


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

Ling-Ling Zhu¹, Quan Zhou² 

¹Geriatric VIP Ward, Division of Nursing, The Second Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou, Zhejiang Province, 310009, People's Republic of China; ²Department of Pharmacy, The Second Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou, Zhejiang Province, 310009, People's Republic of China

Correspondence: Quan Zhou, Department of Pharmacy, The 2nd Affiliated Hospital, School of Medicine, Zhejiang University, Zhejiang, 310009, People's Republic of China, Tel +86-571-8778-4615, Email zhouquan142602@zju.edu.cn

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.

Acknowledgment

This study was supported by the Department of Education of Zhejiang Province (grant number: Y202249568).

Disclosure

The authors report no conflicts of interest in this communication.

References

1. Lopez-Lopez JP, Gonzalez AM, Lanza P, Lopez-Jaramillo P. Benefits of the polypill on medication adherence in the primary and secondary prevention of cardiovascular disease: a systematic review. *Vasc Health Risk Manag*. 2023;19:605–615. doi:10.2147/VHRM.S421024
2. Shu-yi Z, Ling-ling Z, Zhou Q. Optimal time to administer once-daily oral cardiovascular agents: evidence based on randomized clinical trials in the last ten years. *J Geriatr Med Gerontol*. 2018;4:57. doi:10.23937/2469-5858/1510057
3. Zhu LL, Zhou Q, Yan XF, Zeng S. Optimal time to take once-daily oral medications in clinical practice. *Int J Clin Pract*. 2008;62:1560–1571. doi:10.1111/j.1742-1241.2008.01871.x
4. Krasinska B, Paluszkiwicz L, Miciak-lawicka E, et al. The impact of acetylsalicylic acid dosed at bedtime on circadian rhythms of blood pressure in the high-risk group of cardiovascular patients—a randomized, controlled trial. *Eur J Clin Pharmacol*. 2021;77:35–43. doi:10.1007/s00228-020-02997-8
5. Sunaga K, Fujimura A, Shiga T, Ebihara A. Chronopharmacology of enalapril in hypertensive patients. *Eur J Clin Pharmacol*. 1995;48:441–445. doi:10.1007/BF00194332
6. Hermida RC, Ayala DE, Fernández JR, Portaluppi F, Fabbian F, Smolensky MH. Circadian rhythms in blood pressure regulation and optimization of hypertension treatment with ACE inhibitor and ARB medications. *Am J Hypertens*. 2011;24:383–391. doi:10.1038/ajh.2010.217
7. Lafeber M, Grobbee DE, Schrover IM, et al. Comparison of a morning polypill, evening polypill and individual pills on LDL-cholesterol, ambulatory blood pressure and adherence in high-risk patients; a randomized crossover trial. *Int J Cardiol*. 2015;181:193–199. doi:10.1016/j.ijcard.2014.11.176

Dove Medical Press encourages responsible, free and frank academic debate. The content of the Vascular Health and Risk Management 'letters to the editor' section does not necessarily represent the views of Dove Medical Press, its officers, agents, employees, related entities or the Vascular Health and Risk Management editors. While all reasonable steps have been taken to confirm the content of each letter, Dove Medical Press accepts no liability in respect of the content of any letter, nor is it responsible for the content and accuracy of any letter to the editor.

Vascular Health and Risk Management

Dovepress

Publish your work in this journal

Vascular Health and Risk Management is an international, peer-reviewed journal of therapeutics and risk management, focusing on concise rapid reporting of clinical studies on the processes involved in the maintenance of vascular health; the monitoring, prevention and treatment of vascular disease and its sequelae; and the involvement of metabolic disorders, particularly diabetes. This journal is indexed on PubMed Central and MedLine. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <https://www.dovepress.com/vascular-health-and-risk-management-journal>

<https://doi.org/10.2147/VHRM.S440353>