1 (MCP-1), TNF-α, and matrix metalloproteinase 9 (MMP-9), circulating surrogate markers of endothelial function, including NO and endothelin 1 (ET-1), and circulating surrogate markers of adipose tissue inflammation and metabolism, including adiponectin and leptin at baseline and after 6 and 12 months.

Methods/design

Study design

This study is a prospective, single-center (Chinese PLA General Hospital, Beijing, China), open-label, randomized controlled trial of the efficacy of olmesartan medoxomil on coronary atherosclerosis and EAT. Consecutive patients with coronary stenosis greater than 30 % and less than 70 % detected by CCTA will be randomly assigned to olmesartan medoxomil or conventional antihypertensive medication groups (1:1 ratio). Coronary computed tomography angiography will be conducted at the Department of Cardiology (Chinese PLA General Hospital). Primary outcome measures include coronary atherosclerosis progression and EAT volume reduction, as detected by CCTA, at 12 months. Secondary outcome measures include levels of blood lipids, glucose, high-sensitivity C-reactive protein, IL-6, MCP-1, TNF-α, MMP-9, NO, ET-1, adiponectin, and leptin at baseline and

after 6 and 12 months. The study design is summarized in Fig. 1.

Clinical inclusion and exclusion criteria

Clinical inclusion criteria are:

- Age between 18 and 75 years;
- Coronary artery stenosis between 30 % and 70 % determined by CCTA in essential hypertension patients;
- Resting diastolic blood pressure between 90 and 110 mmHg;
- Type A and B for coronary artery vascular lesions.

Clinical exclusion criteria are:

- Secondary hypertension;
- Coronary artery stenosis less than 30 % or greater than 70 %, as determined by CCTA;
- Severe arrhythmia;
- Severe cardiac insufficiency or left ventricular dysfunction (left ventricular ejection fraction < 30 %);
- Severe hepatic or kidney insufficiency;
- Resting systolic blood pressure > 200 mmHg or resting diastolic blood pressure >110 mmHg;
- Contraindications to treatment with olmesartan medoxomil (allergy, glaucoma, digestive ulcer, currently taking phosphodiesterase-5 inhibitor);
- Severe calcification, distortion or type C coronary artery vascular lesions;
- Pregnancy;
- Unwillingness or inability to provide informed consent.

Randomization

Information regarding the study will be provided to the patient at the Department of Cardiology. Once informed consent is obtained, the patient will be randomized at the Department of Cardiology. Subjects will be randomized to either olmesartan medoxomil or conventional antihypertensive medication groups (1:1 ratio). Participants will be randomized before the first treatment using a blocked randomization procedure (computerized random numbers) and will incorporate minimization to ensure matching for age, sex, body mass index, and hypertension grade.

Ethical considerations

The Chinese PLA General Hospital Ethics Committee approved this study on 12 December 2014 (reference number S2014-119-01). This study complies with the Declaration of Helsinki. Informed consent will be obtained from all participating patients. Upon signing informed consent, patients' data will be populated as per protocol.

Details of CCTA examination

CCTA examination procedure

CCTA will be performed on a dual-source CT scanner (Somatom Definition Flash, Siemens Healthcare, Forchheim, Germany). All enrolled patients will be instructed in the breath-holding technique before CCTA to minimize breathing artifacts. Three minutes before CCTA, all patients will be given 0.5 mg nitroglycerin sublingually to dilate the coronary artery. The scan range is from the carina or the pulmonary artery segment down to 1 cm below the diaphragm. Electrocardiography is continuously performed throughout the entire examination for each patient. A dual-head power injector (SCT 210, Medrad, USA) and a nonionic contrast medium (Ultravist®, 370 mg I /ml, Schering AG, Guangzhou, China) will be used. The collimation is 2 × 128 × 0.6 mm, the gantry rotation time is 0.28 ms, the slice thickness is 0.6 mm, the tube voltage is 80 to 120 kV (modified using a care kV, Siemens Medical Solutions, Forchheim, Germany), and the tube current is 290 to 560 mAs/rotation (scout-based automatic reference tube current selection – CareDose 4D, Siemens Medical Solutions, Forchheim, Germany). For double flash acquisition, the pitch is 3.4, and for retrospectively ECG-triggered spiral acquisition, the pitch will vary depending on the patient's heart rate. Total estimated radiation dose for the patient will be recorded.

Patients with a heart rate ≤70 beats/min will be evaluated using double prospective ECG-gated high-pitch CT angiography (double flash mode). For the double flash protocol, the contrast-enhanced CCTA protocol is as follows: a test bolus scan will be performed at the level of the aortic root with administration of 15 ml of contrast medium into the right antecubital vein at a rate of 5.0 ml/s, followed by an injection of 20 ml of saline flush at the same flow rate to obtain a peak enhancement time curve. The double flash acquisition triggered scan

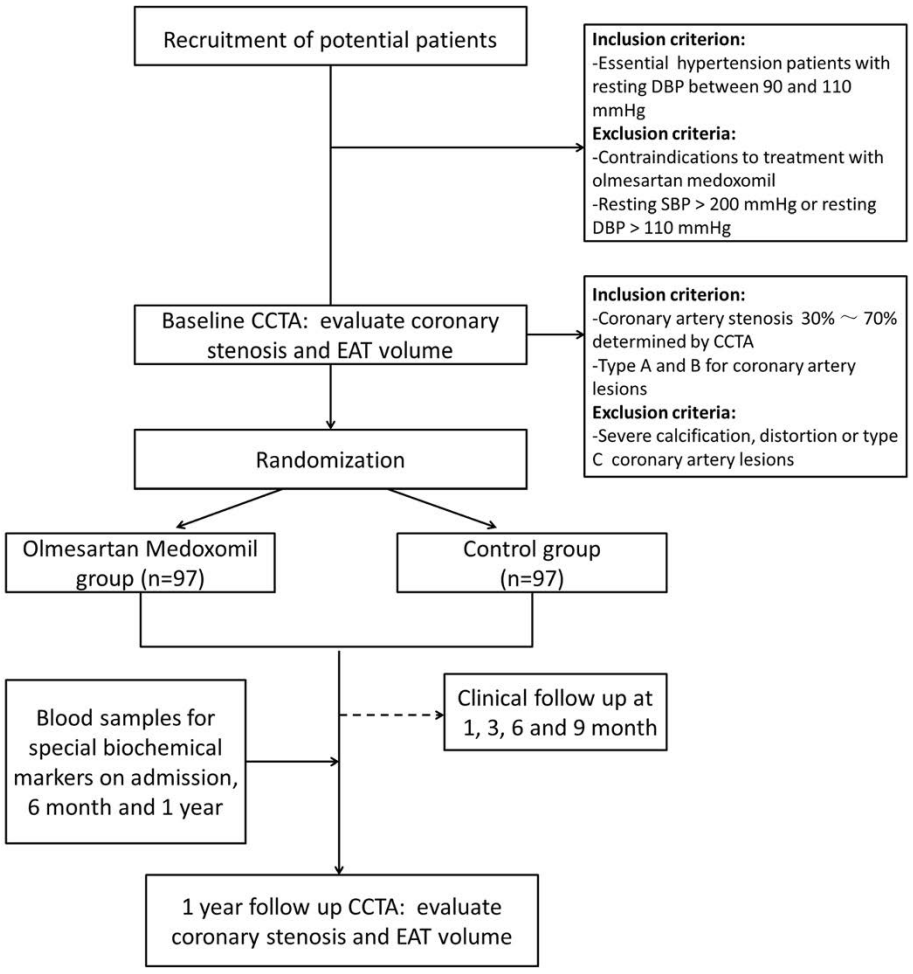

Fig. 1: Study flowchart. CCTA, coronary computed tomography angiography; DBP, diastolic blood pressure; EAT, epicardial adipose tissue; SBP, systolic blood pressure

time is 4 s after the peak enhancement time. After calculating the triggered scan time, double flash acquisition will be performed by injecting 60 to 90 ml contrast medium at a rate of 5.0 ml/s, immediately followed by 35 ml of 70/30 contrast/saline material mixture and 50 ml saline bolus at the same flow rate. The first scan will begin at 60 % of the R-R interval from the craniocaudal direction. The second scan will be acquired at 30 % of the R-R interval 3 s after the first scan during the same contrast injection time.

Patients with a heart rate >70 beats/min will be evaluated using retrospectively ECG-triggered spiral acquisition. The retrospective protocol is as follows: 60 to 90 ml contrast medium is injected into the antecubital vein at a rate of 5.0 ml/s, immediately followed by 50 ml saline solution at the same flow rate. Bolus tracking is used, and the region of interest is set at the root of the ascending aorta. We will perform the scan with a delay of 5 s after the root of the ascending aorta reaches a threshold of 100 Hounsfield units. For this scan mode, the acquisition is from 30 % to 80 % of the R-R interval.

CCTA image post-processing

All CCTA data will be sent to the Syngo Multi-Modality Workplace for post-processing. Two independent experienced observers who are unaware of the patients' clinical information will evaluate the CCTA data in different modes, including maximum intensity projection, volume rendering, curved-planar reconstructions, and the original transaxial images. Disagreements in data analysis between the two readers will be resolved by consensus reading.

Epicardial adipose tissue quantification

The EAT volume will be measured by two experienced radiologists using the same sets of images acquired for the CCTA. The radiologists will be blinded to the purpose of the study, clinical characteristics and patients' anthropometric data.

The EAT volume is defined as the total amount of adipose tissue deposited between the surface of the heart and the visceral pericardium. The region of interest in measuring the EAT volume includes the heart and the surrounding EAT. By manually tracing the epicardium contours in the axial slices from the bifurcation of the pulmonary artery to the diaphragm, the EAT volume is analyzed. The pericardium contour is traced every 10 mm, from the lower visible level of the pulmonary artery bifurcation until the top level of the pulmonary valve, for every 20 mm until the first slice where the diaphragm becomes visible, and for every 10 mm from this point until the last slice where the pericardium is still visible [31]. The pericardium contour is manually outlined by the radiologists, and then the software (Syngo Volume, Siemens Medical Solutions) automatically calculates the total EAT volume. Computed tomography attenuation ranging from −195 to 45 Hounsfield units is applied to isolate the EAT from other tissues. Mediastinal adipose tissue and pericardial adipose fat (fat deposit outside the visceral pericardium and on the external surface of the parietal pericardium) are excluded from the analysis. For the assessment of interobserver agreement, we will randomly select 50 patients, and all EAT measures will be assessed by two experienced radiologists blinded to the other radiologist's measurements.

Definition of coronary atherosclerosis plaque progression

We will use QAngio CT post-processing software (QAngioCT Research Edition version 2.1.0, Medis Medical Imaging Systems, Leiden, the Netherlands) to evaluate all CCTA data. All three vessels will be assessed in each patient using the 15-segment American Heart Association model for coronary segment classification [32]. Only segments with a diameter ≥2.0 mm and without stent implantation will be considered for analysis. Parameters including minimal lumen diameter, percent diameter stenosis, minimum lumen area, plaque burden, plaque volume, vascular remodeling index, plaque type classification (calcification, necrosis, fiber, and fiber lipid plaques) based on segments will be analyzed using QAngio CT post-processing software.

Coronary atherosclerosis progression is defined as ≥10 % diameter reduction or progression of a pre-existing coronary stenosis or ≥0.2 mm reduction or progression of the minimal luminal diameter in the lesion [30].

Medication intervention and control protocols

All patients should accept lifestyle interventions and conventional anti-atherosclerosis treatment. The low-density lipoprotein cholesterol level should be controlled below 100 mg/dl, and the blood pressure should be controlled below 140/90 mmHg.

In the olmesartan medoxomil group, the usual recommended starting dose of olmesartan medoxomil is 20 mg once daily when used as monotherapy in patients who are not volume-contracted. For patients requiring further reduction in blood pressure after 2 weeks of therapy, the dose of olmesartan medoxomil may be increased to 40 mg. Doses above 40 mg do not appear to have a greater effect. Twice-daily dosing offers no advantage over the same total dose given once daily.

In the control group, any antihypertensive medication alone or in combination, including calcium channel blockers, diuretics, beta blockers, or other antihypertensive medication except angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers can be used. The drug dose must be individualized. The patients should take the antihypertensive drugs according to the doctors' recommendations.

Study outcomes

The primary outcome measures are coronary atherosclerosis progression and EAT volume changes, as detected by CCTA at 12 months.

The secondary outcome measures include

1. The relationship between coronary atherosclerosis and EAT;
2. Serum levels of blood lipids, glucose, circulating surrogate markers of atherosclerotic inflammation including high-sensitivity C-reactive protein, IL-6, MCP-1, TNF-α, and MMP-9, individual circulating surrogate markers of endothelial function including NO and ET-1, and individual circulating surrogate markers of adipose tissue inflammation and metabolism including adiponectin and leptin at baseline and after 6 and 12 months.

Biomarkers

Two 10-ml samples of blood will be collected from the antecubital vein by a trained nurse for each individual. Fasting blood samples will be obtained between 7:00 a.m. and 12:00 noon to control for possible diurnal variations. Blood samples will be centrifuged at 4 °C and 3,000 rpm for 15 min. The serum

will be sampled and stored at −80 °C until analysis. Traditional cardiovascular blood risk markers, including fasting blood glucose, triglycerides, total cholesterol, and high- and low-density lipoprotein cholesterol will be assessed. The following proinflammatory markers will be assessed: high-sensitivity C-reactive protein, IL-6, TNF-α, MCP-1, and MMP-9. In addition, NO and ET-1 will be measured, to assess endothelial function. Markers of adipose tissue inflammation and metabolism, including adiponectin and leptin, will also be assessed. These markers will be measured at baseline and 6 and 12 months after treatment.

Follow-up

Clinical follow-up will take place at 1 month (±1 week), 3 months (±2 weeks), 6 months (±2 weeks), 9 months (±30 days), and 1 year (±30 days) by clinical visit or phone interview.

At baseline and 6-month (±2 weeks) and 1 year (±30 days) follow-ups, all patients will provide venous blood for detection of blood lipids, glucose, high-sensitivity C-reactive protein, IL-6, MCP-1, TNF-α, NO, ET-1, MMP-9, adiponectin, and leptin.

At 1 year (±30 days) follow-up, all patients will undergo CCTA (with QAngio CT post-processing software).We anticipated a patient drop-out rate of 10 %.

Sample size calculation

This trial is an open-label randomized clinical trial, so patients will randomly be assigned to olmesartan medoxomil or conventional antihypertensive medication groups (1:1 ratio). The purpose of this study is to verify that olmesartan medoxomil is effective in the treatment of coronary atherosclerosis progression and EAT volume reduction in patients with coronary atherosclerosis detected by CCTA. We also want to elucidate the relationship between coronary atherosclerosis and EAT. The mechanism by which olmesartan medoxomil inhibits coronary atherosclerosis progression will be studied by detecting the serum levels of blood lipids, glucose, circulating surrogate markers of atherosclerosis inflammation including high-sensitivity C-reactive protein, IL-6, MCP-1, TNF-α, and MMP-9, circulating surrogate markers of endothelial function, including NO and ET-1, and circulating surrogate markers of adipose tissue inflammation and metabolism, including adiponectin and leptin.

Studies on coronary atherosclerosis progression rate have had differing results. The combined results of multiple studies indicate that the conventional mean coronary atherosclerosis progression rate is about 30 % [33–35]. We hypothesize that additional olmesartan medoxomil use will reduce the coronary atherosclerosis progression rate to 13 % [36–40]. Using double-side inspection, $\alpha = 0.05$, $\beta = 0.2$, we calculate a total sample size of 176 cases; considering the expected loss to follow-up to be 10 %, the number of cases to be included should be at least $176 \times (1 + 10\ \%) = 194$. Therefore, we aim for 97 cases of each group.

Statistical analysis

Continuous variables will be described using means and standard deviations or median and range in case of asymmetric distribution of data. Categorical variables will be presented using frequency distribution. Univariate analyses will be conducted using chi-square and *t* tests for independent samples. A multiple logistic regression analysis will be performed to correlate coronary atherosclerosis progression with clinical variables and EAT volume, including treatment groups. Statistical significance will be considered for $P < 0.05$. A statistical package (SPSS 16.0) will be used for analysis. The individual will be considered the unit of analysis.

Discussion

To date, there are ample CCTA studies exploring the progression of coronary atherosclerosis following pharmacological manipulation. As studies show that EAT volume is associated with plaque progression and cardiovascular adverse events, treatments aimed at reducing EAT volume may finally achieve an antiatherosclerotic, preventive effect. However, at the time of writing, only a limited number of studies have aimed to reduce both EAT and plaque volume to achieve a preventive effect against atherosclerosis. The novelty of this study is that we intend to explore the effect of olmesartan medoxomil on both plaque volume and epicardial fat. This study will accomplish two goals: (1) it will explain the relationship between EAT volume and coronary atherosclerosis progression and (2) it will verify the effect of olmesartan medoxomil on EAT volume reduction and coronary atherosclerosis progression.

If these hypotheses are supported, the study findings will have significant implications related to clinical practice. Evidence that olmesartan medoxomil is effective on EAT volume reduction and coronary atherosclerosis progression would be very attractive to clinicians and patients. This may further contribute to the care of patients with coronary heart disease.

Trial status

Recruitment for the study is currently ongoing. Patient recruitment began in December 2014.

Abbreviations
CCTA: coronary computed tomography angiography; CT: computed tomography; CYP450: cytochrome P450; EAT: epicardial adipose tissue; ET-1: endothelin 1; IL-6: interleukin 6; MCP-1: monocyte chemotactic protein 1; MMP-9: matrix metalloproteinase 9; TNF-α: tumor necrosis factor α.

Competing interests
The authors declare no competing interests.

Authors' contributions
YZ conceived the study and drafted this manuscript, and will also conduct the CCTA examinations and image analysis. FT and JJ will conduct patient recruitment. JJY will conduct the CCTA examinations and image analysis. JW and TZ performed the statistical analysis and helped to draft this manuscript. YDC is the Head of the Department of Cardiology, conceived the study, and drafted this manuscript. All authors read and approved the final manuscript.

Acknowledgements
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Appendix and References available on request Healthcare.India@springer.com

Source: Ying Zhou, Feng Tian, Jing Wang, Jun-Jie Yang, Tao Zhang, Jing Jing and Yun-Dai Chen. Efficacy study of olmesartan medoxomil on coronary atherosclerosis progression and epicardial adipose tissue volume reduction in patients with coronary atherosclerosis detected by coronary computed tomography angiography: study protocol for a randomized controlled trial. Trials 2016;17:10. DOI 10.1186/s13063-015-1097-z.

Patient with Essential Hypertension and Left Ventricular Enlargement

R. Izzo

A 51-year-old Caucasian male farmer was admitted to the outpatient clinic reporting a more than 2-year-long clinical history of uncontrolled essential hypertension and mild exertional dyspnoea..

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Clinical Case Presentation

A 51-year-old Caucasian male farmer was admitted to the outpatient clinic reporting a more than 2-year-long clinical history of uncontrolled essential hypertension and mild exertional dyspnoea. The average values of home blood pressure (BP) were 180/100 mmHg.

Family History

Both his parents (84-year-old mother and 85-year-old father) and one brother (61 years old) are hypertensive.

Clinical History

Former smoker (about 20 cigarettes per day from the age of 14 to the age of 45), heavy drinker (about 1 L/day), consuming a diet rich in saturated fats and salt. Works about 12 h/day.

Arterial hypertension has been diagnosed 2 years before. His general practitioner prescribed an antihypertensive therapy based on a fixed combination of atenolol/chlorthalidone 100/25 mg, early interrupted after 1 month for drug-related side effects (erectile dysfunction).

Comorbidities

No other comorbidities or known cardiovascular risk factors, associated clinical conditions or non-cardiovascular diseases were reported.

Physical Examination

- Weight: 94 kg
- Height: 173 cm

- Body mass index (BMI): 31.4 kg/m^2
- Waist circumference: 115 cm
- Respiration: normal
- Heart exam: S1–S2 regular, normal and no murmurs
- Resting pulse: regular rhythm with normal heart rate (72 beats/min)
- Carotid arteries exam: no murmurs
- Femoral and foot arteries: palpable

Haematological Profile

- Haemoglobin: 15.1 g/dL
- Haematocrit: 45.2%
- Fasting plasma glucose: 117 mg/dL
- Lipid profile: total cholesterol (TOT-C): 238 mg/dL; low-density lipoprotein cholesterol (LDL-C): 151.4 mg/dL; high-density lipoprotein cholesterol (HDL-C): 61 mg/dL; triglycerides (TG): 128 mg/dL
- Serum electrolytes: sodium, 143 mEq/L; potassium, 4.8 mEq/L
- Serum uric acid: 4.6 mg/dL
- Renal function: urea, 50 mg/dL; creatinine, 0.98 mg/dL; creatinine clearance (Cockroft-Gault), 122.3 mL/min; estimated glomerular filtration rate (eGFR) (MDRD), 103 mL/min/1.73 m^2
- Urine analysis (dipstick): normal
- Albuminuria: 10.8 mg/24 h
- Normal liver function tests
- Normal thyroid function tests

Blood Pressure Profile

- Home BP (average): 184/115 mmHg
- Sitting BP: 180/118 mmHg (right arm); 178/116 mmHg (left arm)
- Standing BP: 176/120 mmHg at 1 min

12-Lead ECG

Sinus rhythm with normal heart rate (70 bpm), prolonged atrioventricular conduction (P-R interval 240 ms), criteria for left ventricular hypertrophy (R(I) + S(III) > 2.00 mV), abnormal repolarization in infero-lateral leads (Fig. 5.1).

Echocardiogram

Eccentric left ventricular hypertrophy (LV max index 59.3 g/m$^{2.7}$; relative wall thickness 0.33) with high left ventricular chamber dimension (LV end-diastolic diameter 57 mm) and volume (87.19 cm^3/m^2), normal ejection fraction (61%), dilated aortic root (43 mm), normal left atrium, no signs of right ventricle and/or pericardium disease. Aortic (++) regurgitation at Doppler ultrasound examination (Fig. 5.2).

Carotid Ultrasound

Both common carotids presented an increase of intima-media thickness (right, 1.0 mm; left, 0.9 mm) without evidence of significant atherosclerotic plaques.

Current Treatment

The patient does not take any medication.

Diagnosis

Essential (stage III) hypertension with hypertension-related target organ damage (left ventricular hypertrophy), hypercholesterolemia, impaired fasting glucose.

Q1: Which is the global cardiovascular risk profile in this patient?
Possible answers are:
1. Low
2. Medium
3. High
4. Very high

Global Cardiovascular Risk Stratification

According to 2013 European Society of Hypertension (ESH)/European Society of Cardiology (ESC) global cardiovascular risk stratification [1], this patient has very high cardiovascular risk (grade 3 HTN + 1 asymptomatic organ damage).

Treatment Evaluation

- Start olmesartan 40 mg + amlodipine 5 mg in a single pill.
- Start atorvastatin 20 mg.

Prescriptions

- Periodical BP evaluation at home according to recommendations from current guidelines
- Regular physical activity and low-calorie and low-salt intake

Follow-Up (Visit 1) After 6 Weeks

At follow-up visit the patient is in good clinical condition. He is regularly practising

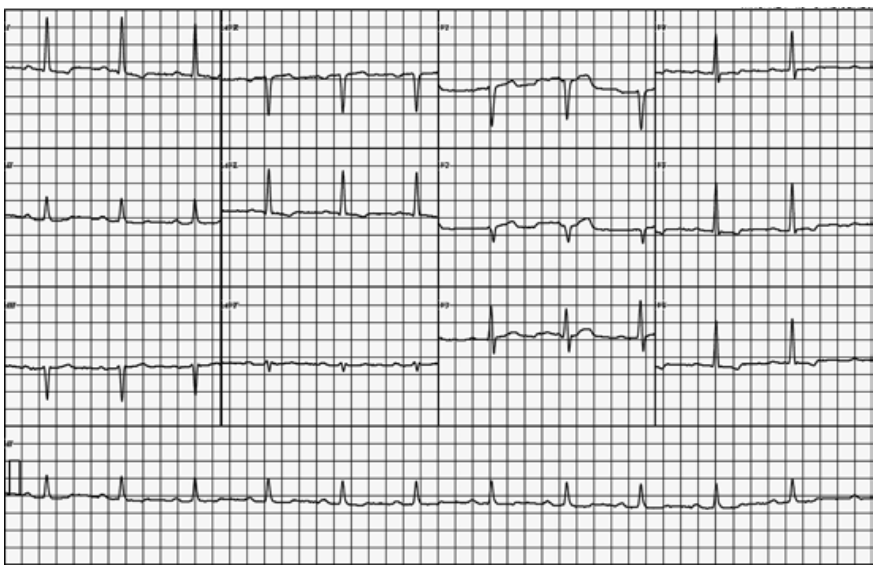

Fig. 1: 12-lead ECG at the first available visit.

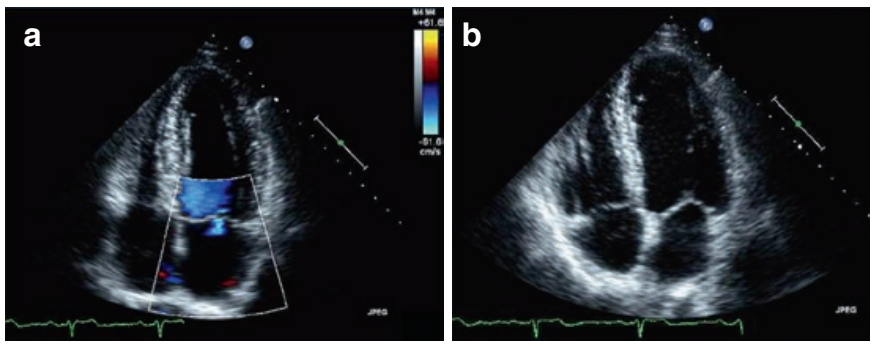

Fig. 2: Echocardiogram at the first visit (Panel a: 4 chamber with color; panel b: 4 chamber without color).

physical activity and following a low-calorie diet. Mean values of BP at home are normal.

Physical Examination

- Weight: 90 kg
- Body mass index (BMI): 30 kg/m^2
- Resting pulse: regular rhythm with normal heart rate (72 beats/min)
- Other clinical parameters substantially unchanged

Blood Pressure Profile

- Home BP (average): 120/85 mmHg
- Sitting BP: 130/88 mmHg
- Standing BP: 128/88 mmHg

Current Treatment

- Olmesartan 40 mg + amlodipine 5 mg
- Atorvastatin 20 mg

Diagnostic Tests for Organ Damage or Associated Clinical Conditions

No other tests were prescribed.

Diagnosis

Essential (stage III) hypertension with hypertension-related target organ damage (left ventricular hypertrophy), hypercholesterolemia, impaired fasting glucose.

Global Cardiovascular Risk Stratification

According to 2013 ESH/ESC global cardiovascular risk stratification [1], this patient has very high cardiovascular risk (grade 3 HTN + 1 asymptomatic organ damage).

Prescriptions

- Olmesartan 40 mg + amlodipine 5 mg (confirmed)
- Atorvastatin 20 mg (confirmed)

Follow-Up (Visit 2) After 3 Months

At follow-up visit after 12 weeks, the patient is still asymptomatic and in good clinical conditions. He reports adherence to treatment and good home values of blood pressure. No drug-related side effects are reported.

Physical Examination

- Weight: 88 kg.
- Body mass index (BMI): 29.4 kg/m^2.
- Resting pulse: regular rhythm with normal heart rate (70 beats/min).
- Mean values at home were normal. Other clinical parameters are substantially unchanged.

Blood Pressure Profile

- Home BP (average): 130/75 mmHg
- Sitting BP: 120/75 mmHg
- Standing BP: 130/70 mmHg

Current Treatment

- Olmesartan 40 mg + amlodipine 5 mg
- Atorvastatin 20 mg

Stress Test

Test performed on cycle interrupted at 150 W. No signs or symptoms of stress-induced myocardial ischaemia were recorded during exercise (Fig. 5.3).

Haematological Profile

Haemoglobin: 16 g/dL
Haematocrit: 47%
Fasting plasma glucose: 100 mg/dL
Lipid profile: TOT-C: 174 mg/dL; LDL-C: 97.2 mg/dL; HDL-C: 53 mg/dL; TG: 119 mg/dL

Prescriptions

- Olmesartan 40 mg + amlodipine 5 mg (confirmed)
- Atorvastatin 20 mg (confirmed)

Follow-Up (Visit 3) at 1 Year

The patient presents to the hypertension clinic for a control visit.

He is asymptomatic, his lifestyle has discretely improved, and he continues to practise moderate physical activity.

Physical Examination

- Weight: 88 kg.
- Body mass index (BMI): 29.4 kg/m^2.
- Resting pulse: regular rhythm with normal heart rate (64 beats/min).
- Mean values at home were normal. Other clinical parameters are substantially unchanged.

Blood Pressure Profile

- Home BP (average): 110/70 mmHg
- Sitting BP: 124/75 mmHg (right arm); 128/76 mmHg (left arm)
- Standing BP: 129/75 mmHg at 1 min

Haematological Profile

- Haemoglobin: 15.9 g/dL
- Haematocrit: 45.5%
- Fasting plasma glucose: 98 mg/dL
- Lipid profile: TOT-C: 167 mg/dL; LDL-C: 100.8 mg/dL; HDL-C: 54 mg/dL; TG: 61 mg/dL
- Electrolytes: sodium, 137 mEq/L; potassium, 4.0 mEq/L
- Serum uric acid: 4.0 mg/dL
- Renal function: urea, 45 mg/dL; creatinine, 0.88 mg/dL; creatinine clearance (Cockroft-Gault), 122.2 mL/min; estimated glomerular filtration rate (eGFR) (MDRD), 114 mL/min/1.73 m^2
- Urine analysis (dipstick): normal
- Albuminuria: 10.2 mg/24 h
- Normal liver function tests

12-Lead ECG

Sinus rhythm with normal heart rate (62 bpm), normal atrioventricular conduction (P-R interval 204 ms), evidence of left

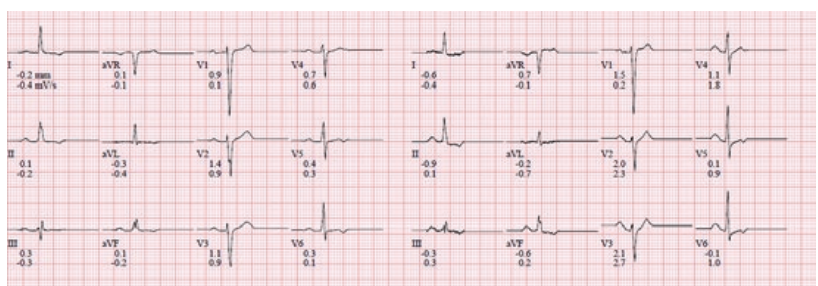

Fig. 3: 12-lead ECG during stress test

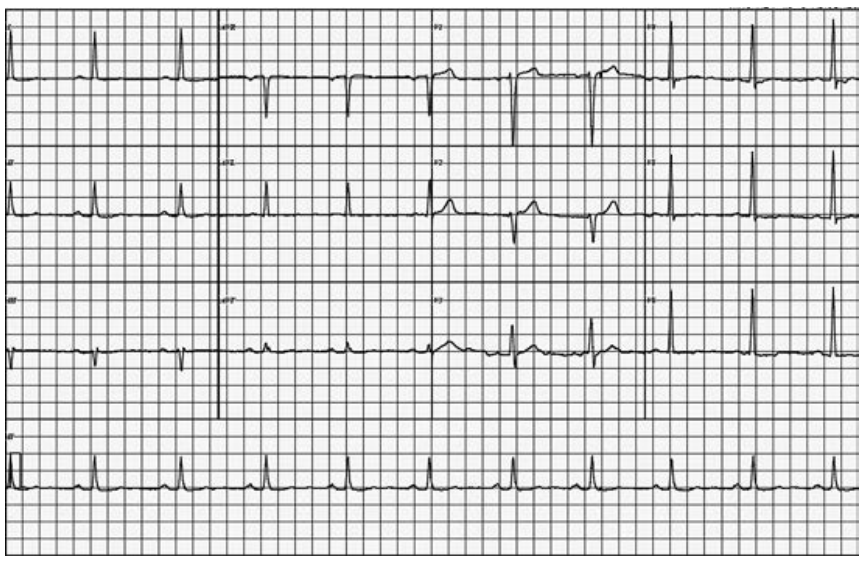

Fig. 4: 12-lead ECG at 1 year (follow-up visit 3).

ventricular hypertrophy (R(I) + S(III) > 2.00 mV) (Fig. 5.4).

Echocardiogram

Eccentric left ventricular hypertrophy (LV max index 57.1 g/m$^{2.7}$; relative wall thickness 0.38) with high left ventricular chamber dimension (LV end-diastolic diameter 52 mm) and volume (82.20 cm^3/m^2), normal ejection fraction (63%), dilated aortic root (42 mm), normal left atrium, absence of pathological findings on the right ventricle and pericardium.

Aortic (++) regurgitation at Doppler ultrasound examination.

Carotid Ultrasound

Both common carotids present an increase of intima-media thickness (right, 1.0 mm; left, 1.0 mm) without evidence of significant atherosclerotic plaques.

Current Treatment

Olmesartan 40 mg + amlodipine 5 mg
Atorvastatin 20 mg

Q2: Which is the best therapeutic option for this patient?
Possible answers are:
1. Increase amlodipine to 10 mg.
2. Stop atorvastatin.
3. Change olmesartan with ramipril.
4. No changes.

Prescriptions

No Changes
- Olmesartan 40 mg + amlodipine 5 mg (confirmed)
- Atorvastatin 20 mg (confirmed)

Discussion

This clinical case describes a patient with unknown grade III hypertension complicated by ventricular enlargement (eccentric left ventricular hypertrophy). Arterial hypertension has been associated with development and progression of cardiac organ damage, namely, left ventricular hypertrophy, which in turn is related to an increased risk of coronary events, myocardial infarction, ischaemic stroke and congestive heart failure. For these reasons, systematic assessment of left ventricular hypertrophy in all hypertensive patients has been recently reaffirmed and promoted by 2013 ESH/ESC guidelines on the clinical management of hypertension [1], in order to properly identify and treat those hypertensive patients at high cardiovascular risk.

In a recent paper we reported that the left ventricular dilatation in hypertensive patients with normal ejection fraction is associated with high cardiovascular risk [2].

The therapeutic choice for this patient was oriented on a fixed combination therapy based on the angiotensin receptor blocker olmesartan and the calcium channel blocker amlodipine. This choice is justified by the particular efficacy of the ARB olmesartan, compared with the ACE inhibitor ramipril [3], and its ability to reduce left ventricular hypertrophy [4] and to improve left ventricular function and to ameliorate the progression of cardiac remodelling [5]. The association with amlodipine is particularly recommended for its ability to reduce the peripheral resistance and consequently the aortic regurgitation.

Take-Home Messages

Arterial hypertension has been associated to the development and the progression of cardiac organ damage.

LV hypertrophy is related to an increased risk of coronary events, myocardial infarction, ischaemic stroke and congestive heart failure.

Left ventricular dilatation in hypertensive patients with normal ejection fractions is associated with high cardiovascular risk.

The fixed combination of ARBs and calcium channel blockers is able to reduce blood pressure and related target organ damage.

Appendix and References available on request Healthcare.India@springer.com

Source: R. Izzo. Patient with Essential Hypertension and Left Ventricular Enlargement. In: R. Izzo, Hypertension and Cardiac Organ Damage. Practical Case Studies in Hypertension Management. 2017; pp. 61-73. DOI 10.1007/978-3-319-56080-9_5.

Comparison Among Recommendations for the Management of Arterial Hypertension Issued by Last US, Canadian, British and European Guidelines

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The management of hypertension is a key factor of primary and secondary cardiovascular disease (CVD) prevention strategies. Hypertension societies have a common goal; to help the medical community understand hypertension complexity and expand the medical knowledge assisting hypertension research.

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Introduction

The management of hypertension is a key factor of primary and secondary cardiovascular disease (CVD) prevention strategies. The American Society of Hypertension was established on 1985 and was followed 4 years later by the establishment of the European Society of Hypertension aiming in the effective blood pressure control. Hypertension societies have a common goal; to help the medical community understand hypertension complexity and expand the medical knowledge assisting hypertension research. All guidelines aim to help the physician to control hypertension especially in high risk patients. Societies frequently collaborate for educational instances for example in the joint meetings of the European and International Society of Hypertension, but medical organizations have formulated guidelines for the management of hypertension which have major differences. Hypertension guidelines were issued from the National Institute for Health and Care Excellence

(NICE) in the United Kingdom on 2011 (updated on 2016) [1], the European Society Hypertension (ESH) and European Society of Cardiology (ESC) on 2013 [2], the Eighth Joint National Committee (NJC 8) from USA on 2014 [3] and lately from the Canadian Hypertension Society on 2015 [4], but also other societies have issued guidelines such as the Chinese, the Japanese, Greek and other. European and Canadian guidelines are more detailed and deal with the diagnosis, assessment of the hypertensive population, prevention and treatment, whereas NICE guidelines are more focused in the cost for the healthcare system of the different treatment and diagnostic approaches. NJC 8 guidelines refer to the blood pressure goals and the treatment strategies but lately have been heavily criticized by the American-Heart-Association.

Differences in guidelines issued from hypertension organizations may cause confusion in physicians that are reading and interpreting them in everyday clinical praxis. Aim of this review is to report differences and similarities among guidelines issued by the NICE, ESH/ESC, Canadian and NJC 8 societies and organizations and to evaluate them for their ability to help the medical community to distinguish what is the best practise for the hypertensive patient.

Diagnostic Evaluation

(a) Measurament of blood pressure and diagnosis of hypertension

Diagnosis of hypertension should be based on measurements at office and out-of-office BP levels according to all guidelines. Office auscultatory (mercury) or oscillometric (electronic) measurements with validated devices are recommended in all guidelines for the measurement of blood pressure at the clinic, except the last Canadian guidelines. In Canadian guidelines auscultatory (mercury, aneroid) is not recommended for office blood pressure measurements, while automated office (unattended) oscillometric (electronic) measurements are recommended as the office BP measurement of choice. In the NICE guidelines, it is recommended that if the clinic blood pressure is 140/90 mmHg or higher, ambulatory blood pressure monitoring (ABPM) should be offered to the patient to confirm the diagnosis of hypertension. ABPM is suggested to have at least two measurements per hour during the person's usual waking hours, giving an average of at least 14 measurements to confirm diagnosis, but desirable goals are not referred. Per this approach nighttime blood pressure measurements are not considering despite that major studies have reported the importance of these measurements [5–11]. European and Canadian guidelines agree about ABPM goals; patients can be diagnosed as hypertensive if the mean awake SBP is ≥ 135 mmHg and or DBP ≥ 85 mmHg or if the mean 24 h SBP is ≥ 130 mmHg and or DBP ≥ 80 mmHg. Home blood pressure measurement (HBPM) has been proposed as a complementary way of measuring out of office blood pressure in the European, Canadian and NICE guidelines. All of them agree about measuring blood pressure twice per day morning and evening for seven days continuously defining home BP hypertension if SBP is ≥ 135 mmHg and or DBP is ≥ 85 mmHg. Canadian guidelines have more details of the HBPM protocol suggesting measuring blood pressure before breakfast and 2 hours after dinner, before taking any medication. Patient also should refrain from drinking coffee or smoking, as well as exercising, 30 min before measurement.

In ESH/ESC guidelines it is considerd that in elderly patients (chronological age of 80 years or higher) the goal for BP should be between 140 and150 mmHg, higher than the values suggested for younger hypertensives.

(b) What are the optimal blood pressure levels according to guidelines

The definition of elderly is different among guidelines. In ESH/ESC guidelines it is considerd that in elderly patients (chronological age of 80 years or higher) the goal for BP should be between 140 and150 mmHg, higher than the values suggested for younger hypertensives. In elderly fit patients with age less than 80 years the goal could be at 140/90 mmHg. In NJC8 [3] treatment should be initiated when BP is higher than 140/90 mmHg (ages 30–59) or higher than 150/90 mmHg (ages 60 and older). In a latest statement of American Heart Association on September 2016 this increased BP goal was not adopted stating that the society maintain the recommendation of initiating treatment starting with lifestyle changes and then medication if necessary at BP levels higher than 140/90 mmHg until the age of 80 years and then at 150/90 mmHg. In the NICE and Canadian guidelines chronological age of 80 years set the goal to 150/90 mmHg.

Patients with comorbidities or additional cardiovascular health problems have also different treatment goals compared to hypertensives having no other cardiovascular risk factors. Blood pressure goals for patients with diabetes are different in guidelines. ESH/ESC guidelines have a BP goal < 140/85 mmHg, NJC8 < 140/90 mmHg, Canadian 130/80 mmHg, ADA 140/80 mmHg [12] and NICE have no specific mention to patients with diabetes. Hypertension treatment for people with chronic kidney disease is suggested when BP is higher than 140/90 mmHg in all guidelines, expept in patients with proteinouria,where ESH/ESC and KDIGO guidelines [13] recommend BP less than 130/80 mmHg. Blood pressure goals according to comorbidities from different societies are described at Table 1. ESH/ESC reffers to the population of patients with previous cardiovascular events, as patients with very high cardiovascular risk and the recomendation for BP goals is similar to the that of most other people i.e < 140/90 mmHg. Reversely, in the recend 2016 Canadian guidelines it is suggested that for high-risk patients, aged ≥ 50 years, with systolic BP levels ≥ 130 mmHg, intensive management to target a systolic BP ≤ 120 mmHg should be considered. Intensive management should be guided by automated unattended office BP measurements. Patient selection for intensive management is recommended and caution should be taken in certain high-risk groups. Recommendations for blood pressure manegement in the obese patients are not mentionted in any guidelines.

(c) Physical examination, mandatory laboratory tests and evaluation of taget organ damage

ESH/ESC describes physical examination step by step, aiming to the identification of patients with secondary hypertension, possible organ damage and obesity parameters. Mandatory laboratory exams are urinary test, blood test with hemoglobin, hematocrit, serum uric acid, electrolytes (potassium, sodium, calcium), fasting glucose, lipid levels, as well as kidney function with estimation of e-GFR and 12-lead electrocardiography. Glycated hemoglobin and lipid levels seems to be important as they play a significant role in the diagnosis of the type 2 diabetes and the high-

Table 1: Blood pressure goals according to different guidelines		
Population	**Guidelines**	**BP goal (SBP/DBP)**
Elderly (aged ≥ 80 years old)	ESC/ESC	< 150/90 mmHg
	NICE	
	Canadian	
	NJC8[a]	
Diabetes mellitus	ESC/ESC	< 140/85 mmHg
	Canadian	< 130/80 mmHg
	NJC8	< 140/90 mmHg
	ADA	< 140/80 mmHg
Chronic kidney disease without proteinouria	ESC/ESC	< 140/90 mmHg
	Canadian	
	NJC8	
	KDIGO	
Chronic kidney disease with proteinouria	ESC/ESC	< 130 mmHg
	KDIGO	< 130/80 mmHg

[a]In NJC8 guidelines, it is defined as age ≥ 60 years old

risk for atherosclerosis dyslipidemic patients. In NJC8 guidelines there is no special report to laboratory exams neither for the diagnosis of the new hypertensive patient nor for the control and monitoring of the already known hypertensive patient.

ESH/ESC guidelines suggest that per findings clinical doctor can undergo Holter monitoring in case of arrhythmias and evaluation of target organ damage with carotid ultrasound, pulse wave velocity and echocardiography. Increased intima media thickness of the carotid arteries or the presence of a plaque and increased stiffness of the large arteries are key factors for the probability of future cardiovascular events. Similarly, left ventricular mass, systolic and diastolic function of the heart seems to be an extra valuable tool for the evaluation of a hypertensive patient, because left ventricular hypertrophy and or systolic and diastolic dysfunction of the heart re-classify hypertensive patients into higher risk categories. At ESH/ESC guidelines, echocardiography is advisable to all hypertensive patients at the initial evaluation, but in Canadian guidelines it is recommended only if ventricular dysfunction or coronary artery disease is suspected, while in NICE guidelines only 12-lead electrocardiograph should be performed.

(d) Assessment of cardiovascular risk in the hypertensive population

The estimation of total cardiovascular risk in hypertensive patients is important for the evaluation and treatment of hypertensive patients. High-risk patients may treat earlier or intensive to prevent an irreversible condition through the years. A score to evaluate the 10-year cardiovascular risk in the population is the Systematic Coronary Risk Evaluation model (SCORE), which have been developed from large European studies. SCORE provides charts for individual countries and estimates the 10 years risk of dying from cardiovascular events. SCORE is calculated from age, gender, smoking, cholesterol and blood pressure levels [14]. There are two available charts, one of the low to moderate cardiovascular risk countries and one for the high-risk countries. ESC recommends the SCORE model in asymptomatic patients with hypertension and free of other health problems as a minimal requirement to evaluate the CV risk.

ESH guidelines having designed their own chart to evaluate the 10-year risk categorizing patients into risk categories from low to elevated risk. Patients are categorized according their blood pressure levels and the presence of cardiovascular risk factors. According to the blood pressure values, patients are divided into four groups; high normal blood pressure (SBP 130–139 or DBP 85–89), grade 1 hypertension (SBP 140–159 or DBP 90–99), grade 2 hypertension (SBP 160–179 or DBP 100–109) and grade 3 hypertension (SBP ≥ 180 or DBP ≥ 110) and according to risk factors (RF) into five groups; no other RF, 1–2 RF, ≥ 3 RF, organ damage or chronic kidney disease (stage 3) or diabetes and finally a group of patients having already symptomatic CV disease or stage 4 chronic kidney disease or diabetes with organ damage. Combining the above groups, patients are classified in low, moderate, high and very high-risk category. For example, a patient with high normal blood pressure and 1–2 RF has low CV risk, while a patient with grade 3 hypertension and 1–2 RF has high risk. All patients with symptomatic CV disease or stage 4 chronic kidney disease or diabetes with organ damage, independently of their blood pressure levels, belong to the very high-risk category.

NICE guidelines suggest using local country tools to evaluate the cardiovascular risk. QRISK is a multifactor cardiovascular disease risk prediction algorithm and was recently developed and validated for use in the United Kingdom. QRISK includes traditional cardiovascular disease risk factors, such as age, sex, systolic blood pressure, smoking and serum cholesterol, but it also includes body mass index, family history of cardiovascular disease, social deprivation and the use of antihypertensive treatment. QRISK 2 score is recommended for patients with type 2 diabetes mellitus and for primary prevention of CV disease in people aged 84 years or older [15]. Patients with type 1 diabetes or an estimated glomerular filtration rate less than 60 ml/min/1.73 m^2 or familiar hypercholesterolaemia or pre-existing cardiovascular disease have already a very high cardiovascular risk. Such patients may be excluded from the use of risk tools because they already have a very high risk. NICE suggest that patients treated for HIV, patients with serious mental health problems, patients treated with medicines that cause dyslipidaemia and patients with autoimmune disorders are high risk populations. Finally, it is recommended that measured score in morbid obese patients with body mass index greater than 40 kg/m^2 is under-estimated and the real patients' score is higher than that measured with the different risk score tools.

Canadian and USA guidelines motivate doctors to use multifunctional risk assessment models to predict CV risk such as Framingham risk score. Framingham Heart Study Model score and Cardiovascular Life Expectancy Model score are recommended as they have been validated to Canadian adult population but also other available risk scores may also be used.

(e) Treatment strategies

Lifestyle Modification

Exercise

Lifestyle seems to be very important in the development of hypertension, diabetes mellitus, hypercholesterolemia and obesity[16–25]. Sedentary lifestyle and unhealthy food eating habits include increased consumption of calories and salt are common in the developed countries. Both ESH/ESC and Canadian guidelines agree that regular aerobic physical activity may be beneficial for both prevention and treatment of hypertension. They recommend at least 30 min of moderate intensity dynamic exercise (walking, jogging, cycling or swimming) for 4–7 days per week. NICE guidelines also recommend regular exercise. NICE and Canadian guidelines suggest reducing the stress and relaxation strategies are recommended.

Weight Reduction

A healthy BMI (about 25 kg/m^2 in ESH/ESC guidelines and 18.5–24.9 kg/m^2 in Canadian guidelines) and waist circumference < 102 cm for men and < 88 cm for women are a safe goal to prevent hypertension in non-hypertensive individuals and to reduce blood pressure in hypertensive patients. NICE guidelines recommend healthy diet without a specific goal for BMI.

In the American population aged more than 18 years with CKD, initial (or add-on) antihypertensive treatment should include an ACEI or ARB to improve kidney outcomes.

Dietary Recommendations

ESH/ESC and Canadian guidelines agree that alcohol consumption should be restricted. In Canadian guidelines, patients may drink less than 14 standard drinks per week for men and 9 for women. European guidelines recommend consumption of less than 140gr alcohol per week for men and 80 g per week for women or 10 standard drinks for men and 6 standard drinks for women weekly. All guidelines recommend healthy diet with increased consumption of fruits, vegetables and low-fat diet. Daily sodium intake should remain low for British and at 5 g daily for Canadians and Europeans. Patients that are not at risk for hyperkalaemia may increase dietary potassium intake to reduce blood pressure and potassium supplementation should be recommended per Canadian guidelines in hypertensives because potassium can decrease blood pressure especially in high salt diet populations.

Smoking Habits

It is recommended from all guidelines to give all smokers advice to quit smoking and to offer medical aid to help them.

Pharmacological Treatment

(a) Initial drug treatment

Initial drug treatment options are also different between guidelines. ESC-ESH guidelines leave the physician free to select between diuretics (thiazides, chlorthalidone, indapamide), beta blockers (BBs), calcium channel blockers (CCBs), angiotensin-converting enzyme inhibitors (ACE-I) or angiotensin II receptor blockers (ARBs). NCJ8 suggest for non-black diuretics, CCBs, ACE-I or ARBs and for blacks diuretics or CCBs. NICE guidelines suggest ACE inhibitor or low-cost angiotensin II receptor for ages lower than 55 and CCB if age is higher than 55 years. Second step is to combine the two classes of drugs if BP is not at goal, then to add a thiazide-like diuretic and finally other drug such as BBs or central acting drugs. Canadians start therapy with a single agent that can be a thiazide-diuretic (strong recommendation), b-blocker (for patients younger than 60 years old), ACE-1, ARB or CCB. Additional antihypertensive therapy is added if blood pressure levels do not achieve the goals.

(b) Treatment in diabetic hypertensive population

Treatment options also differ between ESC-ESH guidelines and NCJ8. Europeans suggest to treat patients with diabetes with a RAAS inhibitor, especially in case of proteinouria and or microalbuminuria. Simultaneous administration of two blockers of the RAS is not recommended and should be avoided in patients with diabetes. Americans suggest that the general nonblack population, including those with diabetes, initial antihypertensive treatment should include a thiazide-type diuretic, CCB, ACE-I, or ARB. Canadian agree with American guidelines. If blood pressure does not reach the goal, then combination therapy should be added. For persons in whom combination therapy with an ACE-I is being considered, a CCB is preferable to a thiazide-diuretic. British guidelines do not have specific suggestions for the diabetic hypertensive patients' management. Finally, American Diabetes Association 2013 guidelines recommend reduction of blood pressure below 140/80 mmHg and treatment with ACE-I or ARB [26].

All patients with left ventricular hypertrophy should be treated with anti-hypertensive drugs. ACE or ARB may better reduce left ventricular mass compared to b-blockers or CCBs.

(c) Treatment in hypertensive population with nephropathy

Per ESH/ESC guidelines, RAS blockers are more effective in reducing albuminuria than other antihypertensive agents, and are indicated in hypertensive patients in the presence of micro albuminuria or overt proteinuria. Aldosterone antagonists are not recommended in chronic kidney disease patients, especially in combination with a RAS blocker, because of the risk of excessive reduction in renal function and of hyperkalemia. In the American population aged more than 18 years with CKD, initial (or add-on) antihypertensive treatment should include an ACEI or ARB to improve kidney outcomes. This applies to all CKD patients with hypertension regardless of race or diabetes status. The same recommendation applies in Canadian guidelines, where the second anti-hypertensive agent should be a thiazide-diuretic except for end stage disease where loop diuretics should be prescribed. Nephology association guidelines (KDIGO 2012) suggest blood pressure goals equal or less than 140/90 mmHg for chronic kidney disease without proteinuria, while when proteinuria is present blood pressure goal is equal or less than 130/80 mmHg and to be treated with ARB or ACE-I [27].

(d) Treatment of hypertension after cerebrovascular disease

In ESC/ESC guidelines, it is not recommended to reduce BP-lowering therapy during the first week after acute ischemic stroke irrespective of BP level, although clinical judgment should be used in extremely high SBP values. Antihypertensive treatment is recommended in hypertensive patients with a history of stroke or transient ischemic attack (TIA), even when initial systolic BP is in the 140–159 mmHg range. In hypertensive patients with a history of stroke or TIA, a systolic BP goal of < 140 mmHg should be considered. In elderly hypertensives with previous stroke or TIA, systolic BP values for intervention and goal may be somewhat higher. All drug regimens are recommended for stroke prevention, if BP is effectively reduced.

Canadians agree about the nonintervention with antihypertensive drug therapy in the acute phase of ischemic stroke except for patients that will undergo thrombolytic therapy where BP should be reduced when is found greater than 185/110 mmHg. After the acute phase of stroke, the blood pressure goal remains the same (< 140/90 mmHg). Canadians prefer for stroke patients ACE-I in combination with thiazide-diuretic drugs.

This trial has showed the importance of lowering blood pressure in a hypertensive elderly population with reductions by 21% in the total mortality, 30% in stroke and 64% in the risk for heart failure.

(e) Treatment of hypertension in heart disease

ESC/ESC guidelines recommend blood pressure reduction ≤ 140 mmHg for patients with coronary heart disease. In recent myocardial infarction, beta blockers are recommended, while in stable coronary heart disease all anti-hypertensive agents are recommended, but beta blockers and calcium channel blockers seems to be a better choice. In patients at risk of new atrial fibrillation ACE-I or ARB should be given. In heart failure with preserved EF there is no evidence for the most beneficial anti-hypertensive agent, while in reduced EF beta blockers and mineralocorticoid receptor antagonists are recommended. Finally, all patients with left ventricular hypertrophy should be treated with anti-hypertensive drugs. ACE or ARB may better reduce left ventricular mass compared to b-blockers or CCBs.

Canadians suggest that hypertensive population with coronary artery disease should be treated with ACE-I or ARB, while for high risk patients ACE-I could be combined with CCB. The initial therapy for recent myocardial infarction should be a combination of beta blocker and ACE-I. Finally, for patients with hypertension and stable angina pectoris but without prior HF, MI or coronary artery bypass surgery, either a beta blocker or a calcium channel blocker can be used as initial therapy. In NICE guidelines, beta blocker should be the first choice if there is evidence of heart failure. Drug treatment in hypertensive population with co-morbidities is summarized at Table 2.

Table 2: The choice of treatment in hypertensive population with co-morbidities

Special condition	Guidelines	Anti-hypertensive drugs
General population	ESH/ESC	Diuretic, ACE-I, ARB, CCB
	NICE	< 55 years old: ACE-I
		≥ 55 years old: CCB
	Canadian	Thiazide-diuretic(Grade A) < 60 years old: BB
	NJC8	Non-black: thiazide-diuretic, ACE-I, ARB, CCB Black: thiazide-diuretic, CCB
Diabetes	ESH/ESC	ACE-I, ARB
	ADA	
	Canadian	Thiazide-diuretic, ACE-I, ARB, CCB
	NJC8	
Chronic kidney disease	ESH/ESC	ACE-I, ARB
	Canadian	
	NJC8	
	KDIGO	
Stroke	ESH/ESC	Thiazide-diuretic, ACE-I, ARB, CCB
	Canadian	ACE-I +/thiazide diuretic
Myocardial infraction	ESH/ESC	Beta-blocker
	Canadian	Beta-blocker +/ACE-I
Coronary heart disease	ESH/ESC	Beta-blocker, CCB
	Canadian	ACE-I, ARB
Left ventricular hypertrophy	ESH/ESC	Thiazide-diuretic, ACE-I, ARB,CCB
	Canadian	ACE-I, ARB
Heart failure	ESH/ESC	No evidence
	NICE	Beta-blocker

Discussion

The main differences between guidelines issued by hypertension associations and societies is the definition of hypertension, the treatment goals in the elderly and the drug of choice for the initial treatment of uncomplicated hypertension and how low should we go with antihypertensive treatment in patients with very-high cardiovascular risk. Guidelines issued by scientific societies may differ from those issued by national authorities due to different perspectives for the cost of treatment.

Diagnosis of hypertension should be based on measurements at office and out-of-office BP levels. If the diagnosis and treatment of hypertension is based only on measurements at office then more than 50% of patients may be misclassified [28]. At least at diagnosis of hypertension before the initiation of treatment, 24 h ABPM (not only daytime) should be offered to exclude white coat and masked hypertension. Home BP monitoring should be guide all follow up visits and treatment changes, but should be done correctly with 7 days measurements,

validated devices with memory and measurements that can be downloaded by the doctor for at least the last week before visit.

The Hypertension in the Very Elderly Trial (HYVET), published in 2008, is the only available clinical trial for hypertensive population with ages greater than 80 years old [29, 30]. This trial has showed the importance of lowering blood pressure in a hypertensive elderly population with reductions by 21% in the total mortality, 30% in stroke and 64% in the risk for heart failure. The study population consisted of patients from Europe, Indonesia, China and Australasia. The main criticism for the study was that most of the patients included were from Eastern Europe and Asia and the patients were too healthy for their age. Despite criticism the results are clear and show that in otherwise healthy octagerians we should reduce BP at levels like that of younger ages. In older ages, according to our view the problem is not how much we have to reduce BP, but how fast we should reduce the BP. In ages higher than 80 years, we should be wise not to reduce BP too quickly but with caution and after several weeks of progressively increasing doses or number of drugs. Such an approach will eliminate the possibility of extremely low for the given patient BP values, that may induce organ hypo-perfusion and damage. It is also important to know the health condition of the vessels in such patients. Arterial stenosis of carotid, coronary or renal arteries should differentiate our approach to BP control in elderly patients. Fragile patients also may be treated more conservative.

Arterial stenosis of carotid, coronary or renal arteries should differentiate our approach to BP control in elderly patients. Fragile patients also may be treated more conservative.

Lifestyle modification that includes moderate physical exercise, weight loss, salt restriction, moderate alcohol consumption and quit smoking is an important first step to reduce high BP according to all guidelines. Clinical trials have showed the importance of lifestyle modification not only in the management of hypertension but also in other cardiovascular risk factors control [31–33]. Weight loss is important to reduce BP. [5, 34, 35]. Finally, clinical trials suggested that a reduction to about 5 g/day of salt consumption can reduce systolic blood pressure about 4–5 mmHg. Salt restriction seems to be beneficial to salt sensitive populations such as black people, elderly, patients with diabetes mellitus, chronic kidney disease and obesity [36–38].

NICE guidelines suggest ACE inhibitor or low-cost angiotensin II receptor for ages lower than 55 and CCB if age is higher than 55 years.

The choice of antihypertensive treatment in uncomplicated hypertension according to ESH guidelines is free to be selected by the doctor from the five available categories of the anti-hypertensive agents. Patients may be treated with β-blockers as initial drug treatment. The idea to treat a patient with older β-blockers like atenolol may be not ideal for a patient when other categories may have similar or greater BP reductions with less side effects and better patient compliance. On the other hand, newer β-blockers such as nebivolol or carvedilol may be used because there are not clinical trials that suggest that are inferior to other drug classes and may be useful in selected patients. NCJ8 suggest for non-black diuretics, CCBs, ACE-I or ARBs. The use of diuretics as a first choice drug treatment in uncomplicated hypertension is not supported by any clinical trials. Diuretics need to be used in high doses to be effective in BP control, but high doses of diuretics have important adverse effects including orthostatic hypotension, electrolytic and metabolic abnormalities and low adherence to treatment especially in younger ages. NICE guidelines suggest ACE inhibitor or low-cost angiotensin II receptor for ages lower than 55 and CCB if age is higher than 55 years. The problem in NICE is the very low cut off value for age not supported by clinical trials and why should not an older patient start treatment with a ACE or ARB.

Most patients with hypertension will need more than one agent to treat hypertension. In our view, the modern approach of hypertension treatment should include more than one drug class with low drug doses. The effect on BP is maximized when multiple mechanisms of BP reduction are used. Vasodilation, reduction in circulating blood volume and cardiac index may synergetic reduce BP. Low drug doses reduce side effects and this may increase patient adherence.

In conclusions, differences between guidelines in the definition of old age from 60 years in USA and 80 years in Europe, in the initial drug treatment, in the definition of normal BP in patients with diabetes and CKD should be addressed in the future with discussion between the societies. We should also be aware that each of our patient is unique and guidelines may not feet well to all. Finally, we should individualize our approach to each patient's hypertension according to the best needs for its health, not taking care only financial numbers but to a more humanistic approach of the disease.

Compliance with Ethical Standards

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Appendix and References available on request Healthcare.India@springer.com

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Drug Evaluation: Olmesartan Medoxomil + Rosuvastatin for the Treatment of Dyslipidemia and Concomitant Risk Factors: A Chance for Better Compliance?

Joanna Gozdzikiewicz-Lapinska and Jolanta Malyszko

Among the established, most common, and well-controlled by pharmacotherapy risk factors of CVD remain high blood pressure and cholesterol abnormalities: increased serum concentration of low-density lipoprotein - cholesterol (LDL) and low levels of high-density lipoprotein – cholesterol (HDL). Commonly used drugs for the treatment of hypertension and dyslipidemia are angiotensin receptor blockers (ARBs) and HMGCoA reductase inhibitors (statins) respectively.

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Despite the progress in prevention, cardiovascular disease (CVD) remains the main cause of death in developed countries [1, 2]. Among the established, most common, and well-controlled by pharmacotherapy risk factors of CVD remain high blood pressure and cholesterol abnormalities: increased serum concentration of low-density lipoprotein - cholesterol (LDL) and low levels of high-density lipoprotein – cholesterol (HDL). Commonly used drugs for the treatment of hypertension and dyslipidemia are angiotensin receptor blockers (ARBs) and HMGCoA reductase inhibitors (statins) respectively. Recent years' trials emphasize the potential pleiotropic actions of these groups of drugs, beyond its conventional indications.

Worth of greater interest are well-known olmesartan medoxomil and rosuvastatin.

Olmesartan Medoxomil

The rennin–angiotensin–aldosteron system (RAAS) is a target for drugs used in the treatment of hypertension. ARBs inhibit the

RAAS by competitive binding to the type 1 receptor for angiotensin II, which blocks the enzyme actions: vasoconstriction, increased aldosteron secretion and sympathetic activation, salt and fluid retention.

Olmesartan, as other ARBs, is a potent angiotensin II type – 1 receptor (AT1 receptor) antagonist, without any effect on angiotensin II type – 2 receptor [3]. Its affinity for the AT1 receptor is greater than that of losartan and similar to that of candesartan [4]. Olmesartan esterification with the medoxomil moiety increases bioavailability of the drug [5]. The mean plasma half-life of olmesartan during chronic treatment is 10–15 h. The drug is excreted mainly in feces, with about 10–16 % excreted in the urine (briefly revised in [6]). Dosage adjustment for patients with renal or hepatic impairment as well as for elderly is not indicated; however, some manufacturers of the drug recommend lower initial dose [6].

Efficacy and tolerability of olmesartan (5–80 mg/day) in the treatment of hypertension in different populations of patients was examined in placebo-controlled trials as well as in the studies comparing it with different other classes of antihypertensives (among others amlodypine, hydrochlorotiazyd, atenolol, captopril) [7–12]. The researchers proved the efficacy of monotherapy as well as combined therapy of olmesartan with calcium channel blocker or diuretic in the treatment of mild to moderate hypertension, masked hypertension, or white coat hypertension. They also showed no more adverse effects of olmesartan as compared to placebo or amlodypine/calcium channel blocker alone, but slightly higher incidence of adverse effects was observed in the elderly population treated with olmesartan and diuretic [7–12]. Other conclusions of these studies were as follow: (1) higher possibility to achieve goal blood pressure with olmesartan than with other hypertensives, (2) olmesartan plus calcium channel blocker could be more effective in reducing risk of stroke than olmesartan plus diuretic in the elderly, (3) higher doses of olmesartan or addition of hydrochlorotiazyd to olmesartan therapy are equally effective and safe for patients who didn't respond to monotherapy with olmesartan alone [7–12].

Efficacy of olmesartan was also compared with other ARBs and summarized in a meta-analysis of 22 randomized controlled trials [13]. The study showed better efficacy of olmesartan in systolic blood pressure (SBP) reduction as compared to losartan or valsartan, and also better efficacy in diastolic blood pressure (DBP) reduction than losartan; when compared with valsartan, olmesartan was equally effective in DBP reduction [13]. No difference in the total number of adverse events was described while comparing olmesartan with losartan and valsartan [13].

Recent years' trials point on a link between hypertension and vascular inflammation/atherosclerosis, where the key player is angiotensin II (Ang II) [14].

Ang II proinflammatory actions are (1) in human endothelial and smooth muscle cells as well as in monocytes, increases the expression of different proinflammatory cytokines and adhesion molecules, such as interleukin 6 (Il-6), interleukin 1 beta (Il-1β), tumor necrosis factor alpha (TNFα), nuclear factor kappa B (NF-kappaB), monocyte chemoattractant protein 1 (MCP-1), and vascular cell adhesion molecule (VCAM); (2) induces recruitment of inflammatory cells; (3) induces production of superoxide anions and activates NADH/NADPH signaling – increases the oxidative stress and decreases nitric oxide bioavailability; (4) induces cell hypertrophy and activates fibrosis [14–19].

The researchers proved the efficacy of monotherapy as well as combined therapy of olmesartan with calcium channel blocker or diuretic in the treatment of mild to moderate hypertension, masked hypertension, or white coat hypertension.

Olmesartan medoxomil as a long-acting antagonist of AT1 receptor is able to improve endothelial dysfunction/atherosclerosis in animal models and human studies.

Olmesartan's influence on oxidative stress mediators was shown in rat studies. After treatment of methotrexate-induced mucositis model in Wistar rats with olmesartan (5 mg/kg/day), reductions in mucosal inflammatory infiltrations, ulcerations, and hemorrhagic areas were observed as well as decrease in concentrations of proinflammatory cytokines Il-1β and TNFα [20]. Moreover, authors noticed an increase in anti-inflammatory cytokine interleukin 10 (Il-10) concentration [20]. In a rat model of high-salt diet-induced glomerular and tubulointerstitial kidney injury, treatment with olmesartan (10 mg/kg/day) as well as with olmesartan and calcium channel blocker (CCB) caused a significant regression of morphological changes [21]. It was explained by the reductions in expression of other proinflammatory cytokines: MCP-1 and tumor growth factor β (TGF-β). Also, decrease in NADPH oxidase activity and NADPH oxidase-dependent superoxide production was observed [21]. Similar decrease in NADPH oxidase activity was noticed in olmesartan-treated rats with a stroke model (permanent middle cerebral artery occlusion) [22]. Significantly better functional scores and reduced infarct sizes were confirmed in a group of rats treated with olmesartan (10 mg/kg/day) 7 days before and 14 days after infarct, but also in the group only pretreated with this ARB or treated after infarct induction [22]. In a previous study, the antioxidative properties of olmesartan measured as the decrease in superoxide production and NADPH oxidase activity were confirmed for the lower dose of ARB – 3 mg/kg/day – in apolipoprotein E knockout mice [23].

Amelioration of oxidative stress in the endothelium improves its function. In spontaneously hypertensive rats treated with olmesartan (5 mg/kg/day) for 4 weeks and subsequently divided into 5 groups – increased dose of olmesartan (10 mg/kg/day) or addition of azelnidipine or temocapril or atenolol or hydrochlorothiazide, endothelial function, assessed by evaluating dilatory response to acetylcholine, was significantly improved compared to the control group [24]. Beneficial effects of olmesartan were probably connected with the upregulation or inhibition of the disruption of endothelial nitric oxide synthase (eNOS) [25, 26]. Antiatherogenic effects of olmesartan administration are further confirmed also by amelioration of atherosclerotic areas in the thoracic aorta, perivascular fibrosis, and medial thickness of the coronary arteries in diabetic apolipoprotein E-deficient mice treated with the combination of this ARB and CCB [26].

Olmesartan's effects on interstitial matrix were also evaluated. In spontaneously hypertensive rats treated with high (15 mg/kg/day) or low (1 mg/kg/day) dose of olmesartan, left ventricular weight–to–body weight ratio (RLVM) was measured, and cardiac, aortic, and glomerular interstitial collagen content was evaluated [27]. Both high and low dose of olmesartan normalized, increased in

control group rats, collagen content in hart, kidneys and aorta. The significantly increased RLVM in untreated rats was decreased in high-dose olmesartan-treated group [27]. In addition, reduction in expression of matrix metalloproteinases 2 and 9 could also contribute to antifibrotic effects of this ARB [20]. Attenuation of cardiac hypertrophy, remodeling, and improved cardiac diastolic function by olmesartan might be also a result of the influence of olmesartan on other molecular pathways: activation of delta-like ligand 4/Notch 1 pathway or calcineurin pathway [28, 29].

Olmesartan's observed renoprotective effects in animal models (based on improvement in urinary protein excretion and histological kidney injury/fibrosis) might be augmented by the increased expression of klotho mRNA in olmesartan + alfadiol-treated chronic renal failure rats [21, 30].

A double-blinded, placebo-controlled study (EUTOPIA), authors showed that 12 weeks of olmesartan therapy (20 mg/day), in contrast to placebo, significantly reduced serum concentration of high-sensitivity C reactive protein (hsCRP), TNF-α, IL-6, and MCP-1.

Not only in study animals but also in hypertensive patients, olmesartan medoxomil therapy results in improvements in endothelial function. In a double-blinded, placebo-controlled study (EUTOPIA), authors showed that 12 weeks of olmesartan therapy (20 mg/day), in contrast to placebo, significantly reduced serum concentration of high-sensitivity C reactive protein (hsCRP), TNF-α, IL-6, and MCP-1 [31]. The effect was observed already after 6 weeks of treatment, and further augmented during the next 12 weeks of therapy [31].

Amelioration of the endothelial function was documented by other authors who investigated arterial dilation after treatment with this ARB. In a Japanese study, 26 patients with essential hypertension, previously untreated, were assigned to the treatment either with olmesartan (20 mg/day; dose was doubled in case of not reaching desirable blood pressure or halved in case of too low blood pressure) or amlodypine for 12 weeks [32]. The protocol resulted in significant increase in the corrected myocardial blood flow and decrease in the change of coronary vascular resistance in the olmesartan group; effects were not observed in amlodypine-treated patients. What more, serum superoxide dismutase (SOD) concentration increased in the olmesartan group during the treatment period, but not in the amlodypine group, and could at least partially explain ameliorated myocardial blood flow [32]. Improved endothelial function evaluated by flow-mediated dilation (FMD) of brachial artery was also found in a 12 week trial of olmesartan vs amlodypine therapy [33].

Other studies concentrated on vascular hypertrophy and remodeling. Hypertensive, nondiabetic patients after a 4 week washout period were randomized to olmesartan (20–40 mg/day) or atenolol (50–100 mg/day) plus additional hypotensive drugs if needed (hydrochlorothiazide, amlodypine, hydralazine) [34]. At baseline and after a year of treatment upon biopsies, subcutaneous gluteal resistance arteries were examined to evaluate remodeling. In the control group, the wall-to-lumen ratio was 11 %. After the treatment period, the wall-to-lumen ratio in the olmesartan-treated group significantly decreased from 14.9 to 11.1 %. No significant change was observed in the atenolol group [34]. In the MORE study, in patients with hypertension and increased cardiovascular risk with carotid wall thickening (measured by means of ultrasound), olmesartan's or atenolol's influence on common carotid intima-media thickness (IMT) and atherosclerotic plaque volume was investigated [35]. After 2 years of treatment, olmesartan and atenolol produced similar significant reductions in IMT. However, only olmesartan reduced the volume of large atherosclerotic plaques [35].

In diabetic patients, olmesartan treatment was shown to be associated not only with delayed onset of microalbuminuria (early predictor of diabetic nephropathy and cardiovascular disease) but also delayed development of left ventricular remodeling [36, 37]. The latter effect was assessed during a randomized trial; signs of left ventricular hypertrophy were evaluated based on a 12-lead ECG at baseline and after 2 years of treatment with olmesartan or placebo (non-RAAS-influencing antihypertensive drugs were allowed) [36].

Rosuvastatin

HMGCoA reductase inhibitors are nowadays commonly used agents for lowering cholesterol concentration and thus preventing cardiovascular events. Competitive inhibition of HMGCoA reductase results in decreased hepatic cholesterol synthesis and apolipoprotein B-containing lipoproteins, increase in hepatic low-density lipoprotein (LDL) receptor expression, and enhanced LDL cholesterol uptake from plasma.

Rosuvastatin is one of the most recently available synthetic statins. It is rapidly absorbed after oral administration (briefly revised in [38]). Half-life of rosuvastatin is 19 h, which results in similar pharmacokinetics of the drug irrespective of the morning or evening dosing [39]. The drug is about 88 % reversibly bound to plasma proteins, mainly to albumin; it is eliminated in 90 % as unchanged drug with feces and remaining 10 % with the urine [38, 39]. In consequence, rosuvastatin administration is contraindicated in patients with active liver disease and unexplained transaminase elevations, and dosage adjustment is needed for patients with eGFR <30 ml/min/1.73 m2 – 5–10 mg/day. However, in end-stage kidney disease patients on continuous ambulatory peritoneal dialysis, pharmacokinetics of 10 mg/day of rosuvastatin was similar as in healthy volunteers [40]. Similar observations were made in a small study of 10 mg of rosuvastatin in 11 hemodialysis patients, suggesting that no dose adjustment is needed for these patients [41].

In diabetic patients, olmesartan treatment was shown to be associated not only with delayed onset of microalbuminuria (early predictor of diabetic nephropathy and cardiovascular disease) but also delayed development of left ventricular remodeling.

Rosuvastatin shows higher efficacy in modifying atherogenic lipid profile in patients with hypercholesterolemia than other statins. In several meta-analyses and clinical trials, rosuvastatin was not only more

efficacious in decreasing LDL cholesterol and increasing HDL cholesterol when compared to simvastatin, fluvastatin, lovastatin, or pravastatin but also in comparison to atorvastatin [42–44]. Rosuvastatin decreased LDL cholesterol levels better at the same dose of atorvastatin and 1:2 dose ratio; no significant difference in lipid profile goals was observed at 4 times higher atorvastatin doses [43]. What more, the same results were observed for different patient age-groups, and the incidence of adverse effects was the same for all the statins compared [42–44]. Rosuvastatin was also better than simvastatin in attaining LDL goals after switching patients from atorvastatin therapy – authors concluded it might be the drug of choice for lipid-lowering therapy in patients who failed to achieve cholesterol goals during atorvastatin treatment [45].

To effectively decrease cardiovascular adverse events in patients with multiple risk factors, it is required to act synergistically against all of them on different fields: change lifestyle to lose weight, change the dietary and exercise habits, and use the pharmacological measures.

Rosuvastatin's efficacy in improving lipid profile and achieving target goals of cholesterol were also studied for so-called high-risk populations including patients with diabetes mellitus (DM) or metabolic syndrome, acute coronary syndrome (ACS) or chronic kidney disease (CKD) [38]. Additional effects of the drug were also observed: (1) rosuvastatin administration (2.5–10 mg/day for 24 weeks) reduced albuminuria, serum cystatin C levels in CKD patients regardless of presence or absence of DM; (2) rosuvastatin administration (2.5–20 mg/day for 24 weeks) decreased hsCRP and malondialdehyde-modified LDL (effect of oxidative stress) in diabetic nephropathy patients with eGFR >60 ml/min/1.73 m2; (3) rosuvastatin (5–20 mg/day for 24 months) induced lasting decrease in carotid plaque lipid content in lipid treatment subjects as assessed by magnetic resonance; (4) rosuvastatin treatment decreased the incidence of heart failure hospitalizations in heart failure patients over 60 years of age; (5) rosuvastatin treatment (10 mg/day for 1 year) significantly improved coronary flow reserve in hypertensive patients without coronary artery disease [46–50].

Rosuvastatin's influence on oxidative stress, independent of lipid-lowering properties, is also under investigation (briefly revised in [51]). This statin is able to ameliorate NADPH oxidase-mediated damage by reducing NADPH oxidase activity in rats and NADPH oxidase-dependent superoxide production in obese rats [52, 53]. Rosuvastatin also inhibits angiotensin II-mediated vascular impairment by decreasing NADPH oxidase-derived oxidant excess, stimulation of endogenous antioxidant mechanisms, and restoring NO availability [54].

In addition, rosuvastatin increases endothelial NO synthesis and attenuates myocardial necrosis (the effect of ischemia and reperfusion) in mice [55]. Inhibiting HMGCoA reductase increases NO bioavailability and improves endothelial function in congestive heart failure rats [56]. Finally, it also upregulates eNOS expression in mice protecting the animals from cerebral ischemia [57]. Rosuvastatin reduces also other prooxidative cytokines like Il-6 or TNFα [58]. The restoration of antioxidant defense is mediated by rosuvastatin-dependent improvement in SOD1 expression [59].

Combination Therapy: Olmesartan with Rosuvastatin – A Chance for Better Compliance

To effectively decrease cardiovascular adverse events in patients with multiple risk factors, it is required to act synergistically against all of them on different fields: change lifestyle to lose weight, change the dietary and exercise habits, and use the pharmacological measures. The doctor should notice that in hypertensive patients with other risk factors not only blood pressure goal achievement but also improved lipid profile or proper glycemia control significantly decreases cardiovascular risk [60]. Patients' adherence to the pharmacological therapy significantly decreases the risk of long-term adverse events including mortality [61]. However, treatment regimens for combined blood pressure, cholesterol, and glycemia control and antiplatelet therapy in high cardiovascular risk is often complicated and for the patients is the main reason for poor compliance [62]. Benefits of the use of single-pill combination therapy are not only good effects of free therapy but also better patient compliance [62].

Patients' adherence to the pharmacological therapy significantly decreases the risk of long-term adverse events including mortality.

Olmesartan medoxomil and rosuvastatin, thanks to its pleiotropic effects, besides blood pressure lowering and lipid lowering respectively, are very attractive for the prescribing doctor and for the patient as well. Lately, a fixed-dose combination tablet of these two drugs (rosuvastatin 20 mg/olmesartan 40 mg) was developed [63]. Pharmacokinetics of the fixed-dose combination tablet was equally effective as coadministration of each drug as a single pill [63].

Appendix and References available on request Healthcare.India@springer.com

Source: Joanna Gozdzikiewicz-Lapinska, Jolanta Malyszko. Drug Evaluation: Olmesartan Medoxomil + Rosuvastatin for the Treatment of Dyslipidemia and Concomitant Risk Factors: A Chance for Better Compliance? In: M. Banach (ed.), Combination Therapy In Dyslipidemia. 2015; pp. 191-200. DOI 10.1007/978-3-319-20433-8_16.

A case report of malignant hypertension in a young woman

Andrea Michelli, Stella Bernardi*, Andrea Grillo, Emiliano Panizon, Matteo Rovina, Moreno Bardelli, Renzo Carretta and Bruno Fabris

Malignant hypertension is a condition characterized by severe hypertension and multi-organ ischemic complications. Incidence of malignant hypertension has remained stable over the years, although mortality and renal survival have improved with the introduction of antihypertensive therapy.

Background

Malignant hypertension is a condition characterized by severe hypertension and multi-organ ischemic complications [1]. Incidence of malignant hypertension has remained stable over the years, although mortality and renal survival have improved with the introduction of antihypertensive therapy. However, progression to end-stage renal disease remains a significant cause of morbidity and mortality [2]. The underlying cause of malignant hypertension can be primary or secondary hypertension, and identification of the latter is mandatory for choosing the correct treatment in order to control blood pressure and improve end-organ damage. However, correct diagnosis can be challenging [3]. This case highlights the difficulty in differentiating between primary and secondary hypertension, particularly when the patient presents with acute renal failure.

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Case presentation

A 33-year-old woman was referred to our Internal Medicine Department by her GP after the recent diagnosis of severe hypertension. While the diagnosis of hypertension dated back to the day before, its onset was actually unknown, as the patient had no memory of having ever measured her blood pressure before, consistent with the low awareness that young adults have of their hypertension [4]. During the visit she complained of fatigue. Otherwise, her medical and family histories were unremarkable. She used to smoke no more than 5 cigarettes per day, did not take any prescription or over-the-counter medications and denied the use of recreational drugs, as confirmed by the negativity of the urine drug screening. On admission, her blood pressure was 240/140 mmHg, but her other vital signs were normal and physical examination was unremarkable. Initial laboratory studies identified the presence of renal failure (creatinine 2.11 mg/dL), hypokalemia (potassium 2.45 mEq/L), and anemia with thrombocytopenia (hemoglobin 10.6 g/dL, platelets 113.000/microm^3), which were likely to be hemolytic as LDH was elevated (572 U/L). There was also an elevated CRP level of 170 mg/L. As for end-organ damage, renal failure was associated with a proteinuria of 1.9 g over 24 h, while ultrasound revealed 2 normal-sized kidneys with echogenic parenchyma. The ECG showed signs of left ventricular hypertrophy, which was confirmed by echocardiography, as the interventricular septum thickness measured 19 mm and LV mass/BSA was 232 g/m^2. The left ventricular ejection fraction was 50 %, and there was no aortic coarctation. Retinal examination revealed grade III hypertensive retinopathy, showing the presence of malignant hypertension, and antihypertensive drugs were promptly administered.

Given that the clinical characteristics suggestive of secondary causes of hypertension include early (i.e. < 30 years) and sudden onset of hypertension in patients without other risk factors, blood pressure levels higher than 180/110 mmHg, and presence of target end-organ damage [5], our next exams were aimed at excluding secondary causes of hypertension. These analyses showed that our patient had a hyperreninemia with a secondary hyperaldosteronism (renin 266.4 microUI/mL, aldosterone 38.1 ng/dL), which could be due to the presence of a renovascular disease, a renin-secreting tumor, or a scleroderma renal crisis [6]. This last hypothesis was

however excluded by the absence of circulating autoantibodies, as well as the absence of other clinical and/or laboratory features suggestive of immunological disorders. Moreover, a week after the start of the antihypertensive therapy, not only CRP, but also hemoglobin, platelets, and LDH normalized, so that we ruled out also other conditions causing renal failure with thrombotic microangiopathy and secondary hypertension, such as the hemolytic uremic syndrome (HUS) and the thrombotic thrombocytopenic purpura (PTT) [7].

Given the severity of the case, the diagnosis of any underlying curable cause of the patient hypertension could not be overlooked. At that stage, taking into account the laboratory exams, we needed to rule out several possible causes of malignant hypertension, including renal artery stenosis, and other insidious diseases such as phaeocromocytomas [8], lymphomas, and other renin-secreting masses [9]. For this reason, according to current guidelines [10, 11], the patient underwent a contrast enhanced computed tomography (CT) of the abdomen. This exam did not show any suspicious masses. Nevertheless, it visualized a stenotic left renal artery (Fig. 1a), suggesting that our patient could have a fibromuscular dysplasia causing renal artery stenosis. Despite most of our results were already strongly suggestive of renal artery stenosis, before prescribing any angiography with angioplasty, we requested a renal duplex ultrasound exam. The analysis of blood flow velocity, which was performed at the renal hilum as well as the intraparenchymal arteries, showed a normal hemodynamic pattern (Fig. 1b). Moreover, both proximal and distal velocimetric indices were normal (Fig. 1c). In particular, the maximal acceleration index, whose sensitivity is 93 % and specificity is 84 % [12], was greater than 9 s^{-1}, at all the sites. So, the renal duplex ultrasound did not confirm -to our surprise- the suspected renal artery stenosis.

Given this result, the renal angiography was put on hold and the patient was treated with medical therapy only, achieving blood pressure normalization over a few weeks. Nevertheless, the persistence of the renal failure, despite blood pressure normalization, led us to perform a kidney biopsy in order to exclude primary renal diseases. Kidney biopsy showed relative sparing of glomeruli with predominant vascular damage (Fig. 2). This finding led us to the final diagnosis of malignant hypertension complicating an underlying primary (essential) hypertension with thrombotic microangiopathy.

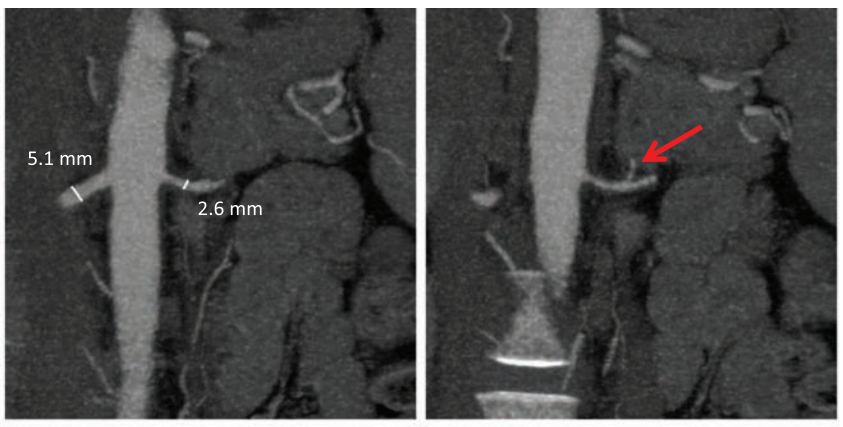
In this case antihypertensive therapy was able to successfully reduce blood pressure and induce end-organ damage recovery (Fig. 3). The echocardiography showed that after 1 year from the start of the therapy the interventricular septum thickness was of 11 mm, the LV mass/BSA was of 61 g/m^2, and that the ejection fraction was of 74 %. The retinal examination did not show any cotton wool spots or flame hemorrhages. Proteinuria disappeared 4 months after hospitalization and renal function progressively ameliorated over the following 2 years (Fig. 3), reflecting a slow recovery process that is likely to include vascular remodeling [6].

Conclusions

This young woman's presentation, marked by malignant hypertension with renal failure, was a diagnostic challenge. On one hand, the clinical presentation, the hyperreninemia with a secondary hyperaldosteronism were suggestive of a secondary form of hypertension, which at the contrast-enhanced CT scan seemed to be that of a renal artery stenosis. On the other hand, the renal duplex ultrasound exam was normal. Had there been a renal artery stenosis, the angiography (with angioplasty) might have been essential to successfully treat both hypertension and renal failure. On the contrary, if this had not been the case, unnecessary contrast media administration could have prevented renal recovery. In the end, we relied on the sensitivity [12] of the renal duplex ultrasound exam and decided to avoid the angiography.

This case highlights the difficulty in differentiating between primary and secondary hypertension in cases of malignant hypertension. More than half of the cases of malignant hypertension are in fact due to essential hypertension [13]. Moreover, be it essential or secondary, the clinical presentation of malignant hypertension can be the same. In addition, if the clinical presentation does not help discriminate, laboratory might not help either, in particular

a



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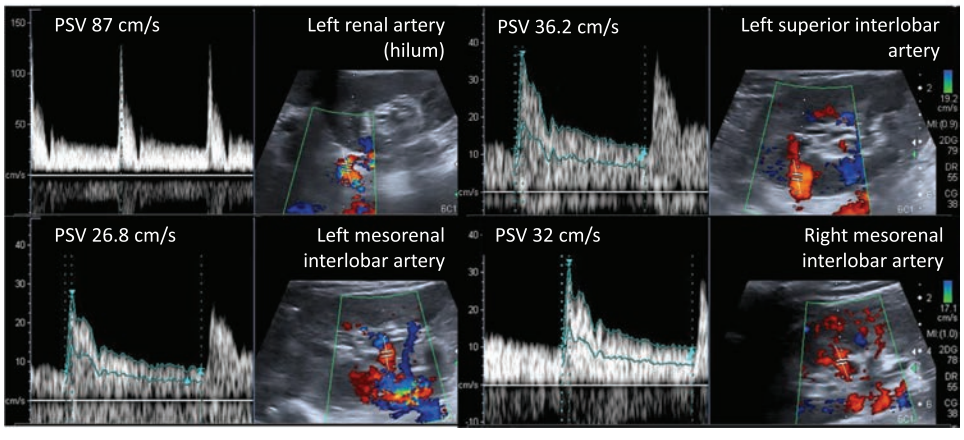

c

Velocimetric indices	Left superior interlobar artery	Cutoff values (12)
ACC (m/sec^2)	7.4	> 4
AI max (Acc/Vs sec^{-1})	20.6	> 9.0
AT (msec)	40	< 80

Fig. 1: a Abdomen CT scan image. The red arrow indicates the suspected left renal artery stenosis. **b** Renal echocolordoppler images and velocimetric indices. PSV, peak systolic velocity; ACC, maximal systolic acceleration, AI_{max}, maximal acceleration index; AT, acceleration time.

when it comes to the measurement of renin and aldosterone. Malignant hypertension is in fact typically associated with an activation of the renin-angiotensin-aldosterone system (RAAS) [14]. Although the exact mechanism of malignant hypertension is unknown, several studies have implicated the RAAS as a key factor to its pathogenesis. The severe elevation of blood pressure would in fact lead to RAAS activation through microvascular damage and renovascular ischemia, and the increased production of Angiotensin II would in turn further increase blood pressure, leading to malignant hypertension [14]. In this setting, it is not unusual to find also other changes due to endothelial dysfunction [15], which might explain the transient microangiopathic hemolysis and increased CRP of our case.

Secondly, this case underlines the importance of performing the renal artery duplex ultrasound as the first-line (screening) exam when a renal artery stenosis is suspected, before considering the renal angiography with angioplasty, which is the reference standard for the anatomic diagnosis and treatment of renal artery stenosis [10]. Given that angiography is an invasive procedure that carries a risk for serious complications, less invasive techniques are advocated for the initial work-up of patients with suspected renal artery stenosis [12]. For this reason, the European consensus on the diagnosis and management of fibromuscular dysplasia suggests starting the patient evaluation with renal duplex ultrasound and then confirming the diagnosis with a CT-angiography prior to angioplasty. As compared to computed tomography, whose sensitivity has not always been found sufficient to rule out a renovascular disease [16], the renal duplex ultrasound exam, by the assessment of intrarenal velocimetric indices, has a high sensitivity and a high negative predictive value [12]. On the other hand, the results of the renal duplex ultrasound exam can be suboptimal if it is performed on obese patients, when apnea is difficult or impossible, and where local expertise is poor [10]. Nevertheless, in our case, given the patient's slender figure and compliance, as well as local expertise, we took a step backward and decided to schedule a renal duplex ultrasound before the angiography. Contrary to the CT scan, the renal duplex ultrasound turned out to be negative. Therefore, given that there had not been technical biases hindering the diagnostic accuracy of the exam, we based our next decision on the high sensitivity and negative predictive value of the duplex ultrasound. This helped avoid the angiography as well as the additional contrast media administration that could have affected negatively the renal recovery [17].

Despite the fact that over the last 40 years the incidence of malignant hypertension has not changed and remains 2-3/100,000/year, its prognosis has improved significantly [13], which can be ascribed to the introduction of modern antihypertensive drugs and a better blood pressure control. Likewise, also renal prognosis has improved, and the probability of renal survival is 84 % and 72 % after 5 and 10 years of follow-up, respectively [18]. In the end, our case confirms that a tight control of blood pressure during follow-up is one of the main predictors of renal outcome in patients with malignant hypertension [18].

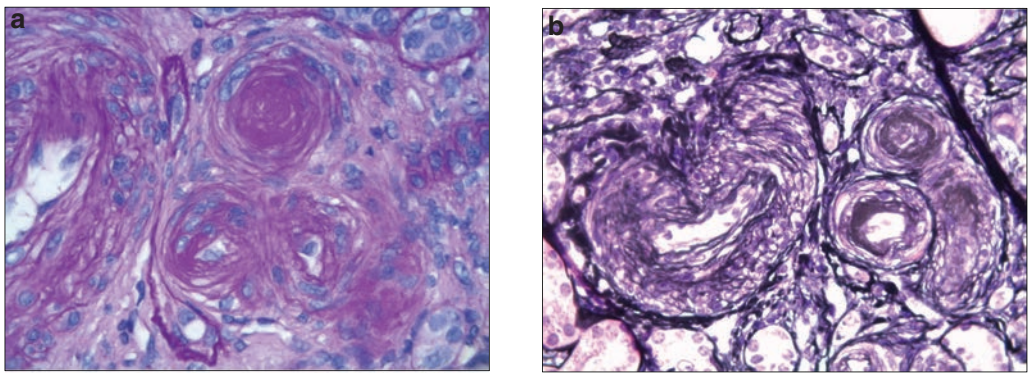

Fig. 2: a-b Representative images of kidney biopsy pathology, where vessel wall thickening with aspects of onionskin hyperplasia, endothelial layer detachment, and intraluminal platelet thrombosis with partial or complete obstruction of the vessel lumina can be seen

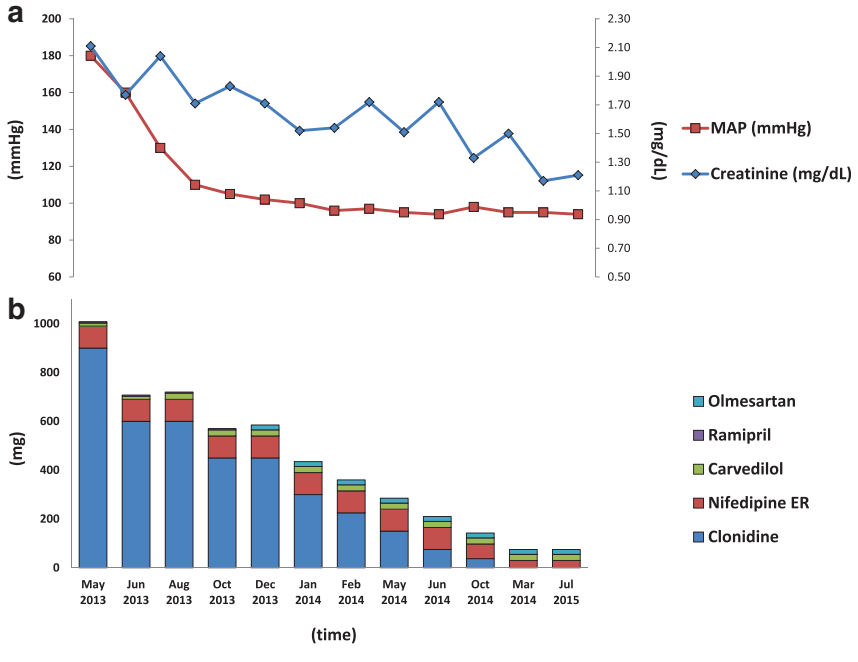

Fig. 3: Mean arterial pressure and creatinine normalization. **a** antihypertensive therapy reduction. **b** over the 2-year follow-up

Availability of data and supporting materials
All information supporting the conclusions of this case report has been included in the article.

Authors' contributions
AM conceived and participated in the design the study, participated in the acquisition, drafted the manuscript. SB conceived the study, participated in its design and coordination and revised the manuscript. AG EP MR participated in the acquisition of data, MB RC participated in the study design and in the revision of the manuscript. BF conceived the study, participated in its design and coordination, and revised the manuscript. All authors read and approved the final manuscript.

Competing interests
None of the authors have any competing interests.

Consent for publication
Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

Ethical approval and consent to participate
Not applicable

Appendix and References available on request Healthcare.India@springer.com

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A case of treatable hypertension: fibromuscular dysplasia of renal arteries

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Renovascular hypertension is due to renal artery stenosis (RAS) leading to reduced renal perfusion activating the renin angiotensin aldosterone system, resulting in hypertension. It accounts for 1–2 % of all cases of hypertension in the general population, and 5.8 % of secondary hypertension, but plays a major role in completely treatable causes of hypertension in the young.

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Background

Renovascular hypertension is due to renal artery stenosis (RAS) leading to reduced renal perfusion activating the renin angiotensin aldosterone system, resulting in hypertension [1]. It accounts for 1–2 % of all cases of hypertension in the general population [2], and 5.8 % of secondary hypertension [3], but plays a major role in completely treatable causes of hypertension in the young. Renovascular hypertension is characterized by features like hypokalemia, young age of onset, and renal bruit [1]. This entity consists of renal vascular atherosclerosis and fibromuscular dysplasia (FMD). Atherosclerosis; accounting for 90 % of RAS, is seen in the elderly and in those with high cardiovascular risk factors. Whereas FMD accounts for less than 10 % of RAS, as is seen in females between 15 and 50 years [1]. FMD is a non-atherosclerotic, non-inflammatory angiopathy which could affect any vascular bed, but mainly affects renal arteries [4]. Other rarer cause of RAS include aortitis, radiation induced arteritis, dissecting aneurysm and von-Recklinghausen's disease. In this paper, we present a case of successfully treated young hypertension due to RAS caused by FMD.

Case presentation

A 29 year old Sinhalese Sri Lankan female, who was apparently well, presented with incidentally detected high blood pressure. She is a mother of two children, but had no history of pregnancy induced hypertension. She denied any family history of hypertension. She also complained of loss

of appetite and subjective weight loss during the past few months.

Her physical examination revealed a blood pressure of 180/120 mmHg on two separate occasions, and was equal in both arms. Her pulse rate was 88 beats per minute, with no radio-radial or radio-femoral delay. There were no renal masses, and no carotid, renal or femoral artery bruits. Her cardiovascular and central nervous system examination was unremarkable, and had no evidence of retinopathy on fundoscopy. She had no peripheral stigmata of atherosclerosis, or endocrinopathies.

Her renal function tests, serum electrolytes, urine full report, full blood count, erythrocyte sedimentation rate, and liver function tests were all normal. Her electrocardiogram and transthoracic echocardiogram were unremarkable.

As she was a recent onset young hypertensive, she was investigated with ultrasound scan of the abdomen which showed non visualization of the left kidney. Therefore, computed tomography angiogram (CTA) and diethylene triamine penta acetic acid (DTPA) renogram was indicated. DTPA renogram showed a small left kidney which was suggested to be either congenital, or due to RAS, with normal perfusion and function of the right kidney. CTA revealed significant stenosis of the left main renal artery, which was suggested to be due to FMD, and an accessory renal artery supplying the lower pole of the left kidney was detected (Figs. 1, 2). After evaluation of her renovascular hypertension, she was referred to a vascular surgeon and underwent left sided nephrectomy, and histology revealed features of FMD of left renal artery. She achieved full recovery with normalization of blood pressure following surgery, and is currently not on any antihypertensive medication.

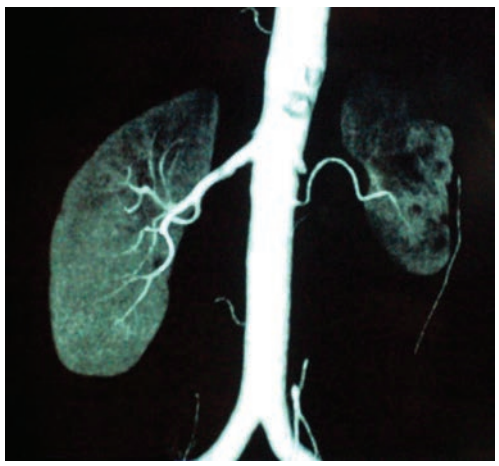

Fig. 1: Close-up of CT angiogram showing significant left sided renal artery stenosis, with an atrophied left kidney, which is supplied by an accessory renal artery. There is normal perfusion and function of the right kidney.

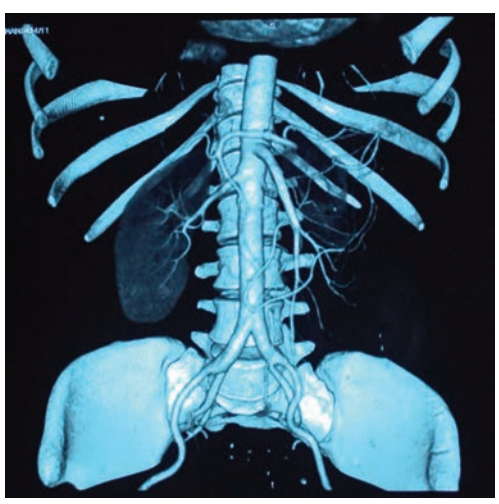

Fig. 2: CT renal angiogram showing atrophic left kidney with non visualization of the left main renal artery.

Discussion

FMD is an uncommon angiopathy that predominantly affects young to middle-aged females [5], which is non-atherosclerotic, and non-inflammatory, and most commonly affecting the renal and internal carotid arteries, but may be seen in any arterial bed [4]. A pathological classification of renal artery FMD was proposed by McCormack et al. [6] and revised by Stanley [7]. Three main subtypes were identified based on the dominant arterial wall layer involved, namely; intimal, medial, and adventitial (perimedial) FMD. Intimal, medial, and perimedial FMD accounts for 5, 85, and 10 % cases of renal artery FMD respectively [2]. A study done by *Alimi* et al found that 66 % of cases had more than one arterial layer involved [8]. Aneurysms and dissections are considered to be complications of FMD [7].

A definite etiology of FMD is not known, though there are various theories. Genetic predisposition is proposed, as a study done by *Rushton* showed 60 % cases to have autosomal dominant inheritance pattern with variable penetrance [9], and a subsequent case report of disease among family members also support this theory [10]. Other proposed mechanisms of etiology are hormonal factors, mechanical trauma, metabolic and immunologic factors, and intrinsic deficiency of elastic fibers [11]. There is evidence that cigarette smoking may be a risk factor [12]. FMD is also associated with pheochromocytoma, neurofibromatosis, Ehlers-Danlos syndrome type IV, Marfan's syndrome, Alport's syndrome, and Takayasu's arteritis [4]. Atherosclerosis, which is its main differential diagnosis, is differentiated by being located at the ostium or proximal portion of the artery in older patients with typical cardiovascular risk factors, where as FMD occurs in the middle or distal arterial segments in younger patients with few cardiovascular risk factors [4]. Unlike RAS due to atherosclerosis, FMD rarely has deterioration of renal function with high serum creatinine levels [2]. The other differential diagnosis is Polyarteritis nodosa which shows pathognomonic multiple focal aneurysms on renal angiography [13].

FMD accounts for 10–20 % of documented RAS, with renovascular hypertension accounting for 1–2 % of hypertensives, and the prevalence of clinically significant renal artery FMD can be estimated to be about 0.4 % [2]. The commonest arterial involvement of FMD is of renal arteries (60–75 %), followed by cervico-cranial arteries with a prevalence of half that of renal arterial involvement [14], with at least two vascular beds involved in up to 28 % cases [15]. The clinical presentation may vary from an asymptomatic condition to a multisystem disease depending on the arterial segment involved, the degree of stenosis, and the type of FMD.

The commonest presentation of FMD is renovascular hypertention; usually grade 2–3, or resistant hypertension. The mechanism depends on whether the stenosis is unilateral (renin-dependent hypertension) or bilateral/unilateral with a single functioning kidney (volume-mediated hypertension) [16]. However 2/3 RAS due to FMD are bilateral [17]. Ultimately there is activation of the renin angiotensin aldosterone system resulting in vasoconstriction, and salt and water retention. FMD may be complicated by renal artery dissection and kidney infarction with abrupt flank pain, haematuria and rapidly progressive hypertension [18].

Various imaging methods are used in the evaluation of RAS. Duplex imaging of the renal arteries can accurately detect elevated blood-flow velocities in the proximal and distal portions of these arteries, but has a 10–20 % failure rate due to operator's inexperience, the presence of obesity or bowel gas, respiratory renal movements, and the fact that the possibility of a stenotic accessory renal artery cannot be excluded by visualization of a single normal renal artery [19]. The current importance of ultrasound scan is the ability to predict functional recovery based on the measurement of resistive index. Captopril renography (DTPA renography) is a safe

noninvasive tool used in the screening for RAS, but data regarding its reliability is inconsistent. Its efficacy is increased by administering 25–50 mg of captopril 1 h prior to injection of radioisotope, and the sensitivity and specificity decreases in the presence of azotemia, bilateral disease, or disease of solitary functional kidney [20]. Computed tomographic angiography is the most specific tool in diagnosis, where as gadolinium enhanced magnetic resonance angiography has the additional advantage of not having radiation exposure, and limited nephrotoxicity. However both modalities have high specificity, but low sensitivity [21]. The gold standard in diagnosing renal artery FMD is intra-arterial angiogram with digital substraction, but is reserved for patients for whom it is clinically justified to proceed with revascularization in the same procedure, as it is an invasive test. Multifocal stenosis with the "string of beads" appearance is characteristic of FMD, which likely indicates the presence of medial type FMD, where as other features are tubular or focal lesions [22].

Pharmacological treatment of hypertension in FMD should follow the guidelines of the Joint National Committee on prevention, detection, evaluation and treatment of high blood pressure [23]. Almost all patients with RAS require at least one antihypertensive agent, and require three or more medications twice as frequently as those with cerebrovascular FMD [24]. Revascularization is the choice of treatment in patients with young hypertension refractory to pharmacological therapy, those who are intolerant to antihypertensive, those who have lost renal volume due to ischaemic nephropathy, and the goal is to cure the disease [4]. Surgical revascularization was the primary treatment modality before the introduction of percutaneous transluminal angioplasty techniques (PTA), and leads to improvement of hypertension in 60–88 % cases [24, 25]. Nowadays PTA has emerged as a mainstay of treatment for patients with FMD who meet the criteria for interventions, and leads to improvement or resolution of hypertension in 60–80 % of cases [24, 25]. It is less costly than surgical revascularization and less invasive, and can be performed on an outpatient basis and has a lower morbidity [4]. Complications of percutaneous interventions occur in 14 % of cases and usually minute but rarely renal artery perforation, dissection or segmental renal infarctions may occur [27, 28, 29]. Successfully performed renal angioplasty results in substantial and rapid reduction in both systolic and diastolic blood pressure to normal values and it correlates with a marked reduction in plasma renin activity and angiotensin II levels [4, 30]. Complete resolution of hypertension without the requirement of antihypertensive medication may be achieved only in 30–50 % cases [24, 25]. Imaging should be performed soon after revascularization process to assess the adequacy of the intervention [31], again in 6 months, 12 months and yearly there after [3]. When the criteria for revascularization are not met, or in extreme hypertension, or following failed primary surgery, or when a kidney is non-viable nephrectomy can be performed as in this case, resulting in complete cure [25].

Conclusions

FMD causing RAS, though a rare cause of renovascular hypertension is essential to be considered in young hypertensives, even in the absence of family history of hypertension. A high index of suspicion is necessary in early diagnosis and prompt treatment, which would result in rapid and complete recovery.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Abbreviations
CTA: computed tomography angiogram; DTPA: diethylene triamine penta acetic acid; FMD: fibro muscular dysplasia; RAS: renal artery stenosis; PTA: percutaneous transluminal angioplasty.

Authors' contributions
Analysis and interpretation of patient data and literature review were done by DMPUKR, KPJ and EMME. DMPUKR guided the other authors in reporting this case and corrected the final manuscript. All authors were involved in the management of the patient. All authors read and approved the final manuscript.

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Competing interests
The authors declare that they have no competing interests.

Appendix and References available on request Healthcare.India@springer.com

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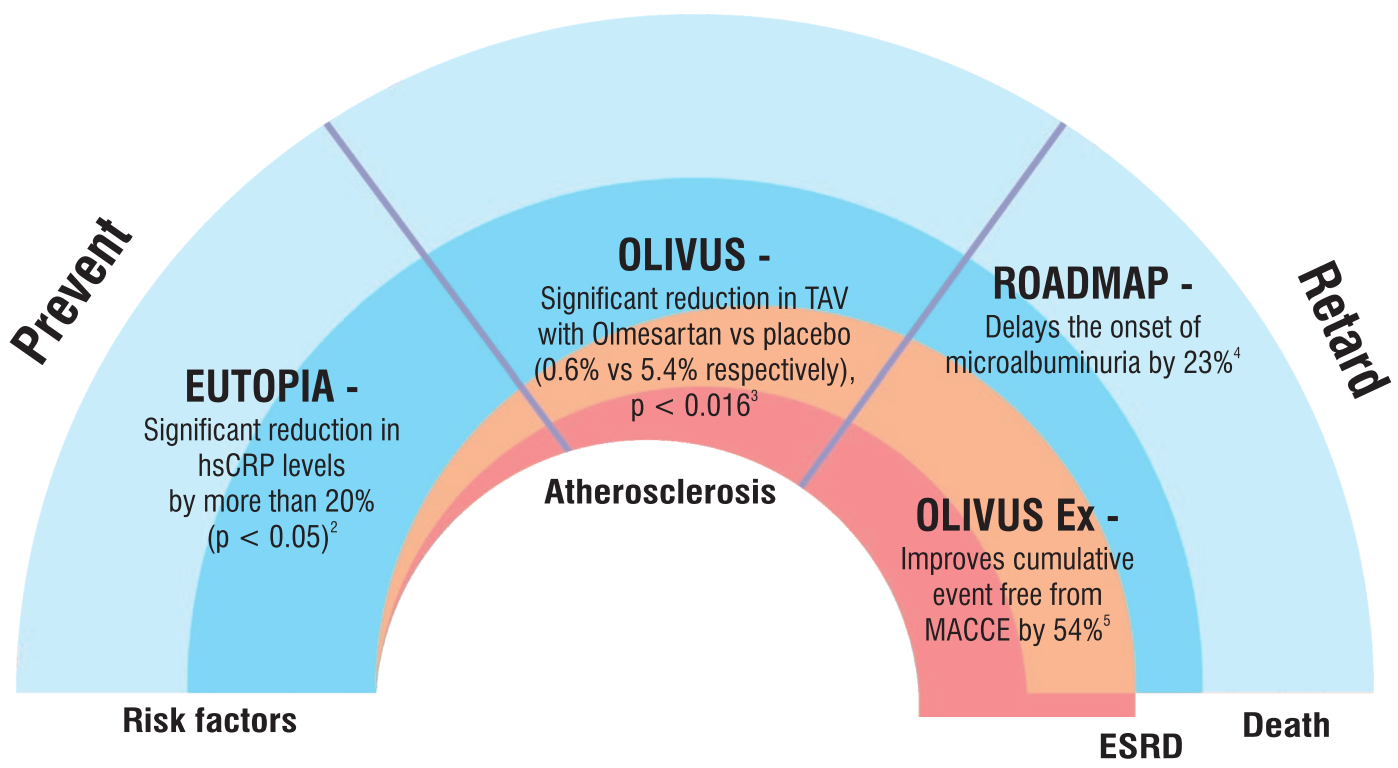

TAV – Total Atheroma Volume, MACCE - Major Adverse Cardio- and Cerebrovascular Events

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