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Polypill, hypertension and medication adherence: The solution strategy?

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ABSTRACT

Introduction: Hypertension is an important global health challenge and a leading preventable risk factor for premature death and disability worldwide. In current cardiology practice, the main obstacles in the management of patients affected by hypertension are comorbidities and poor adherence to pharmacological treatments. The World Health Organization has recently highlighted increased adherence as a key development need for reducing cardiovascular disease.
Methods: Principal observational and clinical trial data regarding adherence, reductions in cardiovascular risk and safety of the polypill approach are summarized and reviewed.
Conclusions: The polypill approach has been conclusively shown to increase adherence relative to usual care in all cardiovascular patients, furthermore, concomitant risk factor reductions have also been suggested. To date, the use of polypill could represent a solution strategy in patients affected by hypertension, comorbidities and non-adherence even though further studies, especially in the real-world settings, are needed in order to better understand its role in clinical practice.

1. Background

Hypertension is an important global health challenge and a leading preventable risk factor for premature death and disability worldwide [1].

The management of hypertension has two main aims: obtaining optimal blood pressure (BP) levels and reducing cardiovascular events and mortality. Therapeutic arsenal for treatment of hypertension includes angiotensin-converting-enzyme (ACE) inhibitors, angiotensin II receptor antagonists (ARBs or sartans), β-blockers, calcium channel blockers (CCBs) and diuretics [2].

ESH-ESC 2013 guidelines recommend to start antihypertensive treatment with diuretics, β-blockers, CCBs, ACE inhibitors and sartans, either alone or in combination. Different pharmacological associations can be considered, in particular ACE inhibitor and diuretic, sartan and diuretic, ACE inhibitor or sartan and CCB [3]. Pharmacological intervention is required when systolic BP (SBP) value is above 160 mm Hg and the goal of treatment is represented by the progressive achievement of values lower than 140 mm Hg. However, the achievement of this value is often difficult and <25% of the patients reported values below 140/90 mm Hg.

In current cardiology practice, the main obstacles in the management of patients affected by hypertension are comorbidities and poor adherence to pharmacological treatments [4].

2. Treatment of hypertension and comorbidities

Treatment of hypertension could be complicated by several comorbidities (e.g., diabetes mellitus, kidney disease, cardiovascular diseases) and, in the real-world population, its management is a matter of debate [5]. Several drugs can be administered in patients with hypertension and comorbidities (ACE inhibitors, sartans, diuretics, β-blockers, CCB) and the choice strictly depends on patient characteristics, comorbidities and risk factors (Table 1).

Different BP target values have been proposed for diabetic patients in order to minimize cardiovascular risk. Few randomized controlled trials have shown that a reduction of SBP to levels of 120–125 mm Hg and/or to 70–75 mm Hg diastolic BP (DBP) could lead to an increased incidence of coronary events, consequent to hypoperfusion of vital organs (the so called "J-curve phenomenon") [6]. In the light of these findings, the previous target of ≤130/80 mm Hg is no longer evidence based. Nevertheless, there is still no homogeneity regarding optimal BP targets. In fact, recent international guidelines [7,8] suggest to start treatment when BP values are ≥140 mm Hg (SBP) and ≥90 mm Hg (DBP) with

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Table 1
Blood pressure values and comorbidities.

Guidelines	Population	BP target (mm Hg)	Pharmacological treatment
JNC 8 [12]	Age ≥ 60 years	<150/90	Thiazide diuretics, ACE inhibitors, sartans, CCBs
	Age < 60 years	<140/90	
	Diabetes	<140/90	
	Chronic kidney disease	<140/90	ACE inhibitors, ARB
ESH/ESC 2013 [3]	Young adults	<140/90	Diuretics, ACE inhibitors, sartans, β-blockers
	Age ≥ 80 years	<150/90	o CCBs
	Age < 80 years	<150/90	
	Diabetes	<140/85	ACE inhibitors or sartans
	Chronic kidney disease without proteinuria	<140/90	
	Chronic kidney disease with proteinuria	<130/90	
American Diabetes Association (ADA) 2016 [8]	Diabetes	<140/90	ACE inhibitors or sartans
Kidney Disease: Improving Global Outcome (KDIGO) 2013 [10]	Chronic kidney disease without proteinuria	≤140/90	ACE inhibitors or ARB
	Chronic kidney disease without proteinuria	≤130/80	
National Institute for Health and Clinical Excellence (NICE) 2014 for chronic kidney disease and 2015 for diabetes [11]	Age ≥ 80 years	<150/90	Patients ≥55 years, CCBs
	Age < 80 years	<140/90	Patients <55 years, ACE inhibitors or sartans
	Type 2 diabetes without macrovascular complications	<140/80	ACE inhibitors, sartans thiazide diuretics, or CCBs.
	Type 2 diabetes with macrovascular complications	<130/80	
	Type 1 diabetes	<135/85	ACE inhibitors, sartans, thiazide diuretics or CCBs
	Type 1 diabetes with complications	<130/80	
	Chronic kidney disease	<140/90	ACE inhibitors or sartans

the aim to reduce SBP <140 mm Hg and DBP <90 mm Hg and, if patients present vascular complications, to achieve a BP target of <130/80 mm Hg.

In these patients, therapy can be started with any antihypertensive medication even if combination therapy is often required to obtain optimal BP levels. ACE inhibitors or sartans should be included in any case, since they exert a protective role in renal disease; subsequently a thiazide diuretic or a CCB can be added if BP levels are not in target with ACE inhibitors or sartans alone [9]. Thiazide diuretics are often administered in combination to drugs acting on renin-angiotensin system (RAS). CCBs have proven useful, especially when combined with a RAS blocker [3].

In patients with diabetic kidney disease and concomitant proteinuria, ESH-ESC 2013 guidelines recommend a SBP reduction of <130 mm Hg, as long as the glomerular filtration rate is monitored. Similar BP target has also been suggested by the Kidney Disease: Improving Global Outcomes (KDIGO) [10], NICE [11] and JNC 8 guidelines [12]. RAS blockers seem to be more effective compared to placebo or other antihypertensive treatment in reducing albuminuria. More controversial are the recommendations for hypertensive haemodialysis patients, since the optimal target pressure is not yet clear. However, all antihypertensive drugs, with the exception of diuretics, can be used, adjusting the dosage in relation to haemodynamic conditions [3].

The context is completely different for the treatment of hypertensive patients with cardiovascular diseases (i.e., atrial fibrillation, myocardial infarction, heart failure, arterial disease). To date, there are no clear evidences in favor of the achievement of SBP values <130 mm Hg in hypertensive patients with coronary artery disease (CAD). However, the SPRINT study demonstrated that among patients at high risk for cardiovascular events, targeting a SBP of <120 mm Hg, as compared with <140 mm Hg, resulted in lower rates of fatal and nonfatal major cardiovascular events and death from any cause [13]. In this group of patients, the cardiovascular risk reduction depends on the appropriate selection of cardiovascular medications other than the achievement of the optimal BP target [3]. In particular, for hypertensive patients with atrial fibrillation (AF) and rapid ventricular response rate, ESH/ESC guidelines recommend the use of β-blockers and non-dihydropyridine CCBs [3]. Treatments with ACE inhibitors and sartans are equally effective in reducing AF in patients with heart failure (HF) [14]. Moreover, both ACE inhibitors and sartans proved to be effective in reducing the risk of new AF, with more robust data for sartans [15]. All antihypertensives medications can be helpful in patients with CAD, but β-blockers and ACE inhibitors demonstrated a superior efficacy in patients with recent myocardial infarction (MI) [3]. In particular, β-blockers exert a positive effect in secondary prevention of MI and sudden cardiac death [16]. Moreover, β-blockers and CCBs are to prefer in case of symptomatic angina. Lastly, ACE inhibitors, diuretics and sartans can slow the progression from HF with preserved ejection fraction to HF with reduced EF and are to be preferred in this kind of patients [3].

3. Hypertension and medication adherence

Adherence to treatment may be defined as the extent to which the patient's history of therapeutic drug-taking coincides with the prescribed treatment (taking practitioner-prescribed medication >80% of the time). Non-adherence in antihypertensive treatment could influence clinical outcomes and represents one of the major risk factors for cardiovascular complications, mainly in patients with comorbidities [17]. Therefore, maximizing adherence to antihypertensive treatment is one of the main goals in order to better control clinical outcome in hypertensive patients. Several factors are associated with non-adherence, e.g. young age, low income, multiple pharmacological treatment or being a new user of the drug.

A cohort study [18] pointed out that non-adherence to any antihypertensive medication was more frequent in people under the age of 65 and with low income.

Furthermore, non-adherence was higher among new users of antihypertensives and in patients taking multiple cardiovascular drugs [19].

Another retrospective cohort study found a significant relation between antihypertensive and antidyslipidemic treatments and the number of prescribers, suggesting that continuity of medication management could be improved by minimizing the number of prescribers involved in a patient's care and by ensuring optimal communication and coordination among prescribers [20].

Adherence could also be different according to drug classes. An Italian prospective study evaluated adherence to antihypertensive treatment in 347 patients. In this study, hypertensive patients were randomly allocated to monotherapy with either ACE-inhibitors, sartans, CCBs, β-blockers or diuretics. After a follow up period of 24 months, persistence of treatment was highest among ACE-inhibitors (64.5%) and sartans (68.5%), when compared to CCBs (51.6%), β-blockers (44.8%) and diuretics (34.4%) [21].

Several interventions in order to improve adherence have been evaluated, e.g. simplification of pharmacological regimens, education and

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