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BCS Editorial

The power of one versus many

Sally Elshafie, MBChB, MRCP, PGCert

ST6 Cardiology Registrar
University Hospitals of Derby and Burton, Derby, United Kingdom

Editor Ahmed Adlan
Deputy Editor Evelyn Brown

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Take Home Messages

- The polypill strategy may help reduce cardiovascular events by improving adherence to medications.
- In selected populations, polypills can improve cardiovascular outcomes in primary prevention settings.
- The SECURE trial, the first randomised control trial assessing cardiovascular outcomes with polypill use as secondary prevention, showed that polypills reduce major acute cardiovascular events and improve medications adherence in secondary prevention setting. However, all-cause mortality and adverse events in the polypill and control arms of the trial were similar.
- Further randomized controlled trials are needed to confirm the findings in this study.
- The components of the polypill used and the targeted population are key factors to the success of Polypills in improving cardiovascular outcomes.

Introduction

It has been proposed that fixed-dose combination (FDC) polypills could reduce major acute cardiovascular events (MACE) and improve medications adherence in secondary prevention of cardiovascular disease (CVD). This editorial will address this and look at the existing evidence in the literature with a focused review on the SECURE trial.

FDC polypill

The polypill strategy was an innovative concept proposed nearly 20 years ago by Wald and Law which involved combining multiple medications in one tablet (1, 2) in the hope of reducing medications non-adherence and therefore improving risk factor control and CVD prevention. Polypills are mainly used in cardiovascular medicine, but they are also commonly used in diabetes (3) and the treatment of infectious disease (e.g. anti-tuberculous, anti-retroviral therapy).

Medications non-adherence is responsible for 194,000 deaths per year in Europe (4), and some of the contributing factors to this include polypharmacy and treatment complexity (5). Several clinical trials have demonstrated improved adherence by using polypills (6-11). **Table 1** demonstrate the benefits and limitations of using polypills.

About the author

Sally Elshafie is currently an ST6 Cardiology registrar in East Midlands Deanery. She is training in devices and heart failure with a specialist interest in inherited cardiac conditions and medical education.

Table 1. Benefits and limitations of using polypills.	
Benefits	**Limitations**
• Reduces polypharmacy since less medications need dispensing. • Increases adherence as a smaller number of tablets need to be taken. • Simpler to prescribe one tablet as a fixed combination medication. • Improves risk factor control due to improved adherence. • Reduces health economic burden.	• Problems with adverse effects and tolerability, i.e. unable to identify causative component of the polypill. • Dose adjustment and titration is difficult. • The size of the polypill may be too big to swallow. • Physician acceptability may be a challenge and education will be required.

FDC polypill in primary prevention

The polypills used in primary prevention CVD trials are summarised in **Table 2** (8, 10-13). Prior studies have demonstrated significant reductions in CVD events (10, 11), blood pressure (BP) and LDL cholesterol levels (8) when compared to standard treatment. In one study there was no difference in CV events compared with placebo (10-13) (**Figure 1**) possibly due to the trial not mandating a specific BP level for entry into the trial. They discovered patients with a systolic BP < 140 mmHg derived no benefit from CV events reduction which was a large proportion of the study population (average systolic BP = 138 mmHg).

Most of the study population amongst the trials were non-white which makes extrapolating data to the United Kingdom (UK) practice challenging with an 80% white population. TIPS-3 participants were mostly Indian, HOPE-3 were 80% non-white, SCCS were 96% black and PolyIran were 100% Persian.

Table 2. FDC polypill combinations in primary prevention trials				
Trial	**Design**	**Patients**	**Formulation of polypill**	**Primary outcome**
HOPE -3 2016 (12, 13)	Randomised controlled trial 2x2 1. Rosuvastatin 10mg vs. Placebo 2. Polypill vs. Placebo 3. Polypill + Rosuvastatin 10mg vs. Placebo	12,705	Candesartan 16mg Hydrochlorothiazide 12.5mg	Composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, revascularisation, heart failure, and resuscitated cardiac arrest. 1. 3.7% vs. 4.8% (HR 0.76; 95% CI 0.64-0.91) 2. 4.1% vs.4.4% (HR 0.93; 95% CI 0.79-1.10) 3. 3.6% vs. 5.5% (HR 0.71; 95% CI 0.56-0.90)
SCCS 2019 (8)	Randomized controlled trial Polypill vs. Usual care (routine care + pre-existing medications)	303	Atorvastatin 10mg Amlodipine 2.5mg Losartan 25mg Hydrochlorothiazide 12.5mg	Change from baseline in SBP and LDL-C. Mean SBP: decrease by 9 mmHg vs 2 mmHg (p=0.003) Mean LDL-C: decrease by 15 mg/dL vs. 4 mg/dL (p<0.001)
PolyIran 2019 (10)	Pragmatic cluster randomised trial Polypill vs. Minimal Care (Lifestyle education)	6838	Hydrochlorothiazide 25mg Aspirin 81 mg Atorvastatin 20mg Enalapril 5mg or Valsartan 40mg	Major cardiovascular events 5.9% vs. 8.8% (adjusted HR 0.66, 95% CI 0.55-0.80) Mortality 5.9% vs. 6.5% (p=0.43)
TIPS-3 2021 (11)	Randomised controlled trial 1:1 then 2x2 1.Polypill vs. Placebo 2.Aspirin vs. Placebo 3.Polypill + Aspirin vs. double placebo	5713	Atenolol 100mg Simvastatin 40mg Hydrochlorothiazide 25mg Ramipril 10mg	Major cardiovascular events plus heart failure, resuscitated cardiac arrest, or arterial revascularisation. 1. 4.4% vs. 5.5% (HR 0.79; 95% CI 0.63-1.00) 2. 4.1% vs. 4.7% (HR 0.86; 95% CI, 0.67-1.10) 3. 4.1% vs. 5.8% (HR 0.69; 95% CI, 0.50-0.97)

CI = confidence interval; HOPE-3 = Heart Outcome Prevention Evaluation-3; HR = hazard ratio; LDL-C = Low-Density Lipoprotein Cholesterol; PolyIran = Effectiveness of polypill for primary and secondary prevention of cardiovascular diseases; SCCS = Southern Community Cohort Study; SBP = systolic blood pressure; TIPS-3 = International Polycap Study

There are notable uncommon practices used in the trials compared with UK practice. Aspirin use for primary prevention was only seen in TIPS-3 and PolyIran trials; in contrast it is commonly used as primary prevention in the UK until recently. Moreover, in the UK anti-hypertensive medications are only prescribed if patients have confirmed hypertension, but in the four trials described, anti-hypertensives were used in all patients regardless of having hypertension.

FDC polypill in secondary prevention

In 2014, the FOCUS project was a randomised controlled trial established to assess the impact of polypill strategy on adherence in post myocardial infarction (MI) patients. The primary end point was a measure of adherence to treatment by using Morisky-Green medication adherence Questionnaire (MAQ) which is a self-reported questionnaire of four questions. Each question is scored 1 to 5 with higher scores indicating higher adherence. The trial showed improved adherence with polypill strategy (5).

More recently, NEPTUNO was a direct observational retrospective study of the real-world impact on outcomes of a polypill on the incidence of MACE for secondary prevention compared with the same components taken separately. Again, polypill strategy showed superiority over the control groups (14).

These studies have led to the development of the SECURE trial which was a randomised controlled trial assessing the efficacy of the same polypill combination used in NEPTUNO (Aspirin, Ramipril, Atorvastatin) on MACE for secondary prevention indications (15) (**Figure 2**) (**Table 3**).

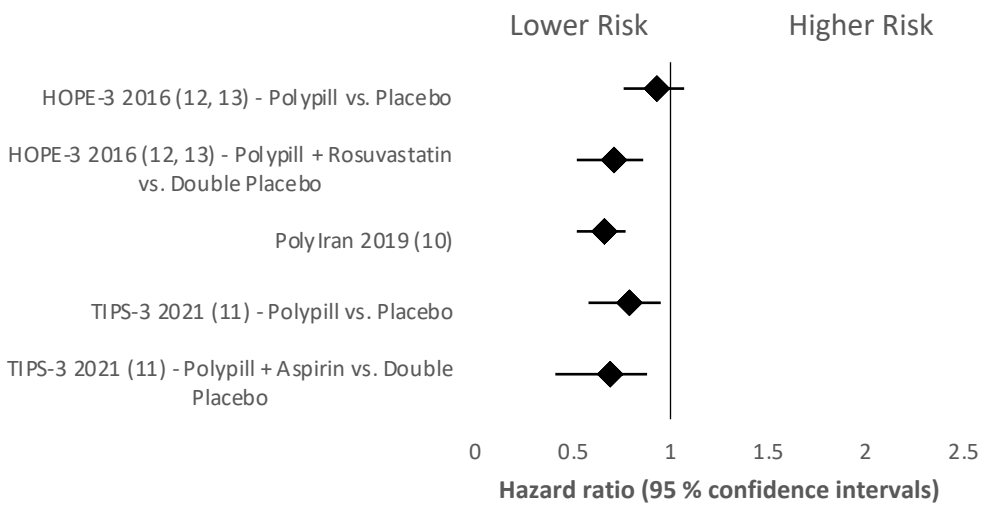

Figure 1. Forest plot demonstrating hazard ratios (95% confidence intervals) for primary outcome events in primary prevention trials (HOPE-3: Polypill vs. Placebo and Polypill + Rosuvastatin vs. Double Placebo, PolyIran, and TIPS-3: Polypill vs. Placebo and Polypill + Aspirin vs. Double Placebo). Adapted from references 10-13.

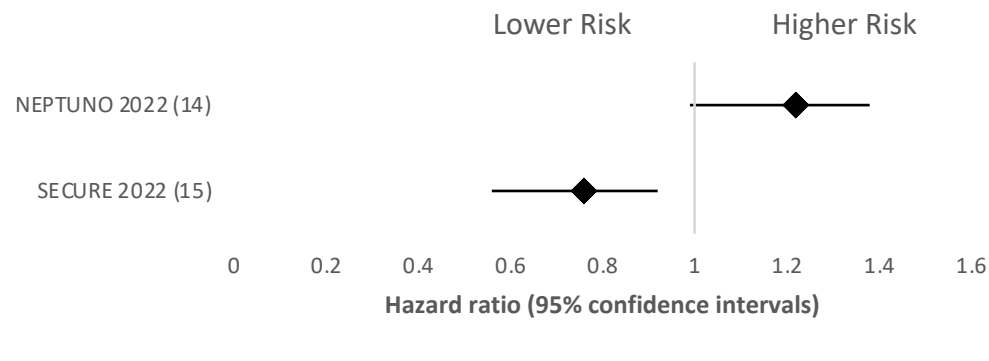

Figure 2. Forest plot demonstrating hazard ratios (95% confidence intervals) for major acute cardiovascular events (MACE) events in the SECURE and NEPTUNO trials on the use of polypills versus usual care in a secondary prevention setting. Adapted from references 14 and 15.

Table 3. FDC polypill combinations in secondary prevention trials

Trial	Design	Patients	Formulation of polypill	Primary outcome
FOCUS 2014 (5)	Randomised controlled trial Polypill vs. control group (the same three medications taken separately)	N=695	Aspirin 100mg Simvastatin 40mg Ramipril 2.5mg, 5mg or 10mg	Adherence using MAQ + pill count: 50.8% vs. 41% (p=0.019) No difference in BP and cholesterol levels
NEPTUNO 2022 (14)	Retrospective observational study Polypill vs. three control groups Control 1: Monocomponents (identical polypill medications taken separately) Control 2: Equipotent medication (Aspirin + Simvastatin or Rosuvastatin + Enalapril or Valsartan) Control 3: Other therapies (other medications than those listed above from ASA, Statin and ACEI/ARB classes)	N=6456	Aspirin 100mg Ramipril 2.5mg, 5mg or 10mg Atorvastatin 20mg or 40mg	Recurrent MACE: Control 1: 19.8% vs. 23.3% (HR 1.22, 95% CI 1.06-1.45) Control 2: 19.8% vs. 25.5% (HR 1.25, 95% CI 1.08-1.43) Control 3: 19.8% vs. 26.8% (HR 1.27, 95% CI 1.10-1.41)
SECURE 2022 (15)	Randomised controlled trial Polypill vs. usual care	N=2499	Aspirin 100mg Ramipril 2.5mg, 5mg or 10mg Atorvastatin 20mg or 40mg	Cardiovascular death, nonfatal type 1 myocardial infarction, nonfatal ischaemic stroke, or urgent revascularisation: 9.5% vs. 12.7% (HR 0.76, 95% CI 0.60-0.96, p<0.001 for non-inferiority, p=0.02 for superiority)

ACEI = angiotensin-converting enzyme inhibitors; ARB = Angiotensin receptor blocker; ASA = acetylsalicylic acid; BP = Blood Pressure; CI = confidence interval; FOCUS = Fixed-dose Combination Drug for Secondary Cardiovascular Prevention; HR = hazard ratio; MACE = Major Acute Cardiovascular Events; MAQ = Morisky-Green Questionnaire; NEPTUNO = CNIC-Polypill reduces recurrent major cardiovascular events in secondary prevention; SECURE = Secondary prevention of cardiovascular disease in the Elderly.

SECURE Trial

The SECURE trial (published in the New England Journal of Medicine) was conducted across seven European countries (Spain, Italy, France, Germany, Poland, Czech Republic, Hungary) and randomly allocated 2499 patients who had type 1 MI within the previous 6 months, to receive a Polypill or usual care over a median of 3 years. The polypill was marketed as Trinomia® which contained two formulations: Polypill AAR40 (Aspirin 100mg, Atorvastatin 40mg, Ramipril) and Polypill AAR20 (Aspirin 100mg, Atorvastatin 20mg, Ramipril). Each formulation had three different doses of Ramipril (2.5mg, 5mg, 10mg). A low dose of Ramipril would be used if patients were not on it before, but those with prior treatment would receive a bioequivalent dose. The statin dose would depend on patients' blood results and symptoms.

The usual-care arm of the trial was of patients treated according to the ESC (European Society of Cardiology) guidelines for secondary prevention. Patients were followed up for a minimum of 2 years and a maximum of 4 years. There were 3 follow up visits at month 6, 12 and 24 and telephone follow up calls at month 18, 36, and 48.

The SECURE trial population were predominantly white (98%) and above 65 years of age which is representative of the acute coronary syndrome (ACS) population in the UK. However, the polypill combination had a higher dose of aspirin, did not include beta blockers and only moderate (rather than high) intensity statins were used.

A striking observation was that alongside the polypill, patients continued their existing medications. In the study, 82% of patients were already taking beta blockers, 94% were taking an additional antiplatelet agent, and 18.5% were taking a calcium-channel blocker. This makes extrapolating data for clinical use challenging. For example, the choice of P2Y12 inhibitor used was not specified and may contribute to any difference in outcomes. Additionally, the treatment for the usual-care group was not clearly defined and difficult to follow making it challenging to draw comparisons. Various types of statins and angiotensin-converting enzyme inhibitors at different strengths were used in this group. Similarly, it is difficult to establish the criteria and rationale for the choice of medications.

Conclusion

The concept of polypills is intriguing and potentially applicable in post-ACS patients who are sent home with multiple new medications. Simplification of management improves medications adherence as supported by the trials described in this editorial; consequently, improving risk factor control. The SECURE trial was the first randomised controlled trial assessing the impact of polypill use on cardiovascular outcomes as secondary prevention. Although the study was positive and showed improved adherence and reduction in MACE with the polypill compared to usual care, it is difficult to make confident conclusions due to a lack of clarity in the usual care arm and differences in UK practice. Further randomised controlled trials are needed to examine the effect of polypills alone compared with the same components taken separately to derive at a more accurate conclusion.

Disclosures

None

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