Artery Research (2017) 18, 49–54

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Review

Practical solutions for hypertensive patients with dyslipidemia☆

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Received 16 October 2016; accepted 17 March 2017

KEYWORDS
ACE inhibitors;
Amlodipine;
Aortic stiffness;
Central pressures;
Dyslipidemia;
Hypertension

Abstract Arterial hypertension and dyslipidemia often coexist and constitute major risk factors of ischemic heart disease. Aggressive treatment of both comorbidities is of paramount importance to decrease global risk. Low adherence is a determinant of poor risk factor control and increases adverse cardiovascular outcomes. Regarding treatment of hypertension, combination therapy is superior in achieving target BP values compared to up-titrating monotherapy and it is recommended in hypertension guidelines. The combined use of drugs in a single pill formulation increases adherence and reduces cardiovascular risk. Our review of the literature indicates that triple therapy with an angiotensin converting enzyme inhibitor, a calcium channel blocker and a statin is associated with a significant reduction in major cardiovascular events. This is attributed to synergy at the vascular, and is translated into efficacy at the clinical level.
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Why should we care?

Hypertension and dyslipidemia are among the leading cardiovascular (CV) risk factors associated with deaths.[1] The two conditions frequently coexist. Two out of three hypertensive patients have dyslipidemia and, conversely, half of dyslipidemic patients are hypertensives.[2,3] In risk score models, high cholesterol levels doubles the CV risk of hypertensive patients.[4] Cardiovascular disease (CVD) is preventable through treatment of risk factors; however, managing global CV risk has received less attention compared with treating individual diseases that affect CV risk, such as hypertension or hypercholesterolemia.

One out of three hypertensive patients are already treated with more than three antihypertensive drugs.[5] In spite of the introduction of drugs that can efficiently reduce blood pressure (BP) and cholesterol levels, a considerable proportion of patients with established CVD

☆ This article was presented as lecture in the symposium on "Protecting arteries against hypertension and dyslipidemia" at the ARTERY 16 Congress in Copenhagen, Denmark (October 13–15, 2016).

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http://dx.doi.org/10.1016/j.artres.2017.03.002
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cannot achieve the guideline-recommended BP and low density lipoprotein cholesterol (LDLc) goals. The European Society of Cardiology European Action on Secondary and Primary Prevention by Intervention to Reduce Events (EUROASPIRE) IV cross-sectional survey reported recently that risk factor control is very poor, with less than half (42.8%) of the patients on BP lowering medications reaching the target of <140/90 mmHg (<140/80 mmHg in people with self-reported diabetes)[6] (Fig. 1A). Also, among treated dyslipidemic patients only 32.7% attained the low-density lipoprotein (LDL)-cholesterol target of <2.5 mmol/l (70 mg/dl)[6] (Fig. 1B). Poor adherence, need for multiple medications, physician inertia and deficiency of health-care systems are important factors that affect control rates of both hypertension and dyslipidemia.

Therefore, current evidence clearly shows that more efforts must be taken to improve CV prevention in people at high CVD risk. The aim of this review article is to explore efficacy of practical solutions such as the use of fixed-dose combinations of antihypertensive agents and a statin, which might improve the management and prognosis of hypertensive patients with coexisting hypercholesterolemia.

What to combine?

Antihypertensive combination therapy

Dual combination therapy is an important component of guideline-recommended therapy in hypertension because it has numerous benefits. Indeed, adding a drug from another class is 5-fold more effective than doubling the dose of the first drug and BP targets are achieved faster; complications are reduced and adherence is enhanced.[7] Overall, better adherence contributes to improved CV protection.

Renin-angiotensin aldosterone system (RAAS) inhibitors are a well-established drug class for the reduction of CVD mortality. Pooled analysis of RAAS inhibitor trials in populations with a high prevalence of hypertension (≥66%) demonstrated a significant reduction in the relative risk (RR) of all cause mortality by 5% and in the RR of all cause mortality by 7% reduction.[8] The observed treatment effect resulted entirely from the class of angiotensin converting enzyme (ACE) inhibitors, which were associated with a significant 10% and 12% reduction in all cause mortality and CVD mortality, respectively, whereas no mortality reduction could be demonstrated with angiotensin receptor blocker (ARB) therapy. The largest reductions in the RR of all-cause mortality (by 13%) occurred in three trials in which the ACE inhibitor perindopril (ASCOT-BPLA, ADVANCE and HYVET − 34,242 patients) (Fig. 2).[8] Also, ACE inhibitors reduced all-cause mortality, CVD mortality and major CV events in patients with diabetes, whereas ARBs had no benefits on these outcomes.[9] In light of these data, ACE inhibitors could be considered as first-line therapy to limit mortality and morbidity in these populations.

The combination of a RAAS blocker and a calcium channel blocker (CCB) is very effective in controlling BP. Further, there is convincing evidence that ACE inhibitors and CCBs may be a particularly useful combination in terms of clinical synergy. Protection from coronary artery disease and stroke conferred by ACE inhibitors and CCBs in hypertensive patients that can be explained by the specific drug is of paramount importance. Interestingly, ACE inhibitors appear to preferentially protect from coronary artery disease, while CCBs appear to protect from stroke, over and beyond BP reduction in meta-regression analyses.[10] Furthermore, recent data support modern antihypertensive regimen based on an ACE inhibitor and a CCB because this combination therapy improve prognosis by furthering reducing CV endpoints compared with an older antihypertensive treatment regimens based on beta-blocker and diuretic, independent of similar BP control.[11,12]

Further to hard endpoints, a favorable side-effect profile is very important for patients' adherence. The addition of ACE inhibition or ARB to CCBs has been shown to reduce peripheral edema, a common adverse effect of therapy with CCBs. According to a meta-analysis, ACE inhibitors seem to be more efficacious than ARBs (by 26% in indirect comparison) in reducing CCB-associated peripheral edema, although head-to head comparisons are desired.[13]

The combination with statins

It has been clearly demonstrated that cholesterol-lowering therapy with statins reduces morbidity and mortality in

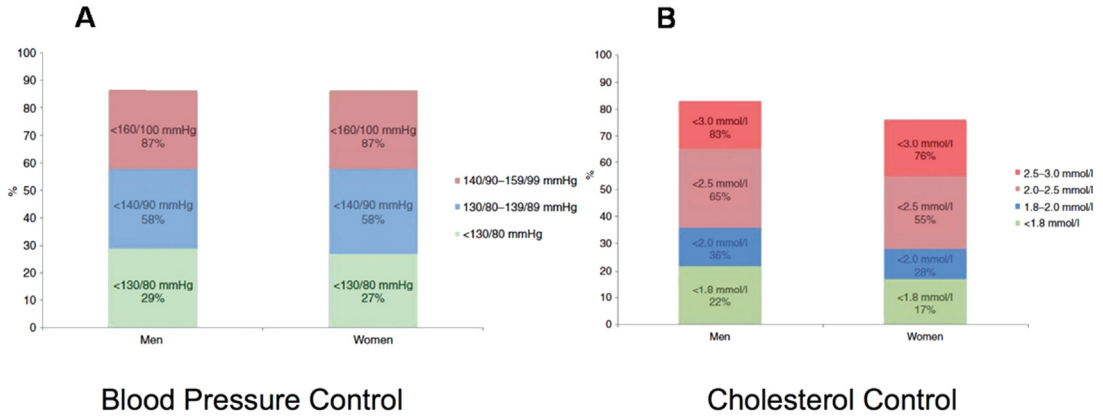

Figure 1 A. Proportions (%) at BP target (<130/80 mmHg, <140/90 mmHg, <160/100 mmHg) in patients on BP lowering medication. B. Proportions (%) at low-density lipoprotein cholesterol target (<1.8 mmol/l, <2.0 mmol/l, <2.5 mmol/l, <3.0 mmol/l) in patients on lipid lowering medication. Modified from: Gyberg V et al. Eur J Prev Cardiol 2015;22(6):753–61.

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