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PERSPECTIVE

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The role of single-pill ACE inhibitor/ccb combination for hypertension: an Algerian view via the nominal group technique

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ABSTRACT

Around one-third of adults in Algeria have hypertension, but > 40% are unaware they have the disease, and of those receiving treatment, only ~ 20–30% have adequate blood pressure (BP) control. Recommended starting treatment is an angiotensin converting enzyme inhibitor (ACEi) or angiotensin receptor blocker plus a calcium channel blocker (CCB) or diuretic. A single-pill combination of perindopril/amlodipine (ACEi/CCB) recently became available in Algeria. Twelve Algerian hypertension experts reviewed the clinical evidence regarding this therapeutic combination to determine its potential role for hypertension management in Algeria. The evidence indicated that this combination reduces cardiovascular outcomes and visit-to-visit BP variability, effectively controls 24-hour BP, and is well tolerated. In conclusion, the perindopril/amlodipine SPC provides a valuable new treatment option for hypertension in Algeria.

PLAIN LANGUAGE SUMMARY

Hypertension (high blood pressure [BP]) is a main cause of heart disease, stroke, kidney disease, and dementia, and the World Health Assembly has a target to reduce the number of people with hypertension by 25% by 2030. Around one-third of Algerian adults have hypertension, but a high proportion of Algerian people with hypertension are unaware that they have the disease. Additionally, most patients receiving hypertension treatment do not have their BP controlled adequately. For most patients, international medical guidelines recommend starting BP treatment with two drugs–one that blocks the renin-angiotensin-aldosterone system (RAAS) plus either a calcium channel blocker (CCB) or a diuretic. Guidelines also recommend that patients receive the two drugs in a single pill (called a 'single-pill combination' [SPC]) because this is more convenient and patients are more likely to take the treatment. Recently, a new SPC containing the angiotensin-converting enzyme inhibitor perindopril (which targets the RAAS) and the CCB amlodipine has become available in Algeria. A meeting of Algerian hypertension experts was held on 3 September 2022, to discuss the evidence for this drug combination in treating hypertension and to define the potential role of the perindopril/amlodipine SPC in treating patients with hypertension in Algeria. The evidence indicated that this combination is effective in controlling BP throughout the 24-hour period between doses, reduces the risk of stroke and heart attack, and is well tolerated (safe). The experts concluded that the perindopril/amlodipine SPC provides a valuable new treatment option for hypertension in Algeria.

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1. Introduction

Hypertension is a leading cause of global morbidity and mortality [1–4], contributing to the development of ischemic heart disease (IHD), stroke, chronic kidney disease (CKD), heart failure (HF), and dementia [5]. Globally, hypertension is the leading risk factor for noncommunicable diseases, causing 19% of deaths each year around the world [3].

The estimated burden of hypertension in North Africa is among the highest in the world [2]. Estimates indicate that more than 1.3 million people in North Africa and the Middle East had hypertension in 2019, and Algeria ranked 20th in the world for the age-standardized prevalence of hypertension in that year [2].

Current guidelines may not include the global population because of the lack of data from and delayed updating of essential medicine lists in all countries [6]. A key goal of the World Health Assembly agenda on noncommunicable disease control is to reduce the prevalence of hypertension (defined as

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Article highlights

The importance of blood pressure (BP) control: an Algerian perspective

- Hypertension is a considerable problem in Algeria, with around one-third of adults affected by the disease.
- Hypertension is underdiagnosed and undertreated in Algeria, with low use of combination therapy, despite current guideline recommendations.

Other considerations

- While the various antihypertensive drugs might reduce BP to a similar degree, they have different effects on cardiovascular event rates.

BP treatment approaches

- Patients may start treatment with a single antihypertensive agent but will frequently need at least two antihypertensive agents to achieve BP control. Guidelines recommend that most patients can start on two antihypertensive drugs, with exceptions (e.g., very frail or old patients).
- Typical recommended combinations include a renin angiotensin aldosterone system inhibitor (RAASi), such as an angiotensin converting enzyme inhibitor (ACEi) or an angiotensin II receptor blocker (ARB), in combination with either a calcium channel blocker (CCB) or diuretic.
- A RAASi plus CCB combination is the first-line therapy of choice for the majority of patients with hypertension.
- Patients with AF should receive a RAASi plus β-blocker; patients with heart failure, or post-stroke patients or patients who are very elderly, are recommended to receive a RAASi plus diuretic.
- Patients with comorbidities such as diabetes, metabolic syndrome, atheroma, or left ventricular hypertrophy can be treated with a RAASi plus CCB combination.
- ACEis and ARBs reduce BP to a similar extent, but only ACEis can significantly reduce the risk of all-cause and cardiovascular mortality, and myocardial infarction.
- Treatment adherence and persistence are typically better when patients are given the dual therapy as a single-pill combination (SPC).

The perindopril/amlodipine SPC

- The perindopril/amlodipine SPC is effective and well tolerated, and this SPC is one of the recommended first-line antihypertensive therapy options according to international guidelines.
- There is a large body of clinical study evidence supporting the use of the perindopril plus amlodipine combination, both from international large well-controlled trials and from studies in real-world settings in a wide range of patients.

Role of the perindopril/amlodipine SPC in Algeria

- A study has shown that 45.4% of patients with hypertension in Algeria are treated with monotherapy and 32% on dual therapy. This may explain why only 37.5% of patients receiving treatment for hypertension in Algeria had BP that met recommended targets for BP control.
- SPCs have the potential to markedly improve adherence, and the recent availability of perindopril plus amlodipine as a SPC in Algeria provides an important treatment option in Algeria.
- Real-world data on the effectiveness of the perindopril/amlodipine SPC in patients with hypertension from two North African countries, Algeria and Morocco, are being collected in the observational SYNERGIA studies.

a systolic blood pressure [SBP] ≥140 mmHg and/or diastolic blood pressure [DBP] ≥90 mmHg) by 25% by 2030, relative to the prevalence in 2013 [7]. Achieving this goal requires effective detection, diagnosis and treatment of hypertension, maintaining target blood pressure (BP), and ensuring ongoing patient adherence.

Given the burden of hypertension and the recent approval of a single-pill combination (SPC) of perindopril (an angiotensin converting enzyme inhibitor [ACEi]) and amlodipine (a calcium channel blocker [CCB]) in Algeria, hypertension experts from Algeria met to review hypertension management in the country and the clinical evidence regarding this therapeutic combination. The experts also sought to clarify the potential role of the fixed combination of perindopril/amlodipine for effective hypertension control in Algeria.

2. Methods

The meeting included 12 Algerian hypertension experts (the authors of this review), who were invited to be a part of this panel by the sponsor via e-mail, and were selected if they were the heads of cardiology departments and clinics in the region and/or active members of the national and regional cardiology scientific societies. Panelists who had accepted a role in the meeting were also allowed to suggest other members of the panel, as appropriate. Eight of the twelve experts made presentations at the meeting (M.C., F.H., A.K., A.B., N.L., Y.A., H.M.A.L., and S. A.). Three presenters moderated discussions arising from the presentations (B.K., Y.B., and M.T.C.B.).

The Advisory Board convened at a meeting held on 3 September 2022, in Algiers, Algeria, to discuss the burden of hypertension in Algeria, the impact of antihypertensive therapy on BP and disease outcomes, and clinical data with perindopril and amlodipine, while focusing on the safety, effectiveness, and cardioprotective effect of the perindopril/amlodipine combination. The eight authors presented their interpretations of the most relevant clinical data available supporting the use of a renin-angiotensin-aldosterone system inhibitor (RAASi, i.e., either an ACEi or an angiotensin II receptor blocker [ARB])/CCB combinations (with/without diuretics) and, more specifically, the perindopril/amlodipine combination. They generated ideas and determined priorities as a group.

Ad hoc searches of PubMed were also conducted in April and November 2023 during the development of this article to identify the best quality and most recent data, although no date limits were set. English and French language papers were eligible for inclusion. Relevant hypertension guidelines were also reviewed, and where data were not available specifically from Algeria, evidence from studies conducted in other countries or multi-national studies were included.

The content was analyzed and organized into themes such as importance of BP control, BP treatment approaches, combinations of drug treatments, AEs, and the role of SPCs in the Algerian context.

3. The importance of BP control: an Algerian perspective

As described above, the burden of hypertension in North Africa is among the highest in the world [2]. According to the 2013 Epidemiological Trial of Hypertension in North Africa (ETHNA), conducted in 28,500 primary care attendees in Algeria, Tunisia, and Morocco, the crude prevalence of hypertension in North Africa was 45.4% [8]. Of note, hypertension was first detected during the study assessment in 29.0% of all individuals with hypertension, indicating a high rate of underdiagnosis [8]. Among patients who were receiving treatment for hypertension in the study, only 35.7% had controlled BP (<140/90 mmHg) [8].

About one-third of adults in Algeria have hypertension [9,10], with slight variation in prevalence reported between

regions: 50.2% in the El-Menia oasis (51.3% in males, 49.7% in females) [11], 46.2% (in males) and 31.6% (in females) in the Blida region [12], and 42.5% (in males) and 34.8% (in females) in the city of Oran [13]. Of concern, only 38% of treated Algerian patients have BP controlled to recommended levels [14].

There are no specific Algerian guidelines for hypertension and the guidelines used in Algeria are generally those from the International Society of Hypertension (ISH) [15] or European Society of Hypertension (ESH) [16]. To understand the potential place of the perindopril/amlodipine SPC in the management of hypertension in Algeria, the authors considered it important to review the recommendations in these guidelines and the available evidence supporting these recommendations.

Formerly, guidelines suggested that BP be treated to achieve BP of < 140/90 mmHg, but the most recent iterations of international guidelines define target BP in most hypertensive patients as < 130/80 mmHg (Table 1), with the option of the less rigorous targets (SBP <140 mmHg and DBP < 80 [ESH] or 90 [ISH] mmHg) in older patients for whom the risk of adverse events (AEs) is higher [15,16].

These recommendations are based on extensive data showing the benefits of BP-lowering in patients with or without concomitant cardiovascular disease (CVD) [17]. A meta-analysis of individual patient-level data from 48 randomized controlled trials (RCTs) in 344,716 patients conducted by The Blood Pressure Lowering Treatment Trialists' Collaboration showed that a 5-mmHg decrease in SBP significantly reduced the incidence of major cardiovascular events in patients with and without CVD [17]. In addition, greater SBP reductions were associated with more marked reductions in cardiovascular risk [17].

The recommendation for lower BP targets is also supported by the results of the SPRINT study, which randomized hypertensive patients to a SBP target of <140 mmHg or a more intensive target of <120 mmHg [18]. The risk of a major cardiovascular event (i.e., composite of myocardial infarction [MI], other acute coronary syndromes, stroke, HF, or cardiovascular death) was 25% lower with intensive treatment compared with standard treatment [18].

4. Other considerations

Research in hypertension is focused on BP recorded in the brachial artery, but each brachial BP measurement is a snapshot in time and in a particular section of the vascular tree. It is also important to consider the effects of hypertension in the central arteries and throughout the 24-hour period, as well as variability in BP over time.

Central BP is highly influenced by arterial stiffness, which determines the magnitude and timing of pulse wave reflection from the periphery, and the load on the left ventricle during filling [19]. Central BP has a close correlation with carotid intima-media thickness and with left ventricular mass, and the relationship between BP and these parameters is stronger for central than brachial pressures [20]. Central BP also correlates with cardiovascular outcomes [20], and central pressure and its amplification are significant predictors of coronary artery atherosclerosis and restenosis after stent placement [21].

Ambulatory BP monitoring has proven to be better than clinic BP monitoring for predicting cardiovascular events because it captures nighttime BP, which is the strongest predictor of outcomes [22]. Variability in BP over time (between visits) is also a predictor of cardiovascular risk. Patients with more marked BP variability have more rapid progression of atheroma in coronary arteries and are at increased risk of cardiovascular events [23]. Differences in the effects of treatment on these parameters may help to explain some of the variance in cardiovascular event rates for similar changes in clinic measures of BP with different antihypertensive drug classes [24].

5. BP treatment approaches

A high proportion of patients with hypertension will not reach their BP target on single-agent antihypertensive therapy [25],

Table 1. Target blood pressure (BP) during treatment in the International Society of Hypertension (ISH) [15] and European Society of Cardiology/European Society of Hypertension (ESC/ESH) [16] guidelines.

	Age <65 years	Age 65–79 years	Specific groups
ESC/ESH guidelines 2023 [16]			
Recommended BP	<130/80 mmHg	<140/80 mmHg (<130/80 mmHg can be considered if treatment well tolerated[b])	Age 65–79 years + isolated systolic hypertension, or age ≥80 years: SBP < 140–150 mmHg (130–139 mmHg can be considered if tolerated and cautiously if DBP <70 mmHg)
Class[a]/LOE	I/A	I/A	–
ISH guidelines 2020 [15]		**Age ≥65 years**	
Recommended BP (essential)		BP reduction of < 20/10 mmHg, ideally to < 140/90 mmHg	
Recommended BP (optimal)	<130/80 if tolerated (but >120/70 mmHg)	<140/90 mmHg if tolerated, but consider individualized target[c]	CAD, stroke, CKD, COPD, diabetes: <130/80 mmHg (<140/80 mmHg in elderly patients) HF: <130/80 mmHg (but >120/70 mmHg)
Class[a]/LOE	NR	NR	NR

[a]Class of recommendation, where I = recommended or indicated and IIa = should be considered [2].
[b]Class of recommendation/LOE for lower target is II/B.
[c]In the context of frailty, independence, and likely tolerability of treatment.
CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; HF, heart failure; LOE, level of evidence; NR, not reported; SBP, systolic blood pressure.

and most require at least two antihypertensive drugs to achieve adequate BP control [26]. The need for combination therapy is recognized in the most recent guidelines, which consistently recommend starting most patients on two antihypertensive drugs [15,16]; the ESH guidelines include some exceptions, specifically young people with grade 1 hypertension and no other cardiovascular risk factors, people with high-normal BP but very high CV risk, or frail, or very old patients [16], all of whom may be managed with monotherapy.

Starting with dual antihypertensive therapy has several advantages over monotherapy [26]. First, the reduction in BP is greater [26,27], so patients are more likely to achieve the lower BP targets defined in recent guidelines [25,26]. The enhanced efficacy does not come at an increased risk of AEs, particularly hypotension, the risk of which is not (or only minimally) increased compared with monotherapy [16,26]. Second, there is a lower potential for therapeutic inertia (where physicians do not escalate treatment as needed to achieve BP goals) because patients are more likely to achieve goal BP with the treatment they start on [16,26]. Third, patients have a lower risk of developing cardiovascular events with low doses of two or three antihypertensive drugs than they do with a standard dose of a single antihypertensive agent [28]. In the view of the authors, it is important for clinicians to understand the principles of dual antihypertensive therapy if they are going to consider prescribing a fixed-combination SPC.

Treatment adherence and persistence are significantly better when patients receive dual antihypertensive therapy as a SPC than when they receive dual therapy as a free combination [29], so SPCs are recommended in guidelines to maximize adherence [15,16].

5.1. Recommended drug classes

European guidelines recommend starting treatment for uncomplicated hypertension with a RAASi, in combination with a CCB or diuretic (Figure 1) [16]. ISH guidelines are similar but recommend first-line treatment with a RAASi plus a CCB, with addition of a diuretic if the BP goal is not reached with the initial combination [15]. This recommendation is based on the fact that CCBs have few contraindications [16] and are less likely to cause new-onset diabetes compared with diuretics [30].

Treatment recommendations may differ a little for patients with comorbidities, although the combination of a RAASi plus CCB or diuretic is also recommended for patients with CKD [16]. Both ISH and ESH guidelines recommend considering a β-blocker as part of the combination for patients with preexisting CVD, HF, atrial fibrillation (AF), or another compelling indication, such as hypertension in pregnancy [15,16].

When the BP target is not achieved, ISH and ESH guidelines recommend additional agents from other antihypertensive classes until the target is reached; patients who do not reach target BP with triple therapy should be investigated for potential reasons, and spironolactone or another antihypertensive agent may be added (Figure 1) [15,16].

The recommendation to start antihypertensive therapy with a RAASi plus CCB is based on data from multiple large-

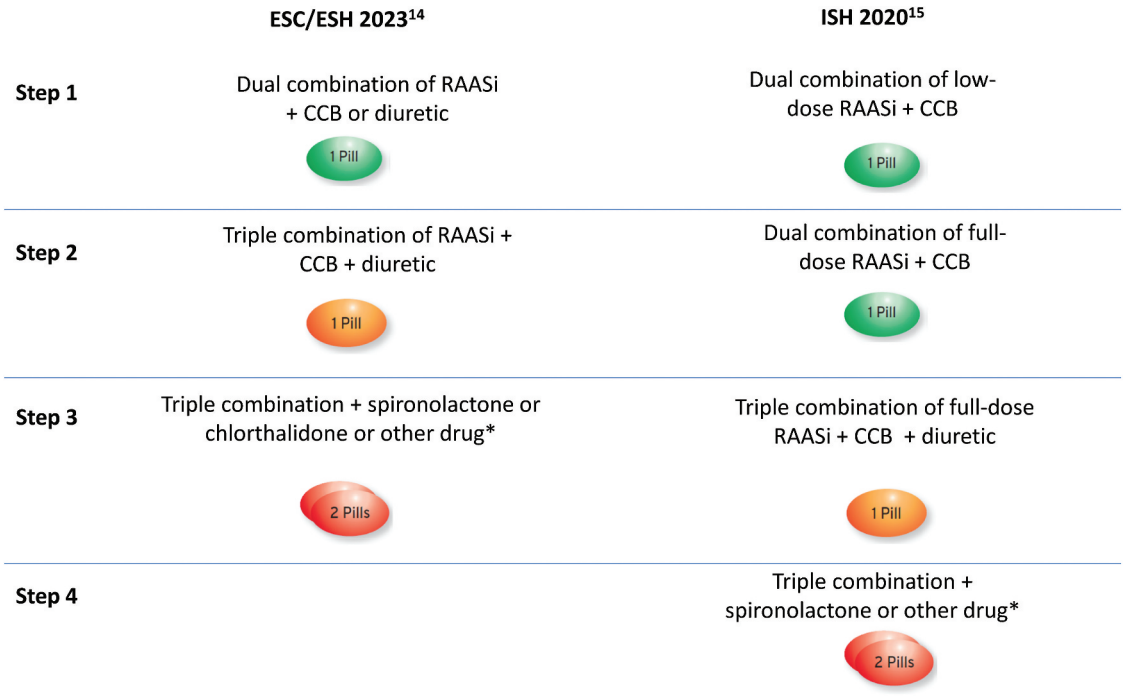

Figure 1. Guideline-recommended approaches to patients with uncomplicated hypertension [15,16]. *spironolactone preferred in patients with estimated glomerular filtration rate (eGFR) ≥30 mL/min/1.73 m^2 and chlorthalidone preferred in patients with eGFR <30 mL/min/1.73 m^2 (not on dialysis). Alternatives are (1) other mineralocorticoid receptor antagonist (eGFR ≥30 mL/min/1.73 m^2) or other thiazide or thiazide-like diuretic (eGFR <30 mL/min/1.73 m^2), or (2) β-blocker or α_1-blocker (irrespective of eGFR), or (3) a centrally acting agent (irrespective of eGFR); consider renal denervation if eGFR is >40 mL/min/1.73 m^2. RAASis are ACEis or angiotensin II receptor blockers. ACEi, angiotensin-converting enzyme inhibitor; CCB, calcium channel blocker; ESC, European society of cardiology; ESH, European society of Hypertension; ISH, international society of Hypertension; RAASi, renin-angiotensin-aldosterone system inhibitor.

scale studies which demonstrated that combinations of these agents are effective at reducing the risk of clinical events, and are generally well tolerated [31–34]. Based on a meta-analysis of outcomes with combination antihypertensive therapy, there is a lower risk of cardiovascular events with the combination of a RAASi plus CCB compared with the RAASi plus diuretic combination [35]. Moreover, the RAASi plus CCB combination has been shown to effectively reduce cardiovascular risk in a range of patients with hypertensive risk and/or comorbidities [32,33], as well as reducing the risk of renal impairment in patients with diabetes and hypertension [36].

5.2. Which combination for which patients?

The guidelines include specific recommendations for which patients should receive the RAASi plus CCB combination and which should receive the RAASi plus diuretic combination. In high-risk patients with hypertension, this decision is driven by whether patients are likely to have arterial stiffness (in which case they should receive a CCB) or volume retention (in which case they should receive a diuretic) [37]. Both of these strategies provide optimal 24-hour BP control and cardiorenal protection (Figure 2) [37], and underlie the rationale for guideline recommendations. However, it is worthy to note that guidelines may provide contrasting recommendations based on race/ethnicity of patients, for example, there are insufficient data on which dual combinations should be prescribed to treat patients of black African origin [38].

5.2.1. RAASi plus CCB

The ISH and ESH guidelines recommend the RAASi plus CCB combination as the first-line therapy of choice for most patients with hypertension [15,16] with a few exceptions. In the ESH guidelines, RAASi plus β-blocker treatment is suggested for patients with AF, and RAASi plus diuretic is suggested for patients with HF (see below) [16]. The RAASi plus CCB combination may be particularly suited to patients with diabetes, metabolic syndrome, subclinical atheroma, left ventricular hypertrophy or obliterative arteriopathy of the lower limbs-abdominal aortic aneurysm, all of whom are likely to have arterial stiffness [37]. The ACCOMPLISH study showed that the combination of an ACEi plus/CCB was more effective than an ACEi plus diuretic in reducing the risk of cardiovascular events in a broad range of patients with diabetes [39].

5.2.2. RAASi plus diuretic

The 2020 ISH guidelines recommend starting a RAASi plus diuretic treatment in post-stroke patients, very elderly patients, those with incipient HF, or those who are unable to tolerate CCBs [15]. The 2023 ESH guidelines also recommend a RAASi as first-line antihypertensive therapy for patients with concomitant HF and reduced ejection fraction, with the addition of a diuretic to manage fluid balance [16].

The combination of an ACEi plus/diuretic may also be considered for patients with diabetes [40], and is an option (along with a RAASi plus CCB) for patients with hypertension and CKD in the ESH guidelines [16]. Other patient groups who may benefit from the RAASi plus diuretic combination are those with a high salt intake, proteinuria, or reduced renal function [37].

Among the options for diuretic therapy, the ISH and ESH guidelines recommend the preferential use of thiazide or thiazide-like diuretics [15,16]. Many SPC combinations with diuretics include thiazide or thiazide-like diuretics, which may simplify treatment. Indapamide, a thiazide-like diuretic, is a logical option, because it has potent BP-lowering effects [41], and thiazide-like diuretics are associated with more cardioprotective benefits compared with thiazides, such as hydrochlorothiazide [42]. However, a loop diuretic is preferred for patients with severe renal failure (estimated glomerular filtration rate <30 mL/min/1.72 m^2) [16].

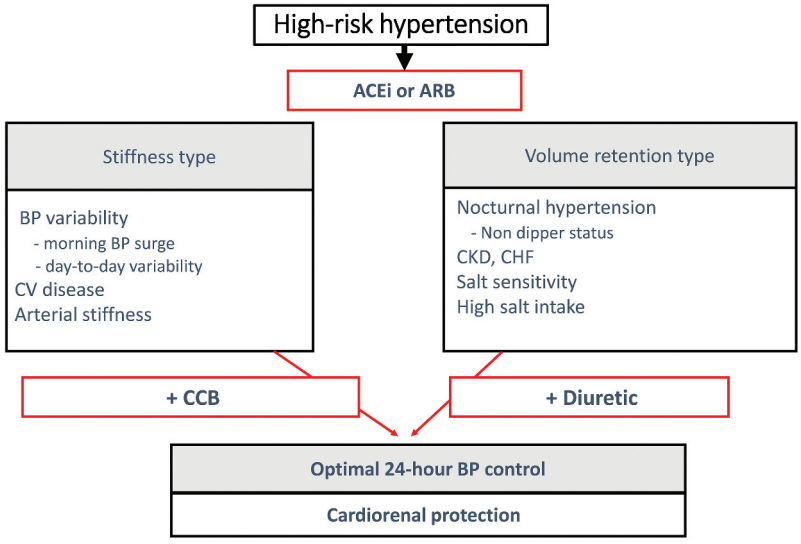

Figure 2. Factors determining the choice of antihypertensive agent to combine with RAASis in patients with high-risk hypertension [37]. Reprinted from journal of the American society of hypertension, vol 4(5), Kario K, proposal of ras-diuretic vs. ras-calcium antagonist strategies in high-risk hypertension: insight from the 24-hour ambulatory blood pressure profile and central pressure, pages 215–218, copyright (2010), with permission from Elsevier. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BP, blood pressure; CCB, calcium channel blocker; CHF, congestive heart failure; CKD, chronic kidney disease; CV, cardiovascular; RAASi, renin-angiotensin-aldosterone system inhibitor.

Table 2. Risk of myocardial infarction, cardiovascular mortality, and all-cause mortality in parallel meta-analyses of placebo-controlled trials of ACEis and ARBs [43]. Reproduced with permission from Strauss MH, hall AS. Angiotensin receptor blockers do not reduce risk of myocardial infarction, cardiovascular death, or total mortality: further evidence for the ARB-MI paradox. Circulation. 2017;135(22):2088–2090. DOI : 10.1161/CIRCULATIONAHA.117.026112. American heart association.

	ACE inhibitor vs placebo				ARB vs placebo			
Patients	N	MI	CV death	All-cause death	N	MI	CV death	All-cause death
High CV risk [42]	62,398	0.83 (0.78–0.90)	0.83 (0.78–0.99)	0.89 (0.80–1.00)	66,282	0.93 (0.85–1.03)	1.02 (0.92–1.14)	1.01 (0.96–1.06)
High CV risk [44]	53,791	0.81 (0.75–0.88)	0.90 (0.78–1.03)	0.91 (0.85–0.98)	54,421	0.90 (0.80–1.02)	1.03 (0.85–1.26)	1.01 (0.94–1.08)
Diabetes mellitus [43]	21,997	NA	0.83 (0.70–0.99)	0.89 (0.79–0.99)	13,304	NA	1.21 (0.81–1.80)	1.03 (0.89–1.18)
Hypertension [45]	49,440	NA	0.87 (0.78–0.98)	0.91 (0.85–0.98)	65,256	NA	1.03 (0.94–1.13)	1.01 (0.97–1.06)

Risk is expressed as hazard ratio with 95% confidence intervals.
ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CV, cardiovascular; MI, myocardial infarction; NA, not assessed.

5.2.3. ACEi or ARB?

Both ACEis and ARBs block the RAAS, but the two drug classes do not have identical pathophysiological or clinical effects. ACEis and ARBs reduce BP to a similar extent [41], but ACEis can significantly reduce the risk of all-cause and cardiovascular mortality, whereas this risk is not reduced with ARBs (Table 2) [43–47]. ACEis are also more effective than ARBs at reducing the risk of MI [48].

The beneficial effects of ACEis may be explained by their action on bradykinin, while the effects of ARBs are mediated by blocking type 1 angiotensin receptors [49]. Downstream, this upregulates angiotensin II levels, which may have a pro-inflammatory and proatherogenic effect [49].

A small proportion of patients receiving ACEis develop cough, and this is not dose-related [50]. The incidence varies between ACEis, but has been shown to be < 5% with perindopril [51], which is lower than the incidence reported with most other ACEis [52,53]. For patients who are unable to tolerate ACEis, ARBs are the preferred drug class for initial combination antihypertensive therapy [54].

RAASis reduce the peripheral edema that may occur with CCBs by counteracting the microcirculatory effects [36,55]; this effect is more marked with ACEis than with ARBs [55].

6. The perindopril/amlodipine SPC

The combination of the ACEi perindopril and the dihydropyridine CCB amlodipine in a single pill (Coveram®; Servier) to be taken once daily has recently become available in Algeria, and is the only ACEi/CCB SPC available there. The SPC of perindopril/amlodipine is indicated in Algeria for the treatment of hypertension and coronary artery disease (CAD). Such an ACEi plus CCB combination is recommended for the first-line treatment of hypertension according to international guidelines [15,16] and there are extensive data supporting the use of perindopril/amlodipine specifically for the management of hypertension.

6.1. Evidence of benefit for the perindopril plus amlodipine combination

The large-scale, randomized, Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA) trial compared the BP-lowering efficacy, tolerability and impact on cardiovascular outcomes of perindopril plus amlodipine and atenolol (a β-blocker) plus bendroflumethiazide (a thiazide diuretic) in 19,257 patients with hypertension [32]. There was a significant reduction in fatal and nonfatal stroke, total cardiovascular events and procedures, and all-cause mortality in the perindopril plus amlodipine group compared with the atenolol plus bendroflumethiazide group (Figure 3) [32]. Both SBP and DBP showed significantly greater reductions in the perindopril plus amlodipine group than in the atenolol plus bendroflumethiazide group, with mean between-group differences of −2.7 and −1.9 mmHg, respectively [32]. However, the better cardiovascular protective effect of perindopril plus amlodipine compared with atenolol plus bendroflumethiazide could also be explained by better effects on other BP parameters (e.g., nighttime BP, central BP and BP variability), which were demonstrated in ASCOT-CAFÉ, a substudy of ASCOT-BPLA [24].

The EUROPA trial also showed the benefits of the perindopril plus amlodipine combination in patients with stable CAD, with a reduction in the primary endpoint (composite of cardiovascular death, MI, or cardiac arrest) by 50%, total mortality by 69%, cardiovascular death by 71%, MI by 71%, and hospitalization for HF by 86% compared with placebo [31]. In these patients, the benefits may have been at least partially mediated by favorable effects of perindopril on endothelial function [56].

In addition to benefits on brachial BP and cardiovascular outcomes, perindopril plus amlodipine has been shown to significantly reduce visit-to-visit BP variability [57], and this has been proposed as the reason for the lower risk of stroke in the perindopril/amlodipine arm than the atenolol/thiazide arm of the ASCOT-BPLA study [58]. The combination of perindopril and amlodipine also maintains BP throughout the 24-hour dosing interval [59], and provides superior control of central BP compared with atenolol/thiazide [24].

Taken together, our interpretation of these data are that perindopril and amlodipine not only work synergistically on BP stability, but they also have favorable effects on the pathophysiological mechanisms responsible for coronary lesions and long-term cardiovascular events.

6.2. Evidence of benefit for a SPC of perindopril/amlodipine

The perindopril/amlodipine SPC was compared with an irbesartan-based regimen in a randomized phase 3 study [60]. In

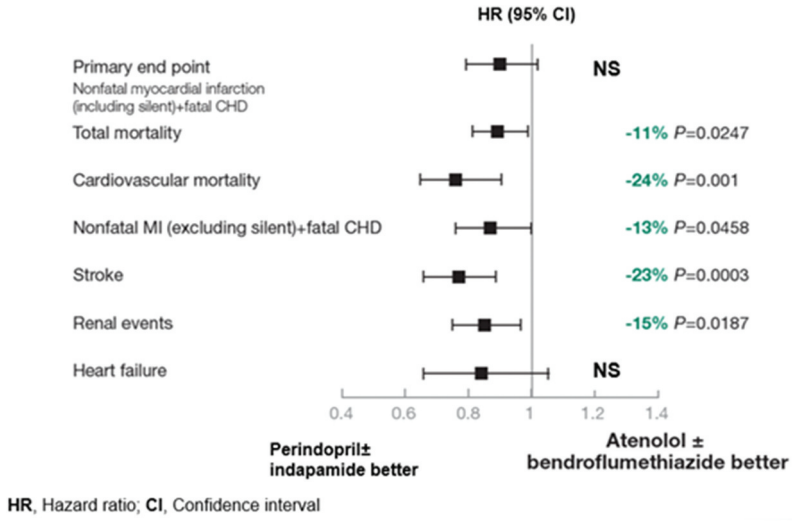

Figure 3. Forest plot showing the effect of perindopril-amlodipine ($n = 9639$) versus atenolol-bendroflumethiazide ($n = 9618$) in hypertensive patients with 3 or more cardiovascular risk factors: results of the ASCOT-BPLA study [32]. Reprinted from the lancet, vol 366, dahlöf B, sever PS, Poulter NR, wedel H, beevers DG, Caulfield M, Collins R, Kjeldsen SE, Kristinsson A, McInnes GT, Mehlsen J, Nieminen M, O'Brien E, Ostergren J, ASCOT investigators.

Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicenter randomized controlled trial, Pages 895–906, Copyright (2005), with permission from Elsevier. CHD, coronary heart disease; CI, confidence interval; HR, hazard ratio; MI, myocardial infarction; NS, not significant. The study was stopped prematurely by the Data Safety Monitoring Board because of the significantly higher rate of mortality in the atenolol-bendroflumethiazide arm at interim analysis. This likely explains the non-significant difference in the primary endpoint.

both treatment arms, the dose was titrated upwards at monthly intervals to achieve the BP goal (<130/80 and < 140/90 mmHg for patients with and without diabetes, respectively). In the perindopril/amlodipine group, the starting dose was 3.5/2.5 mg, increasing to 7/5, 14/5 and 14/10 mg, while in the comparator arm, treatment started with irbesartan alone at 150 mg, then titrated to irbesartan/hydrochlorothiazide (HCTZ) 150/12.5 mg, increasing to 300/12.5 and 300/25 mg. Both treatments significantly reduced BP and increased BP control at each incremental dose, but perindopril/amlodipine significantly reduced the risk of clinical events (composite of cardiovascular events, diabetes and glucometabolic impairment, and renal impairment) after 9 months of treatment (hazard ratio [HR] 0.811; $p = 0.036$), as well as significantly reducing the risk of renal impairment (HR 0.118; $p < 0.0001$) [60].

In a separate randomized study, first-line treatment with the perindopril/amlodipine SPC led to more rapid BP control compared with a stepped-care strategy starting with ARB monotherapy (in this case, valsartan) and adding amlodipine in patients with hypertension [61].

While RCTs are considered the 'gold standard' for robust demonstration of clinical efficacy, it is also important to show that antihypertensive treatment strategies are effective in patients with diverse clinical characteristics under real-world clinical conditions [62]. The perindopril/amlodipine SPC has been shown to be effective in a wide range of patients in real-world clinical practice settings [63–66]. For example, the STRONG study examined the effectiveness of the perindopril/amlodipine SPC in 1250 primary care patients with hypertension, including patients who were previously untreated (32.6%), those who had uncontrolled BP on monotherapy (40.5%) or combination therapy (24.7%), and patients who had controlled BP but had poor adherence (1.2%) or experienced AEs (1.0%) with dual therapy; 12.9% of the patient group had SBP >180 mmHg [63]. Adherence was high and the perindopril/amlodipine SPC rapidly reduced SBP (within 15 days) in the overall population by −21/−11 mmHg [63]. BP targets of < 140/90 mmHg or < 130/80 mmHg in patients with diabetes were reached in 66.1% of the overall population after 60 days of treatment with perindopril/amlodipine [63]. A similar trend was seen in different patient subgroups; target BP control was achieved in 68.3% of previously untreated patients, 68.4% of patients uncontrolled on monotherapy and 59.9% of patients inadequately managed on another combination [63]. Clinical data for patients from geographies typically excluded from large international pivotal randomized controlled trials are also valuable, in our view. As described further below, two observational studies in North Africa on the management of hypertension with the SPC combination of perindopril/amlodipine are awaited with interest.

Several other observational studies have confirmed that treatment with the perindopril/amlodipine SPC rapidly reduces BP in patients who were not achieving BP targets with their previous antihypertensive therapy, including those receiving any previous monotherapy or dual therapy [65], an ACEi and/or a CCB (alone or in combination) [64], a free combination of perindopril and amlodipine [64], or ARB-based dual therapy (ARB with a diuretic, CCB, β-blocker or moxonidine) [67].

In an observational study in 1907 patients with hypertension and CAD, 90.3% of whom had uncontrolled BP at baseline, BP control was achieved in 81.5% of patients after 4 months of treatment with the perindopril/amlodipine SPC [66]. In these patients, mean office BP decreased from 156.5/89.9 mmHg at baseline to 130.8/78.2 mmHg after 4 months of perindopril/amlodipine treatment ($p < 0.001$) [66].

6.3. AEs and treatment discontinuation of SPCs

The STRONG study revealed that the perindopril/amlodipine SPC was safe and well tolerated (0.7% of patients withdrew from treatment because of AEs of cough, ankle edema and cerebral hemorrhage) [63], and a meta-analysis of outcomes with combination antihypertensive therapy, demonstrated that the risk of withdrawal due to AEs was lower with the combination of RAASi plus CCB compared with the RAASi plus diuretic combination [35]. In the ASCOT-BPLA study, the incidence of AEs was generally lower in the perindopril plus amlodipine group than in the atenolol plus bendroflumethiazide group, with significantly fewer discontinuations due to AEs in the ACEi plus CCB group (2% vs 3%; $p < 0.001$) [32]. Bradycardia, chest pain, diarrhea, dizziness, dyspnea, erectile dysfunction, fatigue, lethargy, peripheral coldness, and vertigo were more common with atenolol plus bendroflumethiazide, while cough, joint swelling, eczema, and peripheral edema were more common with perindopril plus amlodipine [32]. The risk of rare AEs is also dependent on ethnic and population-based differences, such as the occurrence of angioneurotic edema is higher in black African patients who are prescribed ACEIs [16].

7. Role of the perindopril/amlodipine SPC in Algeria

Algeria is a country in transition, with an increasing burden of non-communicable diseases [68]. The leading cause of death in both sexes in Algeria is IHD, followed by stroke [69], and the burden of these diseases is increasing with an aging population [68]. Moreover, it is common for Algerian patients with CAD to have atherosclerotic disease in more than one arterial bed, e.g., peripheral or carotid arteries [70]. The transition in prevalent morbidities from infectious to non-communicable conditions follows an increase in the prevalence of multiple cardiovascular risk factors in Algeria in recent years, including obesity, type 2 diabetes and hypertension [68]. Another risk factor of cardiovascular disease is metabolic syndrome, which is highly prevalent in South Algeria [71].

As described earlier, hypertension is a major health concern in Algeria in terms of prevalence, awareness and control (Table 3) [8–10,14]. In Algeria, the reported prevalence is between 30% and 40% of the adult population [9,10], but differs between rural and urban areas and is highest (~67%) in elderly women, irrespective of urban/rural setting [72]. In a representative adult population in Algeria, only 58.9% of individuals with hypertension were aware that they had the disease [9]. Among those who are receiving treatment, BP control is poor. In the ETHNA study conducted in Algeria, Morocco, and Tunisia, only 35.7% of patients receiving antihypertensive treatment had BP controlled to < 140/90 mmHg [8]. The recent PACT II study in Algeria reported that, while 38.0% of patients receiving treatment for hypertension had BP of < 140/90 mmHg, only 17.4% had BP that met the ESC 2018 guidelines criteria for BP control (<130/80 mmHg) [14].

Poor BP control in Algeria is likely the result of undertreatment in the region. The ETHNA study found that 10% of hypertensive patients receive no treatment, 45% receive monotherapy, and only 32% receive dual therapy [8], despite guideline recommendations of starting dual therapy in most patients [15,16]. The most commonly prescribed medications in the ETHNA study were diuretics (45%), ACEis (35%), CCBs (29%), and ARBs (28%) [8]. An observational study of 1027 hypertensive patients seen by private or public cardiologists in Algeria found that 44.5% were receiving monotherapy; among patients newly diagnosed with hypertension at the cardiology visit, 69.3% were prescribed monotherapy and approximately 50.0% were prescribed ARBs [73].

In the authors' combined clinical practice experience, ACEis are generally considered to be underutilized and ARBs are overprescribed in Algeria despite the availability and reimbursement of ACEis. This under-prescription is puzzling given the proven benefits of ACEis on cardiovascular outcomes [43–48]. Similarly, data from the abovementioned observational study [73] and from the ETHNA [8] study suggest that dual antihypertensive therapy is under prescribed in Algeria, despite international recommendations [15,16]. In the PACT II study, 43.7% of patients were receiving dual therapy, 28.2% were receiving triple therapy and 4.6% received more than 3 antihypertensive therapies [14]. Among the 875 patients receiving dual therapy, 255 (29.1%) were receiving separate agents instead of SPCs [14].

Fixed dose combinations of perindopril/amlodipine have proven benefits in reducing BP and improving BP control, in both RCTs and observational studies [31,32,63–66] and are also associated with significant decreases in adverse cardiovascular outcomes and all-cause mortality in RCTs [31,32]. In an analysis of medical insurance claims in South Africa,

Table 3. Hypertension awareness, diagnosis and control in Algeria.

Reference	Population	N	Prevalence, % of total population	Awareness, % of hypertensive population	Control[a], % of treated hypertensive population
Algeria, Tunisia and Morocco					
Nejjari et al. [8]	Adult patients attending primary care physicians	28,500	45.5	71.0	35.7
Algeria					
Brouri et al. [10]	Adult patients at general medicine centers; Algerian subgroup of the Africa/Middle East Cardiovascular Epidemiological Study	410	39.5	NR	NR
Moussouni et al. [9]	Representative sample of adult population	6765	31.6	58.9	NR
Nibouche et al. [14]	Nationally representative sample of adult patients with hypertension seeing cardiologists, internists or general practitioners at 100 sites (PACT II cross-sectional study)	2000	NR	NR	38.0

[a]BP of < 140/90 mmHg.
NR, not reported.

perindopril-based treatment was associated with a lower rate of cardiovascular events over 5 years compared with enalapril- or losartan-based regimens [74]. Perindopril-based regimens also provided better cost outcomes compared with other treatments.

An observational study called SYNERGIA is underway to investigate the effectiveness of the perindopril/amlodipine SPC in ~ 1000 Algerian patients with uncontrolled hypertension [75]. The results will help to clarify the role of this combination for patients with hypertension in Algeria. A similar study in 1614 patients with uncontrolled hypertension conducted in Morocco has recently been completed (SYNERGIA-Morocco) [76,77], which will add to the evidence of the SCP for the treatment of hypertension in North African populations, and may also be of interest for Algerian clinicians.

If a RAASi plus diuretic combination is indicated, or if patients require a diuretic to be added to the first-line combination to reach their BP target, in the authors' view, indapamide is a logical choice as it is a thiazide-like diuretic with potent BP-lowering effects [41,42]. The combination of perindopril plus indapamide has been proven to reduce the risk of cardiovascular events in hypertensive and non-hypertensive patients with a history of stroke or transient ischemic attack (PROGRESS study) [78], in hypertensive patients ≥80 years of age (HYVET study) [79], and in patients with type 2 diabetes and at least one cardiovascular risk factor (ADVANCE study) [80].

8. Strengths and limitations

It is the authors' view that the availability of the perindopril/amlodipine SPC fills an important gap in the available antihypertensive treatments in Algeria, providing guideline-recommended first-line therapy of a SPC. The perindopril/amlodipine SPC is indicated for both hypertension and stable CAD in Algeria, providing a convenient option for a range of patients. The once-daily, fixed combination is likely to increase adherence, which has been suggested as the most important strategy to manage hypertension in North Africa [81].

Some limitations of the methodology of this article includes a lack of representativeness of the panel and lack of a consensus protocol, which may limit the interpretability of our findings.

9. Conclusion

Hypertension is highly prevalent but undertreated in Algeria. The perindopril/amlodipine SPC has proven benefits in reducing BP, reducing the risk of cardiovascular events and decreasing all-cause mortality, and represents a convenient treatment option for a range of patients with hypertension. The availability of the perindopril/amlodipine SPC in Algeria fills an important gap in available therapy options for patients with hypertension and stable CAD, and results from the SYNERGIA studies with this combination in patients with hypertension from Algeria and Morocco are awaited with interest.

9.1. Future perspective

- A wider variety of treatment options for the management of hypertension in a broad range of patients will greatly assist meeting therapeutic goals in Algeria and wider North Africa.
- Results from the SYNERGIA studies in Algeria and Morocco will be published in the next few years, and should provide additional evidence from the North African region regarding the effectiveness of a single-pill combination of an ACEi and CCB for treating hypertension.
- A roadmap for the next 5 to 10 years may assist clinicians and policy makers in translating existing knowledge into effective action, such as the road map developed by the Pan-African Society of Cardiology for the treatment and control of hypertension in sub-Saharan Africa [82].
- There are already proposals for key strategic actions to be implemented to reduce the burden of hypertension in Africa (the ACHIEVE initiative), and hopefully the next 5 to 10 years will see the fruits of such initiatives [83].
- Most progress in the next decade will likely come from patient education on the impact of uncontrolled hypertension, addressing physician treatment inertia, improved physician training, as well as changes in healthcare policies and the provision of healthcare to promote the detection and treatment of hypertension, rather than the discovery/development of completely novel anti-hypertensive treatments.

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Author contributions

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Ethical declaration

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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Data availability statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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