The 2016 Joint European Prevention Guidelines and the uses of polypills: time to update the evidence

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The 2016 European Guidelines on cardiovascular disease prevention in clinical practice[1] were the first major international guideline to address the potential uses of polypills (single dose formulations including a statin, anthihypertensives and aspirin), which is important because the first polypill has recently been launched throughout Europe. However, the Guidelines largely did not address the most obvious use of polypills – as a strategy to increase uptake and adherence to guideline-recommended medicines. Instead the Guidelines focused on a still-controversial use of polypills, in primary prevention for everyone over a certain age. ~~Moreover, the need for cardiovascular endpoint trials was emphasized. This is a "straw man" approach: asking the question "should the polypill be given universally?", rather than a much more relevant question "for what patients could currently available polypills provide worthwhile improvements in adherence?".~~

Elsewhere in the Guidelines the importance of providing statin, aspirin and BP lowering therapy to patients with CVD is emphasised, along with acknowledging the importance of adherence and the need for new strategies because current levels of adherence to cardiovascular medications are generally poor. A major intended use of the polypill is as a strategy to overcome these barriers to uptake and access to guideline recommended treatments – as reflected in many of the early publications[2-4] and the majority of subsequent trials. We suggest that the discussion on the potential role of a polypill in improving adherence to cardio-protective drugs should be updated in the Guidelines in the light of additional evidence. This article attempts to provide a suggested framework for considering the randomized evidence~~, and discusses when a cardiovascular endpoint trial should and should not be required~~. With the guidelines due for review and updating ~~in 2019~~shortly, and additional trial evidence available, it is timely to reconsider the polypill narrative within the guidelines.

Suggested ~~criteria~~ use cases for ~~discussing uses~~updating the evidence for ~~of~~ the polypill in CVD prevention

The guidelines currently note publication of a recent meta-analysis[5] showing improved risk factor levels with use of a polypill, however criticize this meta-analysis as having multiple comparators and diverse composition and doses of included polypills. The rationale behind the various polypill trials conducted thus far has varied from establishing short-term effects on risk factors and side effects of polypills vs placebo thus demonstrating efficacy and safety of the product, through to establishing effectiveness against usual care of these patients within pragmatic trial settings. The type of patient targeted by each trial has also varied including secondary prevention,[6,7] high-risk primary prevention[7,8], and age over 55 years.[9] This explains the diversity of comparators. And the diversity of doses and agents is to be expected

– there are millions of permutations of recommended drugs, and so it is to be expected there will be numerous polypill versions.

~~Along with other colleagues w~~We suggest that it would be useful to consider the potential benefit and the scientific evidence for use of polypills in ~~four distinct potential areas~~two distinct patient groups:

1. Established indications for all polypill medicines (ie. Guidelines and approved labels recommend drugs should be used in this patient group), patient taking drugs already as separate pills. This use can be called "established indications, straight substitution"
2. Established indications for all polypill medicines, but not taking them all due to barriers in uptake and/or adherence. This use can be called "established indications, step-up substitution", since patients who are taking some but not all therapy (eg. aspirin and statin but no blood pressure lowering) ~~stop that therapy (at least the aspirin and statin component) and~~ are switched to a polypill containing aspirin, statin and blood pressure lowering.
3. ~~Established indications for some of the polypill medicines, and patient-level prediction that absolute benefits will exceed risks – "high risk primary prevention". In this use, all patients would have a raised risk of cardiovascular disease, as a result of a constellation of clinical conditions and/or a high global cardiovascular risk score, and would be treated with the polypill as a global risk reduction strategy in which it is expected that benefits would exceed side effects. This might include use of some component medicines in a way that did not match current approved labels (eg. aspirin for patients without symptomatic atherosclerotic vascular disease, blood pressure lowering for patients without hypertension)~~
4. ~~No established indications, but estimation that individual and population-level benefits will be worthwhile eg. a strategy to provide polypills to everyone aged over >55yrs. No drug has a registered indication of "age >55 years" and so this use would be in addition to currently approved labelling.~~

~~The guidelines currently note publication of a recent meta-analysis[5] showing improved risk factor levels with use of a polypill, however criticize this meta-analysis as having multiple comparators and diverse composition and doses of included polypills. The reason for the disparity of comparator groups and patient populations was because different trials were testing different use indications. The rationale behind the various polypill trials conducted thus far has varied from establishing short-term effects on risk factors~~

~~and side effects of polypills vs placebo (mostly with relevance to uses 3 and 4 above), through to establishing effectiveness against usual care of these patients within pragmatic trial settings (testing uses 1 and 2 above). The type of patient targeted by each trial has also varied including secondary prevention,[6,7] high risk primary prevention[7,8], and age over 55 years.[9] This explains the diversity of comparators. And the diversity of doses and agents is to be expected – there are millions of permutations of recommended drugs, and so it is to be expected there will be numerous polypill versions.~~

Evidence for improved adherence with use of polypills in patients with established ~~disease or at high risk vs moderate risk primary prevention~~indications for component drugs.

The 2016 guidelines noted that only two trials[6,10] have shown improved adherence in patients with established indications - this requires updating considering a large and clinically relevant improvement in adherence has been seen in four trials now, UMPIRE, IMPACT, Kanyini-GAP and FOCUS (Figure).[6,10-12] Of note, the polypill used in the FOCUS trial contained different blood pressure lowering component (Ramipril at difference doses) to the polypill used in the other 3 trials (combination of lisinopril and hydrochlorothiazide, or lisinopril and atenolol). The FOCUS trial assessed the 1st use indication and randomized 695 patients with CHD to polypill-based care or treatment with the same drugs as three separate pills.[6] At 9 months' follow-up they observed a 10% absolute increase in adherence in the intervention group compared to the control group (65.7% vs 55.7%, p=0.012). The authors concluded that polypills could be of use to improve adherence to recommended medications in secondary prevention after myocardial infarction. The SPACE trials[10-12] (3140 patients with CVD or high risk, testing polypill-based care vs usual care) tested the polypill in uses 1 and 2 ie. Straight and step-up substitution. The comparator in these trials was usual care with no restrictions resulting in a range of different medication regimes in the usual care arm. Meta-analysis of these three SPACE Collaboration trials confirmed improvement in adherence of 30% for polypill based care compared to usual care (regardless of usual care regimen used).[7] The benefits were considerably larger for step-up substitution than for straight substitution. There were also corresponding improvements in SBP and LDL cholesterol levels over 12 months of 2.5 mmHg (95% CI -4.5 to -0.4mmHg; p=0.02) and 0.1 mmol/L (95%CI -0.2 to 0.0; p=0.04) respectively when polypill use was compared with usual care, despite the wide variety of usual care regimes that were utilized and the potential to 'tweak' therapy to maximize outcomes in that arm. ~~Benefits were seen across every subgroup of patient that was examined with no detrimental effect on safety.~~

Within all these trials no excess of side effects was seen outside of the components' ~~-~~well-established safety profiles.[13] The Guidelines currently state "potential adverse effects of a single drug component of the FDC cannot be specifically corrected and therefore may also affect treatment adherence to the other components" however we suggest that all four of these trials ~~were specifically designed to evaluate the balance of any benefits from improved adherence with any unintended adverse consequences – and~~ consistently showed that the adherence benefits were sufficiently large to outweigh the potential problems of fixed-dose combination approach.

We suggest that this provides sufficient evidence to confirm that use of polypills in patients with established disease or at high risk of developing CVD improves adherence to recommended CVD preventive medications with consequent improvement in CVD risk factor levels. Recommended medications for CVD prevention may change over time with changing evidence (e.g. recent updates to aspirin recommendations in primary prevention). For clarity, we are proposing that the concept of fixed dose combinations (polypills) containing *guidelines recommended therapies (currently statins, blood pressure lowering agents and anti-platelet therapy for secondary prevention and some high risk primary prevention)* be considered part of the armamentarium of the clinician in managing CVD risk. [14]

The need for CV endpoint trials

The Guideline ends with the statement that "Until we have the results of ongoing trials with major CVD as the endpoint, the polypill cannot be recommended for prevention of CVD and cannot be prescribed to all individuals." However, this only addresses one possible role of the polypill. As a tool to increases adherence to guideline-recommended treatments, it is not necessary or appropriate to "re-require" evidence of benefit on CV endpoints. Fixed dose combinations in many areas, such as HIV/AIDS and TB, have not been required to re-demonstrate the benefits already established for individual agents. Blood pressure combination drugs are not required to repeat the endpoint trials conducted for their components – it is now considered sufficient for the guidelines to recommend that clinicians consider prescribing dual combination therapy as initial therapy for hypertension to improve compliance. We suggest that the combination of statins, blood pressure lowering and aspirin should not be any different. We do however suggest endpoint trials may be required if the polypills are used in patient populations beyond those who have existing approved indications, such as in patients at moderate risk or using age based inclusion criteria~~, such as uses 3 and 4 above~~. A large ~~high-risk~~ primary prevention trial is ongoing

(TIPS3) funded by The Wellcome Trust, Canadian Institutes of Health Research and Heart and Stroke Foundation of Ontario and this will provide additional evidence as to the risk-benefit ratio of polypills in ~~this population~~patients without established indications for component therapy. Although highly persuasive arguments can be mounted that the evidence for individual components is overwhelming, including evidence of benefit in the presence of other components, the key factor is that drug regulations do not currently allow such usage until new supportive clinical trial evidence is provided.

Conclusion

There is now a polypill available throughout Europe – Trinomia® containing atorvastatin, ramipril and aspirin. Additional polypills containing different blood pressure components are also likely to be launched, and some combination therapies without aspirin (e.g. Triveram®) for patients with a contraindication for aspirin are also now on the market. The Guidelines have an important opportunity to guide clinicians on the potential role of this new strategy to help patients and prescribers reach guideline goals. A consistent high level of patient and prescriber acceptability has been demonstrated for polypills as a strategy to improve adherence to guideline-recommended therapy.[15] We support the revision of the guidelines to include recommendations around the use of the polypill as a tool to improve adherence in those with established indications for aspirin, statin and blood pressure lowering therapy and more broadly for combination therapy containing statin and blood pressure lowering medication.

Contributions of authors

All authors conceived and refined the paper idea. RW drafted and revised the paper. All authors provided critical input and commentary.

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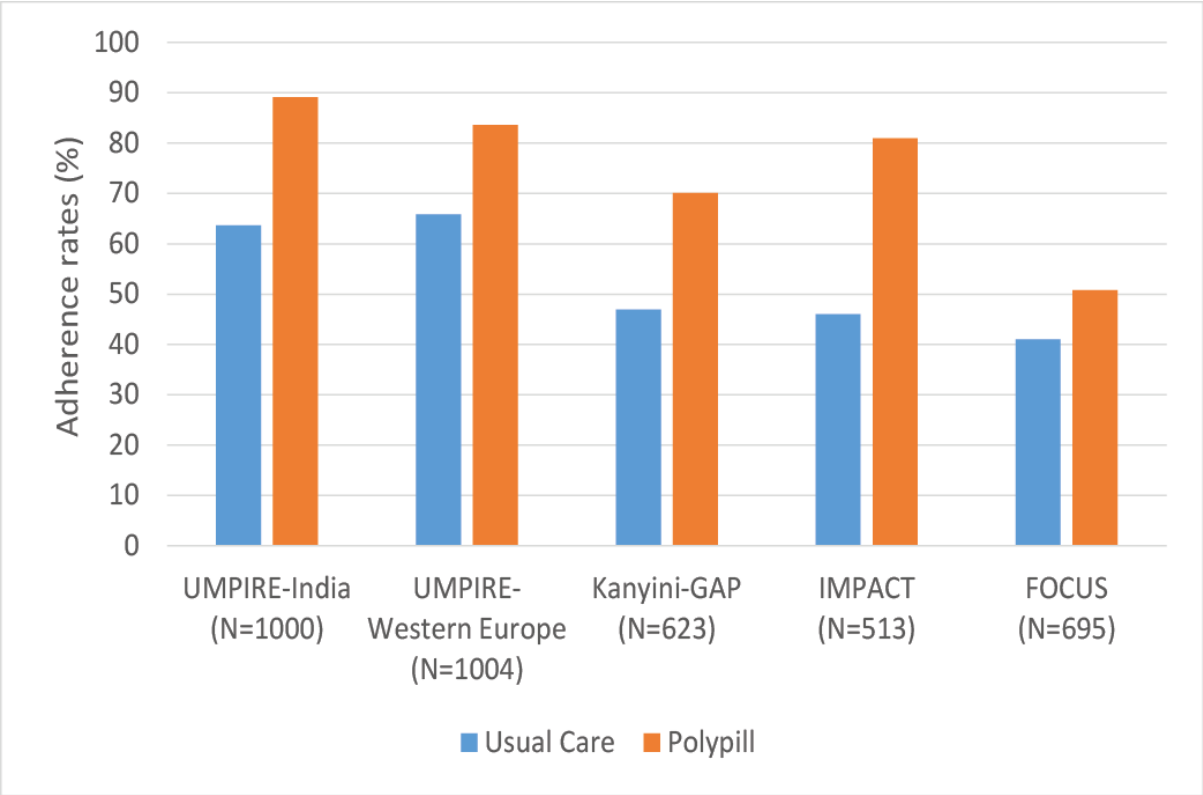

Figure 1. Proportion of trial participants adherent to combination therapy at end of study in participants with either established CVD or at high calculated risk. Adherence defined as taking antiplatelet, statin and ≥ 2 BP lowering drugs at least 4 days of the last 7 at end of study in UMPIRE[10], Kanyini-GAP[11] and IMPACT[12]. Adherence defined in the FOCUS[6] trial as pill count between 80 and 110% at end of study plus a score of 20/20 on the Morisky-Green questionnaire.