"Polypill": Pros and Cons

Patricia Olsen

Speaking at a symposium held during the 2004 European Society of Cardiology Congress, Peter Sleight, MD, University of Oxford (Oxford, UK), declared that he is "sympathetic" to the polypill idea originally proposed by Wald and Law in a paper published in the *British Medical Journal* in 2003.[1,2] According to that paper, the polypill -- a single daily pill containing 6 drugs and vitamins to treat 4 cardiovascular risk factors -- could be used to reduce ischemic heart disease events and stroke by more than 80%. However, Prof. Sleight said that he favored some modifications to the components of the proposed polypill, which included low-dose aspirin and folic acid combined with half-doses of a thiazide diuretic, a beta blocker, an angiotensin-converting enzyme (ACE) inhibitor, and a statin. The proposed polypill was intended for high-risk patients over the age of 55.

Prof. Sleight, who is the Deputy Chairman of the Heart Protection Study Steering Committee, reminded delegates of the importance of identifying and treating known risk factors for cardiovascular disease (CVD). He referenced a retrospective analysis, conducted at Oxford University, that followed a large number of patients for approximately 14 years. Researchers found that high blood pressure (BP) carries a greater burden of risk for both coronary artery disease (CAD) and stroke than previously appreciated. Specifically, the researchers found that the vascular event rate for each decade of age was approximately half that among participants whose BP was 20 mm Hg lower at the start of each decade compared with participants who had higher BP levels at baseline.

In the INTERHEART study -- also presented at the ESC Congress 2004 and recently published in *The Lancet*[3] -- lipids plus smoking emerged as the most important population-attributable risk factors for myocardial infarction (MI), predicting two thirds of the global risk. Relevant risk factors in the INTERHEART study were apolipoprotein B/apolipoprotein A, current smoking, diabetes, hypertension, abdominal obesity, psychosocial issues, daily consumption of fruits and vegetables, exercise, and alcohol intake. According to Prof. Sleight, in the 52 countries that participated in the INTERHEART study, "risk factors operated at the same level...and nine risk factors accounted for 90% of the risk of coronary risk disease. So if you have a high risk population, a polypill makes sense." Recent data from Europe suggest that approximately 70% of patients are discharged on 3 or 4 drugs following an ST segment elevation MI (STEMI), "which is terrific," he said, "and which makes a good advertisement for a STEMI polypill."

He went on to note that the more drugs that high-risk patients receive for secondary prevention, the better the outcome. As an example of this, he cited a recent German study in which STEMI patients who received combination therapy consisting of aspirin, a beta-blocker, an ACE inhibitor, and a statin had a significantly better prognosis at 1 year than those who received fewer drugs.

"This is a simple, powerful message," said Prof. Sleight, "and we should be giving patients everything [since] each drug has different [cardioprotective] mechanisms." He suggested that one of the most compelling arguments in favor of a polypill is the likelihood of improving adherence both in patients "who like to take one rather than four pills, and from physicians...who prefer to write one prescription rather than four."
Safety may also be improved by the polypill, provided that it is composed of proven drugs at proven doses. Nevertheless, real challenges remain before any CVD-protective polypill can be launched, not the least of which is whether patients will be able to swallow what will likely be a very large pill.

Prof. Sleight pointed out that Industry has made it clear that there are technical difficulties to overcome in combining a variety of different drugs together; the resulting tablet might not be exactly what one would always expect. Pharmacokinetic and pharmacodynamic studies of any combination pill would clearly have to be done, and dosing as well as scheduling issues would have to be considered in order to work out any unforeseen problems.

The polypill would also be costly to develop, predicted Prof. Sleight. Prof. Sleight also alluded to some other limitations, as well as the importance of addressing specific -- as opposed to all -- morbidities. "I am sympathetic to the concept of a polypill but I think six components is over-ambitious and I think we would [do] better to concentrate on polypills for indications which are common and important, like hypertension, post-MI, diabetes [and] heart failure," he concluded.

**Improving Adherence**

During the same symposium, Xavier Girerd, MD, Hôpital Pitié Salpêtrière (Paris, France), spoke about patient compliance.[4] He cited 1 study in which over 22% of one group of more than 19,000 hypertensive patients had stopped taking the original antihypertensive drug prescribed at 1 year, while more than 31% of patients had stopped their medication and then restarted.

In their own adherence evaluation test, Prof. Girerd and colleagues found that only 39% of a group of 484 hypertensive patients had what was judged to be "good" adherence; 53% showed signs of minor nonadherence, while 8% of the group had evidence of major nonadherence. "Complex treatment regimens clearly affect adherence, while monotherapy with simple dosing schedules and less frequent dosing help adherence," he noted.

Nevertheless, Prof. Girerd felt that the number of pills a patient must take is only part of the problem, and physicians need first and foremost to explain to patients why it is important to adhere to the prescribed regimen.

"A take-home strategy for improving adherence is to keep the regimen as simple as possible and to give clear instructions and ensure patients understand the function [of the medication]," Prof. Girerd advised. "You also need to discuss any problems the patient might be having with the regimen at each visit, and you should probably congratulate the patient[s] for what they have been able to accomplish even if it isn't perfect."

**Alternative "Polypill"**

Lars Rydén, MD, Karolinska University Hospital (Solna, Sweden), did not argue with the need to reduce vascular events including MI and stroke in high-risk patients.[5] But he cautioned that the efficacy and safety -- particularly the safety -- of any polypill developed for CVD protection must be thoroughly tested. Prof. Rydén also pointed out that the original proponents of the polypill did not take into account modifiable risk factors including smoking and physical inactivity when calculating how large an impact a polypill may have on CVD risk. Both of these risk factors contribute to a substantial proportion of CAD morbidity and mortality and they could be reversed if encouragement is provided by public health officials as well as individual physicians, he believes.

"Exercise is a polypill in your feet," Prof. Rydén said, pointing out that it is well established that regular physical activity corrects many of the underlying abnormalities that contribute to CVD risk. By walking a minimum of 3 km a week and avoiding weight gain, Prof. Rydén said, patients can do much to reduce their risk of vascular events.

**References**

1. Sleight P. A strategy to reduce cardiovascular disease by more than 80%. Program and abstracts from the European Society of Cardiology Congress 2004; August 28 - September 1, 2004; Munich, Germany.
2. Wald NJ, Law MR. A strategy to reduce cardiovascular disease by more than 80%. BMJ. 2003;326:1419.


4. Girerd X. The issue of patient compliance: Is the number of pill the problem? Program and abstracts from the European Society of Cardiology Congress 2004; August 28 - September 1, 2004; Munich, Germany.

5. Rydén L. Is there a real need for a fixed combination therapy? Program and abstracts from the European Society of Cardiology Congress 2004; August 28 - September 1, 2004; Munich, Germany.

Copyright © 2004 Medscape.