

Polypill Brings Benefits to Patients with Cardiovascular Disease, Both Improving Medication Adherence and Demonstrating the Concept of Chronotherapy [Letter]

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Dear editor

We read with great interest the systematic review conducted by Lopez-Lopez et al,¹ which shows the benefits of the polypill on medication adherence in the primary and secondary prevention of cardiovascular disease (CVD), and a positive impact on reducing major adverse cardiovascular events in secondary prevention. We especially appreciate the methodological quality criteria defined by PRISMA. We found several points worthy of discussion and we would like to share our perspectives in the following paragraphs.

Encouragingly, the timing of oral administration of polypill is basically not in conflict with chronotherapeutic strategies which has aroused the attention of clinicians. We summarized optimal time to administer once-daily oral cardiovascular agents based on randomized clinical trials.^{2,3} The polypill usually include multiple kinds of the following components: aspirin, statins (eg, simvastatin, atorvastatin), renin-angiotensin system (RAS) inhibitors (eg, enalapril, lisinopril, ramipril, valsartan), hydrochlorothiazide and atenolol.¹ What is appropriate administration time of a polypill? Let us evaluate each component. Bedtime dosing is more suitable for aspirin (eg, favourable drop in the ambulatory BP measurements in the high-risk group of CVD patients), statin (eg, more LDL-C reduction, lower high-sensitivity C-reactive protein level), enalapril (eg, a more marked effect on the asleep than awake BP, and less occurrence of drug-induced cough by a switch from morning dosing to night-time dosing), and valsartan (eg, greater therapeutic effect on asleep BP, plus normalization of the circadian BP profile toward a more dipping pattern).²⁻⁶ Although healthcare providers will likely tell patients to take hydrochlorothiazide in the morning because the drug may cause patients to urinate more in the hours following the dose and thus might interfere with sleep, prescribing information for hydrochlorothiazide does not specify dosing time. For atenolol orally once a day, there is no specific requirement on administration time. Additionally, PubMed search identified only one randomized crossover trial investigating whether the efficacy of polypill could exhibit circadian changes. Evening dosing of a polypill containing aspirin, simvastatin, lisinopril and hydrochlorothiazide was more effective in lowering LDL-cholesterol, and achieved similar ambulatory BP levels compared to morning dosing.⁷ Therefore, cardiovascular polypills taken in the evening or at bedtime not only embodies the requirement of chronotherapy strategy, but also plays the advantage that it can promote medication compliance.

There are, of course, several concerns with polypill, including the risk of discontinuing the intact polypill in case of side-effects of any one of the components, inconvenience of dose adjustments if the therapeutic goals are not reached, and inaccessibility of cardiovascular polypill formulation in many countries.

Anyway, Lopez-Lopez et al's study convinces us the benefits of polypill strategy to break down barriers to the control of CVD risk factors, especially in patients who have received individual pills without obvious side effects, and those

without need to receive intensive lipid lowering therapy. We cannot expect polypill strategy to solve every problem, but at least it can offer hope for a better quality of life for many patients with poor adherence. When a patient's treatment goal after polypill is not met, doctors can add other drugs. This is a very promising therapeutic idea.

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Disclosure

The authors report no conflicts of interest in this communication.

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