WHAT IS THE FUTURE OF STROKE PREVENTION: POLYPILL OR INDIVIDUALIZED RISK FACTOR MODIFICATION?

INDIVIDUALIZED RISK FACTOR MODIFICATION

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The concept of the polypill is superficially attractive, but a single pill for all patients is not only not achieveable; it is fundamentally inappropriate[1]: the best treatment for any patient is the right medication, in the right dose, by the right regimen, and this must be individualized. A polypill containing, for example, ASA, folic acid, simvastatin, metoprolol and enalapril, will have the following problems for at least some of the patients:

ASA: patients with a history of peptic ulceration or allergy to ASA cannot take it

Metoprolol: contraindicated in asthma (~7% of people), and with a huge variation in drug metabolism, so the appropriate dose cannot be achieved for most patients. This drug is metabolized by CYP2D6; some patients are superfast metabolizers, others slow metabolizers, so the blood levels achieved with a given dose range 150-fold!

Folic acid: aggravates renal function in patients with diabetic nephropathy, may increase risk of bowel cancer, not needed in jurisdictions that have folate fortification of the grain supply. Unrecognized vitamin B12 deficiency is a much more important problem than folate deficiency.

Simvastatin: will cause myopathy in some patients and myalgias in many; subject to huge drug interactions, with 15-fold increase in blood levels and the risk of rhabdomyolysis and renal failure, with drugs that inhibit CYP3A4 (such as erythromycin, itraconazole, ketoconazole), and with grapefruit or its juice.

Enalapril: needs to be taken twice a day, will cause a dry cough in 8% of patients and angioedema in some; more importantly it is not appropriate for all patients with hypertension. Especially for patients with African ancestors, it is important to individualize the treatment of hypertension, according to the physiology of the underlying problem that is causing the hypertension. Once rare causes such as pheochromocytoma, licorice and adult coarctation of the aorta are excluded, most cases of hypertension can have their therapy appropriately tailored by measuring plasma renin and aldosterone[2] (preferably in a stimulated condition, for example after diuretic administration). If the renin is low and the aldosterone is high, the problem is primary aldosteronism, and the primary treatment is aldosterone antagonists (Spironolactone for women, eplerenone for men, who get gynecomastia with Spironolactone). In jurisdictions where eplerenone is not available, high-dose amiloride can be used to control the blood pressure, but it will not block the cardiac and vascular problems from inflammation due to aldosterone. This condition is usually due to bilateral adrenocortical hyperplasia, so adrenalectomy should be reserved for patients who cannot be controlled medically If the renin is low and the aldosterone is low, the problem is fluid retention due to a mutation of the sodium channels in the renal tubule (Liddle's syndrome and variants), and the specific treatment is amiloride. Liddle's and variants account for 5-6% of hypertension in patients with African ancestors (20% of indigenous Koi San people in South Africa). If the renin is high and the aldosterone is high, the problem is secondary hyperaldosteronism due to a renal or renovascular cause. Some patients may need relief of obstruction, or revascularization, but most should be treated with angiotensin receptor antagonists or aliskiren. ACE inhibitors are less effective because of non-ACE pathways for formation of angiotensin II. The table below summarizes this algorithm.

	Primary aldosteronism	Liddle's and variants	Renal/renovascular
Renin	Low	Low	High
Aldosterone	High	Low	High
Primary treatment	Spironolactone or eplerenone (Amiloride) Rarely surgical	Amiloride	ARB or aliskiren Rarely surgical

References:

Spence,J.D. Polypill:for Polyanna. *Intl J Stroke* **3**, 92-97 (2008).

Spence,J.D. Physiologic tailoring of treatment in resistant hypertension. *Current Cardiology Reviews* **6**, 213-219 (2010).