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CORONARY HEART DISEASE (JA FARMER, SECTION EDITOR)

Prevention of Coronary Artery Disease: Recent Advances in the Management of Hypertension

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Abstract As coronary artery disease (CAD) still represents the leading cause of death worldwide, more efforts should be made to improve CAD prevention with both lifestyle changes and medical treatment. Elevated blood pressure has been identified as a risk factor for CAD; however, recent evidence suggests that lowering blood pressure too much could be harmful in patients at high cardiovascular risk. Despite the availability of a wide selection of antihypertensive drugs, new strategies and treatments are needed to improve blood pressure control and reduce cardiovascular risk factors associated with elevated blood pressure. New fixed-dose combinations have been recently approved; they usually contain an inhibitor of the renin–angiotensin system, a calcium antagonist and/or a diuretic. Although research and development related to new antihypertensive drugs has slowed in recent years, some new antihypertensive compounds with novel mechanisms of action or dual activity are currently in clinical development.

Keywords Coronary artery disease · Cardiovascular diseases · Hypertension · Blood pressure · Lifestyle · Prevention · J curve · Antihypertensive treatment · Fixed-dose combination

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Introduction: Cardiovascular Disease and Coronary Artery Disease Death Rates

In 2009, the WHO stated that "coronary heart disease is now the leading cause of death worldwide; it is on the rise and has become a true pandemic that respects no borders" [1••]. Indeed, even if something has changed in the past decade, cardiovascular diseases (CVD) and, in particular, coronary artery disease (CAD), still represent the leading cause of death worldwide.

Almost half of the deaths in Europe are caused by CVD, accounting for over four million deaths per year [1••, 2]. From that portion of deaths, almost half (1.8 million per year) are caused by CAD [2].

If we take into account the past three decades, we can see that the age-adjusted mortality rates due to CAD decreased in many European countries [2, 3], but, as shown by different studies such the Multinational Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) project, the variability of CAD death rates in the different European countries is high [4].

A greater decrease in CAD mortality rates is found in the north and west of Europe, but in some countries, in particular in the east of Europe, the rates are still high [2, 3].

Similarly to Europe, also in the USA the age-specific CAD death rates decreased in recent decades [5]. However, in the population between 45 and 54 years, this reduction of CAD death rate lost its momentum in part around 1990 [6, 7].

Therefore, even if the CAD mortality rates are somewhat reduced in some countries, they are still high worldwide, and together with the negative trends of the young population, they underline the importance of improving prevention of this disease.

Prevention

Lifestyle Modification

The latest European guidelines on CVD prevention suggest that both lifestyle changes and treatment are important for reducing CVD and CAD mortality [1••].

According to several studies, lifestyle interventions such as cessation of tobacco smoking, increased physical activity and modified diet (i.e. restriction of salt intake, reduction of alcohol consumption, reduction of cholesterol intake as well as saturated and total fat) in general can prevent and reduce CVD risk and improve survival in CAD patients [8–12].

Moreover, these guidelines underline that ideally prevention should be a lifelong approach and that it should address not only men and women with established CVD or at high risk but also people at moderate risk and young people [1••].

Tobacco smoking has a well-known adverse effect on cardiovascular risk [10, 13, 14]. In Europe, about 20% and 3% of deaths from CVD in men and in women, respectively, are due to smoking, and an even higher proportion of premature deaths are caused by smoking [2, 14]. For this reason, the guidelines advise hypertensive patients stop smoking (e.g. with use of nicotine replacement, bupropion therapy or varenicline) [1••].

European guidelines also recommend weight reduction in overweight individuals, restriction of alcohol consumption to a maximum ethanol intake of 20 g/day for men and 10 g/day for women, reduction in the use of sodium chloride to less than 5 g/day and regular physical activity in sedentary individuals. Concerning diet modification, these guidelines suggest that hypertensive patients should eat more fruits and vegetables and reduce their intake of saturated fat and cholesterol [1••]. However, such well-meant lifestyle recommendations are not easy to follow.

The European Action on Secondary and Primary Prevention by Intervention to Reduce Events (EUROASPIRE) III, a survey of 13,935 CAD patients, conducted in 2006–2007 in 22 countries in Europe, suggested that large proportions of coronary patients do not adhere to the lifestyle recommendation for CVD prevention [15]. In particular, in this survey, nearly one third of patients were smokers in the month before the coronary event, and the half of them persisted with smoking at interview. Only one patient in seven patients was advised to attend a smoking cessation service, and only one third of those attended a smoking cessation clinic. Despite the fact that in EUROASPIRE III most patients reported modification in their diet since the coronary event, the results were not validated. Moreover, two fifths of the patients had not increased their physical activity, and only one third reported they did some regular exercise. EUROASPIRE III also underlines that the prevalence rates of being overweight and obese were high in all the countries studied (i.e. four fifths of patients had a BMI of 25 kg/m^2 or more and over one third were obese). These data reflect the trends of the general population, and as well as being an independent risk factor for CVD, obesity contributes to other risk factors, such as high blood pressure (BP), dyslipidaemia and diabetes [13, 15].

The EUROASPIRE programme of the European Society of Cardiology (ESC) includes three different surveys: the first EUROASPIRE survey was done in 1995–1996 (in nine European countries), the second was done in 1999–2000 (in 15 countries) and the third was done in 2006–2007 (in 22 countries) [13, 15–18].

Taking together these three surveys, one can evaluate the lifestyle trends in Europe in the past decade: this analysis shows that there are adverse lifestyle trends. In particular, even if the number of patients who are smokers has not changed, there is an increased proportion of younger female smokers, and, in addition, there is an increase in obesity rates [13].

These data demonstrate that CVD prevention in daily clinical practice is inadequate and that there is still room for improving preventive care in order to reduce risk factors and death in CAD patients.

Blood Pressure

A meta-analysis of data involving one million adults without known vascular disease in 61 prospective studies on deaths from CVD found that BP is directly correlated to fatal CAD, fatal stroke and overall mortality from BP levels as low as 115/75 mmHg upwards [19].

Since elevated BP has been identified as a risk factor for CAD among other factors, the latest guidelines universally recommend lowering systolic BP to below 140 mmHg and diastolic BP to below 90 mmHg in all hypertensive patients [1••], and the 2007 guidelines of the European Societies of Hypertension and Cardiology (ESH/ESC) on CVD prevention suggested a goal of decreasing BP below 130/80 mmHg in patients with established CVD or diabetes [20].

The analysis of the three EUROASPIRE surveys reveals that in the last decade, despite increased use of antihypertensive drugs, BP control has not improved, underlining that more efforts should be made to control hypertension [13].

Moreover, the BP target recommended by the guidelines have recently been the centre of debate because they are not always supported by evidence from prospective randomized intervention trials and because of the growing fear that lowering BP too much can lead to a negative effect on cardiovascular outcome [20, 21].

Lower Is Not Always Better

Earlier randomized trials showed that lower BP targets would engender a proportionally greater risk reduction independently

of the medication [22–24], leading to the idea of "the lower, the better" for BP without any limit. However, conflicting data have been published [25•] suggesting that this avenue of thinking may not correctly reflect reality; in fact, lowering systolic BP below 130 mmHg may even be harmful with respect to CAD [26, 27].

Several studies have recently provided evidence questioning the idea of "the lower, the better". They reported the existence of a J-curve distribution that describes the relationship between BP and cardiovascular outcomes in CVD, and in particular in CAD patients. This kind of distribution is characterized by an increased risk at high BP, a decreased risk with lowered BP and a subsequent increased risk when BP reaches the nadir [28, 29, 30•, 31•]. Such a J-curve phenomenon was first observed by Cruickshank [32] in patients with CAD, and was later confirmed by other studies.

However, whether antihypertensive treatments are linked by a causality relation to this phenomenon is still unclear [25•]. The Framingham Study with a cohort of 5,209 subjects reported the existence of a significant J-shaped relationship between diastolic BP and CAD death in patients with myocardial infarction, for both subjects receiving antihypertensive treatment and those not receiving it [33]. Conversely, other studies reported a treatment-induced J-curve relationship between BP and cardiovascular risk [25•].

The International Verapamil-Trandolapril Study(INVEST) was a randomized blinded end-point study in 22,576 hypertensive CAD patients performed in 14 countries [34]: analysis of the data from this study revealed a J-shaped relationship between BP and all-cause mortality and myocardial infarction with a nadir at 119/84 mmHg [28].

The same J-shaped curve was found in an additional post hoc analysis of the INVEST data for 2,699 patients with CAD and peripheral arterial disease. This analysis suggested a J-shaped relationship between BP (both diastolic and systolic) and the primary outcome, demonstrating the lowest risk for the primary outcome at 135–145 mmHg/60–90 mmHg compared with the risk at lower and higher BP levels [35].

In addition, an observational analysis of 4,162 patients in the Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction (PROVE IT-TIMI) trial shows that the relationship between BP and the incidence of vascular events follows a J-curve association. The curve was relatively flat for systolic BPs of 110–130 mmHg and diastolic BPs of 70–90 mmHg and revealed a nadir BP of 136/85 mmHg (range 130–140 mmHg systolic BP and 80–90 mmHg diastolic BP) that was associated with the lowest risk of vascular events and mortality [36].

In accordance with these studies, a subanalysis of the Treating to New Targets (TNT) trial, which randomized 10,001 CAD patients, showed a J-shaped curve with a nadir of 146/81 mmHg. Also in this study it emerged that there was a relatively flat part for systolic BPs between 120 and 140 mmHg and diastolic BPs between 70 and 80 mmHg and an exponential part that described an increase in the incidence of cardiac events for BPs lower than 110–120/60–70 mmHg; however, for the outcome of stroke, there was not a J-shaped relationship with systolic BP [30•].

An analysis of the data obtained in the multicenter Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET), which enrolled 25,588 patients with coronary, peripheral or cerebrovascular disease or diabetes mellitus with end-organ damage, reported an association between systolic BP and higher cardiovascular mortality [27]. In this study a J pattern was present for the incidence of cardiovascular mortality, with a nadir at 130 mmHg, and the incidence of myocardial infarction, with a nadir at 126 mmHg; However, also in this analysis, a relationship between the incidence of stroke and BP was not described by a J curve [27].

In a recent observational study of a cohort of 5,788 patients with symptomatic vascular disease (CAD, peripheral arterial disease and/or CVD) enrolled in the Secondary Manifestations of Arterial Disease (SMART) study, the relationship between BP and the occurrence of vascular events followed a J curve with the nadir BP of 143/82 mmHg [31•, 37].

As previously underlined by Mancia et al. [38•], and as supported by the data presented above, since the relation between BP and cardiovascular outcomes in patients with CAD can often be described by a J curve, it may be prudent not lower BP below 130/80 mmHg in these patients because this procedure may not induce a further reduction but, on the contrary, may even cause an increase in the incidence of coronary events.

Antihypertensive Treatments in CAD Patients

A post hoc analysis of the INVEST data demonstrated that BP control in hypertensive patients with CAD is strongly related to a decrease in the incidence of cardiovascular events [39].

Moreover, ESH/ESC guidelines recognize that administration of antihypertensive treatments such as β-blockers, angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) in patients surviving a myocardial infarction reduces the incidence of recurrent myocardial infarction and death [20, 40–42].

These guidelines also advise treating hypertensive patients with chronic coronary heart disease with antihypertensive drugs in monotherapy or in combination, including calcium-channel blockers. Besides, for patients with congestive heart failure, the ESH/ESC guidelines suggest treatment with thiazide and loop diuretics and/or β-blockers, ACE inhibitors, ARBs and antialdosterone drugs in addition to diuretics [20].

Antihypertensive therapies include renin–angiotensin–aldosterone system antagonists (ACE inhibitors, ARBs and

mineralocorticoid receptor blockers), diuretics, calcium-channel blockers and β-blockers [43, 44•]. These groups of drugs display variably efficacy in lowering BP in hypertensive patients [44•]. Statistical analysis of data from eight countries that participated in the three EUROASPIRE surveys suggests an increase in the use of antihypertensive drugs in 10 years (from EUROASPIRE I to EUROASPIRE III). Unfortunately, the trend of a growing use of antihypertensive drugs did not result in improved BP control [13]; this highlights the need for new strategies in CVD prevention as far as hypertension is concerned.

What's New?

Even in the presence of a wide collection of antihypertensive drugs, new treatments are needed in order to find a better way to improve BP control and reduce the cardiovascular risk factors associated with elevated BP.

"Negative" Studies

In 2007, the first renin inhibitor orally active antihypertensive drug, aliskiren, was approved as a monotherapy but, recently, alarming data arose from the ALTITUDE trial. This study aimed to evaluate whether a combination of aliskiren and an angiotensin II type 1 receptor (AT1R) antagonist or ACE inhibitor reduced cardiovascular and renal morbidity and mortality compared with "placebo" in patients with type 2 diabetes [45, 46•]. However, an increase in the incidence of adverse events and a lack of benefits among patients in the aliskiren group caused the premature termination of the trial [46•].

Another "negative" issue for an antihypertensive drug emerged from the Randomized Olmesartan and Diabetes Microalbuminuria Prevention (ROADMAP) trial.

The results of this multicenter randomized controlled study of 4,447 patients performed in 19 European countries showed that nearly 80% of patients treated with the ARB olmesartan achieved the target BP compared with 71% of the placebo group [47•]. Although olmesartan treatment was effective in significantly preventing the new onset of albuminuria [47•], "positive study", and was slightly more effective in preventing non-fatal cardiovascular events, it was, unexpectedly, associated with a higher incidence of fatal cardiovascular events [48].

Combination Treatment and Fixed-Dose Pills

Current European guidelines recommend combination treatment of complementary antihypertensive drugs in patients with mild-to-severe hypertension in the case of impossibility to continue treatment because of side effects or in the case of insufficient lowering of BP with monotherapy [1••, 20].

These recommendations reflect a reality in which only at most one third of the hypertensive population achieves BP control with monotherapy, and most of the population need three or at least two agents in combination [49].

Combination therapy of complementary classes, in fact, can produce a more effective decrease in BP because each drug can block the counter-regulatory system activity of the other [50] and might reduce the incidence of side effects [51••].

Several trials demonstrated a positive relation between the addition to the treatment of another antihypertensive drug and a decrease in mortality rates in patients with heart failure [52].

Interest in fixed-dose pills is growing for their potential improvement of BP control compared with monotherapy, reduction of the incidence of side effects and amelioration of patient compliance compared with the use of free combinations of the same agents [53, 54, 55•, 56–59].

Three fixed-dose combinations have recently been approved: olmesartan, amlodipine and hydrochlorothiazide; aliskiren, amlodipine and hydrochlorothiazide; and aliskiren and amlodipine [51••].

The efficacy of the olmesartan, amlodipine and hydrochlorothiazide triple combination was investigated in the TRINITY study; its results demonstrated an increased capability of this triple combination to lower BP compared with the double-drug combinations [58]. Recently, a further double-blind, active-treatment-controlled trial in mild-to-severe hypertensive patients showed that the fixed-dose triple combination of aliskiren, amlodipine and hydrochlorothiazide induced a higher BP reduction than three two-drug combinations [58].

The ALTITUDE trial [45, 46•] is another large clinical trial investigating a combination treatment with aliskiren but, as before mentioned, this study was prematurely stopped because of an increase in the incidence of adverse events in the aliskiren group [46•], leading to the idea that in diabetic patients, combination of aliskiren with an AT1R antagonist or an ACE inhibitor should be avoided.

Most of the existing double or triple fixed-dose combinations employ amlodipine and/or hydrochlorothiazide. Nevertheless, the FDA recently approved in the USA a double fixed dose of the new AT1R blocker azilsartan medoxomil and the diuretic chlorthalidone. This combination has been reported to be more effective in reducing BP than the hydrochlorothiazide–azilsartan medoxomil combination [60] or the olmesartan–hydrochlorothiazide combination [61].

Therefore, new combinations are expected to introduce calcium-channel blockers and diuretics different from those that are currently included in combinations.

New Drugs

During the past 2 years, only one new drug has been approved for hypertension treatment: the AT1R blocker azilsartan medoxomil. The antihypertensive effectiveness of this novel molecule was demonstrated by randomized studies of almost

6,000 mild-to-severe hypertensive patients [62, 63]. These studies reported an increased lowering of 24-h mean BP induced by azilsartan medoxomil compared with placebo, olmesartan or valsartan. However, additional studies are needed in order to evaluate long-term morbidity and mortality rates.

Despite the fact that only one new drug has been recently approved, eight novel antihypertensive compounds are in clinical development [51••]. These new drugs comprise compounds with novel mechanisms of action or dual activity: two dual-action AT1R blockers (LCZ 696 and PS433540), an aldosterone synthase inhibitor (LCI 699), a dual endothelin-converting enzyme and neutral endopeptidase inhibitor (daglutril), a natriuretic peptide receptor A agonist (PL 3994) and a soluble epoxide hydrolase inhibitor (AR 9281). Furthermore, included in these eight compounds, there are two modified formulations of already known drugs: a modified-release formulation of the calcium-channel antagonist lercanidipine and a controlled-release formulation of the α_2-adrenergic agonist clonidine. In addition, an angiotensin AT2 receptor (AT2R) agonist, compound 21, is in preclinical development [51••]. This compound is unique in that it combines strong anti-inflammatory, antiproliferative and tissue-regenerative characteristics without lowering BP [64, 65•]. Thus, it will not be developed as an antihypertensive but as one of the first representatives of a new class of tissue-protective agents in CVD and other indications.

LCZ 696 is the most promising dual AT1R and neutral endopeptidase antagonist: a phase II, double-blind, placebo- and active-treatment-controlled clinical trial in 1,215 patients with mild-to-moderate hypertension demonstrated that LCZ 696 (200 and 400 mg) induced a significantly greater reduction in systolic and diastolic BP compared with valsartan (160 and 320 mg) [66]. Furthermore, in this study LCZ 696 was well tolerated and no angio-oedema was reported in the 8-week treatment period [66].

Encouraging results have been also shown with PS433540. This dual AT1R and endothelin A receptor blocker was evaluated in a phase II, randomized, double-blind, placebo- and active-treatment-controlled clinical trial in patients with stage 1–2 hypertension. This study reported a greater efficacy of PS433540 in lowering BP compared with placebo and at the highest dose also compared with irbesartan. Moreover, all doses of PS433540 (200, 400, and 800 mg) displayed improved BP control (less than 140/90 mmHg) compared with irbesartan at 12 weeks [67].

In 2010, the first study of the aldosterone synthase inhibitor LCI 699, in 14 primary aldosteronism patients, showed that twice-daily administration of LCI 699 (0.5 or 1.0 mg) induced a decrease in supine plasma aldosterone concentration and in 24-h ambulatory systolic BP after 4 weeks of treatment [68].

A more recent double-blind, randomized trial in 524 patients with primary hypertension demonstrated that all doses of LCI 699 tested (0.25 mg once daily, 0.5 mg once daily, 1.0 mg once daily and 0.5 mg twice daily) induced significant reductions in clinical systolic BP and in 24-h ambulatory BP (systolic and diastolic) compared with placebo at 8 weeks. However, only the 1.0-mg dose of LCI 699 once daily was significantly more effective than placebo in reducing seated diastolic BP. Moreover, this once-daily dose of LCI 699 resulted in a BP reduction comparable to that achieved with 50 mg eplerenone twice daily. The trial also reported that safety and tolerability were similar among the different groups (LCI 699, placebo and eplerenone) [69]. Even if more detailed data are needed on the effect of this new compound on BP, available data suggest a possible use of this drug as once-daily dosing. However, this trial also reported that LCI 699 suppressed adrenocorticotropic hormone stimulation of cortisol in approximately 20% of patients, raising the question as to whether this effect might interfere with a clinically useful response to stress, thus compromising the safety of this drug [51••].

In a phase IIa study in 21 patients with controlled essential hypertension, consistent with a phase I trial in healthy volunteers [70], it was demonstrated that the natriuretic peptide A receptor agonist PL 3994 dose-dependently increased plasma cyclic GMP levels, and reduced BP. In this study, three of five patients taking both PL 3994 and ACE inhibitors reached the maximum tolerated dose at 0.3 μg/kg, displaying a greater BP reduction than for any other class of antihypertensive, therefore suggesting an interaction between natriuretic peptide A receptor agonism and ACE blockade [71].

The soluble epoxide hydrolase inhibitor AR 9281 was demonstrated to lower BP, to reduce renal damage and to improve vascular function in a rat model of angiotensin II induced hypertension [72, 73]. However, in a study performed in healthy human volunteers, AR 9281,despite being well tolerated up to a 1,000-mg single dose or 400 mg every 8 h for 7 days, did not reduce BP [74].

Conclusion

CAD prevention is mainly by means of lifestyle changes in the entire population and in the entire life of an individual; when lifestyle changes fail or are no longer sufficient to prevent CAD, antihypertensive treatment plays a key role in prevention.

In the past, an uncontrolled policy of lowering BP without limits was executed. Since it has been shown that the relation between BP and the incidence of cardiovascular events can often be described by a J-shaped curve, and that lowering BP too much may even be harmful with respect to CAD, special care should be given to the limit of BP lowering, especially in high-risk populations.

Despite the fact that new antihypertensive treatments are needed, only one novel compound has been approved in the past 2 years: the AT1R blocker azilsartan medoxomil. However, new potentially promising drugs with novel mechanisms of action or dual activity are in clinical development. Single-pill multidrug fixed-dose combinations seem to be the future for antihypertensive treatment in most cases, although more studies are needed and new triple combinations will have to be investigated.

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