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Editorial

Polypill revisited – Unity in diversity

Almost two decades have passed since a cardiovascular polypill was proposed. The rationale for this initiative was the fact that cardiovascular diseases (CVD) kill more than 1/3 of individuals which implies a population-based approach. Moreover, as only less than 20% of future events comes from patients with CVD, the role of primary prevention is essential. Also, it was clearly proven that lifestyle measures alone are not sufficient to prevent CVD. From the 75% estimated efficacy of multidrug approach in preventing CVD, the real effectiveness is only 21% [1] and the lack of adherence is responsible for 50% of this failure. In 2003 Wald and Law [2] postulated that a polypill containing 6 agents (3 antihypertensive drugs, a statin, folic acid and aspirin) would reduce the incidence of CVD by 80% in individuals older than 55 years. However, this concept was rejected by the scientific community as being unprovable and unrealistic. Nevertheless, substantial evidence has accumulated in the last years reinforcing this concept and its applicability, although with slight modification compared previous concepts. In the second Polycap study [3], taking into account the possible cumulative benefit of statins, ACE inhibitors, beta-blockers and aspirin, a polypill containing ramipril, atenolol, thiazide diuretic, simvastatin and aspirin (in two different dosages) plus potassium supplement administered to 518 individuals with previous CVD or diabetes, significantly decreased blood pressure and cholesterol with a low discontinuation rate. In the UMPIRE study [4] two different types of polypill were studied in patients with established CVD (containing aspirin, a statin, an ACE inhibitor and a beta-blocker or a thiazide diuretic), depending on presence of comorbidities. The study was able to detect a small but statistically significant improvement of blood pressure (BP) and control of cholesterol (Chol) levels, with an improved adherence at 15 months, but no significant decline in CV events. Similar improvement in adherence with two polypill strategies was noticed by IMPACT study [5]. In the very interesting FOCUS project [6] a polypill containing low-dose aspirin (100 mg), ramipril in different dosages and simvastatin (40 mg), was tested in post-myocardial infarction patients and compared with the 3 drugs given separately. The study demonstrated increased adherence for fixed dosage combination (FDC) as compared with individually administrated drugs, with no differences regarding BP, Chol level, adverse effects or death.

One large scale study realized in Iran [7] and another study done in US [8] in primary prevention confirmed the better adherence and the better control of BP and LDL Chol levels with the polypill strategy and the first one demonstrated also a decrease in atherosclerotic CV disease (ASCVD) in the polypill group, as compared with usual care comparison group. The ongoing studies TIPS 3 – The International Polycap study 3 (NCT01646437) and SECURE (NCT02596126) aim to investigate the effect of polypill strategy on ASCVD development.

Despite these positive results, a Cochrane systematic review and meta-analysis [9] evaluating polypill strategy for primary and secondary prevention failed to demonstrate any difference in ASCVD events and mortality with the polypill strategy. Moreover, a small increase in adverse effects was noted, likely because of improved adherence to a multidrug regimen in the polypill treated patients. The differences between the meta-analysis and the aforementioned trials could be explained by a limited power for ASCVD, a shorter duration of included trials, and the comparison with usual care only, with no appropriate control groups [10].

A paper published in this Journal [11] evaluated 1193 patients combining primary and secondary prevention in a post-hoc observational and non-comparative prospective registry in Mexico after a polypill treatment with a compound containing aspirin (100 mg), simvastatin (40 mg) and ramipril (5 or 10 mg) for a 12 months period. This study is of potential clinical importance for the studied population, because in Mexico more than a half of population is considered at high risk. In the studied cohort 57.6% of patients had pre-existing CVD. The authors demonstrated a significant decrease in total Chol, LDL Chol, triglycerides and some atherogenic lipid-dependent indices (including remnant cholesterol, Castelli's risk index-I, atherogenic index, atherogenic coefficient, a surrogate of insulin resistance, atherogenic index of plasma, and the lipoprotein combined index). Also, the likelihood that patients attained their corresponding target LDL-Chol and triglyceride levels was almost three-fold and seven-fold higher, respectively, as compared with the prediction from pre-treatment usual care. Of note, the decrease in LDL was smaller than that observed in a previous study of exclusive secondary prevention in a Mexican population [12]. One potential explanation for this difference could reside into the higher LDL Chol values included in the later study. Although conducted as an open-label study with no control group, in a small but representative population, this study supports the validity and the applicability of the polypill concept.

As for all new concepts, the real enemies reside in the dogmatic application of the concept following the "one fits all" approach. Several misconceptions should be addressed before a final conclusion can be correctly drawn from studies and applied in clinical practice [10]. One of these is the assumption that there is only one polypill and that when given to a patient such a drug could not be titrated and no other drug could be added to a background polypill therapy. As already shown, several studies have already included different dosage polypills and additional drugs. Another

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frequent belief is that the main discriminator for polypill indication is the age. Instead, the risk for the ASCVD (including the "vascular age") should be considered as the basis of indication. Some could suspect that a polypill strategy is not able to sustain an optimal care, even if in other circumstances (as in hypertension) FDC strategy has been proven largely beneficial. Finally, sometimes there is also believed that the polypill strategy is applicable only for low income countries or developing countries. This misconception was disproved by positive studies with polypills in high income countries where the gaps and disparities in the health systems still exist.

In conclusion, the polypill is a valuable strategy under continuous development indicated [13] for CVD prevention in patients non-adherent to one or more components of the drug treatment, for patients not at target for blood pressure or LDL-Chol level when non-adherence is suspected, or as a substitution therapy in patients with controlled blood pressure or lipid profile treated with individual drugs. Future studies should further refine the polypill concept by addressing and validating the selection of drugs based on their potency, dosage, expected synergism, along with considering inclusion of additional drugs such as antidiabetic drugs.

Declaration of Competing Interest

There is no conflict of interest linked to this paper.

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