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Optimizing treatment benefit: individualized therapy or the polypill?

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In their News & Views commentary, Webster and Rodgers address the controversy surrounding the use of the polypill in patients with cardiovascular disease (Webster, R. & Rodgers, A. Prevention: Coronary artery calcium and polypill therapy. *Nat. Rev. Cardiol.* **11**, 7–8 [2014]).[1] On the basis of data from the Multi-Ethnic Study of Atherosclerosis (MESA),[2] they propose that patients most likely to benefit from prophylactic therapy can be identified using the coronary artery calcium (CAC) score. In MESA, patients with a CAC score of 0 had a very low event rate, and the authors of the MESA report suggest that treatment might be unnecessary in these individuals, thereby reducing the number of individuals considered for polypill therapy.[1,2]

Tailored therapy with preventive cardiovascular drugs has been extensively studied. Since the advent of the polypill concept, attitudes to this approach have diverged widely. Some physicians favour the use of a single polypill, which could increase patient compliance by simplifying drug intake. Whereas others are against the use of the polypill, because the ability to control the potential adverse effects of the individual drug components can be lost. Webster and Rodgers should have addressed this issue in more detail in their commentary,[1] especially given that the effect of each drug, a patient's characteristics, and their response to the drug are unique. The variation in drug response between individuals is well known, in terms of both pharmacokinetic and pharmacodynamic effects. This point is illustrated by our analysis of angiotensin-converting-enzyme (ACE) inhibitors as an example of tailoring therapy to those patients most likely to benefit rather than 'group therapy' with a polypill.[3–5]

In our study, we investigated 8,907 patients with stable coronary artery disease participating in the randomized, placebo-controlled EUROPA trial.[3–5] We studied the genes involved in the direct pharmacodynamic pathway of ACE inhibitors, the renin–angiotensin system (12 candidate genes in total, using 52 haplotype tagging single nucleotide polymorphisms covering common genetic variations within these genes).[3,4] The primary end point was the incidence of cardiovascular mortality and nonfatal myocardial infarction in patients treated with perindopril or placebo (mean follow-up 4.2 years).[3–5] We found three genetic variants in the type I angiotensin II receptor and bradykinin type I receptor (also known as the B1 bradykinin receptor) genes that substantially modified the treatment benefit of perindopril, after adjustment for confounders and correction for multiple testing. A clear heterogeneity in treatment benefit of ACE inhibitor therapy with perindopril was observed in these patients, revealing nonresponders and responders (a well-known concept in cardiovascular pharmacotherapy).[3–5] This finding was not detected in previous studies on the consistency of treatment benefit assessed using clinical characteristics alone.[6] By using a pharmacogenetic risk profile, we could identify patients with a more-pronounced treatment benefit relative to the overall trial results (73.5% of the patients) and those with an absence of treatment benefit (26.5% of the patients).[3–5] Ineffective treatment for 4 years could have been prevented in these patients.

To our knowledge, this study was the first in which genetic determinants of treatment benefit of ACE inhibitor therapy were identified. The pharmacogenetic risk score that we developed could be used to optimally treat patients, and as a way to target ACE inhibitor therapy to those patients most likely to benefit. Similar heterogeneity in efficacy is likely to exist for other preventive drugs in cardiovascular medicine. In my opinion, detecting heterogeneity in treatment benefit mentioned in clinical trials is contrary to any concept of the polypill.

Bearing in mind the individuality in drug effect and patient response, I advise others to remain critical to accepting the use of polypill therapy, which is based on homogeneity between patients that does not exist. Patients should, therefore, be treated individually. Tailored use of single drugs is the next step forward rather than the use of polypills as a general group therapy.

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Competing interests
The author declares no competing interests.

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