

The Polypill: A Cocktail of Uncertainty or a Stroke of Genius?

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Throughout humanity's history, finding effective treatments for disease has been the primary difficulty facing physicians. Now, in the 21st century, with a plethora of therapies on the market and a pharmaceutical revolution in full swing, it seems that the greatest hurdles facing physicians are: 1) making a correct diagnosis of patients' symptoms and 2) selecting suitable treatments.

As such, the processes involved can be rather time-consuming and inefficient, especially when diseases are multifaceted and have risk factors endemic in society. Moreover, the diagnostic process is further complicated in cases where people display only a slight increase in individual risk factors but in actuality have an overall increased risk of developing a disease [1]. One such disease is cardiovascular disease (CVD). Responsible for one in every three deaths in the United States [2], it is the leading cause of morbidity and mortality in the Western world [3]. In 2007, CVD cost the United States approximately US\$286 billion (A\$270 billion) [4] in both direct and indirect expenses, with 95 per cent of all heart attack and stroke deaths occurring in people aged 55 and over [5].

While most patients who have CVD are on secondary preventative medication (so termed because it is prescribed *after* diagnosis), a majority of the at-risk population is not on any primary preventative medication, or if so, is on only one type of medication. While monotherapy (single therapy) is effective in some diseases, CVD cannot simply be treated by a single drug because it is actually characterised by a wide variety of abnormalities. These include high blood pressure, unhealthy cholesterol levels and composition, abnormal platelet function, and high serum homocysteine levels. Therefore, an across-the-board approach to treat these components individually yet simultaneously in an all-embodying drug termed the "polypill" has been proposed. At the moment, a majority of studies on the polypill are aimed at CVD prevention. However, this form of treatment could potentially be extended to other diseases, such as diabetes, in the near future.

While many have acknowledged the polypill's potential benefits [6], a great deal of controversy surrounds its implementation in society, with its supporters envisioning that it be given as a "population medicine". What this means is



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that all people over 55, regardless of their underlying risk factors, take the polypill daily. This notion received considerable backlash, as medicine is widely seen to be grounded upon individualised patient care and not “one size fits all” treatments. It is this dissociative treatment policy, alongside arguments relating to drug efficacy, adherence, potential side effects and cost that make the polypill such a contentious medical issue.

What Is in It?

CVD is multifaceted and patients at risk of developing it often exhibit several signs and biomarkers indicative of the disease. One score used to estimate the 10-year cardiovascular risk of an individual is the Framingham Risk Score [7]. This score takes into account the following factors:

- Age
- Gender
- Total cholesterol
- High-density lipoprotein (HDL) cholesterol
- Smoker/non-smoker
- Systolic blood pressure
- Current blood pressure-lowering medication

While factors such as age and gender are largely unalterable, many other aspects of this score can be improved with medication. This is where the polypill comes into play.

The original polypill outlined by Wald and Law in 2003 [6] contained six drugs to treat four risk factors for developing CVD:

- A statin for low-density lipoprotein (LDL) cholesterol level reduction, as raised LDL is a significant risk factor for CVD [3]
- Three anti-hypertensives to lower blood pressure
 - A beta-blocker
 - An angiotensin-converting enzyme (ACE) inhibitor
 - A thiazide diuretic
- Aspirin to reduce the risk of arterial blood clots (anti-platelet function)
- Folic acid to reduce homocysteine levels in blood

Still, despite all the factors outlined in the Framingham Risk Score, the greatest risk indicator of developing CVD is age [8]. Thus, when Wald and Law outlined their methodology of deciding who was in need of the polypill, age was the deciding factor. Wald later stated that the polypill’s potential in effectively treating the at-risk population would be limited if individuals were required to see a physician periodically for prescriptions [9]:

“By offering the polypill on the basis of age alone, prevention is greatly simplified and the population receiving the polypill are not medicalised, because they do not have to become patients to receive it” [10].

Do We Need It?

Revolutionary as this concept is, it is not immune to controversy, with detractors of the polypill highlighting the potential dangers of medications being available outside

the prescription paradigm. In a study where United States physicians were surveyed on their willingness to administer the polypill, 83.0 per cent responded that “they would ‘definitely’ or ‘probably’ prescribe it for high risk patients” [9]. Yet, an even greater 89.2 per cent were opposed to the idea of doing this without a prescription despite being told it halved the risk of CVD events such as myocardial infarction and stroke [9]. While physicians understand the benefits of the polypill, it seems that they are of the view that there is a greater necessity to monitor these individuals as patients through prescription-based treatment. Whether through a perceived lack of paternalistic control over their patient population or as a result of ingrained prescribing habits, physician’s perceptions may prove to be a significant barrier to the polypill’s introduction.

However, there are strong arguments for administering the polypill as a population medicine rather than through prescriptions. One such argument is the “prevention paradox”. The majority of cases of a disease arise in the low to moderate-risk population while only a minority come from the high-risk population [1,11,12], thus supporting the need for greater primary preventive treatment across the entire population.

In addition, many physicians face problems ensuring that patients comply with specifications outlined with their prescribed medications. The most common problems are patients forgetting to take medication or stopping medication after self-diagnosing a perceived recovery. It is precisely to circumvent these problems that the polypill was designed to reduce the treatment routine to just one single pill, allowing for easy dosage. This is sound reasoning according to Dr Geraldine Moses, an information pharmacist from Mater Health Services:

“It’d be a wonderful idea if all six were in one pill and then the burden of having to juggle taking six tablets a day in your busy routine would be eliminated in one gulp” [13].

While pragmatically sound with regard to treatment adherence, the polypill also displays other intrinsic benefits, including improved tolerance and efficacy. Combined pharmacotherapy can be more effective in achieving desired results than monotherapy. Multiple studies have demonstrated that when a greater number of agents are given at lower doses as opposed to a single agent at standard dosage, the desired result is improved [11]. Wald and Law recently conducted a meta-analysis comparing the reduction in blood pressure after using a monotherapeutic and a polytherapeutic (consisting of two drugs at half-standard dose). The latter was found to be five times more effective in reducing blood pressure [14]. Other clinical trials have further strengthened the evidence for polytherapy, demonstrating that three drugs are more effective than two in reducing blood pressure [15].

The three anti-hypertensives contained in the proposed polypill are each at half the usual effective dose for monotherapy [6]. As a result, these agents are less likely to reach harmful concentrations whereby positive effects are accompanied by unwanted side effects. Yet all these benefits come at a cost: the polypill may be inflexible as a population medicine and have other unwanted side effects.

A Roadblock to Population Medicine: Unwanted Side Effects

Multiple agents working at lower concentrations to yield a greater overall physiological response is a key advantage of the polypill. This factor, along with reduced side effects, makes for a strong argument in favour of the polypill. Yet there are some situations where this situation may not be entirely accurate.

An Achilles heel for those in favour of the polypill is its inflexibility to treat a diverse population. For example, people from both genders have slightly different risk factors; each individual has different states of health and responsiveness to medication. Increasing the number of components in a pill increases the proportion of individuals in the population who may react adversely to any one or more of the component medications.

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For example, some patients can develop a serious condition known as rhabdomyolysis, which involves skeletal muscle breakdown following statin treatment [16]. Beta-blockers have an unwanted secondary effect of increasing the risk of developing diabetes [17], and are not included in the list of first-line treatments for high blood pressure by the National Institute for Clinical Excellence due to this very risk [18]. A common symptom of ACE inhibitors is a persistent dry cough [19], and in some patients has been known to cause renal failure [20]. Finally, even aspirin has not escaped controversy. While aspirin is effective if prescribed following a CVD event (e.g. myocardial infarction or stroke) [21], studies regarding its effects as a primary preventive have not been conclusive [22,23]. The risks involved with aspirin use ranges from gastric and intracranial bleeding [24,25] to allergy-like symptoms (e.g. swelling or headache) as a result of salicylate intolerance found in some people [26].

While the polypill is a cocktail of uncertainty regarding its side effects, this is not the primary reason its development has been relatively languid. Frankly, to many large pharmaceutical companies, an investment in the polypill is seen as risky because it exhibits low profit margins and further studies are needed to prove its potential to save lives [27].

Big Pharma Not So Big on Polypill

Almost a decade since Wald and Law’s landmark papers, only a moderate effort has been made by pharmaceutical companies to manufacture a CVD polypill. One may wonder why the development of such a potentially effective, beneficial, and widely-used population medicine is moving at a snail’s pace. As with so many things, it all comes down to dollars.

Before a pharmaceutical company can produce and distribute a drug on the market, they are first required to conduct a large-scale clinical trial. This trial is usually broken down into several phases, where the safety, tolerability, and efficacy of the drug are tested. The trial must be large enough and encompass sufficiently diverse demographics to ensure consumer safety.

Unfortunately (for the pharmaceutical companies, not consumers), despite being a potential big seller on the market, the polypill is composed of components that are now all off-patent. This dramatically lowers the market price and profit margins. Needless to say, no company is likely to spend millions of dollars trialling a drug that only costs a few cents. It is genuinely unfortunate for the consumer that our health and intellectual property systems make it economically unviable for a polypill to be designed and implemented.

Professor Malcolm Law of the Wolfson Institute of Preventive Medicine in London has stated that the drugs used in manufacturing the polypill are

“off-patent and cost pennies. You might be talking in terms of 50p a day. There’s no way it is going to drain resources. It is not going to make megabucks for anyone, but it’s a public health thing” [27].

However, thanks to a number of companies in India, the polypill dream may well become a reality.

Where Are We Now?

Until recently, little was known clinically about the effectiveness of the polypill for preventative CVD treatment, and instead relied on extrapolating data from meta-analyses. This soon changed with The Indian Polycap Study (TIPS), which laid the foundations for a new pharmaceutical revolution. TIPS was a double-blinded study that measured the reduction in CVD risk [28,29] from taking a polypill developed by Indian firm Cadila Pharmaceuticals [30]. Their results indicated a 60 per cent reduction in CVD risk as a result of daily polypill usage [30]. Other companies in India have also taken the polypill idea on board, including Dr Reddy’s Laboratories and Cipla [31]. Dr Denis Xavier of St John’s Medical College, Bangalore, India and a co-investigator of the TIPS trial was interviewed regarding the target price and market for the polypill:

“I am unable to comment on pricing at this point. It is the company’s call here, and to the best of my knowledge they have not yet priced it. What I do know for sure is that ... it will be priced in such a way that the majority of the lower-middle class in India would be able to afford it long term, and the same will apply to other developing countries, too. In developed countries, it will be priced higher” [30].

While good medical care is preferable to polypill implementation, it holds great promise for lesser-developed regions that require better CVD treatment. Although many physicians are opposed to the polypill being given without a prescription, there may be parts of the world where the need outweighs the risk. Physician surveys conducted in the

United States to gauge reactions to polypill implementation demonstrated greater support originating from physicians in the Southern parts of the United States, where CVD is a relatively greater burden compared to the rest of the country [9,32].

This is also the case in Australia where certain populations, especially Aboriginals and Torres Strait Islanders, are disproportionately affected by CVD [33]. With various other groups, they are now undergoing a clinical trial titled the “Kanyini GAP Study” that aims to address whether patients prescribed polypill treatment have greater adherence and improved clinical outcomes compared to those given conventional cardiovascular treatment [34].

Where to?

Easy, convenient and inexpensive pharmacoprevention is the underlying message of the polypill: treat individuals at risk before they become patients. Even though the population-based approach to CVD primary prevention proposed by Wald and Law is complex and has its shortcomings, the World Health Organisation has described such approaches as the most effective method of attaining genuine health reform [35], with numerous examples to date having produced profound effects. Population-based medicine can be comprehensively effective, be it immunisation in children and adults [36], public health awareness with campaigns on exercise and good diet, food regulation with salt-reduced and iodised-salt foods, and even fluoride in public drinking water to help reduce tooth decay [37]. Recent studies have shown that taking the polypill daily would equate to spending £400

(US\$650, A\$600) a year with an average benefit of gaining approximately 11 years of life [5,6], a price many would be willing to pay if the polypill were available.

While the polypill may seem to be a “magic bullet” for CVD and other devastating diseases responsible for high morbidity and mortality, it strikes at the heart of the issue that medicine should be tailored to individual patients’ needs. The polypill is aimed at reducing disease in a large proportion of the population, and opposes the traditional approach to preventative medicine of targeting the upper percentile of risk. With the polypill being given a population role, individual risk factors such as blood pressure and cholesterol levels need not be measured in order to obtain a prescription. Thus, the tailored approach is lost. While this methodology may have drastic repercussions in the medical world, could this indeed be the way of the future?

While there are numerous obstacles to the implementation of the polypill in modern medicine, be it potential side effects, an unsupervised treatment regime, or a lack of development incentive, the polypill has been demonstrated to be a cheap, practical, and effective prevention strategy for reducing the risk of CVD. While further studies into the polypill’s effectiveness are needed, it may merely be a matter of time before its benefits are recognised and the polypill approach prevails as the norm for preventative medicine. ■

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References

- Rose G. Sick individuals and sick populations. *Int J Epidemiol.* 1985;14(1):32-8.
- Lloyd-Jones D et al. Heart disease and stroke statistics—2010 update: a report from the American Heart Association. *Circulation.* 2010;121(7):e46-e125.
- Gluckman TJ et al. A practical and evidence-based approach to cardiovascular disease risk reduction. *Arch Intern Med.* 2004;164(14):1490-500.
- Roger VL et al. Heart disease and stroke statistics—2011 update: a report from the American Heart Association. *Circulation.* 2011;123(4):e18-e209.
- Wald DS, Wald NJ. The polypill in the primary prevention of cardiovascular disease. *Fundam Clin Pharmacol.* 2010;24(1):29-35.
- Wald NJ, Law MR. A strategy to reduce cardiovascular disease by more than 80%. *BMJ.* 2003;326(7404):1419-23.
- Lloyd-Jones DM et al. Framingham risk score and prediction of lifetime risk for coronary heart disease. *Am J Cardiol.* 2004;94(1):20-4.
- Lewington S et al. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet.* 2002;360(9349):1903-13.
- Viera AJ et al. Acceptance of a Polypill approach to prevent cardiovascular disease among a sample of U.S. physicians. *Prev Med.* 2011;52(1):10-5.
- Trial begins of polypill that could prevent heart attacks and strokes. [Internet]. *The Guardian Reader*; [updated 2011 Jan 4]. Available from: <http://www.guardian.co.uk/society/2011/jan/04/heart-attack-stroke-polypill-trial-begins>.
- Hingorani AD, Psaty BM Primary prevention of cardiovascular disease: time to get more or less personal? *JAMA.* 2009;302(19):2144-5.
- Wald NJ, Hackshaw AK, Frost CD. When can a risk factor be used as a worthwhile screening test? *BMJ.* 1999;319(7224):1562-5.
- Caulfield J. Polypills: Pie in the sky or brave new world? *Australian Pharmacist*; [updated 2007]. Available from: <http://www.psa.org.au/site.php?id=1506>.
- Wald DS et al. Combination therapy versus monotherapy in reducing blood pressure: meta-analysis on 11,000 participants from 42 trials. *Am J Med.* 2009;122(3):290-300.
- Calhoun DA et al. Triple antihypertensive therapy with amlodipine, valsartan, and hydrochlorothiazide: a randomized clinical trial. *Hypertension.* 2009;54(1):32-9.
- Golomb BA, Evans MA. Statin adverse effects: a review of the literature and evidence for a mitochondrial mechanism. *Am J Cardiovasc Drugs.* 2008;8(6):373-418.
- Elliott WJ, Meyer PM. Incident diabetes in clinical trials of antihypertensive drugs: a network meta-analysis. *Lancet.* 2007;369(9557):201-7.
- Mayor S. NICE removes beta blockers as first line treatment for hypertension. *BMJ.* 2006;333(7557):8.
- Robinson TD, Celermaier DS, Bye PT. How to stop ACE-inhibitor-induced cough. *Lancet.* 1997;350(9070):3-4.
- Woo KT et al. ACE inhibitor use and the long-term risk of renal failure in diabetics. *Kidney Int.* 2006;70(7):1376-8.
- Lievre M, Cucherat M. Aspirin in the secondary prevention of cardiovascular disease: an update of the APTC meta-analysis. *Fundam Clin Pharmacol.* 2010;24(3):385-91.
- Garg MK. Weighing the benefits and risks of aspirin for primary prevention of vascular disease. *J Assoc Physicians India.* 2010;58:331.
- Aspirin and primary cardiovascular prevention. Uncertain balance between benefits and risks. *Prescrire Int.* 2010;19(110):258-61.
- Derry S, Loke YK. Risk of gastrointestinal haemorrhage with long term use of aspirin: meta-analysis. *BMJ.* 2000;321(7270):1183-7.
- Delaney JA et al. Drug drug interactions between antithrombotic medications and the risk of gastrointestinal bleeding. *CMAJ.* 2007;177(4):347-51.
- Raithel M et al. Significance of salicylate intolerance in diseases of the lower gastrointestinal tract. *J Physiol Pharmacol.* 2005;56(5):89-102.
- Lister S. Five-in-one Polycap pill could slash heart problems. *The Times*; [updated 2009 Mar 31]. Available from: http://www.timesonline.co.uk/tol/life_and_style/health/article6004996.ece.
- Yusuf S et al. Effects of a polypill (Polycap) on risk factors in middle-aged individuals without cardiovascular disease (TIPS): a phase II, double-blind, randomised trial. *Lancet.* 2009;373(9672):1341-51.
- Wald NJ, Law MR. The Indian Polycap Study (TIPS). *Lancet.* 2009;374(9692):781-2.
- Nainggolan L. First polypill data show promise; larger trials next step. *Heartwire*; [updated 2009 Mar 30]. Available from: <http://www.theheart.org/article/953881.do>.
- Wald NJ, Wald DS. The polypill concept. *Heart.* 2010;96(1):1-4.
- Lanska DJ, Kuller LH. The geography of stroke mortality in the United States and the concept of a stroke belt. *Stroke.* 1995;26(7):1145-9.
- Brown A. The Context of Indigenous Cardiovascular Disease. *Central Australian Rural Practitioners Association*; [updated 2004 Mar]. Available from: http://www.carpa.org.au/documents/nl36_indig_cardio.pdf.
- Scientific Facts on Drug-resistant Tuberculosis. *GreenFacts*; [updated 2008 Dec 18]. Available from: <http://www.greenfacts.org/en/tuberculosis/l-2/1-mdr-tb-xdr.htm>.
- Secretariat. WHO medicines strategy. Revised procedure for updating WHO’s Model List of Essential Drugs. *World Health Organization*; [updated 2001 Dec]. Available from: http://apps.who.int/gb/archive/pdf_files/EB109/eeb1098.pdf.
- Nichol KL et al. The effectiveness of vaccination against influenza in healthy, working adults. *N Engl J Med.* 1995;333(14):889-93.
- McGrady MG, Ellwood RP, Pretty IA. Water fluoridation as a public health measure. *Dent Update.* 2010;37(10):658-64.
- Available at: <http://www.flickr.com/photos/emagineart/4741451457/>