High Blood Pressure & Cardiovascular Prevention (2025) 32:255–273
https://doi.org/10.1007/s40292-025-00710-3

Online ISSN 1179-1985

REVIEW ARTICLE

# Aortic Remodeling in Patients with Arterial Hypertension: Pathophysiological Mechanisms, Therapeutic Interventions and Preventive Strategies—A Position Paper from the Heart and Hypertension Working Group of the Italian Society of Hypertension

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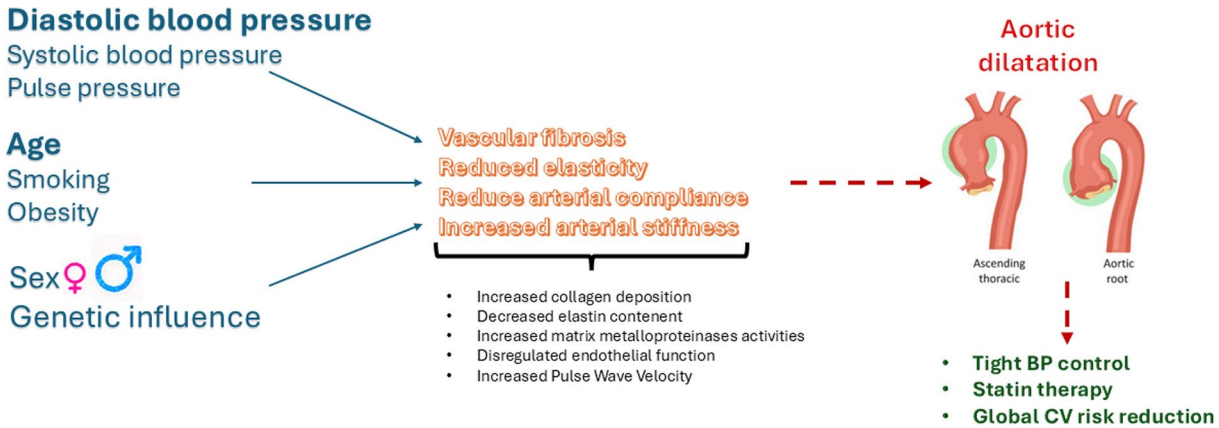
Received: 25 November 2024 / Accepted: 18 February 2025 / Published online: 14 March 2025


## Abstract

In patient with arterial hypertension the whole aorta is exposed to increased wall stress due to pressure overload. Different blood pressure (BP) components have been reported as main determinant of aortic remodelling. In particular increased diastolic BP has been associated with aortic dilatation across all its segments with smaller increase in aortic root and ascending aorta related to increased systolic BP and pulse pressure. Optimal BP control is crucial to prevent development of aortic aneurysm and acute aortic disease. Many studies have evaluated the role of different antihypertensive drug classes for prevention of adverse aortic remodelling including beneficial effects of ACEIs, ARBs, dihydropyridinic calcium channel blockers and Beta-blockers. The present review discusses pathophysiological mechanisms, therapeutic interventions and preventive strategies for development of aortic remodeling in patients with arterial hypertension.

## Graphical Abstract




**Keywords** Aortic aneurysm · Hypertension · Cardiovascular prevention

Extended author information available on the last page of the article

## 1 Introduction

Aorta is exposed to a very high shear and pressure stresses throughout the life [1]. Its unique elastic properties permit to store and redistribute energy-captured form from the blood flow ejected from the heart, a mechanism known as the "Windkessel phenomenon". Structural and functional changes may contribute to maladaptation of aortic properties leading to pathological dilatation of the vessel. In particular endothelial cells, vascular smooth muscle cells and network of collagen fibers are involved in the remodeling process of aortic wall [2, 3]. Recent evidence also suggests that risk of aortic dissection is related not only to aortic diameter but to other anatomical abnormalities involving aortic length and ascending-to-arch angle [4, 5]. Different epidemiological studies have demonstrated a close link between hypertension and aortic remodeling. Compared to normotensive subjects, patients with arterial hypertension have larger aortic diameter including aortic root, ascending aorta and aortic arch [6] resulting in an increase of wall stress, further augmented by the presence of hypertension, which is associated with an higher risk of development of aortic aneurysm and dissection [7–9]. Remodeling of aorta, starting from the aortic root through ascending and descending aorta down to the abdominal aorta, is influenced differently by the different blood pressure (BP) components. Diastolic BP (DBP) plays a pivotal role in the development of aortic dilatation across all its segments, mainly due to the fact that its effect of distending pressure stretches the aortic wall when the aortic valve is closed [10, 11]. Systolic BP (SBP) and pulse pressure (PP) are associated with a smaller increase in aortic root and ascending aorta dimensions and exert a smaller influence on abdominal aorta compared to DBP [9, 12]. Both European and American guidelines on the management of aortic disease highlight the need of BP control in patients with thoracic aortic aneurysm (TAA) while evidence supporting specific pharmacological therapy are lacking and are mostly related to patients with Marfan syndrome (MFS, [13, 14]). The aim of the present review is to highlight the pathophysiological mechanisms related to the development of aortic remodeling in patients with arterial hypertension. Furthermore, we deeply analyze the influence of different antihypertensive drugs on aortic remodeling providing also preventive strategies for development of aortic aneurysm

## 2 The Pathophysiological Mechanisms of Aortic Remodeling in Hypertension

### 2.1 Hemodynamic Mechanisms

Blood pressure, particularly central systolic and pulse pressure, deeply affects large arteries, such as the aorta, and their remodeling [15]. Mechanical stimuli and inflammatory responses driven by elevated blood pressure values are responsible for arterial morphological and functional modifications. The intricate aortic remodeling process results from various changes, including cell size increase leading to thicker arterial walls, reduced organized elastin fibers, and collagen apposition [16]. These changes ultimately reduce arterial compliance and elasticity, resulting in arterial stiffening and, eventually, dilation. With aging, arterial hemodynamic stress becomes even more pronounced, exacerbating the structural changes in the walls of large arteries [17]. The arterial hypertrophic response, which is primarily an adaptive mechanism in response to increased mechanical stress, involves both the proliferation of vascular smooth muscle cells and the rearrangement of extracellular matrix components in arterial walls, and further results in alteration of arterial architecture [18].

An increase in wall shear stress may stimulate endothelial cells to develop arterial dilation, while the progression of small atheroma may weaken the medial and adventitial layers, leading to plaque's outward expansion [19]. Additionally, arterial wall remodeling could be driven by the migration of smooth muscle cells from the media to the intima and ischemic thinning of the medial layer, influenced by various immune-mediated signals, including the release of growth factors and cytokines, further leading to cell apoptosis and vascular fibrosis [20].

The evaluation of arterial stiffness, a sign of aortic remodeling, can be determined using various metrics, including central systolic blood pressure, central pulse pressure, augmentation index, and pulse wave velocity [21]. These parameters play a significant role in identifying "early vascular aging," emphasizing the accelerated progression toward target organ damage, which increases the risk of cardiovascular diseases and mortality [22, 23]. Remarkably, arterial stiffness measurements can reflect an early involvement of arterial remodeling, thus related to subclinical organ damage, and are proven to be robust predictors of cardiovascular events [24]. Therefore, they are instrumental in identifying individuals with elevated cardiovascular risk beyond traditional risk factors.

### 2.2 Non-hemodynamic Mechanisms

Several non-hemodynamic mechanisms are involved in the pathogenesis of aortic remodelling in hypertension. First, age is a main determinant of increased aortic stiffness and aortic dilatation over time and different epidemiological longitudinal studies have indeed demonstrated an impact of age on aortic root and ascending aorta dimension [25, 26]. Gender related differences have also been described in women showing absolute smaller aortic size compared to men [27]. However, among hypertensive patients women have been reported to be more prone to develop aortic root dilatation over time [10]. Different mechanisms related to hormonal factors have been described as main determinants of sex differences in aortic remodelling [28]. Epidemiological studies have demonstrated that smoking may influence aortic root dilatation over time and is associated with increased risk of acute aortic complication [29]. Different in vitro studies have demonstrated a durable alteration in vascular smooth muscle cells and abnormalities of inflammatory cell function related to tobacco exposure [30]. Interestingly, smoking cessation has been found to be associated with a consistent reduction in the risk of acute aortic mortality [31]. Genetic factors influence the susceptibility to abnormal aortic remodeling leading to familial clustering of aortic dilatation and aneurysm [32]. The concomitant presence of CV risk factors including diabetes and obesity should also be regarded as a main contributor to aortic remodeling. In particular, obesity has been associated with larger aortic dimensions and has been related to the development of aortic dilatation in hypertensive patients [10, 11]. On the other hand, diabetes seems to be associated with reduced aortic dimension and lower risk of acute aortic disease [33].

## 3 Influence of Blood Pressure Components on Aortic Remodeling

Studies that have analyzed the relationship between BP components and aortic remodeling yielded mixed results [34–36]. This uncertainty largely depends on the variable contribution of other determinants such as age, gender and body size [26], duration of hypertension [36], methods used to measure aortic diameter [37, 38], as well as the level at which the aorta is assessed in the different studies. Moreover, while most work has relied on office BP measurements, central hemodynamics and ambulatory BP monitoring (ABPM) might be stronger predictors of aortic remodeling [36, 39, 40]. Different methods for measuring BP may therefore play an important role in this setting.

### 3.1 Aortic Root

The overall body of evidence suggests that patients with arterial hypertension have larger aortic root diameter compared to normotensive subjects [11, 41]. In a sample of patients from the Framingham Heart Study, a direct correlation was found between DBP and aortic root diameter [42]. In the Strong Heart Study cohort, aortic root size was directly correlated to DBP, with negligible effects for SBP. Such findings were consistent both on office and central BP measurements [11]. In patients with obstructive sleep apnea (OSA), greater aortic root diameter was associated with higher DBP, measured both with office BP measurement and 24-h ABPM [43]. Intriguingly, nighttime DBP evaluated by ABPM seems to be particularly associated with aortic root size both in hypertensive patients [36] and subjects with obstructive sleep apnea [44], in line with the growing evidence that nocturnal BP may have a superior prognostic value than awake BP in predicting CV morbidity and mortality [45]. Intriguingly, PP seems to be inversely related to aortic root size [46, 47]. In a recent study using two-sample Mendelian randomization, both genetically-predicted reduced PP and increased DBP were associated with aortic size [48]. In patients with isolated systolic hypertension, an inverse relation between PP and aortic diameter was demonstrated even after adjustment for several confounders including age, sex, aortic wall stiffness, AIx, and mean BP [49]. While DBP seems to contribute to the development of aortic root dilatation, as it reflects the distending pressure stretching the aortic wall when the aortic valve is closed [10], increased PP could be the consequence rather than the cause of reduced aortic root dimension, possibly related to an anticipated ad augmented backward pressure reflection [49]. However, a reverse causal relationship between PP and aortic size is also possible [48] and remains a hypothesis worth exploring in the future.

### 3.2 Ascending Aorta and Aortic Arch

While the majority of published research have exclusively investigated the aortic root, little is known about the relationship between BP components and dimension of other aortic segments. In a prospective echocardiographic study, aortic enlargement at the sino-tubular junction and aortic arch levels was highly prevalent in patients with hypertension [6]. Among 345 untreated and treated essential hypertensive patients, Milan et al. observed a slight increase of central SBP, PP, and Augmentation Index in patients with proximal ascending aorta dilation, suggesting that the latter is associated to arterial stiffness [50]. We previously demonstrated that among treated hypertensive patients DBP is a main determinant of ascending aorta dilatation [51]. Both

ascending and descending aorta have been associated with increased BP (systolic, diastolic and PP) as reported in a recent study using CT scan [52].

### 3.3 Abdominal Aorta

Several observational studies and meta-analyses have also evaluated the association between BP and abdominal aorta aneurysm (AAA), with mixed results [53, 54]. In a systematic review and meta-analysis of 21 cohort studies, a 20 mmHg increase in SBP and a 10 mmHg increase in DBP were associated with a 14% and 28% increase in the risk of developing AAA, respectively. In particular, a strong non-linear dose-response relationship was found with DBP. Accordingly, the authors suggested that DBP has a larger impact on AAA development than SBP [9]. Further research should elucidate the relationship between BP components and aortic size at these less-investigated levels, including ABPM and central BP assessment results.

## 4 Influence of Different Antihypertensive Drugs on Aortic Remodeling

Assessing aortic stiffness and central hemodynamics stands as a primary method for physicians to evaluate aortic remodeling.

Drug treatment may change the natural history of aortic remodeling. The aim of the antihypertensive treatment is to reduce the pressure within the vascular system. Therefore, a reduction in vessel wall remodeling may help to achieve this goal. This effect may be obtained with multiple molecules interfering with different pathways and possibly acting synergistically. In-vivo studies indicated that ACEIs [55–61], ARBs [55, 60, 61], and dihydropyridinic calcium channel blockers (CCBs, [62]) reduce vascular remodeling obtaining a decrease in aortic stiffness, possibly due to reduced collagen deposition within the media layer [55] and producing an improvement in endothelial dysfunction ([57, 59, 61, 62], Fig. 1).

Angiotesin II (Ang II) effects are mostly mediated by the activation of the subtype 1 of angiotensin II receptor (AT1, [63]). Focusing on large arteries, antihypertensive drugs may have both a direct and indirect effect on the vascular wall. Treatment with ACEIs, ARBs, mineralocorticoid receptor antagonists, or CCBs has shown the potential to change the mechanical properties of aortic wall by decreasing vascular stiffness [64, 65]. Reducing the effects of Ang II with ACEIs or by direct AT1 receptor blockade also increases the bioavailability of nitric oxide [62, 66] improving endothelial function. Other antihypertensive drugs do not have the same effect despite some beta-blockers may improve small artery endothelium-dependent relaxation [57, 67]. These effects may be also due to the downregulation of the expression of transforming growth factor-beta (TGF-β). In particular, Angiotensin II exerts growth and profibrotic effects [68] also via TGF pathway. This may support the hypothesis that renin-angiotensin-aldosterone system inhibitors can reduce arterial stiffness partly through this mechanism. Moreover, ARBs also act by reducing the matrix metalloproteinases (MMPs) 2 and 9 levels and inflammatory mediators, leading to a reduced PWV and thus vascular remodeling, whereas ACEIs do not [69, 70]. Using invasive monitoring, it was shown that dihydropyridinic CCBs exert favorable hemodynamic effects, including significant reductions in aortic pressure, resistance, and acute changes in some wave components in less than 15 min [71], obtaining also a reduction in total arterial resistance in invasive long term evaluation [72]. Beta-blockers do not appear to reduce vascular stiffness to the same extent. Thus, in some clinical trials there was a lower efficacy of beta-blockers compared to renin-angiotensin-aldosterone system inhibitors [73]. In these studies the small differences in BP control leave open the question of whether the BP differences rather than specific effects attributable to each antihypertensive class may entirely explain the different outcomes. In experimental hypertensive animals it is difficult to dissociate BP reduction from reversal of vascular remodeling or changes in blood vessels' function. However, despite similar BP reductions, several studies in hypertensive patients reported no improvement

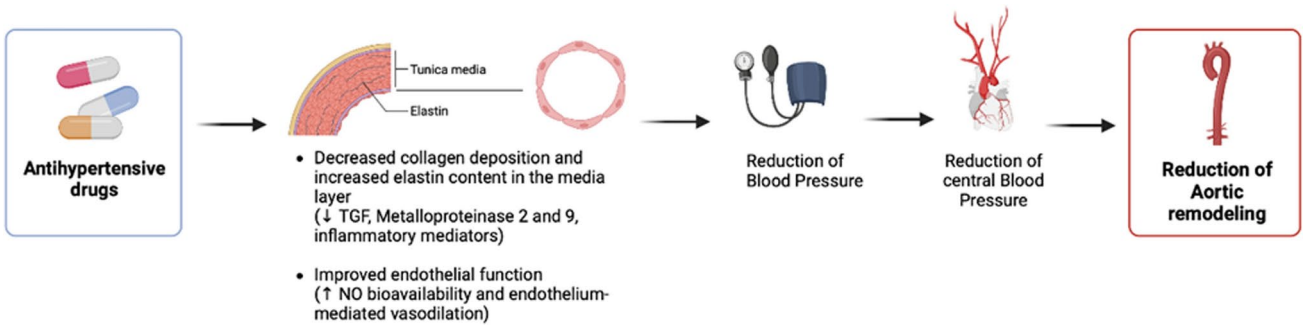



**Fig. 1** Effect of antihypertensive drugs on aortic remodeling

in either structural remodeling or endothelial dysfunction using beta-blockers, while participants under treatment with ACEIs, ARBs or CCBs showed a shift of vascular structure and function toward normal [74–76]. Evaluating stiffness in hypertensive patients, ARBs, ACEIs and CCBs but not beta-blockers are effective in reducing PWV [70, 77–80] also when combined together [81]. A recent meta-analysis [82] evaluated the role of antihypertensive drugs on aortic and vascular stiffness in patients with hypertension. They found a significant role of ACEIs, ARBs, beta-blockers, CCBs, and renin inhibitors as single agents as well as the combination of thiazide diuretics with ACEIs and ARBs or ACEIs with CCBs, especially for patients with hypertension who have higher degrees of arterial stiffness. These results were more significant in individuals treated with thiazide diuretics, ACEIs, ARBs, and the ACEIs or ARBs plus CCBs combinations, if treatment with antihypertensive drugs was longer than 6 months (Table 1, Fig. 2). Beta-blockers with vasodilator properties have peculiar effect on aortic remodeling [83, 84]. Nebivolol exerts protective effects on aortic remodeling reducing oxidative stress thought different pattern while carvedilol inhibits calcium channels in vascular smooth muscle cells with vasodilating and antiproliferative effects. [85, 86]

## 5 Blood Pressure Target in Patients with Aortic Aneurysm

The therapeutic goal of BP control in aortic aneurysm is to delay the growth and to prevent complications (i.e. aortic dissection or rupture and severe aortic valve regurgitation), as well as to reduce related non-aortic atherothrombotic events, such as myocardial infarction and stroke [87]. All these aims require rigorous and persistent BP control. The mechanisms through which high BP can produce a worsening of aortic aneurysms is related to the increased wall stress, the disruption of the endothelial layer and function, and the damage of *vasa-vasorum* which may contribute to weaken the aortic wall [88]. For these reasons, uncontrolled hypertension represents a well-known and strong modifiable risk factor for both aortic aneurysms growth and their dissection and acts synergistically with other risk factors like smoking and high cholesterol level [13]. Therefore, optimal BP control should be achieved in patients with aortic wall bulging and aneurysms. However, evidence on the BP target that should be ideally obtained to reduce the risk of aortic complications in patients with aortic aneurysms are very scanty as no specific randomized clinical trials have evaluated which BP threshold is best to be achieved under therapy. This is also related to the difficulties in designing prospective studies in a condition which is often characterized by a very long, and often asymptomatic, natural history. Studies on this topic are mostly focused on MFS (see specific paragraph) and AAA patients and have more frequently investigated which drug class is more effective in slowing the aortic size growth (see specific paragraph). In the absence of specific evidence, international guidelines are predominantly based on expert opinion. The latest 2023 European Society of Hypertension (ESH) Guidelines for the Management of Arterial Hypertension identify a 24-h SBP target of <130 mmHg for patients with aortic aneurysm, similar to that recommended for most hypertensive patients aged 18–65 years [89]. The 2022 American College of Cardiology and American Heart Association guidelines for the Diagnosis and Management of Aortic Disease suggest to achieve an optimal target of SBP/DBP of <130/80 mmHg. A more intensive target of <120 mmHg is recommended in selected patients with TAAs and AAAs not undergoing surgical repair, when tolerated [13]. Other international guidelines, as for instance the 2020 International Society of Hypertension guidelines and the 2014 European Society of Cardiology guidelines on aortic disease [14], do not cover this aspect at all or do not provide specific information on the optimal BP targets. Also, the 2017 American College of Cardiology and American Heart Association (ACC/AHA) guidelines for arterial hypertension management in the chapter dedicated to aortic diseases declare that specific trials are not available and general studies on arterial hypertension do not provide insights into the optimal blood pressure target in patients with TAA, aortic dissection, or aortic disease" [90]. For these reasons, no specific BP target was recommended and only the possible effects of specific drug classes were discussed (see specific paragraph). Despite the lack of data and mandatory recommendations, it is reasonable to conclude that there is a consensus on reaching at least SBP levels below 130 mmHg, targeting a goal of 120 mmHg SBP in patients who can tolerate such levels (Table 3). Further studies would be highly desirable to clearly define what BP target should be achieved to delay or prevent the growth of aortic aneurysms and to reduce their complications.

## 6 Aortic Diseases and BP Targets in Patients with Marfan Syndrome

The MFS is an autosomal dominant inherited connective tissue disorder with a prevalence ranging from 1.5 to 17.2 per 100,000 individuals [91]. MFS is caused by pathogenic variants in the FBN1 gene encoding for the ECM protein fibrillin-1 located on chromosome 15q21.1 [92–94]. The involvement of the aorta, subjected to progressive dilatation, dissection and/or rupture, is the leading cause of death in MFS patients [95]. Drugs with anti-hypertensive effects,

**Table 1** Main studies on the influence of antihypertensive drugs and aortic stiffness

| Author, year [ref] | Population | Drug class and dosage | Exposure time | Method of assessment aortic remodeling | Results |
|---|---|---|---|---|---|
| Wysocki M., 1992 [1] | European hypertensive men (n = 14), mean age 58 years | Isradipine i.v. from 2.5 mg to 7.5 mg BID until DBP was < 90 mmHg. Double-blind placebo-controlled cross-over trial | 9 weeks (~2 months) | Invasive hemodynamics (intraarterial and intravenous catheters). CO was measured by the dye-dilution technique (indocyanine green). Total arterial compliance was calculated as SV/PP and renal arterial compliance as RBF/HR + PP | Antihypertensive effect of the dihydropyridine calcium antagonist isradipine was the result of functional modulation of the small and large arteries, the venous system and the flow properties of blood being unaffected |
| Ting C.T., 1995 [2] | Chinese normotensive group (n = 14, 10 men, mean age 33 years) and hypertensive group (n = 12, 8 men, mean age 49 years) | Sublingual nifedipine (mean dosage 24 mg) | 15 min | Invasive aortic catheterization (micromanometers, velocity sensors and flowmeter). Ascending aortic cross-sectional area during baseline was obtained from two-dimensional echocardiograms | Nifedipine demonstrated significant reductions in aortic pressure, resistance, and certain wave components, as well as an increase in heart rate, total external power, and aortic compliance across different pressures |
| Wang Y., 2021 [3] | 269 Chinese adults with treated or untreated hypertension (118 men, mean age 59 years) | Double-dummy treatment with lacidipine (4–6 mg/day) or amlodipine (5–7.5 mg/day) | 5 months | Brachial-ankle PWV was measured using the fully automated VP-2000 PWV/ABI device | Both CCBs significantly decreased PWV, with similar clinic and ambulatory BP lowing efficacy |
| Shi R., 2017 [4] | 119 Chinese with hypertension (mean age 63 years) | Randomized, parallel, case-controlled trial with amlodipine 10 mg, valsartan 160 mg, amlodipine 5mg+valsartan 80mg QD | 3 months | The automated wave form analyzer (Colin VP-1000, Colin Medical Instruments Corp, Komaki, Japan) was used to measure brachial-ankle PWV | PWV was lowered by all 3 antihypertensive schemes; the degree of which from strongest to weakest were valsartan, combination and amlodipine |
| Xu S-K., 2019 and 2021 [5, 6] | 540 hypertensive Chinese not responsive to monotherapy [270 men, average age 53 years] | Randomized, active controlled trial with valsartan/amlodipine 80/5 mg single-pill vs. nifedipine GITS 30 mg QD | 3 months | Brachial PP, radial AIx and brachial-ankle PWV were obtained by oscillometric Vascular Profiler-1000 device (Omron Healthcare, Kyoto, Japan) | Brachial PP significantly decreased in both treatment arm, with a greater reduction in the combination therapy arm. No differences in AIx were observed. PWV was significantly reduced in the valsartan/amlodipine group but not in nifedipine group |
| Saito Y., 1990 [7] | 202 Japanese with terminal renal failure under dialysis (average of 49 years) | Nifedipine 10–20 mg/day versus untreated age-matched control hemodialysispatients | 2 years | PWV was measured using PWV 200 (Fukuda Elect. Co., Tokyo) by Hasegawa's modified method | PWV in the control group increased by 11% after 2 years. In contrast, nifedipine group experienced no initial increase in PWV during the first year and a significant 2% decrease by the end of the second year |
| Hayoz D., 2012 [8] | 125 European postmenopausal hypertensive women (mean age 61 years) | RCT with valsartan 320 mg ± hydrochlorothiazide or amlodipine 10 mg ± hydrochlorothiazide 12.5 mg | 9.5 months | cfPWV was determined from transcutaneous Doppler flow recordings and the foot-to-foot method triggered by simultaneous ECG (HDI-Lab software) | Both treatment regimens reduced PWV in to a similar degree, despite differences in central BP lowering suggesting that the effect of RAS blockade to influence PVW may partly be independent of central BP with a slightly larger PWV decrease in the valsartan treatment group |
| Rajzer M., 2003 [9] | 118 European adults with mild-to-moderate essential hypertension (mean age 54 years, 64 women) | RCT with 10 mg/d amlodipine (group 1), 20 mg/d of quinapril (group 2), or 2 × 50 mg/d of losartan (group 3) | 6 months | cf PWV was evaluated using an automatic device Complior (Colson AS, Paris, France) | Only quinapril-treated patients showed a significant decrease in PWV |

**Table 1** (continued)

| Author, year [ref] | Population | Drug class and dosage | Exposure time | Method of assessment aortic remodeling | Results |
|---|---|---|---|---|---|
| Park J.B., 2014 [10] | 391 Korean adults with essential hypertension (mean age 48 years, 74% male) non responsive to low-dose monotherapy for 1 month prior to randomization | Prospective, open-label, randomized, active-controlled, multicenter study on nifedipine GITS 30 mg plus valsartan 80 mg (N30 + V80), nifedipine GITS 60 mg (N60), or valsartan 160 mg (V160) | 1 month | Arterial applanation tonometry and pulse wave analysis (SphygmoCor device) | Low-dose nifedipine plus valsartan or high-dose nifedipine was more effective in improving central hemodynamics than high-dose valsartan in patients with hypertension, mostly because of the improvement in peripheral (brachial) hemodynamics |
| Sumbria M, 2014 [11] | Asian hypertensive adults, mean age 45 years | N = 106 data N = 100<br>N = 50 metoprolol (25–200 mg)<br>N = 50 telmisartan (20–160 mg) | 2–4 weeks | Arterial stiffness was measured non- invasively by recording pulse wave velocity (PWV) using periscope (Genesis medical system) | Telmisartan resulted in significantly greater reduction in arterial stiffness index (ASI) in left and right lower limb arterial bed |
| Matsui Y, 2011 [12] | Asian hypertensive adults, mean age 68 years | N = 207<br>N = 104 olmesartan [20 mg] + HCTZ [12.5 mg]<br>N = 103 olmesartan [20 mg] + azelnidipine [16 mg] | 24 weeks | The PWV measurement was performed by using a SphygmoCor device (version 7.0; AtCor Medical, Sydney, Australia). The aPWV was measured from sequentially recorded electrocardiogram-gated carotid and femoral artery waveforms. The aortic augmentation index (AIx), a measure of wave reflec- tion, was determined from radial waveforms using the same device | aPWV and mean arterial pressure in the azelnidipine group decreased more than those in the HCTZ group |
| Matsui Y, 2012 [13] | Asian hypertensive adults, mean age 68 years | N = 104 olmesartan (20 mg) + HCTZ (12,5 mg)<br>N = 103 olmesartan (20 mg) + Azelnidipine (16 mg) | 24 weeks | The cfPWV measurement was obtained with a SphygmoCor device (version 7.0; AtCor Medical, Sydney, Australia). The AASI was defined as 1 minus the regression slope of DBP over SBP readings obtained from individual 24-h BP recordings | The changes in the AASI and symmetrical AASI were similar between the two groups, while cfPWV in the azelnidipine group decreased more than in the HCTZ group ($P < 0.001$). The change in AASI was not significantly correlated with change in cfPWV ($r = 0.08$, $P = 0.26$), whereas the change in symmetrical AASI was significantly but weakly correlated with change in cfPWV ($r = 0.22$, $P < 0.001$) |
| Liu Q, 2016 [14] | Asian hypertensives adults, mean age 70 years | N = 193 elderly patients with EH were randomized to olmesartan 20 mg<br>N = 193 normotensive controls | 3 months | Ba-PWV was measured by an automatic waveform analyzer (model VP-1000; Nippon Colin Ltd, Komaki, Japan) | Olmesartan may increase TAS, yet inhibit oxidative stress, AP-1, inflammatory, and heart rate with improved artery stiffness in elderly hypertensive patients |

**Table 1** (continued)

| Author, year [ref] | Population | Drug class and dosage | Exposure time | Method of assessment aortic remodeling | Results |
|---|---|---|---|---|---|
| Metoki H, 2015 [15] | Asian hypertensive adults mean age 61 years | N = 314 for at least 4 weeks run-in period: losartan potassium 50 mg, candesartan cilexitil 8 mg, valsartan 80 mg, telmisartan 40 mg, or olmesartan medoxomil 20 mg<br>N = 101 losartan potassium 100 mg, candesartan cilexitil 12 mg, valsartan 160 mg, telmisartan 80 mg, or olmesartan medoxomil 40 mg<br>N = 99 losartan 50 mg/ hydrochlorothiazide 12.5 mg | 12 weeks | The HEM-9000AI first analyzes radial arterial waveform and determines the first (SBP1) and second systolic peaks (SBP2). The HEM-9000AI automatically performed detection of the second peak of the radial pressure wave form (late systolic inflection; SBP2 based on the second maximum of the fourth derivative of the radial pressure waveform to determine the radial AIx) | The maximum ARB regimen decreased AIx significantly from 86 ± 12.6 to 8% ± 11.4% (p 0.03) at week four, although the difference was not significant at week eight<br>The decrease in AIx tended to be greater with the maximum ARB regimen than with the combination regimen at week eight, but this difference was not significant |
| Kim EJ, 2014 [16] | Asian hypertensive adults, mean age 49 years | N = 201 (data 182)<br>N = 88 losartan<br>N = 94 carvedilol | 24 weeks | PP-1000 semi-automatic aortic PWV analyzer (Hanbyul Meditech, Jeonju, Korea) | After 24 weeks, there were no between-group differences in the brachial BP, cfPWV, AIx@HR75 or central BP changes, except for a more favorable AIx effect with losartan |
| London GM, 2004 [17] | European hypertensive adults, mean age 55 years | N = 469<br>N = 235 perindopril 2 mg+indapamide 0,625 mg<br>N = 234 atenolol 50 mg<br>N = 181 PW analysis<br>N = 88 perindopril + indapamide<br>N = 93 atenolol | 12 months | The Complior (Colson, Paris, France).<br>For pulse wave analysis, measurements were performed in 181 subjects, involving 144 subjects for the carotid artery and 110 for the aorta | Under Per/Ind, but not atenolol, normalization of brachial SBP is achieved with a significantly greater reduction of central SBP. This hemodynamic profile reflects changes of wave reflections issued from distal arterial and arteriolar territory, where Per/Ind, but not atenolol, is known to improve vessel wall structure |
| Park S, 2013 [18] | Asian hypertensive adults mean age 51 years | N = 209<br>N = 105 (data 96) bisoprolol 5 mg<br>N = 104 (data 95) atenolol 50 mg titration up to bisprolol 10 mg and atenolol 100 mg allowed at the 4th week | 12 weeks | (SphygmoCor; AtCor Medical, Sydney, Australia) | No significant difference between the two groups in reducing aortic SBP, aortic DBP, AIx, PPA and carotid– femoral pulse wave velocity (cfPWV) at week 4 and week 12. Subgroup analysis according to age (under or over 55 years), sex and baseline HR (under or over 66 years) did not show any significant difference for changes in aortic pulse pressure, aortic SBP, aortic DBP, AIx, PPA and cfPWV as well |
| Asmar RG, 2001 [19] | European hypertensive adults, mean age | N = 471<br>N = 204 Per/Ind<br>N = 202 atenolol<br>During the follow-up, 184 subjects in the Per/Ind group and 170 subjects in the atenolol group completed the active treatment period (12 months) | 12 months | Aortic pulse wave velocity (PWV) was determined by an automatic device, the Complior (Colson, Paris), which | The carotid and aortic AI and PP amplification were, respectively, significantly lower and higher with Per/Ind compared with atenolol. With Per/Ind, the AI decreased. The decrease was significant at the aortic (P50.002) but not the carotid level (within-group comparison). The AI decrease on Per/Ind contrasted with the increase on atenolol with a significant difference between the 2 groups (P50.036 for the carotid AI; P, 0.001 for the aortic AI). The significance disappeared after adjustment to heart rate |

**Table 1** (continued)

| Author, year [ref] | Population | Drug class and dosage | Exposure time | Method of assessment aortic remodeling | Results |
|---|---|---|---|---|---|
| Boutouyrie P, 2010 [20] | European hypertensive adults, mean age 57 years | N = 393<br>N = amlodipine valsartan 5/80 mg and then 10/160 mg<br>N = amlodipine atenolol 5/50 mg and then 10/100 mg | 24 weeks | (SphygmoCor; AtCor Medical, Sydney, Australia) | The difference in rough AIx reduction was − 6.5% (95% CI − 8.3 to -4.7; $P <$ 0.0001) in favor of amlodipine-valsartan. AIx adjusted on heart rate was significantly reduced in favor of amlodipine-valsartan (− 2.8% [95% CI − 4.92 to − 0.68]; $P$<0.01). Heart rate decreased significantly more with amlodipine-atenolol (difference: − 11 bpm [95% CI − 14 to −8 bpm]; $P < 0.001$). Pulse wave velocity decreased by 0.95 m/s in both groups with no significant difference. Differences in central systolic BP and rough AIx remained significant after adjustment to the changes in heart rate. The amlodipine-valsartan combination decreased central (systolic and pulse) pressure and AIx more than the amlodipine-atenolol combination |
| Jin Y, 2011 [21] | European hypertensive adults, mean age 55 years | N = 94 atenolol 50 mg<br>N = 107 perindopril + indapamide 2/0.6 mg | 1 year | Complior (Colson, Paris, France). | The changes in AASI (− 0.001 vs. − 0.014; $P = 0.44$) and aPWV (− 0.89 vs. − 0.69 m s(− 1); $P = 0.45$) were similar in the two treatment groups. AASI and aPWV showed significant concordance (r=0.21, P=0.003) after adjustment for covariables |
| Sluyter JD, 2016 [22] | Hypertensive adults, mean age 66 years | N = 2933<br>N = 1292 untreated<br>N = 355 ACEi<br>N = 51 alfa e beta<br>N = 77 ARB<br>N = 134 BB<br>N = 125 CCB<br>N = 86 diuretics<br>N = 73 ACEi+BB<br>N = 81 ACEi+CCB<br>N = 199 ACEi+D<br>N = 44 ARB+D<br>N = 54 BB+D<br>N = 34 CCB+D<br>N = 43 ACEi+BB+CCB<br>N = 82 ACEi+BB+D<br>N = 108 ACEi+CCB+D<br>N = 62 ACEi+BB+CCB+D | | Matlab software (Mathworks, Natick, MA) | Forest plots of single-drug class comparisons across regimens with the same number of drugs (for between 1- and 3-drug regimens) revealed that AIx, Pb, RI and/or loge(EPI) were higher (maximum difference=5.6%, 2.2 mmHg, 0.0192 and 0.13 loge(mmHg·s), respectively) with the use of a beta-blocker compared with vasodilators and diuretics, despite no brachial systolic and diastolic BP differences. These differences were reduced (by 34–57%) or eliminated after adjustment for heart rate, and similar effects occurred when controlling for systolic ejection period or diastolic duration |
| Matsui Y, 2012 [23] | Asian hypertensive adults mean age 68 years | N = 207 olmesartan for 12 weeks<br>THEN<br>N = 104 olmesartan 20 mg + HCTZ 12,5 mg<br>N = 103 olmesartan 20 mg + azlnidipine 16 mg | 36 weeks (12 + 24) | SphygmoCor device (version 7.0; AtCor Medical, Sydney, New South Wales, Australia). | In the azelnidipine group, the change in aortic pulse wave velocity was independently associated with the change in SD of home systolic BP (regression coefficient ± SE = 0.79 ± 0.37; $P = 0.036$) |
| Liu Y, 2018 [24] | Asian hypertensive adults, mean age 55 years | N = 566<br>N = 294 HCTZ 25 mg<br>N = 272 sprironolactone 25 mg | 4 weeks | (Atcor Medical Blood Pressure Analysis System, Sydney Australia) | Both systolic BP and cf-PWV were reduced more profoundly in spironolactone group versus HCTZ group ($P$ <.05). |

Detailed references have been reported as supplementary material

such as beta-blockers (propranolol, atenolol, nebivolol) or ARBs (irbesartan, losartan), have been found to effectively slow the progression of aortic dilation, even when administered to normotensive patients [96]. A recent individual patient data meta-analysis of 10 trials with more than 1800 patients with MFS [97] showed that that ARBs reduce the rate of annual increase of the aortic root Z score by about a half as compared to placebo. Interesting, any relationship

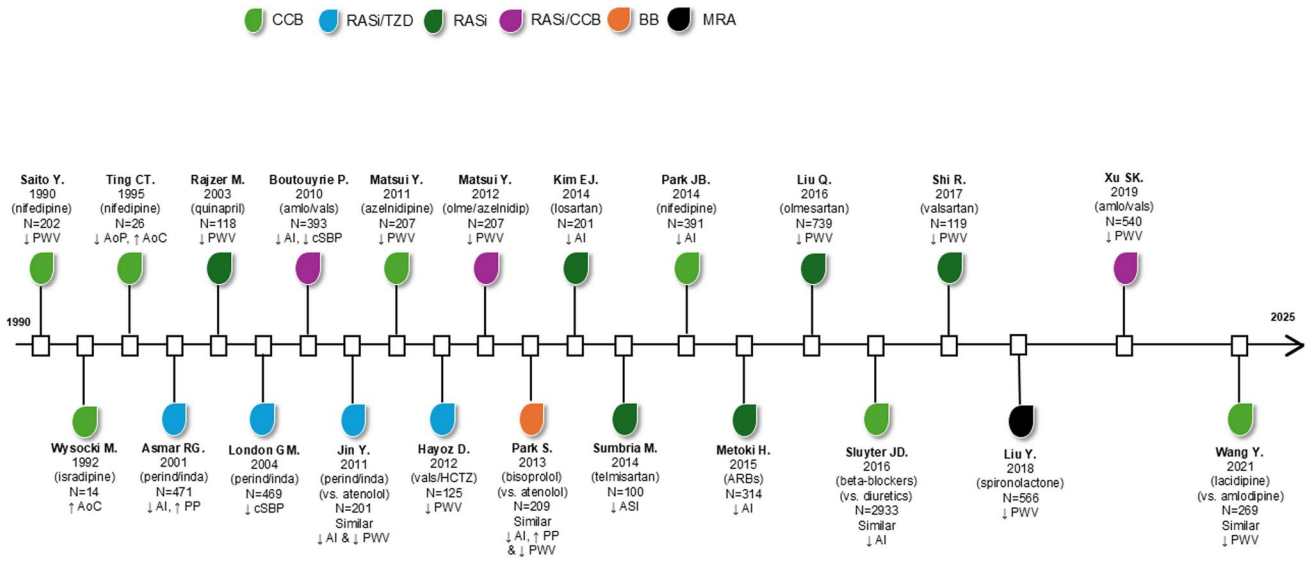



**Fig. 2** Studies evaluating impact different antihypertensive drugs on aortic remodeling

between the rate of progression of aortic dilation and changes in BP was found in trials included in the meta-analysis which explored this aspect [96, 98]. ARBs such as losartan demonstrated greater efficacy among patients with proven pathogenic mutations in the FBN1 gene [99]. The meta-analysis also showed that there is no association between baseline aortic root diameter and the effectiveness of treatment, whereas a greater decrease in the aortic root Z score over time when treatment was started at younger ages. Results of this meta-analysis are also supported by a large population-based retrospective cohort study of 7000 patients with aortic dissection [100], in which the long-term use of beta blockers, angiotensin-converting enzyme inhibitors (ACEIs) or ARBs was associated to a lower of all-cause mortality and of all-cause hospital readmission than patients received other antihypertensive drugs. Based on these findings, the ACC/AHA guidelines for the diagnosis and management of aortic disease recommend (class of recommendation 1 and level of evidence A) treatment with either a beta-blocker or an ARB, in maximally tolerated doses, to reduce the rate of aortic dilation [101, 102]. They also suggest (class of recommendation 2A, level of evidence C) the use of both a beta-blocker and an ARB, at maximally tolerated doses, to reduce the rate of aortic dilation [98, 103], although there is inconclusive evidence supporting this specific statement (Table 3). Furthermore, despite the latest ESH guidelines for the treatment of hypertension and the ACC/AHA guidelines for the management of aortic disease expanded their recommendations of treatment targets of 24-h SBP below 130 mmHg [13, 89] also to patients with MFS, there is no available randomized clinical trial which has been conducted to test different optimal thresholds for BP reduction to mitigate the risk of aortic complications in this special population. This also applies to treatment target of around 110 mmHg of SBP, to be achieved in the acute phase and possibly even in the chronic phase, if tolerated [104].

## 7 Risk Stratification for Acute Aortic Dissection: Role of Aortic Diameter and Aortic Elongation

Age, body size and gender are the main determinants of aortic diameters [105, 106], but less is known about factors able to predict a pathological evolution over time. Aortic dilatation was hdefined using absolute diameter criteria [40 mm in men and 38 mm in women, [46]]. Previous studies reported an exponential increase in the risk of dissection for diameters >60 mm, even if the absolute risk is quite low: 0.6, 1.6, and 4% in patients of 40, 60, and 80 years old, respectively, for diameter at baseline of 55 mm [106]. Though current American and European guidelines provide recommendations regarding intervention for non-Marfan TAA based on absolute values of 55 mm and progression over time ( > 5 mm over six months), [13, 14], 59% of patients experience aortic dissection at diameters below 55 mm and 40% at less than 50 mm, that is the current threshold for elective aortic repair [107, 108], suggesting that current surgical guidelines might fail to prevent a relevant number of events [109]. For this reason, current evidence suggests to take into account body dimensions [110, 111], indexing aortic diameters for body surface area in normal body sizes and for height in obese patients. Eventually, Z score can be used to describe aortic diameter in terms of standard deviations (SD) from the average value of

the variable considered in the general population: proximal thoracic aorta diameters exceeding by more than 2 SD the expected for age, gender and body size in healthy subjects can be defined dilated [38, 112, 113]. Aortic dilatation is classically coupled with increased wall stress and high BP [34]: it is a common clinical feature in hypertensive patients [114], reaching 17% of cases depending on the definition and reference values used [50]. The great majority of previous studies [115, 116] referred to dilatation of sinus of Valsalva tract, but current evidence suggests that proximal ascending aorta could be a high prevalence condition with a greater prognostic value [117], strictly related to other CV HMOD in terms of left ventricular hypertrophy and arterial stiffness defined as carotid-femoral PWV [50]. Reducing surgery thresholds in asymptomatic TAA may not automatically result in a net advantage, but it could expose a considerable proportion of healthy subjects to significant surgical risk. Searching for enhanced risk-stratification tools, it was observed that an elongation in the ascending tract evaluated by CT angiography (CTA) can be also observed with ageing [118]. Longitudinal dilatation is measured from the midpoint of the sino-tubular junction plane to the midpoint of the plane of origin of the brachiocephalic trunk artery [109]. It correlated with age, height [119] and gender [120], and it is more frequently observed in patients with aortic dissection than among healthy subjects [121, 122]. Additionally, it has superior diagnostic accuracy than absolute diameter threshold [123]. It has been theorized that wall stress leads to a faster fracture and rupture of elastin fibers and eventually to aortic dilatation and elongation [124, 125], potentially explaining the loss of longitudinal elasticity, a decrease of vascular compliance and an increased risk of intimal rupture [126]. On the basis of these studies, many scores based on ascending aortic diameter and length have been proposed [5, 124] in order to improve the management of patients whose ascending aortic diameters are borderline for surgical referral.

## 8 BP Target in Patients with Acute and Chronic Aortic Dissection

The mainstays of the medical management of the hemodynamically stable patients presenting with acute aortic dissection (AAD) is to lower BP and heart rate in order to reduce aortic wall stress and prevent disease progression. It is also needed to provide pain control while evaluating possible endovascular or surgical repair approach [13]. In particular, the maximum reduction of change in pressure over time (dP/dt) should be sought, as it is tightly associated with the rate of progression of intimal tears. Intravenous beta-blockers are the most commonly used drugs in this setting since, differently from other hypotensive agents, they do not induce reflex inotropic and chronotropic response, that can paradoxically increase the shear stress despite global BP reduction [127–130]. Guidelines generally agree in suggesting to achieve a SBP target of less than 120 mmHg and a heart rate target between 60 to 80 beats per minute. However, many experts suggest reducing SBP to the lowest possible level sufficient to maintain adequate organ perfusion. Data come from observational studies as randomized control studies are lacking [13, 89, 131]. Among intravenous beta-blockers, the most commonly used are esmolol and labetalol. In particular, due to its short half-life, esmolol can be used also in patients who are potentially intolerant to beta-blockers. Commonly used doses are: for esmolol, 500 mcg/kg loading dose over 1 min, then i.v. infusion at 25 to 50 mcg/kg/min; maximum of 300 mcg/kg/min; for labetalol, boluses of 20 mg initially, followed by 20 to 80 mg every 10 min to a total dose of 300 mg. Labetalol can also be administered as an infusion of 0.5 to 2 mg/min. When beta-blockers alone are not sufficient to reach BP targets, direct vasodilators such as nitroprusside can be added. In patients not tolerant to beta-blockers, non-dihydropyridine CCBs such as verapamil (5 to 10 mg IV; may repeat after 5 to 10 min) and diltiazem (initial bolus of 0.25 to 0.35 mg/kg IV followed by continuous infusion of 5 to 20 mg/h) can be administered (Table 2, [132]). A toxicologic screening should be performed in every patient presenting with AAD, as cocaine and methamphetamine assumption can trigger acute aortic syndrome. The detection of cocaine abuse is particularly important because beta-blockers (in particular non-selective ones) are generally avoided in these patients due to the risk of unopposed alpha stimulation that can increase BP. However, the use of agents with mixed activity (alpha and beta-blockade) such as labetalol may be reasonable [133–135]. Obtaining an adequate pain control has a pivotal role in the management of AAD. Apart from the obvious role of relieving the patient from suffering, an uncontrolled pain can lead to an increase in BP and heart rate due to sympathetic nervous system activation, thus reducing the efficacy of anti-impulse therapy and leading to disease progression and worse outcomes [136]. Anti-impulse therapy does not end its role in the acute setting; in fact, following surgical or endovascular repair, as well as in chronic B type dissection conservatively managed, patients need to follow long term BP and heart rate control in order to reduce future adverse events and sequelae. BP and heart rate targets are similar to those pursued in the acute setting, namely SBP less than 120–130 mmHg and heart rate from 60 to 80 bpm [13, 137, 138]. The most commonly used drugs are beta-blockers, ACEIs/ARBs and CCBs ([8, 100, 139, 140], Table 3). A special note should be made on long term use of CCBs in MFS patients, as detrimental effects

**Table 2** Drug types, dose and characteristics for treatment of acute aortic dissection

| Drug | Onset of action | Duration of action | Dose | Contraindications | Adverse effects |
|---|---|---|---|---|---|
| Esmolol | 1 min | 10–30 min | 0.5–1 mg/kg i.v. bolus; 50–300 μg/kg/min i.v. infusion | Second-degree or third-degree AV block, systolic heart failure, asthma, bradycardia | Bradycardia |
| Metoprolol | 1–2 min | 5–8 h | 2.5–5 mg i.v. bolus over 2 min; may repeat every 5 min to a maximum dose of 15 mg | Second-degree or third-degree AV block, systolic heart failure, asthma, bradycardia | Bradycardia |
| Labetalol | 5–10 min | 3–6 h | 10–20 mg i.v. bolus in 1 min; incremental doses ≥20 mg may be administered i.v. at 10 min intervals (max 80 mg) or 1–3 mg/min i.v. infusion until goal BP is reached | Second-degree or third-degree AV block; systolic heart failure, asthma, bradycardia | Bronchoconstriction, fetal bradycardia |
| Nitroglycerine | 1–5 min | 5–10 min | 5–200 μg/min i.v. infusion, 5 μg/min increase every 5 min | | Headache, reflex tachycardia |
| Nitroprusside | Immediate | 1–3 min | 0.3–0.5 μg/kg/min i.v. infusion, increase by 0.5 μg/kg/min every 5 min until goal BP (dose of 3 mcg/kg/min is usually enough for 30 to 40% reduction of BP values) | Liver/kidney failure (relative) | Cyanide intoxication |

**Table 3** BP target and pharmacological treatment for patients with aortic aneurysm and previous aortic dissection

| | Blood pressure target | Suggested drug therapy |
|---|---|---|
| Aortic aneurysm | BP below 140/90 mmHg aiming to 120/80 mmHg | Beta-blockers, ARB, Statins |
| Previous aortic dissection | SPB 120–130 mmHg DBP 60–80 mmHg | Beta-blockers, ACEIs/ARB, CCBs* |

*Not in patients with Marfan syndrome

have been reported either in mouse models as in case-control studies; thus should be avoided unless absolutely necessary to achieve BP targets [141].

## 9 Preventive Strategies for Acute Aortic Syndromes in Patients with Arterial Hypertension

### 9.1 Preventive Non-pharmacologic Strategies

Risk factors associated with the onset of acute aortic syndrome are all those events that can generate an increase in wall stress (hypertension and physical trauma) and/or aortic media abnormalities (syndromic and non-syndromic genetic diseases, [142, 143]). Systemic hypertension is present in approximately 75–80% of patients with AAD [144]. If ethnic-related differences are considered in AAD, hypertension and cocaine abuse are identified predominantly as the cause of AAD in Blacks [145, 146]. Other risk factors that can accelerate the development of acute aortic syndrome are also exposure to cigarette smoke and alcohol consumption [147]. Preventive strategies include healthy lifestyle measures that should be adopted from childhood, as with other forms of CV disease [148]. More precisely, it is mandatory to promote in all the patients at risk: Healthy diet (low in saturated fat, with a focus on whole-grain products, vegetables, fruit and fish); avoid cocaine and other stimulating drugs, such as methamphetamine; avoid exposure to tobacco in any form; avoid excessive alcohol intake; mild to moderate aerobic exercise (3–5 METs) can be performed for >30 min on most days of the week, for a total of 150 min per week; participation in a Cardiac Rehabilitation program is advised (in-hospital, at a community center and/or home-based, [88]).

Despite remarkable progress in diagnostic and therapeutic techniques, the burden of aortic diseases remains high. Therefore, allocating specific resources to design and implement prevention and screening programs for this pathology is necessary.

### 9.2 Preventive Pharmacologic Strategies

Pharmacologic strategies aim to stabilize and to prevent the aneurysm progressing using statins, beta-blockers and ARBs [87]. From a systematic review and meta-analysis

involving more than 80000 patients, clinical investigations have demonstrated that statins are associated with reductions in AAAs growth, rupture rate and perioperative mortality. Although the exact mechanism is not yet fully understood, several theories have been postulated and the most accredited is that statins reduce intramural aortic MMPs expression [149] beyond of action of reducing cholesterol levels. For this reason, physicians should consider starting statins in all aneurysmatic aortic patients even in the absence of other cardiovascular indications for statin therapy. In addition, limited data warrant caution in prescribing prophylactic antiplatelet therapy for patients with aortic disease without symptomatic atherosclerosis because no evidence of effectiveness of antiplatelet therapy to lower the risk of complications with trend toward higher bleeding risk although some studies suggest the use of anti-platelet medications correlated to the platelets ability to synthesize MMP-9, contributor to aortic aneurysm formation [150, 151]. Finally, is important to advise that the use of fluoroquinolones in clinical practice should be avoid in patients with aortic dilatation. In fact, several studies showed the link between fluoroquinolones exposure and an increased risk of aortic aneurysm or dissection. According to these studies, the use of fluoroquinolones significantly increased MMP-2 and MMP-9 expression in the aortic wall, promoting ECM destruction [152]. However, the effectiveness of preventive therapies should be validated by multi-center clinical trials.

## 10 Research Perspectives

Further investigations are needed to focus on fine-tuning BP control to more effectively prevent aortic remodeling in hypertension, particularly by refining the specific roles of systolic, diastolic, and pulse pressure in driving aortic dilatation and aneurysm formation. As imaging techniques and advanced analytic methods become more sensitive, physicians may be able to detect early signs of pathological changes in the aortic wall—including shifts in collagen and elastin microarchitecture—long before clinically significant dilation occurs. Parallel efforts in genetic and molecular research aimed at identifying common and rare variants predisposing individuals to accelerate aortic stiffening and aneurysm formation may open the door to precision medicine approaches, ensuring that therapies can be tailored to each patient's genetic risk profile. In addition, a deeper exploration of the interplay between hemodynamic factors and associated comorbidities such as obesity, diabetes, and dyslipidemia could elucidate the mechanisms that render specific subgroups especially vulnerable to rapid aortic expansion and dissection. Comparative and long-term studies will be crucial in determining whether renin–angiotensin–aldosterone system inhibitors, calcium channel blockers, or specific beta-blocker subtypes provide an edge in slowing disease progression, particularly in high-risk contexts like connective tissue disorders. Adopting emerging vascular stiffness indices and biomarker-based assessment into routine clinical practice holds promise for enabling earlier risk-based interventions. Equally important are concerted efforts to optimize lifestyle-focused prevention, emphasizing the additive benefits of smoking cessation, alcohol moderation, regular exercise, and balanced nutrition for lowering the overall burden of disease. By integrating these insights, future management strategies will likely become increasingly individualized, aiming to reduce aortic diameter progression and acute aortic events and minimize the broader cardiovascular morbidity and mortality associated with long-standing hypertension

## 11 Conclusion

In patients with arterial hypertension aortic remodeling is strongly influenced by hemodynamic and non-hemodynamic mechanism leading to development of aortic dilatation in different segments. Preventive strategies for acute aortic syndrome include tight control of BP and all cardiovascular risk factors, especially in patients with aortic aneurysm. Among antihypertensive drugs betablockers, ACEIs, ARBs and CCBs have been demonstrated to influence aortic remodeling although specific randomized control trial aim to assess prevention of aortic aneurysm and acute aortic syndrome are lacking.

**Supplementary Information** The online version contains supplementary material available at https://doi.org/10.1007/s40292-025-00710-3.

**Funding** Open access funding provided by Università degli Studi di Napoli Federico II within the CRUI-CARE Agreement.

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